Washington State Health Care Authority

Health Technology Assessment

Catheter Ablation Procedures For Supraventricular Tachyarrhythmia

Including Atrial Flutter & Atrial Fibrillation

Final Evidence Report - Appendices

April 17, 2013

Health Technology Assessment Program (HTA)

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Catheter ablation procedures for supraventricular tachyarrhythmia (SVTA) including atrial flutter and atrial fibrillation

Provided by:

Spectrum Research, Inc.

Final Report
APPENDICES

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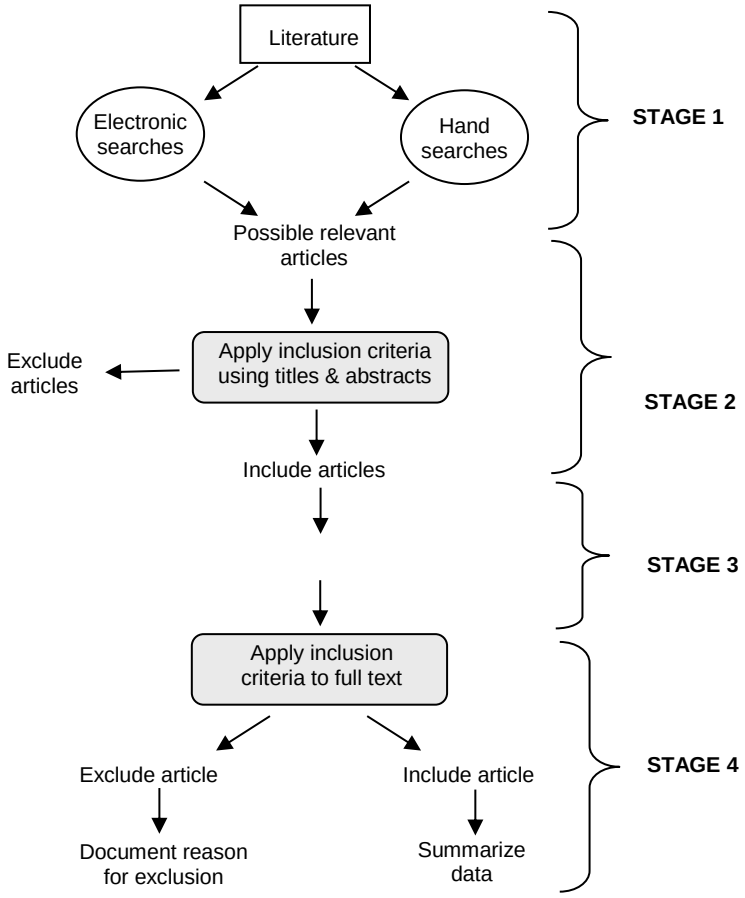
Appendix A. Algorithm for Article Selection



Appendix B. Search Strategies

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources.

Atrial fibrillation:
Search performed through 09/25/2012
PubMed Search strategy: identify studies published after AHRQ HTA's search period (through November, 2008)
Limits Activated: Publication date from 2008/11/01; Humans; English

	Search terms	Number of Articles
1.	atrial fibrillation OR Atrial Fibrillation[MeSH]	7974
2.	*ablation OR pulmonary vein* OR Pulmonary Veins[MeSH] OR "Pulmonary vein isolation" OR "Pulmonary vein antrum isolation" OR Heart Catheterization[MeSH] OR Cryoablation OR "cryoballoon ablation" OR (Cryosurgery[MeSH} AND ablat*) OR (("atrioventricular node" OR "AV node" OR "AV nodal" OR "atrioventricular junction" OR "AV junction") AND ablat*))	14,440
3.	#1 AND #2	2282
4.	Addresses[Publication Type] OR Bibliography[Publication Type] OR Case Reports[Publication Type] OR Comment[Publication Type] OR Editorial[Publication Type] OR Lectures[Publication Type] OR Legal Cases[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Newspaper Article[Publication Type]) OR Review[Publication Type]	545,983

	Search terms	Number of Articles
5.	#3 NOT #4	1336
	Additional studies identified through hand searching and searching PubMed for related literature	34
	Additional studies included in the AHRQ HTA	113
	Final number of studies identified to assess for inclusion (with publication data starting in November, 2008)	**1483**

Atrial flutter:
Search performed through 09/27/2012
PubMed Search strategy: identify studies published starting in January, 2000 in order to focus on studies using newer catheter tips, to include irrigated catheters and 8 mm tip catheters. Conventional tips are considered outdated for catheter ablation of atrial flutter.
Limits Activated: Humans; English; Publication Date 01/01/2000 to present

	Search Terms	Number of Articles
1.	(atrial flutter) OR Atrial Flutter[MeSH] OR (macroreentrant atrial tachycardia*) OR (typical flutter) OR (atypical flutter) OR (isthmus AND flutter)	2368
2.	*ablation OR pulmonary vein* OR Pulmonary Veins[MeSH] OR "Pulmonary vein isolation" OR "Pulmonary vein antrum isolation" OR Catheter Ablation[MeSH] OR Ablation OR Cryoablation OR “cryoballoon ablation” OR (Cryosurgery[MeSH} AND ablat*) OR (microwave AND ablat*)	27,870

	Search Terms	Number of Articles
3.	#1 AND #2	1068
4.	(Addresses[Publication Type] OR Bibliography[Publication Type] OR Case Reports[Publication Type] OR Comment[Publication Type] OR Editorial[Publication Type] OR Lectures[Publication Type] OR Legal Cases[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Newspaper Article[Publication Type]) OR Review[Publication Type])	1,674,101
5.	#3 NOT #4	707
	Additional studies identified through hand searching and searching PubMed for related literature	6
	Final number of studies identified to assess for inclusion (with publication data starting in November, 2008)	**713**

Supraventricular tachyarrhythmias:
Search performed through 09/27/2012
PubMed Search strategy: identify studies published starting in January, 1985 in order identify all studies that report on catheter ablation of SVTs. Our clinical expert advised that conventional tips are still in use to treat SVTs, thus they will be included in the evaluation.
Limits Activated: Humans; English; Publication Date 01/01/1985 to present

	Search Terms	Number of Articles
1.	(((Supraventricular AND (arrhythmia* OR tachycardia*)) OR Tachycardia, Supraventricular[MeSH])	6945

	Search Terms	Number of Articles
2.	((sinus AND (tachycardia* OR tachyarrhythmia*)) OR Tachycardia, Sinus[MeSH])	4581
3.	(((Atrioventricular OR accessory OR node OR nodal OR extranodal OR reciprocating) AND (arrhythmia* OR tachycardia*)) OR AVNRT OR AVRT OR (Wolf AND Parkinson AND White) OR Wolf-Parkinson-White Syndrome[MeSH])	8293
4.	((Junctional AND (tachycardia* OR tachyarrhythmia)) OR Tachycardia, Ectopic Junctional[MeSH])	705
5.	(((focal OR multifocal atrial) AND (arrhythmia* OR tachycardia*)) OR Tachycardia, Ectopic Atrial[MeSH])	1346
6.	#1 OR #2 OR #3 OR #4 OR #5	15,299
7.	*ablation OR pulmonary vein* OR Pulmonary Veins[MeSH] OR "Pulmonary vein isolation" OR "Pulmonary vein antrum isolation" OR Catheter Ablation[MeSH] OR Ablation OR Cryoablation OR “cryoballoon ablation” OR (Cryosurgery[MeSH} AND ablat*) OR (microwave AND ablat*)	37,773
8.	#6 AND #7	4502

	Search Terms	Number of Articles
9.	(Addresses[Publication Type] OR Bibliography[Publication Type] OR Case Reports[Publication Type] OR Comment[Publication Type] OR Editorial[Publication Type] OR Lectures[Publication Type] OR Legal Cases[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Newspaper Article[Publication Type]) OR Review[Publication Type])	2,778,248
10.	#8 NOT #9	2438
	Additional studies identified through hand searching and searching PubMed for related literature	64
	Final number of studies identified to assess for inclusion (with publication data starting in November, 2008)	**2502**

Summary of combined literature searches

When results from all three literature searches were combined and duplicate references were deleted, there were a total of 4295 citations.

Parallel strategies were used to search the Cochrane Library, EMBASE and others listed below. Keyword searches were conducted in the other listed resources.

Electronic Database Searches

The following databases have been searched for relevant information:
Agency for Healthcare Research and Quality (AHRQ)
Cumulative Index to Nursing and Allied Health (CINAHL)
Cochrane Database of Systematic Reviews
Cochrane Registry of Clinical Trials (CENTRAL)
Cochrane Review Methodology Database
Database of Reviews of Effectiveness (Cochrane Library)
EMBASE
PubMed
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database
HSTAT (Health Services/Technology Assessment Text)
EconLIT

Additional Economics, Clinical Guideline and Gray Literature Databases

AHRQ - Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

Appendix C. Excluded Articles

Table C1. Articles excluded as primary studies after full text review, with reason for exclusion.

	Citation	Reason for Exclusion
	Studies considered and excluded for Key Question 1: atrial fibrillation (n = 12)	
1.	Bunch TJ, Crandall BG, Weiss JP, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. J Cardiovasc Electrophysiol 2011;22:839-45.	Not clear that AF ablation patients were treated with PVI; Database study, we have higher quality studies (RCTs) available to evaluate this key question.
2.	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). J Am Coll Cardiol 2011;58:493-501.	Treatments used not specified beyond "rhythm control" or "rate control".
3.	Carnlof C, Insulander P, Pettersson PH, Jensen-Urstad M, Fossum B. Health-related quality of life in patients with atrial fibrillation undergoing pulmonary vein isolation, before and after treatment. Eur J Cardiovasc Nurs 2010;9:45-9.	Indirect comparison (ablation versus published cohort study of control group)
4.	Dong K, Shen WK, Powell BD, et al. Atrioventricular nodal ablation predicts survival benefit in patients with atrial fibrillation receiving cardiac resynchronization therapy. Heart Rhythm 2010;7:1240-5.	AV node ablation, not PVI
5.	Hunter RJ, McCready J, Diab I, et al. Maintenance of sinus rhythm with an ablation strategy in patients with atrial fibrillation is associated with a lower risk of stroke and death. Heart 2012;98:48-53.	Indirect comparison (ablation versus published cohort study of medically managed patients)
6.	Liu Z, Ling Z, Su L, et al. The effect of different treatment strategies on left atrial size in patients with lone paroxysmal atrial fibrillation-a prospective cohort study. J Interv Card Electrophysiol 2008;23:167-73.	Duplicate study with Lan 2009 but with fewer outcomes reported

	Citation	Reason for Exclusion
7.	Oral H, Chugh A, Yoshida K, et al. A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. J Am Coll Cardiol 2009;53:782-9.	All patients had previously received ablation
8.	Pappone C, Radinovic A, Manguso F, et al. Atrial fibrillation progression and management: a 5-year prospective follow-up study. Heart Rhythm 2008;5:1501-7.	Results not stratified by treatment given, except freedom from arrhythmia, but this outcome was reported for less than 100 patients.
9.	Pokushalov E, Romanov A, Corbucci G, et al. Use of an implantable monitor to detect arrhythmia recurrences and select patients for early repeat catheter ablation for atrial fibrillation: a pilot study. Circ Arrhythm Electrophysiol 2011;4:823-31.	All patients had previously received ablation
10.	Reynolds MR, Gunnarsson CL, Hunter TD, et al. Health outcomes with catheter ablation or antiarrhythmic drug therapy in atrial fibrillation: results of a propensity-matched analysis. Circ Cardiovasc Qual Outcomes 2012;5:171-81.	Not clear that AF ablation patients were treated with PVI; Database study, we have higher quality studies (RCTs) available to evaluate this key question.
11.	Reynolds MR, Walczak J, White SA, et al. Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. *Circ Cardiovasc Qual Outcomes* 2010;3:615-23.	Same data as reported in Wilber (2010) study[1]; the additional data on SF-36 outcomes (reported after 3 months follow-up) were analyzed according to treatment given, not treatment allocated.
12.	Schutte F, Ludorff G, Grove R, Kranig W, Thale J. Atrioventricular node ablation is not a prerequisite for cardiac resynchronization therapy in patients with chronic atrial fibrillation. Cardiol J 2009;16:246-9.	AV node ablation, not PVI
	Studies considered and excluded for Key Question 1: atrial flutter (n = 2)	
13.	Luria DM, Hodge DO, Monahan KH, et al. Effect of radiofrequency ablation of atrial flutter on the natural history of subsequent atrial arrhythmias. J Cardiovasc Electrophysiol 2008;19:1145-50.	High risk of bias (historical control from "preablation era" (195=65 – 1995), and no information provided on how the control group was selected (59 patients selected from patient base of 567 patients)

	Citation	Reason for Exclusion
14.	Natale A, Newby KH, Pisano E, et al. Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter. J Am Coll Cardiol 2000;35:1898-904.	84% of patients in the ablation group received ablation with a 4 mm conventional tip only.
15.	Schmidt M, Daccarett M, Segerson N, et al. Atrial flutter ablation in inducible patients during pulmonary vein atrum isolation: a randomized comparison. Pacing Clin Electrophysiol 2008;31:1592-7.	All patients received ablation
	Studies considered and excluded for Key Question 1: SVTs	
16.	Bathina MN, Mickelsen S, Brooks C, et al. Radiofrequency catheter ablation versus medical therapy for initial treatment of supraventricular tachycardia and its impact on quality of life and healthcare costs. *The American journal of cardiology* 1998;82:589-93.	Duplicate study (to the included Goldberg 2002 study) but with shorter follow-up.
17.	Lau CP, Tai YT, Lee PW. The effects of radiofrequency ablation versus medical therapy on the quality-of-life and exercise capacity in patients with accessory pathway-mediated supraventricular tachycardia: a treatment comparison study. Pacing Clin Electrophysiol 1995;18:424-32.	Less than 10 patients per treatment group.
18.	Mainigi SK, Almuti K, Figueredo VM, et al. Usefulness of radiofrequency ablation of supraventricular tachycardia to decrease inappropriate shocks from implantable cardioverter-defibrillators. The American journal of cardiology 2012;109:231-7.	Exclude: outcomes not of interest (focus on further inappropriate ICD therapies)
19.	Nagamoto Y, Inage T, Yoshida T, et al. Atrioventricular nodal ablation versus antiarrhythmic drugs after permanent pacemaker implantation for bradycardia-tachycardia syndrome. Heart Vessels 2012;27:174-8.	AV node ablation + pacemaker
	Studies considered and excluded for Key Question 1a: Atrial flutter	
1.	Wang F, Huang CX, Chen G, et al. Safety and efficacy of cryothermal and radiofrequency catheter ablation in treatment of typical atrial flutter. *Chin Med J (Engl)* 2007;120:1007-9.	Less than 10 patients per treatment group.
	Studies considered and excluded for Key Question 1a: SVTs	

	Citation	Reason for Exclusion
2.	Kimman GP, Theuns DA, Szili-Torok T, et al. CRAVT: a prospective, randomized study comparing transvenous cryothermal and radiofrequency ablation in atrioventricular nodal re-entrant tachycardia. *European heart journal* 2004;25:2232-7.	Duplicate study (same patient set as Kimman 2006).
3.	Park KM, Rhee KS, Jin ES, et al. Effects of slow pathway ablation on fast pathway function in patients with atrioventricular nodal reentrant tachycardia: cryo- vs. radiofrequency ablation. *Circ J* 2012;76:1091-6.	No clinical results reported.
	Studies considered and excluded for Key Question 2	
1.	Bittner A, Monnig G, Zellerhoff S, et al. Randomized study comparing duty-cycled bipolar and unipolar radiofrequency with point-by-point ablation in pulmonary vein isolation. Heart Rhythm 2011;8:1383-90.	Compares different types of catheter tips.
2.	Boersma LV, Castella M, van Boven W, et al. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST): a 2-center randomized clinical trial. Circulation 2012;125:23-30.	Used conventional 4 mm tip only.
3.	Breda JR, Breda AS, Ragognette RG, et al. Comparison of uniatrial and biatrial radiofrequency ablation procedures in atrial fibrillation: initial results. Heart Surg Forum 2011;14:E271-5.	Surgical ablation only.
4.	Bulava A, Hanis J, Sitek D, et al. Catheter ablation for paroxysmal atrial fibrillation: a randomized comparison between multielectrode catheter and point-by-point ablation. Pacing Clin Electrophysiol 2010;33:1039-46.	Compares different types of catheter tips.
5.	Dixit S, Marchlinski FE, Lin D, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. Circ Arrhythm Electrophysiol 2012;5:287-94.	All patients had previously undergone ablation for AF.
6.	Estner HL, Hessling G, Ndrepepa G, et al. Electrogram-guided substrate ablation with or without pulmonary vein isolation in patients with persistent atrial fibrillation. Europace 2008;10:1281-7.	Nonrandomized comparison.

	Citation	Reason for Exclusion
7.	Hunter RJ, Diab I, Tayebjee M, et al. Characterization of fractionated atrial electrograms critical for maintenance of atrial fibrillation: a randomized, controlled trial of ablation strategies (the CFAE AF trial). Circ Arrhythm Electrophysiol 2011;4:622-9.	Data for the outcome of interest only reported for 6 patients in one group and 8 patients in the other group.
8.	Khaykin Y, Skanes A, Champagne J, et al. A randomized controlled trial of the efficacy and safety of electroanatomic circumferential pulmonary vein ablation supplemented by ablation of complex fractionated atrial electrograms versus potential-guided pulmonary vein antrum isolation guided by intracardiac ultrasound. *Circ Arrhythm Electrophysiol* 2009;2:481-7.	Assessment of different types of guidance seems to be the main focus.
9.	Kojodjojo P, O'Neill MD, Lim PB, et al. Pulmonary venous isolation by antral ablation with a large cryoballoon for treatment of paroxysmal and persistent atrial fibrillation: medium-term outcomes and non-randomised comparison with pulmonary venous isolation by radiofrequency ablation. Heart 2010;96:1379-84.	Nonrandomized comparison.
10.	Kuhne M, Suter Y, Altmann D, et al. Cryoballoon versus radiofrequency catheter ablation of paroxysmal atrial fibrillation: biomarkers of myocardial injury, recurrence rates, and pulmonary vein reconnection patterns. Heart Rhythm 2010;7:1770-6.	Nonrandomized comparison.
11.	Lan X, Su L, Ling Z, et al. Catheter ablation vs. amiodarone plus losartan for prevention of atrial fibrillation recurrence in patients with paroxysmal atrial fibrillation. Eur J Clin Invest 2009;39:657-63.	Nonrandomized comparison.
12.	Oral H, Chugh A, Yoshida K, et al. A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. J Am Coll Cardiol 2009;53:782-9.	Exclude- not a true RCT for the purposes of assessing ablation approach: all patients underwent PVAI, then those who failed were randomized to receive ablation of CFAEs or cardioversion.
13.	Senga M, Fujii E, Sugiura S, et al. Efficacy of linear block at the left atrial roof in atrial fibrillation. J Cardiol 2010;55:322-7.	Nonrandomized comparison.

	Citation	Reason for Exclusion
14.	Tamborero D, Mont L, Berruezo A, et al. Circumferential pulmonary vein ablation: does use of a circular mapping catheter improve results? A prospective randomized study. Heart Rhythm 2010;7:612-8.	Approach the same in both groups, evaluated the use of additional circular mapping catheter.
15.	Verma A, Sanders P, Macle L, et al. Selective CFAE targeting for atrial fibrillation study (SELECT AF): clinical rationale, design, and implementation. J Cardiovasc Electrophysiol 2011;22:541-7.	Study design only.
	Studies considered and excluded for Key Question 3: atrial fibrillation	
1.	Bohnen M, Stevenson WG, Tedrow UB, et al. Incidence and predictors of major complications from contemporary catheter ablation to treat cardiac arrhythmias. *Heart Rhythm* 2011;8:1661-6.	Less than 1000 AF patients included
2.	Hoyt H, Bhonsale A, Chilukuri K, et al. Complications arising from catheter ablation of atrial fibrillation: temporal trends and predictors. *Heart Rhythm* 2011;8:1869-74.	Less than 1000 AF patients included
3.	Hussein AA, Martin DO, Saliba W, et al. Radiofrequency ablation of atrial fibrillation under therapeutic international normalized ratio: a safe and efficacious periprocedural anticoagulation strategy. *Heart Rhythm* 2009;6:1425-9.	Not clearly a prospective study
4.	Contreras-Valdes FM, Heist EK, Danik SB, et al. Severity of esophageal injury predicts time to healing after radiofrequency catheter ablation for atrial fibrillation. *Heart Rhythm* 2011;8:1862-8.	Not clearly a prospective study (Considered for esophageal lesions)
5.	Kuwahara T, Takahashi A, Kobori A, et al. Safe and effective ablation of atrial fibrillation: importance of esophageal temperature monitoring to avoid periesophageal nerve injury as a complication of pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2009;20:1-6.	Not clearly a prospective study (Considered for esophageal lesions)
6.	Chilukuri K, Sinha S, Berger R, et al. Association of transseptal punctures with isolated migraine aura in patients undergoing catheter ablation of cardiac arrhythmias. *J Cardiovasc Electrophysiol* 2009;20:1227-30.	Not clearly a prospective study (Considered for procedure-induced migraines)

	Citation	Reason for Exclusion
7.	Noheria A, Roshan J, Kapa S, et al. Migraine headaches following catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol* 2011;30:227-32.	Retrospective (Considered for procedure-induced migraines)
8.	Kidouchi T, Suzuki S, Furui S, et al. Entrance skin dose during radiofrequency catheter ablation for tachyarrhythmia: a multicenter study. *Pacing Clin Electrophysiol* 2011;34:563-70.	Not clearly a prospective study (Considered for radiation exposure)
Studies considered and excluded for Key Question 3: SVTs		
9.	Kay GN, Epstein AE, Dailey SM, et al. Role of radiofrequency ablation in the management of supraventricular arrhythmias: experience in 760 consecutive patients. *Journal of cardiovascular electrophysiology* 1993;4:371-89.	Not clearly a prospective study
10.	Rostock T, Risius T, Ventura R, et al. Efficacy and safety of radiofrequency catheter ablation of atrioventricular nodal reentrant tachycardia in the elderly. *Journal of cardiovascular electrophysiology* 2005;16:608-10.	Not clearly a prospective study
11.	Schwieler JH, Zlochiver S, Pandit SV, et al. Reentry in an accessory atrioventricular pathway as a trigger for atrial fibrillation initiation in manifest Wolff-Parkinson-White syndrome: a matter of reflection? *Heart Rhythm* 2008;5:1238-47.	Not clearly a prospective study
12.	Rosenthal LS, Mahesh M, Beck TJ, et al. Predictors of fluoroscopy time and estimated radiation exposure during radiofrequency catheter ablation procedures. *The American journal of cardiology* 1998;82:451-8.	Not clearly a prospective study (Considered for radiation exposure)
13.	Scanavacca M, d'Avila A, Velarde JL, et al. Reduction of radiation exposure time during catheter ablation with the use of pulsed fluoroscopy. *International journal of cardiology* 1998;63:71-4.	Not clearly a prospective study (Considered for radiation exposure)
14.	Rogers DP, England F, Lozhkin K, et al. Improving safety in the electrophysiology laboratory using a simple radiation dose reduction strategy: a study of 1007 radiofrequency ablation procedures. *Heart* 2011;97:366-70.	Purpose was to evaluate varying techniques to improve safety by reducing radiation exposure- not to measure radiation exposure during typical ablation procedures. (Considered for radiation exposure)

	Citation	Reason for Exclusion
	Studies considered and excluded for Key Question 5: atrial fibrillation	
1.	Khaykin Y, Morillo CA, Skanes AC, et al. Cost comparison of catheter ablation and medical therapy in atrial fibrillation. *J Cardiovasc Electrophysiol* 2007;18:907-13.	Assumes RFA to be more effective and compares cost of RFA vs. medical therapy. **Only accounts for costs.**
2.	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. *J Cardiovasc Electrophysiol* 2009;20:7-12.2009[2]	A more detailed cost comparison over time using a decision tree model to compares cost of RFA vs. AAD. Does not address relative effectiveness. **Only accounts for costs.**
3.	Kim MH, Lin J, Kreilick C, et al. Total costs and atrial fibrillation ablation success or failure in Medicare-aged patients in the United States. *Adv Ther* 2010;27:600-12.	Tests for statistically significant difference in cost of successful vs. unsuccessful ablation. **Only accounts for costs. No comparator.**
4.	Ladapo JA, David G, Gunnarsson CL, et al. Healthcare utilization and expenditures in patients with atrial fibrillation treated with catheter ablation. *J Cardiovasc Electrophysiol* 2012;23:1-8.	Uses regression to model how ablation procedures affect resources and expenditures. Looks at costs and resource use over time. **No comparator or effectiveness measure.**
5.	Medical Advisory Secretariat. Ablation for atrial fibrillation: an evidence-based analysis. Toronto: Ontario Health Technology Assessment Series, 2006:62.	Examines costs and effectiveness separately. Mentions an incomplete cost-utility analysis. Also includes a brief non-primary review of cost effectiveness (p. 43). **Cost-only.**
6.	Noro M, Kujime S, Ito N, et al. Cost effectiveness of radiofrequency catheter ablation vs. medical treatment for atrial fibrillation in Japan. -Cost performance for atrial fibrillation. *Circ J* 2011;75:1860-6.	Conducts a cost comparison between medical therapy and RFA. Mentions advantages of RFA but no quantitative comparison of effects is given. **Primarily a costing study.**
	Studies considered and excluded for Key Question 5: atrial flutter	
7.	Rodgers M, McKenna C, Palmer S, et al. Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation. *Health Technol Assess* 2008;12:iii-iv, xi-xiii, 1-198.	Exclude- cost effectiveness analysis limited to paroxysmal AF, not extended to atrial flutter

	Citation	Reason for Exclusion
	Studies considered and excluded for Key Question 5: SVTs	
8	Bathina MN, Mickelsen S, Brooks C, et al. Radiofrequency catheter ablation versus medical therapy for initial treatment of supraventricular tachycardia and its impact on quality of life and healthcare costs. *The American journal of cardiology* 1998;82:589-93.	Cost study only. Tests for the difference in quality of life between medical therapy and ablation using SF-36 score. Also gives the associated costs of the treatments. **Does not quantitatively relate the two measures.**
9	Goldberg AS, Bathina MN, Mickelsen S, et al. Long-term outcomes on quality-of-life and health care costs in patients with supraventricular tachycardia (radiofrequency catheter ablation versus medical therapy). *The American journal of cardiology* 2002;89:1120-3.	Duplicate of Bathina, same reasons for exclusion.
10.	de Buitleir M, Bove EL, Schmaltz S, et al. Cost of catheter versus surgical ablation in the Wolff-Parkinson-White syndrome. *The American journal of cardiology* 1990;66:189-92.	Notes a difference in effectiveness between procedures and shows surgical ablation to be more expensive. **Only accounts for costs.**
11.	de Buitleir M, Sousa J, Bolling SF, et al. Reduction in medical care cost associated with radiofrequency catheter ablation of accessory pathways. *The American journal of cardiology* 1991;68:1656-61.	Mentions potential effectiveness improvements but primarily focuses on cost of surgical vs. catheter ablation. **Focuses mainly on costs.**
12.	Kalbfleisch SJ, Calkins H, Langberg JJ, et al. Comparison of the cost of radiofrequency catheter modification of the atrioventricular node and medical therapy for drug-refractory atrioventricular node reentrant tachycardia. *Journal of the American College of Cardiology* 1992;19:1583-7.	Compares cost of RFA to medical therapy. Small sample size. **Only accounts for costs.**
13.	Kleinman NL, Rohrbacker NJ, White SA, et al. Economic impact to employers of treatment options for cardiac arrhythmias in the US health system. *J Occup Environ Med* 2011;53:405-14.	Looks at the cost from the perspective of an employer of patients with and with out ablation. **No comparator and only accounts for costs.**
14.	Man KC, Kalbfleisch SJ, Hummel JD, et al. Safety and cost of outpatient radiofrequency ablation of the slow pathway in patients with atrioventricular nodal reentrant tachycardia. *The American journal of cardiology* 1993;72:1323-4.	Gives detailed description of procedure and presents associated costs does not provide any effectiveness measure or comparator. **Only accounts for costs.**

	Citation	Reason for Exclusion
15.	Noorani HZ, Yee R, Marshall D, et al. Radiofrequency catheter ablation for cardiac arrhythmias: a clinical and economic review: Canadian Coordinating Office for Health Technology Assessment, 2002:66.	Systematically reviews cost-effectiveness studies, quality of life studies and cost-only. **Non-primary evaluation.**
16.	Weerasooriya HR, Murdock CJ, Harris AH, et al. The cost-effectiveness of treatment of supraventricular arrhythmias related to an accessory atrioventricular pathway: comparison of catheter ablation, surgical division and medical treatment. *Australian and New Zealand journal of medicine* 1994;24:161-7.	Analyzes the costs of catheter ablation, surgical treatment and drug therapy. **Only accounts for costs.**

Appendix D. Class of Evidence And QHES Determination

Example (Please see proposal appendices for additional information on critical appraisal methods)

Each study is rated against pre-set criteria that resulted in an evidence rating (Class of Evidence I, II, III, or IV) and presented in a table. The criteria are listed in the Tables below.

Table D1. Definition of the class of evidence and risk of bias for studies on therapy

		Studies of Therapy	
Class	**Bias Risk**	**Study Design**	**Criteria**
I	**Low risk:** Study adheres to commonly held tenets of high quality design, execution and avoidance of bias	Good quality RCT	• Random sequence generation • Allocation concealment • Intent-to-treat analysis • Blind or independent assessment for important outcomes • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size
II	**Moderately low risk:** Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias	Moderate or poor quality RCT	• Violation of one of the criteria for good quality RCT
		Good quality cohort	• Blind or independent assessment in a prospective study, or use of reliable data* in a retrospective study • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size • Controlling for possible confounding†
III	**Moderately High risk:** Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results	Moderate or poor quality cohort	• Violation of any of the criteria for good quality cohort
		Case-control	• Any case-control design
IV	**High risk:** Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes	Case series	• Any case series design

* Outcome assessment is independent of healthcare personnel judgment. Reliable data are data such as mortality or re-operation.
† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Table D2. Definition of the class of evidence and risk of bias for studies on prognosis

		Studies of Prognosis	
Class	**Risk of bias**	**Study design**	**Criteria**
I	**Low risk;** Study adheres to commonly held tenets of high quality design, execution and avoidance of bias	Good quality cohort*	• Prospective design • Patients at similar point in the course of their disease or treatment • F/U rate of ≥ 80%† • Patients followed long enough for outcomes to occur • Accounting for other prognostic factors‡
II	**Moderately low risk:** Study has potential for some bias; does not meet all criteria for class I but deficiencies not likely to invalidate results or introduce significant bias	Moderate quality cohort	• Prospective design, with violation of one of the other criteria for good quality cohort study • Retrospective design, meeting all the rest of the criteria in class I
III	**Moderately high risk:** Study has flaws in design and/or execution that increase potential for bias that may invalidate study results	Poor quality cohort Good quality case-control or cross-sectional study	• Prospective design with violation of 2 or more criteria for good quality cohort, or • Retrospective design with violation of 1 or more criteria for good quality cohort • A good case-control study§ • A good cross-sectional study**
IV	**High risk:** Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group	Poor quality case-control or cross-sectional Case series§	• Other than a good case-control study • Other than a good cross-sectional study • Any case series†† design

*Cohort studies follow individuals with the exposure of interest over time and monitor for occurrence of the outcome of interest.

†Applies to cohort studies only.

‡Authors must consider other factors that might influence patient outcomes and should control for them if appropriate.

§A good case-control study must have the all of the following: all incident cases from the defined population over a specified time period, controls that represent the population from which the cases come, exposure that precedes an outcome of interest, and accounting for other prognostic factors.

**A good cross-sectional study must have all of the following: a representative sample of the population of interest, an exposure that precedes an outcome of interest (e.g., sex, genetic factor), an accounting for other prognostic factors, and for surveys, at least a 80% return rate.

††A case-series design for prognosis is one where all the patients in the study have the exposure of interest. Since all the patients have the exposure, risks of an outcome can be calculated only for those with the exposure, but cannot be compared with those who do not have the exposure. For example, a case-series evaluating the effect of smoking on spine fusion that only recruits patients who smoke can simply provide the risk of patients who smoke that result in pseudarthrosis but cannot compare this risk to those that do not smoke.

Determination of Overall Strength of Evidence

Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence" for the relevant question or topic is determined. Methods for determining the overall strength of evidence are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI's method incorporates the primary domains of quality (LoE), quantity of studies and consistency of results across studies as described by AHRQ.

The following four possible levels and their definition will be reported:

- **High** – High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** - Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low** - Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and likely to change the estimate.
- **Insufficient** – Evidence either is unavailable or does not permit a conclusion.

Table D3. Methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table.

Baseline strength: Risk of bias (including control of confounding) is accounted for in the individual article evaluations. HIGH = majority of articles Level I/II. LOW = majority of articles Level III/IV.

DOWNGRADE: Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *apriori* and no test for interaction (2)

UPGRADE: Large magnitude of effect (1 or 2); Dose response gradient (1)

Outcome	Strength of Evidence	Conclusions and Comments	Baseline	DOWGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** Level I/II studies	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Level III studies	**NO** consistent, direct, and precise estimates	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** Level I/II studies	**YES (2)** Inconsistent Indirect	**NO**

*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

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[3]. QHES embodies the primary components relevant for critical appraisal of economic studies[3, 4]. It also incorporates a weighted scoring process and 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.

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 (eg, 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 (eg, 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 (eg, similar protocols, follow-up procedures, evaluation of outcomes, etc)?
- How were the data and/or patients selected or sampled (eg, 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? (eg, were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. For the purposes of this HTA, overall strength was determined by:

- Quality of the individual studies: Where the majority of quality indicators described in the QHES met and were the methods related to patient/claim selection, patient population considerations and other factors listed above consistent with a high quality design?
- Number of formal analyses (3 or more)
- Consistency of findings and conclusions from analyses across studies.

QHES evaluation of economic studies

Study: Assasi 2010	Points	Yes	No	Notes:
1. Was the study objective presented in a clear, specific, and measurable manner?	7	■		*Canada specific cost–utility evaluation of AF ablation with AAD measured in cost per QALY*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	■		*Publicly funded health care system*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	■		*Detailed literature review using clinical reviews when possible.*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	■		*Not applicable*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	■		*Used one-way sensitivity analysis to measure impact of several key variables; including age, gender, risk of stroke, time horizons, discounting, and effectiveness measures.*
6. Was incremental analysis performed between alternatives for resources and costs?	6	■		*Base case results given in $/QALY*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	■		*Derived from literature review and when combining studies gave details of calculations in appendix*
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	■		*Chosen because of the short-term nature (12 months) of the randomized clinical trials comparing AF ablation with AAD. Alternative time horizons were tested in a sensitivity analysis. Discounted at 5% (CADTH guidelines.*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	■		*Cost broken down by treatment type (p.57). Quantities 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	■		*Given in table 19. Different time frames were addressed.*
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	■		*Justifications were given when necessary (p. 53)*
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	■		*Markov decision model and structure clearly defined.*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	P 6		*Assumptions given, and limitations discussed (p.71). Minimal justifications were provided.*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6		■	*Not explicitly*
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	■		*Conclusions tied closely to results and comparable with similar studies.*
16. Was there a statement disclosing the source of funding for the study?	3		■	*Conflicts of interests were given on p .ii but not stated within paper.*
TOTAL POINTS	**100**	**90**		

Study: Chan 2006	Points	Yes	No	Notes:
1. Was the study objective presented in a clear, specific, and measurable manner?	7	■		*"compare the cost-effectiveness of left atrial catheter ablation (LACA), amiodarone, and rate control therapy in the management of atrial fibrillation (AF)."*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		■	*States societal, but only payer costs used, therefore most would not consider it societal.*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	■		*Thorough literature review.*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	■		*Not applicable*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	■		*Used one-way sensitivity and multivariate to simulate possible parameters.*
6. Was incremental analysis performed between alternatives for resources and costs?	6	■		*Base case results gave costs and QALY. AAD treatment of dominated.*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	■		*Derived from literature review. Provided reasons for inclusion and exclusion.*
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	■		*Used a life long time horizon. Discounted at 3%*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	P 5		*Costs derived from literature review and author's estimates.*
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	■		*Given in Table 2.*
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	■		*Given in supplement appendix table A1.*
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	■		*Markov decision model and structure clearly defined (figure 1).*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	P 5		*Assumptions given, and limitations discussed Minimal justifications were provided.*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	■		*Addressed selection bias (p. 2515,6,8) and adjust the model conservatively to compensate.*
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	■		*Conclusions tied closely to results and comparable with similar studies.*
16. Was there a statement disclosing the source of funding for the study?	3		■	None
TOTAL POINTS	**100**	**88**		

Study: Eckard 2009	Points	Yes	No	Notes:
1. Was the study objective presented in a clear, specific, and measurable manner?	7	■		*"Assess the lifetime costs and health outcomes of RFA compared to AAD" measured in $/QALY*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		■	*Says Swedish societal, but actually just health care payer costs are used*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	■		*Detailed literature review relying on RCTs and national registries*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	■		*Not applicable*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	■		*Used one-way sensitivity analysis to measure impact of reversion to uncontrolled AF*
6. Was incremental analysis performed between alternatives for resources and costs?	6	■		*Base case results gave costs and QALY. AAD treatment of dominated.*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	■		*Derived from literature review. Provided reasons for inclusion and exclusion.*
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	■		*Used a life long time horizon. Discounted at 3%*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	P 5		*Costs grouped in general categories and were derived from literation and registries.*
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	P 5		*Given in Table 2: Only costs and QALY*
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	■		*Relied on national registries and RCT found in a literature review.*
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	■		*Markov decision model and structure clearly defined.*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	P 5		*Assumptions given, (p.462). Minimal justifications were provided.*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	P 3		*Mentioned but not explicitly addressed*
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	■		*Conclusions tied closely to results and comparable with similar studies.*
16. Was there a statement disclosing the source of funding for the study?	3		■	none
TOTAL POINTS	**100**	**84**		

Study: Reynolds 2009	Points	Yes	No	Notes:
1. Was the study objective presented in a clear, specific, and measurable manner?	7	■		*Evaluate the cost effectiveness of AAD alone vs AAD + RFA . Measure in terms of $/QALY*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	■		*United States health care system*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	■		*Inputs for the model were drawn from a variety of sources, including completed clinical trials, a large registry of new-onset AF patients, prospectively collected data from patients treated at our institution, and analysis of Medicare claims data.*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	■		*Not applicable*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	■		*Used one-way sensitivity analysis to measure impact of several key variables; found time horizon, ablation cost, and utility inputs to be used. Provided and overview of effects of varying each.*
6. Was incremental analysis performed between alternatives for resources and costs?	6	■		*Base case results given in $/QALY*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	■		*Derived from literature review and when combining studies gave details of justification in supplement.*
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	P 4		*Modeled a 5 year time horizon and argued most changes in variables could be captured in that time frame. Sensitivity analysis showed time horizon carried significant influence over results. Did not specify base year price.*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	■		*Cost specified in detail in supplement.*
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	■		*Given in table 1 of supplement. Different time frames were addressed.*
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	■		*Given in table 1 of supplement. Justified p. 1 of supplement.*
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	■		*Markov decision model and structure clearly defined and illustrated (figures in appendix)*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	P 4		*Assumptions given. Minimal justifications were provided.*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	P 3		*Attempts made to correct some inputs for potential bias. In such instances, assumed conservative estimates.*
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	■		*Conclusions tied closely to results and comparable with similar studies.*
16. Was there a statement disclosing the source of funding for the study?	3	■		*Funding details provided p. 8. Conflicts of interests were given on p. 1.*
TOTAL POINTS	**100**	**91**		

Study: Rodgers 2008	Points	Yes	No	Notes:
1. Was the study objective presented in a clear, specific, and measurable manner?	7	■		*Evaluate the cost effectiveness of RF catheter ablation (without long term use of AAD) and Long-term AAD alone. Measure in terms of $/QALY*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	■		*UK's NHS and Personal Social Services*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	■		*When possible model parameters came from RCTs and a sensitivity analysis was performed comparing authors choice of parameters to literature values.*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	■		*Not applicable*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	■		*Thorough sensitivity analysis was given looking at many key input variables.*
6. Was incremental analysis performed between alternatives for resources and costs?	6	■		*Base case results given in $/QALY*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	■		*In detail.*
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	■		*Took time horizon into consideration and presented several alternative. Offered rationale for choices made.*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	■		*Used a combination of first hand, country specific cost and literature review. Methodology 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	■		*The results clearly given in Tables 27-8. Outcomes were presented with consideration for various timeframes.*
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	■		*Health outcomes came from first hand RCTs and verified with literature review.*
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	■		*Markov decision model and structure clearly defined.*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	■		*Assumptions given and model's use is justified p. 57*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	■		*Certain potential explicitly discussed on p. 70.*
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	■		*Conclusions tied closely to results and comparable with similar studies.*
16. Was there a statement disclosing the source of funding for the study?	3	■		*Commission by NIHR HTA Programme*
TOTAL POINTS	**100**	**100**		

Study: Cheng 2000	Points	Yes	No	Notes:
1. Was the study objective presented in a clear, specific, and measurable manner?	7	■		*Compare the cost effectiveness of radiofrequency ablation with that of medical management of supraventricular tachycardia.*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	P 2		*State societal but really health care system costs.*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	■		*Table 1 gives level of confidence*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	■		*Not applicable*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	■		*Used one-way, mult-way, and best-case vs. worst case sensitivity analysis.*
6. Was incremental analysis performed between alternatives for resources and costs?	6	■		*Base case results given in $/QALY*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	■		*Methodology given p. 868.*
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	■		*Patient lifetime used as time horizon. Discounts made 3%*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	P 4		*Cost variables given in table 1. Not elaborate it detail.*
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	■		*Given in table 2 of supplement.*
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	■		*Given in table 2 of supplement.*
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	■		*Markov decision model and structure clearly defined and illustrated in figure 1.*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	P 4		*Assumptions given. Minimal justifications were provided.*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	P 3		*Sensitivity analysis considers some potential biases however study does not address bias explicitly.*
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	■		*Conclusions tied closely to results and comparable with similar studies.*
16. Was there a statement disclosing the source of funding for the study?	3	■		*Grant support from Agency for Healthcare Research and Quality and from Veterans Affairs Health Services Research and Development Services.*
TOTAL POINTS	**100**	**88**		

Study: Hogenhuis 1993	Points	Yes	No	Notes:
1. Was the study objective presented in a clear, specific, and measurable manner?	7	■		*Compare 5 different treatments for WPW*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		■	*Not specified*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	P 2		*Table 2 and 3 give estimate. Sources include literature review and expert opinion. Author opinion was used to estimate utility levels. (one study was from 1964.*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	■		*5 different treatment types*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	■		*Used one-way sensitivity analysis tested possible input ranges.*
6. Was incremental analysis performed between alternatives for resources and costs?	6	■		*Base case results given in $/QALY*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	P 2		*Author determined utility levels.*
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	■		*Patient lifetime used as time horizon. Discounts made 5%*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	P 3		*Cost variables given in table 2. Estimated using Clinical Cost Manager and small convenience sample from hospital. Not elaborate it detail.*
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	■		*Given in table 5*
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	■		*Given in table 3.*
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	■		*Markov decision model and structure clearly defined and illustrated in figures.*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	P 4		*Assumptions given. Minimal justifications were provided.*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6		■	*Study does not address bias explicitly.*
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	■		*Conclusions followed from results. Different from similar study.*
16. Was there a statement disclosing the source of funding for the study?	3	■		*Supported by grants from the National Library of Medicine and from the John A. Hartford Foundation.*
TOTAL POINTS	**100**	**73**		

Appendix E. Class of Evidence Evaluation.

Table E1: Methodological quality of therapeutic studies evaluating efficacy or effectiveness following catheter ablation compared with another treatment (Key Question 1)

Methodological Principle	Forleo 2009[5]	Jais 2008[6]	Krittayaphong 2003[7]	MacDonald 2011[8]	Oral 2006[9]	Pappone 2006/2011[10, 11]	Stabile 2006[12]	Wazni 2005[13]
Study design								
Randomized controlled trial	✓	✓	✓	✓	✓	✓	✓	✓
Prospective cohort study								
Retrospective cohort study								
Case-control								
Case-series								
Random sequence generation*	✓			✓	✓		✓	✓
Statement of concealed allocation*	✓			✓			✓	✓
Intention to treat*	✓	✓		✓	✓	✓	✓	✓
Independent or blind assessment				✓	✓	✓	✓	
Co-interventions applied equally	✓	✓	✓			✓		✓
Complete follow-up of ≥80%	✓	✓	✓	✓	✓	✓	✓	✓
Adequate sample size	✓	✓	✓		✓	✓	✓	✓
Controlling for possible confounding†	✓	✓	✓			✓	✓	
Evidence Level	**II**	**II**	**II**	**II**	**II**	**II**	**II**	**II**

Methodological Principle	Wilber 2010[1]	Lan 2009[14]	Pappone, Augello 2003[15]	Rossillo 2008[16]	Sonne 2009[17]	STOP AF Pivotal Trial 2010[18]	Stulak 2011[19]
Study design							
Randomized controlled trial	✓					✓	
Prospective cohort study		✓	✓				
Retrospective cohort study				✓	✓		✓
Case-control							
Case-series							
Random sequence generation*	✓						
Statement of concealed allocation*							
Intention to treat*						✓	
Independent or blind assessment	✓		✓		✓	✓	
Co-interventions applied equally	✓						✓
Complete follow-up of ≥80%		✓	✓		✓	✓	
Adequate sample size	✓	✓	✓		✓	✓	
Controlling for possible confounding†	✓	✓	✓		✓	✓	
Evidence Level	**II**	**III**	**III**	**III**	**III**	**II**	**III**

*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented
Blank cells indicate that the criterion was either not met or that it could not be determined

Methodological Principle	Da Costa 2006[20]	D'Este 2007[21]	Kimman 1999[22]	Lin 1998[23]	Natale 1993[24]	Pappone 2003[25]	Goldberg 2002[26]	Weerasooriya 1994[27]
Study design								
Randomized controlled trial	✓					✓		
Prospective cohort study		✓	✓	✓			✓	
Retrospective cohort study					✓			✓
Case-control								
Case-series								
Random sequence generation*						✓		
Statement of concealed allocation*								
Intention to treat*	✓							
Independent or blind assessment	✓							
Co-interventions applied equally	✓				✓		✓	
Complete follow-up of ≥80%	✓	✓	✓		✓	✓	✓	
Adequate sample size	✓			✓		✓		
Controlling for possible confounding†	✓					✓	✓	
Evidence Level	**II**	**III**	**III**	**III**	**III**	**II**	**III**	**III**

*Applies only to randomized controlled trials

†Groups must be comparable on baseline characteristics or evidence of control for confounding presented

Blank cells indicate that the criterion was either not met or that it could not be determined

Forleo (2009)[5]

- RCT
- Random sequence generation: credit
  - Patients randomized according to a computer-generated study list.
- Allocation concealment: credit
  - Credit- randomization performed by computer after patient enrollment.
- Intent to treat: credit
  - All patients received the assigned treatment
- Independent or blind assessment: no credit (hard outcome)
  - Primary outcome was AF recurrence, and was defined as any electrocardiographically confirmed episode of AF or atypical flutter lasting > 30 seconds, however no information that the assessor was independent/blinded.
- Co-interventions applied equally: credit
- Complete f/u of ≥ 80%: credit (100%)
- Adequate sample size: credit
  - Statistically significant difference in primary outcome between treatment groups
- Controlling for possible confounding: credit
  - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups

Jais (2008)[6]

- RCT
- Random sequence generation: no credit,
  - No info on how patients were randomized
- Allocation concealment: no credit (no info)

- Intent to treat: credit (explicit statement)
- Independent or blind assessment: no credit-
    - Primary outcome could be patient-reported; patients not blinded to treatment group.
    - Primary outcome: freedom from AF recurrence (defined as AF lasting at least 3 minutes and documented by ECG OR reported by the patient as AF even in the absence of ECG confirmation)
- Co-interventions applied equally: credit
- Complete f/u of ≥ 80%: credit (96%)
    - Note that the authors write that 108/112 had complete follow-up, however, data for the primary outcome (AF recurrence) was reported for 107/112 patients (52 (of 53 enrolled) ablation and 55 (of 59 enrolled) AAD patients).
- Adequate sample size: credit
- Controlling for possible confounding: credit
    - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups

Krittayaphong (2003)[7]

- RCT
- Random sequence generation: no credit,
    - No info on how patients were randomized
- Allocation concealment: no credit (no info)
- Intent to treat: no credit
    - One patient in the ablation group did not receive treatment and was excluded from analysis.
- Independent or blind assessment: no credit
    - No information on how recurrence was determined
- Co-interventions applied equally: credit
- Complete f/u of ≥ 80%: credit (93%)
- Adequate sample size: credit
    - Statistically significant difference in primary outcome between treatment groups (recurrence)
- Controlling for possible confounding: credit
    - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups

MacDonald (2011)[8]

- RCT
- Random sequence generation: credit
    - Randomization done on 1:1 basis by computer generated sequence
- Allocation concealment: credit
    - Treatment allocation concealed from investigators in numbered envelopes until patients had been through baseline assessments
- Intent to treat: credit (explicit statement)
- Independent or blind assessment: credit
    - Primary outcome (reversion to AF at follow-up) determined by ECG monitoring
- Co-interventions applied equally: no credit
    - Patients in medical treatment (rate control) group received "continued medical treatment" even though all patients had persistent AF and were likely being treated with AADs already- thus these patients received no change in treatment.
- Complete f/u of ≥ 80%: credit (93%)
- Adequate sample size: no credit
    - No statistical analysis on our primary outcome (reversion to AF)
- Controlling for possible confounding: no credit
    - 20 month difference in duration of AF between groups, this difference was not controlled for

Oral (2006)[9]

- RCT
- Random sequence generation: credit
  - Computer-generated randomization table used
- Allocation concealment: no credit (no info)
- Intent to treat: credit (explicit statement)
- Independent or blind assessment: credit
  - Primary outcome- freedom from recurrence. All patients given an event monitor for one year and asked to record their rhythm at least 5 days/week for 3 minutes and whenever they had symptoms suggestive of AF. All rhythm tracings were interpreted in a blinded fashion by two physicians not otherwise involved in the study.
- Co-interventions applied equally: no credit
  - For enrollment, patients had to have chronic AF (defined as AF that had been present for more than six months without intervening spontaneous episodes of sinus rhythm and that recurred within one week after cardioversion.) Also, patients had previously used a mean of 2.1 ± 1.2 AADs that were ineffective (no info on which ones). Patients in control group received amiodarone for 6 months and cardioversion- these are not clearly "new" treatments to the patients, rather they are treatments that most likely have a history of being ineffective.
- Complete f/u of $\geq$ 80%: credit (100%)
- Adequate sample size: credit
  - While the difference in the primary outcome (freedom from recurrence) was not statistically significant between groups, it was nearly so (P = .05) AND the absolute difference in the percentage of patients with freedom from recurrence between groups seems adequately large (74% (57/77) vs. 58%(40/69)), and statistical predictions were done to determine the sample size to determine adequate study power.
- Controlling for possible confounding: no credit
  - No Table 1 or robust description of baseline characteristics

Pappone (2006)/(2011)[10, 11]

- RCT
- Random sequence generation: no credit (no information provided)
- Allocation concealment: no credit (no information provided)
- Intent to treat: credit (explicit statement)
- Independent or blind assessment: credit
  - Primary outcome- freedom from recurrence. All patients given an event monitor and asked to record their rhythm 1-3 times daily and whenever they had symptoms suggestive of AF. All 1-minute rhythm tracings and echocardiograms were interpreted in a blinded fashion by two physicians.
- Co-interventions applied equally: credit
  - ADT therapy given to control group had never been used by the patients
- Complete f/u of $\geq$ 80%: credit (100% for 2006, 95% for 2011)
- Adequate sample size: credit
  - Statistically significant difference in primary outcome between treatment groups (recurrence)
- Controlling for possible confounding: credit
  - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups

Stabile (2006)[12]

- RCT
- Random sequence generation: credit
  - Randomization was computer generated at the statistical analysis coordinating center.
- Allocation concealment: credit
  - Randomization done at a coordinating center.

- Intent to treat: credit (explicit statement)
- Independent or blind assessment: credit
    - Transtelephonic ECG and Holter monitoring were analyzed and interpreted by two independent and blinded physicians.
- Co-interventions applied equally: no credit
    - Amiodarone was the preferred treatment given to the AAD group, yet 66% of patients in this group had previously used this drug. In both treatment groups 30-34% patients were treated with an AAD that had previously failed, however, the AAD patients didn't receive any additional treatment, unlike the ablation group.
- Complete f/u of ≥ 80%: credit (97%)
- Adequate sample size: credit
    - Statistically significant difference in primary outcome between treatment groups (recurrence)
- Controlling for possible confounding: credit
    - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups, the three factors that were statistically different between groups at baseline were then controlled for using the Benjamini and Hochberg False Discovery Rate correction to adjust p-values for multiple testing bias.

Wazni (2005)[13]

- RCT
- Random sequence generation: credit
    - Computer-generated
- Allocation concealment: credit
    - Randomization performed at an outside clinic
- Intent to treat: credit
    - No explicit statement, but it appears that patients were analyzed as randomized, also, physicians advised to keep patients in the same treatment group during the 1-year follow-up period.
- Independent or blind assessment: Independent or blind assessment: no credit
    - Primary outcome determined by ECG and Holter monitoring (hard outcomes) but no report that assessor was blinded/independent.
- Co-interventions applied equally: credit
    - Patients were excluded from study if they had previously taken AADs. The AADs given for the medical treatment group were a first-line treatment.
- Complete f/u of ≥ 80%: credit (96%)
- Adequate sample size: credit
    - Statistically significant difference in primary outcome between treatment groups (recurrence)
- Controlling for possible confounding: no credit
    - Table 1 wasn't very robust, doesn't even include patient sex

Wilber 2010[1]

- RCT
- Random sequence generation: credit
    - Upon enrollment, patients were assigned a sequential identification number at each site and a corresponding sealed envelope was opened. Randomization sequences were generated by the sponsor statistical by using SAS and stratified by site with a block size 11 (7 to ablation and 4 to ADT).
- Allocation concealment: no credit
    - no mention that the corresponding sealed envelopes were opaque; no mention whether the treatment was concealed after allocation
- Intent to treat: no credit
    - It is not clear that data were analyzed using the ITT principle. Further, only patients who had not failed treatment (and for the ADT group, patients who failed could receive ablation) were analyzed for the SF-36 outcomes (1 of 3 outcomes).

- Independent or blind assessment: credit.
    - Recurrence : Independent core laboratories were used to process and analyze transtelephonic, Holter monitors, and CT or MRI scan results. An independent data and safety monitoring committee reviewed and adjudicated causality of all adverse events.
- Co-interventions applied equally: credit
    - Control group was treated with a previously unused AAD.
- Complete f/u of ≥ 80%: no credit
    - Can't determine the percentage of patients followed for the primary outcome. No other outcome reported fully out to 9 months (latest f/u).
- Adequate sample size: credit
    - Statistically significant difference in primary outcome between treatment groups (recurrence)
- Controlling for possible confounding: credit
    - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups

Lan 2009[14]

- Prospective cohort study
- Independent or blind assessment: no credit
    - Recurrence (primary outcome) defined as AF > 30 seconds in duration documented by 12 lead ECG or Holter between 1 and 12 months; but no report that the assessor was independent/blinded.
- Co-interventions applied equally: no credit
    - Patients in AAD group treated with amiodarone; patients were excluded from study if they had been refractory to amiodarone in the past, however it wasn't necessarily a new drug.
- Complete f/u of ≥ 80%: credit (100%)
    - "For all patients, echocardiography and Holter were performed at the … 12th month…."
- Adequate sample size: credit
    - Statistically significant difference in primary outcome between treatment groups (recurrence)
- Controlling for possible confounding: credit
    - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups, AND "Cox proportional hazards model was used to examine the association between the treatment group and AF recurrence AFTER adjusting for covariates." "Cox proportional hazards model demonstrated a significant beneficial effect of segmental pulmonary vein isolation in preventing recurrence after adjusting for age, gender, frequency of AF episode, history of AF, BMI, left ventricular EF, LAD, systolic blood pressure, and diastolic blood pressure."

Pappone, Augello 2003[15]

- Prospective cohort study
- Independent or blind assessment: credit
    - Recurrence defined as a symptomatic episode lasting more than 10 minutes and confirmed by ECG: an independent committee classified all events after masked review of the data.
- Co-interventions applied equally: no credit
    - Not clear that patients in medical treatment group were given an AAD that was new to them
- Complete f/u of ≥ 80%: credit (98.4%)
- Adequate sample size: credit
    - Statistically significant difference in primary outcome between treatment groups (recurrence)
- Controlling for possible confounding: credit
    - Adequate Table 1, AND a Cox proportional-hazards model was used to estimate the effect of treatment on all-cause mortality and freedom from adverse events or AF recurrence while adjusting for other prognostic factors.

Rossillo 2008[16]

- Retrospective cohort study

- Independent or blind assessment: no credit
  - How recurrence was detected after the first three months was not clearly defined.
- Co-interventions applied equally: no credit
  - Patients had been refractory to AADs in the past and may have continued on them. Patients in the AAD group also received electrical cardioversion; no info provided as to whether or not they had previously undergone cardioversion.
- Complete f/u of ≥ 80%: no credit
  - Follow-up not reported
- Adequate sample size: no credit
  - Statistical analysis not done on primary outcome (recurrence).
- Controlling for possible confounding: no credit
  - No multivariable analysis to control for potential confounding baseline variables.

Sonne 2009[17]

- Retrospective cohort study
- Independent or blind assessment: credit
  - Recurrence not reported, so primary outcome become survival (only outcome reported), which is a hard outcome.
- Co-interventions applied equally: no credit
  - Patients had been refractory to AADs in the past and may have continued on them. Patients in the AAD group also received electrical cardioversion; no info provided as to whether or not they had previously undergone cardioversion.
  - group were considered to have permanent AF (which meant in part that cardioversion failed).
- Complete f/u of ≥ 80%: credit (82%)
- Adequate sample size: credit
  - Statistically significant difference in primary outcome between treatment groups (death)
- Controlling for possible confounding: credit
  - Adequate Table 1, AND a multivariate Cox regression was used to identify significant predictors of AF (listed); all potential confounders were entered into the model regardless of their statistical significance.

STOP AF Pivotal Trial[18]

- RCT
- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit (explicit statement)
  - "modified ITT: pre-specified modified ITT included all subjects (82 control, 163 ablation) who were enrolled [at time of database locking] randomized, and received treatment"
- Independent or blind assessment: credit
  - Treatment success defined as freedom from any chronic treatment failure events and as acute procedural success for ablation group). Chronic treatment failure defined as detectable AF during the non-blanked period, use of non-study AF drugs, or an AF intervention. Acute procedural success defined as the electrical isolation of at least 3 PVs from the left atrium. Arrhythmia recurrence elvauated at 9 month assessment via telephone interview, used of Study AF Drugs and concomitant cardiovascular meds, occurrence of AF interventions and an adverse event review. Subjects were trained in the use of the transtelephonic monitoring and instructed to obtain and transmit a recording to the ECG Core Lab every week at a scheduled time and whenever symptomatic. At 6- and 12-months, 24-hour Holter monitoring was performed.
- Co-interventions applied equally: credit
  - No information that patients were given a drug they hadn't previously received.
- Complete f/u of ≥ 80%: credit (93%)
- Adequate sample size: credit
- Controlling for possible confounding: credit

- Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups

Stulak 2011[19]

- Retrospective cohort study
- Independent or blind assessment: no credit
  - A cardiologist evaluated all ECGs and 24-hour Holter monitor reports. Recurrence required documentation of the arrhythmia by either method. However no info that the assessor was blinded/independent.
- Co-interventions applied equally: credit
  - No obvious differences between the treatment groups; treatments performed during same time period
- Complete f/u of ≥ 80%: no credit
  - % f/u unclear, as how the 97 patients were selected from a pool of 448 patients who underwent Cox-Maze was not explained
- Adequate sample size: no credit
  - No statistically significant difference between groups in major outcome (overall freedom from AF)
- Controlling for possible confounding: no credit
  - Table 1 is very limited- inadequate description of baseline characteristics

Da Costa (2006)[20]

- RCT
- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit (explicit statement)
- Independent or blind assessment: credit
  - AF was determined by outpatient f/u on the basis of recurring symptoms or palpitations and ECG and Holter monitoring. Holter monitoring was performed for 7 days. The R-Test Evolution event recorder performed a continuous ECG analysis combined with automatic storage of abnormal events detected in a 20 minute solid state memory with autonomy up to 7 days. In addition, the patient could trigger the Holter manually. The RTE was programmed to recognize 10 types of arrhythmic events. Patients instructed to record symtpoms that would have occurred during the recording. Events were considered symptomatic if there was a temporal correspondence b/w symptoms described in logbook and the occurrence of arrhythmia during this period. All recordings analyzed by 2 separate observers.
- Co-interventions applied equally: credit
  - For inclusion, patients could not have had previous AAD treatment. Patients also received electrocardioversion in control group.
- Complete f/u of ≥ 80%: credit (99%)
- Adequate sample size: credit
  - Statistically significant difference in primary outcome between treatment groups (death)
- Controlling for possible confounding: credit
  - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups

D'Este (2007)[21]

- Prospective cohort study
- Independent or blind assessment: no credit
  - Only outcome was whether patients became asymptomatic, but patients were not blinded to treatment received (ablation vs. AADs vs. no drugs/short drug therapy).
- Co-interventions applied equally: no credit

    - Some patients received no treatment, which is not "equal" to receiving a new treatment like ablation.
- Complete f/u of ≥ 80%: credit (86%)
- Adequate sample size: no credit
    - No statistical analysis done on primary outcome (being asymptomatic)
- Controlling for possible confounding: no credit
    - No Table 1, little demographic info, no multivariate analysis to control for potential confounding variables.

Kimman (1999)[22]

- Prospective cohort study
- Independent or blind assessment: no credit- recurrence evaluated by ECG or Holter recordings (hard outcome)
    - If a patient experienced symptoms of palpitations, a 24 hour Holter recording or a self-activating ambulatory single channel ECG recording and exercise testing were performed. An electrophysiological study was scheduled if recurrence of AVNRT could not be confirmed while symptoms remained present. HOWEVER no information reported as to whether the assessor was independent/blinded.
- Co-interventions applied equally: no credit
    - Co-interventions given during different time periods.
- Complete f/u of ≥ 80%: credit (100%)
- Adequate sample size: no credit
    - Statistical a nalysis not done for the primary outcome (recurrence)
- Controlling for possible confounding: no credit
    - No controlling done for potential confounders.

Lin (1998)[23]

- Prospective cohort study
- Independent or blind assessment: no credit
    - Primary outcome: recurrence; no info that the outcome was measured in an independent/blinded fashion.
- Co-interventions applied equally: no credit
    - Appears that control group received no treatment.
- Complete f/u of ≥ 80%: no credit (follow-up not reported)
    - Not clear how the 27 patients in the study were selected from the pool of 520 patients who received ablation for AVNRT
- Adequate sample size: credit
    - Statistically significant difference between groups in primary outcome (recurrence)
- Controlling for possible confounding: no credit
    - No Table 1, little demographic info, no multivariate analysis to control for potential confounding variables.

Natale (1993)[24]

- Retrospective cohort study
- Independent or blind assessment: no credit- not clear how recurrence was evaluated.
    - Patients complaining of palpitations were evaluated by Holter recordings and telephone transmitter monitoring- but no other info given.
- Co-interventions applied equally: credit
    - Ablation vs surgery
- Complete f/u of ≥ 80%: credit (100%) ("all patients were followed clinically")
- Adequate sample size: no credit
    - Statistical analysis not done for the primary outcome (recurrence)
- Controlling for possible confounding: no credit

- No Table 1 demonstrating baseline characteristics; multivariate analysis not done to control for potential confounders.

Pappone, Santinelli (2003)[25]

- Random sequence generation: credit
  - Randomization performed in 1:1 fashion according to a computer-generated randomization scheme, in permutated blocks of four to ensure a balance b/w groups in the two centers involved in the trial.
- Allocation concealment: no credit (no info)
- Intent to treat: no credit
  - After randomization, four patients withdrew consent and were excluded from the study.
- Independent or blind assessment: no credit
  - Primary outcome: occurrence of symptomatic arrhythmic events. Patients asked to report any palpitations, asthenia, dyspnea, dizziness, chest pain, blurred vision, or syncope. Events reviewed by an independent blinded committee. However, no info was provided on how the outcome was measured. However, patients reported their symptoms, and patients were not blinded to treatment received.
- Co-interventions applied equally: no credit
  - Control group received no treatment
- Complete f/u of ≥ 80%: credit (95%)
- Adequate sample size: credit
  - Statistically significant difference in primary outcome between treatment groups (arrhythmic-event free survival)
- Controlling for possible confounding: credit
  - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups

Goldberg (2002)[26]

- Prospective cohort study
- Independent or blind assessment: no credit
  - Only outcomes reported were symptoms and SF-36 scores, both of which are patient-reported, and patients were not blinded to treatment received (patients chose treatment).
- Co-interventions applied equally: credit
  - Medical therapy and ablation were both the initial treatment strategy for patients with paroxysmal SVT.
- Complete f/u of ≥ 80%: credit (87%)
- Adequate sample size: no credit
  - Only between-group statistical analyses done at 5 years, when results were reported separately for patients that initially underwent ablation, those who took meds, or those who crossed over to ablation at five years.
- Controlling for possible confounding: credit
  - Multivariate analysis done to control for potential effects of age and sex on outcomes

Weerasooriya (1994)[27]

- Retrospective cohort study
- Independent or blind assessment: no credit
  - Primary outcome (remaining asymptomatic) was patient-reported; patients were not blinded to the treatment received.
- Co-interventions applied equally: no credit
  - Surgical treatment and medical treatment took place in the 5 years preceeding ablation, not concurrently.
- Complete f/u of ≥ 80%: no credit (% follow-up not reported)
- Adequate sample size: no credit

    - No statistical analysis done
- Controlling for possible confounding: no credit
    - No Table 1 demonstrating baseline characteristics; multivariate analysis not done to control for potential confounders.

Table E2: Methodological quality of therapeutic studies evaluating efficacy of radiofrequency ablation compared with cryoablation (Key Question 1a)

Methodological Principle	Collins 2006	Kuniss 2009	Malmborg 2009	Thornton 2008
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	✓	✓	✓	✓
Random sequence generation*				
Statement of concealed allocation*				
Intention to treat*			✓	✓
Independent or blind assessment		✓		
Co-interventions applied equally	✓	✓	✓	✓
Complete follow-up of ≥80%	✓		✓	✓
Adequate sample size		✓		
Controlling for possible confounding†				
Evidence Level	**II**	**II**	**II**	**II**

Methodological Principle	Deisenhofer 2010	Kardos 2007	Kimman 2006	Zrenner 2004
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	✓	✓	✓	✓
Random sequence generation*		✓		✓
Statement of concealed allocation*			✓	
Intention to treat*	✓	✓	✓	✓
Independent or blind assessment				
Co-interventions applied equally	✓	✓	✓	✓
Complete follow-up of ≥80%	✓	✓	✓	✓
Adequate sample size	✓			✓
Controlling for possible confounding†	✓			✓
Evidence Level	**II**	**II**	**II**	**II**

*Applies only to randomized controlled trials

†Groups must be comparable on baseline characteristics or evidence of control for confounding presented

Blank cells indicate that the criterion was either not met or that it could not be determined

Collins 2006
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: no credit (no info provided)
- Intent to treat: no credit
  - Four patients were randomized and then excluded from analysis due to factors identified during the ablation procedure.
- Independent or blind assessment: no credit (no info provided)
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (88% f/u)
- Adequate sample size: no credit
  - Statistical significance of primary outcome of interest (freedom from recurrence) not assessed.
- Controlling for possible confounding: no credit
  - Table 1 demonstrates differences in baseline characteristics that were not controlled for (sex, persistent flutter, previous cardioversion, previous AF, current AAD therapy, and IHD).

Kuniss 2009
RCT

- Random sequence generation: no credit (not enough info provided to assess how randomization was done- the algorithm used was not described)
  - "Random sorting algorithm was used"
- Allocation concealment: no credit (no info provided)
- Intent to treat: no credit
  - Ten patients were randomized and then excluded from analysis due to factors identified during the ablation procedure.
- Independent or blind assessment: credit
  - Primary outcome: persistent bidirectional conduction block; "all measurements were documented on paper and reviewed by two independent and experienced electrophysiologists in a double-blind manner."
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: no credit (63.4% f/u (121/191))
- Adequate sample size: credit
  - Statistical significance between treatment groups of primary outcome of interest (persistent bidirectional conduction block) was demonstrated.
- Controlling for possible confounding: no credit
  - Table 1 demonstrates difference in history of coronary artery disease between groups ($P < .05$) that was not controlled for.

Malmborg 2009
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit
  - No explicit statement but data appear to have been handled this way- there were crossovers but patients appear to have been analyzed in the treatment group they were randomized to.
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence- no info reported that this was analyzed in a blind/independent manner.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: no credit

    - No statistical significance of primary outcome of interest (freedom from recurrence) between treatment groups.
- Controlling for possible confounding: no credit
    - Table 1 demonstrates difference in history of ischemic heart disease between groups that was not controlled for.

Thornton 2008
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit
    - No explicit statement but data appear to have been handled this way- all patients randomized were included in the results, and no crossovers were permitted.
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence- no info reported that this was analyzed in a blind/independent manner.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: no credit
    - No statistical significance of primary outcome of interest (freedom from recurrence) between treatment groups.
- Controlling for possible confounding: no credit
    - Table 1 did not give a robust list of baseline characteristics/ potential confounding variables- limited to age, sex, and history of AF.

Deisenhofer 2010
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit
    - No explicit statement but data appear to have been handled this way.
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence- no info reported that this was analyzed in a blind/independent manner.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (97.2% f/u (495/509 for freedom of recurrence))
- Adequate sample size: credit
    - Statistical significance between treatment groups of primary outcome of interest (freedom from documented recurrence) was demonstrated.
- Controlling for possible confounding: credit
    - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups

Kardos 2007
RCT

- Random sequence generation: credit
    - Patients randomized by "computer generated random numbers."
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit
    - No explicit statement but data appear to have been handled this way.
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence- no info reported that this was analyzed in a blind/independent manner.

- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: no credit
    - No statistical significance of primary outcome of interest (freedom from recurrence) between treatment groups.
- Controlling for possible confounding: no credit
    - No robust list of baseline characteristics/ potential confounding variables- limited to age, sex, and diagnosis.

Kimman 2006
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: credit
    - Patients randomized "by an independent institution".
- Intent to treat: credit
    - No explicit statement but data appear to have been handled this way.
- Independent or blind assessment: no credit
    - Primary outcome: freedom from patient-reported palpitations- no info that patients were blinded to treatment received.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: no credit
    - Statistical significance of primary outcome of interest (freedom from recurrence) between treatment groups not assessed.
- Controlling for possible confounding: no credit
    - No robust list of baseline characteristics/ potential confounding variables- limited to age, sex, and diagnosis.

Zrenner 2004
RCT

- Random sequence generation: credit
    - Patients randomized by "computer-generated randomization schemes; blocks of 50 patients were used to enable equal numbers in each group, no stratification was used."
- Allocation concealment: no credit (no info)
- Intent to treat: credit
    - No explicit statement but data appear to have been handled this way.
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence- no info reported that this was analyzed in a blind/independent manner.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: credit
    - Statistical significance of primary outcome of interest (procedural success + freedom from recurrence + freedom from permanent AV block) demonstrated between treatment groups.
- Controlling for possible confounding: credit
    - Adequate Table 1 showing similar distribution of baseline characteristics between treatment groups

Table E3: Methodological quality of therapeutic studies evaluating efficacy of different catheter ablation approaches in atrial fibrillation patients (Key Question 2)

Methodological Principle	Arentz 2007	Chen 2011	Chilukuri 2011	Corrado 2010	Deisenhofer 2009	Di Biase 2009	Elayi 2011	Elayi 2008
Study design								
Randomized controlled trial	✓	✓	✓	✓	✓	✓	✓	✓
Prospective cohort study								
Retrospective cohort study								
Case-control								
Case-series								
Random sequence generation*				✓		✓		✓
Statement of concealed allocation*						✓		✓
Intention to treat*	✓		✓		✓	✓	✓	✓
Independent or blind assessment								
Co-interventions applied equally	✓	✓	✓	✓	✓	✓	✓	✓
Complete follow-up of ≥80%	✓	✓	✓	✓	✓	✓	✓	✓
Adequate sample size	✓					✓		✓
Controlling for possible confounding†	✓	✓		✓	✓	✓	✓	✓
Evidence Level	**II**	**II**	**II**	**II**	**II**	**II**	**II**	**II**

Methodological Principle	Estner 2011	Fassini 2005	Gaita 2008	Gavin 2012	Haissaguerre 2004	Hocini 2005	Karch 2005	Katritsis 2011
Study design								
Randomized controlled trial	✓	✓		✓	✓	✓	✓	✓
Prospective cohort study								
Retrospective cohort study								
Case-control								
Case-series								
Random sequence generation*			✓	✓			✓	
Statement of concealed allocation*								
Intention to treat*	✓	✓	✓	✓	✓	✓	✓	✓
Independent or blind assessment	✓						✓	
Co-interventions applied equally	✓	✓	✓	✓	✓	✓	✓	✓
Complete follow-up of ≥80%	✓	✓		✓	✓	✓	✓	✓
Adequate sample size		✓		✓		✓	✓	✓
Controlling for possible confounding†	✓	✓	✓	✓	✓	✓	✓	✓
Evidence Level	**II**	**II**	**II**	**II**	**II**	**II**	**II**	**II**

*Applies only to randomized controlled trials

†Groups must be comparable on baseline characteristics or evidence of control for confounding presented

Blank cells indicate that the criterion was either not met or that it could not be determined

Methodological Principle	Kim 2010	Liu, Dong 2006	Liu, Long 2006	Mikhaylov 2010	Mun 2012	Nilsson 2006	Oral 2005	Oral 2004
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	✓	✓	✓	✓	✓	✓	✓	✓
Random sequence generation*		✓	✓					
Statement of concealed allocation*								
Intention to treat*	✓	✓	✓	✓	✓	✓	✓	✓
Independent or blind assessment		✓						
Co-interventions applied equally	✓	✓	✓	✓	✓	✓	✓	
Complete follow-up of ≥80%	✓	✓		✓	✓		✓	✓
Adequate sample size		✓						
Controlling for possible confounding†	✓	✓	✓	✓	✓	✓	✓	✓
Evidence Level	**II**	**II**	**II**	**II**	**II**	**II**	**II**	**II**

Methodological Principle	Oral 2003	Pappone 2004	Pokushalov 2009	Pontoppidan 2009	Sawhney 2010	Sheikh 2006	Tamborero 2009	Verma 2010
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	✓	✓	✓	✓	✓	✓	✓	✓
Random sequence generation*		✓		✓			✓	✓
Statement of concealed allocation*		✓						✓
Intention to treat*	✓	✓	✓	✓	✓	✓		
Independent or blind assessment		✓		✓			✓	✓
Co-interventions applied equally	✓	✓	✓	✓	✓	✓	✓	✓
Complete follow-up of ≥80%	✓	✓	✓	✓	✓	✓	✓	✓
Adequate sample size	✓	✓	✓					✓
Controlling for possible confounding†	✓	✓	✓	✓	✓	✓	✓	✓
Evidence Level	**II**	**I**	**II**	**II**	**II**	**II**	**II**	**II**

*Applies only to randomized controlled trials

†Groups must be comparable on baseline characteristics or evidence of control for confounding presented

Blank cells indicate that the criterion was either not met or that it could not be determined

Methodological Principle	Wang 2008	Wazni 2003	Willems 2006
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	✓	✓	✓
Random sequence generation*	✓		✓
Statement of concealed allocation*			
Intention to treat*	✓	✓	✓
Independent or blind assessment	✓		
Co-interventions applied equally	✓	✓	✓
Complete follow-up of ≥80%	✓	✓	✓
Adequate sample size			✓
Controlling for possible confounding†	✓	✓	✓
Evidence Level	**II**	**II**	**II**

*Applies only to randomized controlled trials

†Groups must be comparable on baseline characteristics or evidence of control for confounding presented

Blank cells indicate that the criterion was either not met or that it could not be determined

Arentz 2007
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way (for primary outcome, data reported for all 55 patients randomized per treatment group; also, if second ablation procedure performed, the technique was the same as the first ablation except in three patients who received additional lines; Figure 4 also implies patients were analyzed in the group they were randomized to).
- Independent or blind assessment: no credit (no info provided)
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: credit
    - Statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Chen 2011
RCT

- Random sequence generation: no credit (inadequate information)
    - "Randomization was done by sealed envelopes."
- Allocation concealment: no credit (inadequate information)

  - "Randomization was done by sealed envelopes."
- Intent to treat: credit
  - Although "patients with inducible AF after the initial ablation procedure were then crossed over to the other ablation technique", results for primary outcome (freedom from recurrence) analyzed within the group they were randomized to.
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (99% f/u (117/118))
- Adequate sample size: no credit
  - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
  - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Chilukuri 2011
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (97% f/u)
- Adequate sample size: no credit
  - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: no credit
  - Statistically significant difference in mean left atrial size b/w treatment groups that was not controlled for

Corrado 2010
RCT

- Random sequence generation: credit
  - "Randomization was performed by a computer-generated randomization scheme."
- Allocation concealment: no credit (no info provided)
- Intent to treat: no credit
  - Patients in PVAI + SVCI group who did not undergo SVCI isolation (due to risk of injury of the phrenic nerve or because of lack of SVC potentials) were not analyzed in results
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; the person analyzing the ECG monitoring data was not blinded or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (92% f/u (294/320))
- Adequate sample size: no credit
  - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit

- Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Deisenhofer 2009
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit (explicit statement)
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; the person analyzing the ECG monitoring data was not blinded or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (96% f/u (94/98))
- Adequate sample size: no credit
  - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
  - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Di Biase 2009
RCT

- Random sequence generation: credit
  - "Treatments balanced within a block size of 3, with the block randomly assigned to each center using a web-based centralized control program."
- Allocation concealment: credit
  - Patients randomized with a centralized program
- Intent to treat: credit (explicit statement)
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: credit
  - Statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
  - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Elayi 2011
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: no credit

    - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Elayi 2008
RCT

- Random sequence generation: credit
    - "Patients were randomized into 3 groups using a centralized web-based program with permuted blocks."
- Allocation concealment: credit
    - Use of centralized program for randomization
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: credit
    - Statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Estner 2011
RCT

- Random sequence generation: no credit (no mention as to how randomization was performed).
    - "Patients were assigned on the day before the procedure to one of the two ablation strategies according to the randomization code contained in sealed envelopes."
- Allocation concealment: no credit
    - Envelopes sealed but no mention of opacity.
- Intent to treat: credit (explicit statement)
- Independent or blind assessment: credit??
    - Recurrence determined by analyzing Holter recordings, "and the evaluation of the clinical outcome was performed by medical personnel unaware of the randomly assigned treatment." (recurrence was the main outcome reported)
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: no credit
    - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Fassini 2005
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit (explicit statement)

- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: credit
    - Statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Gaita 2008
RCT

- Random sequence generation: credit
    - To randomize patients 2:1, "the randomization process was built as follows: a random X was extracted from a uniform distribution for any new patient. If X was < .034, the patient was assigned to PVI ablation scheme, to PVI plus left linear ablation otherwise."
- Allocation concealment: no credit (no info)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: no credit (not clear)
- Adequate sample size: no credit
    - Statistical analysis not done for primary outcome (recurrence) without further splitting groups into AF type (paroxysmal versus persistent)
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Gavin 2012
RCT

- Random sequence generation: credit
    - "Patients were randomized by a random number generator."
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: credit
    - Statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Haissaguerre 2004
RCT

- Random sequence generation: no credit (no info provided)
- Allocation concealment: no credit (no info provided)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: no credit
  - Statistical significance of primary outcome between treatment groups was not reported.
- Controlling for possible confounding: credit
  - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Hocini 2005
RCT

- Random sequence generation: no credit (insufficient info provided)
  - "Patients were prospectively randomized in a 1:1 ration into 2 ablation strategies…"
- Allocation concealment: no credit (insufficient info provided)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; the person analyzing the ECG monitoring data was not blinded and/or independent (was the referring physician).
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: credit
  - statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
  - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Karch 2005
RCT

- Random sequence generation: credit
  - "Patients were randomly assigned according to the randomization code contained in sealed envelopes…"
- Allocation concealment: no credit
  - No indication that the envelopes were opaque.
- Intent to treat: credit (explicit statement)
- Independent or blind assessment: credit
  - "Both the analysis of Holter recordings and the evaluation of the clinical outcome were performed by medical personnel unaware of the randomly assigned treatment."
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: credit
  - Statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit

- Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Katritsis 2011
RCT

- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: credit
  - Statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
  - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Kim 2010
RCT

- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (85%)
- Adequate sample size: no credit
  - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
  - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Liu, Dong 2006
RCT

- Random sequence generation: credit
  - "Randomization was performed according to a computer-generated randomization scheme."
- Allocation concealment: no credit (no info)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: credit
  - "Two independent investigators who had no knowledge of procedural data analyzed all follow-up data."
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% implied)
- Adequate sample size: credit

    - Statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Liu, Long 2006
RCT

- Random sequence generation: credit
    - "Randomization was performed according to a computer-generated randomization scheme."
- Allocation concealment: no credit (no info)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: no credit (only patients with at least 9 months follow-up were included in study)
- Adequate sample size: no credit
    - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Mikhaylov 2010
RCT

- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: no credit
    - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Mun 2012

- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)

- Adequate sample size: no credit
    - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Nilsson 2006
RCT

- Random sequence generation: no credit (inadequate methodology/info)
    - "The randomization sequence, which was administered by an independent clerk, was stratified according to sex, age, atrial diameter, and presence of structural heart disease."
- Allocation concealment: no credit (insufficient info)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way (repeat ablations were done using same technique as in the first procedure)
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: no credit (% f/u NR)
- Adequate sample size: no credit
    - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Oral 2005
RCT

- Random sequence generation: no credit (insufficient info)
- Allocation concealment: no credit (sealed but not opaque envelopes)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100%)
- Adequate sample size: no credit
    - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Oral 2004
RCT

- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit

    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: no credit
    - All patients received LACA; those whose sinus rhythm was restored (n = 40) constituted group 1; the remaining patients were randomized to receive no further ablation (group 2, n = 40) or additional left atrial ablation (group 3, n = 30). (Patients not in SR after these procedures underwent pharmacological or transthoracic cardioversion.)
- Complete f/u of ≥ 80%: credit (100%)
- Adequate sample size: no credit
    - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Oral 2003
RCT

- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100%)
- Adequate sample size: credit
    - statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Pappone 2004
RCT

- Random sequence generation: credit
    - "Randomization was performed according to a computer-generated randomization scheme in permuted blocks of 4."
- Allocation concealment: credit
    - "Assignments were concealed in opaque, sealed envelopes that were numbered consecutively."
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: credit
    - "An independent blinded committee evaluated all [recurrence] events."
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100%)
- Adequate sample size: credit
    - statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Pokushalov 2009
RCT

- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: credit
  - statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
  - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Pontoppidan 2009
RCT

- Random sequence generation: credit
  - Block randomization
- Allocation concealment: no credit (no info)
- Intent to treat: credit (explicit statement)
- Independent or blind assessment: credit
  - Primary outcome: freedom from recurrence; the person analyzing the Holter monitoring data was blinded
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (96% (143/149))
- Adequate sample size: no credit
  - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
  - Statistically significant difference in history of hypertension b/w treatment groups. However, subgroup analysis to determine whether hypertension influenced recurrence (among others) was done, and "none of the prespecified clinical variables were predictors of AF/AFL recurrences."

Sawhney 2010
RCT

- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: no credit
  - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit

- Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Sheikh 2006
RCT

- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
  - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: no credit
  - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit?
  - Table 1 demonstrates similarities in baseline characteristics between treatment groups, however no statistical analysis was performed.

Tamborero 2009
RCT

- Random sequence generation: credit
  - "Randomization was performed according to a computer-generated algorithm in blocks of 20 patients."
- Allocation concealment: no credit (no info)
- Intent to treat: credit
  - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: credit
  - "The ablation group was blinded to…the physicians evaluating the outcome of the procedure."
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: no credit
  - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
  - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Verma 2010
RCT

- Random sequence generation: credit
  - "Randomization was done by random allocation centrally at the clinical trial center and was stratified by site."
- Allocation concealment: credit
  - "Allocation concealment was maintained at all sites by sequentially numbered opaque, sealed envelopes."
- Intent to treat: no credit
  - "One patient randomized to PVI did not end up undergoing ablation, so only 32 (of 33 randomized) were available for analysis in this group." No info provided as to why this patient did not undergo ablation (ie, did the patient not meet the inclusion criteria?)
- Independent or blind assessment: credit

    - "Data were collected, managed, and analysed by a central, independent monitoring group with a restricted access database."
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (99%)
- Adequate sample size: credit
    - statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Wang 2008
RCT

- Random sequence generation: credit
    - "Randomization was generated by a computer after enrollment but prior to electrophysiology study and catheter ablation."
- Allocation concealment: no credit (no info)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: credit
    - "Electrocardiograms and Holters were analyzed by reviewers blinded to patient assignment."
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: no credit
    - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Wazni 2003
RCT

- Random sequence generation: no credit (no info)
- Allocation concealment: no credit (no info)
- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u implied)
- Adequate sample size: no credit
    - No statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Willems 2006
RCT

- Random sequence generation: credit
    - "The randomization sequence was generated by a random number table."
- Allocation concealment: no credit (no info)

- Intent to treat: credit
    - No explicit statement but data appears to have been analyzed this way
- Independent or blind assessment: no credit
    - Primary outcome: freedom from recurrence; no info as to whether the person analyzing the ECG or Holter monitoring data was blinded and/or independent.
- Co-interventions applied equally: credit (no obvious differences between treatment groups)
- Complete f/u of ≥ 80%: credit (100% f/u)
- Adequate sample size: credit
    - statistically significant difference in primary outcome (freedom from recurrence) between treatment groups
- Controlling for possible confounding: credit
    - Robust Table 1 demonstrates no statistically significant differences in a number of baseline characteristics between treatment groups

Appendix F. Evidence Tables For Included Studies

Table F1. Atrial Fibrillation Study Characteristics

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
PVI versus AADs (anti-arrhythmic drugs)					
Forleo (2009)[5] Italy Funding NR (last author receives lecture fees from St. Jude Medical and serves on the advisory board of Biosense-Webster)	RCT CoE II	• N = 70 • Age (mean): 64 years • Male: 61% • All patients had diabetes mellitus type 2 (DM2) • Paroxysmal AF: 41% • Symptom duration: 38.9 months (mean) (range, 17-66 months) • CHF: NR • LAD (mean): 4.5 cm • LVEF (mean): 54%	Intervention groups: • RFA (cPVI): n = 35 • ADT: n = 35 RFA characteristics: • PVI? Yes • Isolation (% success, patients): 100% • Definition of isolation: creation of a circumferential line around each PV vestibule or adjacent vestibules of two ipsilateral PV associated with complete elimination of PV potentials as measured by the loop-shaped multipolar mapping catheter at the PV ostium and subsequent demonstration of bidirectional block. • Other ablation? -Bidirectional cavotricuspid isthmus block: (100%) -Mitral isthmus ablation (23%) -Roofline ablation (9%) • Checked inducibility? NR • Catheter tip: 3.5 mm cooled-tip • Energy, watts: 35 • Max temp (°C): 45 • Total ablation time (min): 207 ± 54 Post-RFA anti-arrhythmics: • Patients discharged on AADs • Discontinuation of any AAD was considered on a case-by-case basis • Discontinuation of AADs was complete: within 1 month in the absence of	Inclusion: • DM2 patients • Symptomatic paroxysmal or persistent AF for ≥ 6 months refractory to ≥ 1 class 1-3 AADs Exclusion: • Age <18 or >75 years • Ejection fraction <30% • Left atrial size >55mm • Absence of informed patient consent • Any condition that would make survival for 1 year unlikely • Prior cardiac surgery • History of previous ablation for AF	Follow-up: • 12 months • 100% f/u Outcomes: • Freedom from recurrent AF • Discontinuation of anticoagulation therapy • Discontinuation of AADs • Hospitalizations • QoL (SF-36 general health) • QoL (SF-36 social functioning) • QoL (SF-36 physical functioning) • QoL (SF-36 bodily pain) • QoL (SF-36 role emotional) • Adverse events (PV stenosis, cardiac tamponade, stroke, esophageal perforation, peripheral vascular complications, 30-day mortality, other (bleedings, pharmacological therapy related adverse events)) Subgroup analysis? • No subgroup analysis Blanking period?

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			structural heart disease; OR within 3 months in the remaining patient <u>AAD characteristics:</u> • Patients received new ADT (antiarryhthmic drug treatment) • ADT at maximum tolerable dose of single drug or combination • In patients with persistent AF, cardioversion performed under a new ADT to maintain sinus rhythm • Recommended regimen: flecainide (100 mg/12 hours), propafenone (150-300 mg 3X/day), sotalol (initial dose of 80 mg 3X/day), and amiodarone (600 mg/day for 2 weeks, then 400 mg/day for next 2 weeks, then 200 mg/day thereafter) • If early recurrence (within 1 month), patients offered additional trial of ADT <u>Other important characteristics:</u> • All patients received the assigned treatment		• Blanking period of 5 weeks for both treatment groups
Jais (2008)*[6] France, US, Canada <u>Funding</u>: Biosense Webster, St. Jude Medical, Bard, Medtronic, Biotronik, Canada Research Chair in Electrophysiology and Adult Congenital Heart Disease, Canadian Institute of Health Research, Fonds de Recherche en Sante, Boston Scientific, CryoCath Technologies	RCT CoE II	• N = 112 • Age (mean): 51 years • Male: 84% • Paroxysmal AF: 100% • Symptom duration: 5.5 years (median) • CHF: NR • LAD (mean): 4.0 cm • LVEF (mean): 64%	<u>Intervention groups:</u> • RFA (cPVI): n = 53 • Medical: n = 59 <u>RFA characteristics:</u> • Circumferential PVI + additional ablation (see below for details) • PVI? yes • Isolation (% success, patients): 100% (LPVs), 98% (RSPV), 94% (RIPV) • Definition of isolation: NR • Other ablation? Roof (17%); Mitral isthmus lines	<u>Inclusion</u>: • > 18 years • Symptomatic paroxysmal AF ≥ 6 months <u>Exclusion</u>: • Contraindication to >2 AADs in different classes • Contraindication to oral anticoagulants • Contraindication to the discontinuation of oral anticoagulation • Intracardiac	<u>Follow-up:</u> • 12 months • 96% f/u (107/112) <u>Outcomes</u>: • Freedom from recurrent AF (including asymptomatic AF) • Discontinuation of anticoagulation therapy • LAD • LVED

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			(30%) (LA); Cavo-tricuspid isthmus line (64%) (RA); Targeted foci (23%) (non-venous structure) • Checked inducibility? No • Catheter tip: 3.5 mm or 5 mm irrigated tip • Energy, watts: up to 35 W • Max temp: up to 50 °C • Total ablation time (min): NR <u>Post-RFA anti-arrhythmics</u>: • None <u>AAD characteristics:</u> • Once in the study, patients received "new" AADs (i.e., monotherapy or combinations of drugs never administered before enrollment) • Acceptable AADs (alone or in combination): amiodarone, quinidine, disophramide, flecainide, propafenone, cibenzoline, dofetilide, solatol. • Specific regimen: none, physicians encouraged to comply with published guidelines <u>Other important characteristics:</u> • Number of attempts to achieve freedom from arrhythmia (allowed up to 90 days from randomization during treatment stabilization period): • RFA group: Up to 3 attempts to achieve freedom from arrhythmia (i.e., up to 2 repeat ablations) (n = 23, 43%) • Pharm group: Up to 4 attempts (i.e., up to 3 attempts for modification of pharmacologic therapy	thrombus • AF from a potentially reversible cause • Pregnancy	• LVEF • QoL (SF-36 physical component) • QoL (SF-36 mental component) • Adverse events (PV stenosis, cardiac tamponade, stroke, esophageal perforation, peripheral vascular complications, 30-day mortality, other) <u>Subgroup analysis?</u> • No subgroup analysis <u>Blanking period?</u> • Blanking period of 90 days

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			such as altering drugs) • Treatment failure and crossover: at the time of treatment failure during the follow-up period, crossover to the alternative therapy was allowed.		
Krittayaphong (2003)*[7] Thailand Funding: Faculty of Medicine, Siriraj Hospital	RCT CoE II	• N = 30 • Age (mean): 52 years • Male: 63% • Paroxysmal AF: 67% • Symptom duration: 56 months (mean) • CHF: NR • LAD (mean): 3.9 cm • LVEF (mean): 63%	Intervention groups: • RFA (cPV + additional lines): n = 15 • AADs: n = 15 RFA characteristics: • Circumferential PV and additional lines ablation with transient concurrent antiarrhythmics • PVI? Yes • Isolation (% success, patients): not applicable, only the assessment of the completeness of these lines was performed • Definition of isolation: not applicable • Other ablation? LA: WACA + mitral line; RA: cavotricuspid isthmus line, SVC-IVC, and mid-RA horizontal line • Checked inducibility? No • Catheter tip: 8 mm (Navistar) • Energy, watts: NR • Max temp: 55°C • Total ablation time (min): 212 Post-RFA anti-arrhythmics: • New drug treatment • 3 months (amiodarone 200 mg qd without loading dose) AAD group: • Amiodarone • Loading dose: 1200 mg qd (1 week); 600 mg qd (2 weeks) • Maintenance dose: 200	Inclusion: • Male or female, 15-75 years • Symptomatic (>6 months) paroxysmal or persistent AF • Refractory to at least 1 of the following: class IA/IC, digitalis, beta-blocker, or Ca-blocker • No prior amiodarone Exclusion: • Transient AF or treatable cause • Bleeding disorder • Thyroid disorder • Previous stroke • Other comorbidity with less than 1-year life expectancy • Psychiatric disorder • Valvular heart diseases • Unwilling to participate	Follow-up: • 12 months • 93% f/u (28/30) Outcomes: • Freedom from recurrent AF (including asymptomatic AF) • SF-36 general health score • SF-36 physical fitness score • Adverse events (PV stenosis, cardiac tamponade, stroke, esophageal perforation, peripheral vascular complications, amiodarone-related complications) Subgroup analysis? • No subgroup analysis Blanking period? • NR • Note: no relapse cases reported in the RFA arm during the first three-month period

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			mg qd • Patients with persistent AF could undergo external cardioversion		
MacDonald (2011)[8] Scotland, UK Funding: Chief Scientist Office, Scotland (grant number CZB4475)	RCT CoE II	• N = 41 • Age (mean): 63 years • Male: 78% • All patients had advanced heart failure (coronary heart disease) • NYHA functional class II: 10% • NYHA functional class III: 90% • NYHA functional class IV: 0% • Paroxysmal AF: 0% • Symptom duration: RFA: 3.7 years month; medical: 5.3 • CHF: NR • LAD (mean): NR • LVEF (mean): RFA: 16.1%; medical: 19.6%	Intervention groups: • RFA (cPVI): n = 22 • AAD: n = 19 RFA characteristics: • PVI? Yes • Isolation (% success, patients): NR • Definition of isolation: NR • Other ablation? Roof; at other sites of complex fractionated electrograms • Checked inducibility? No • Catheter tip: NR • Energy, watts: NR • Max temp (°C): NR • Total ablation time (min): 254 (ablation + fluoroscopy time) Post-RFA anti-arrhythmics: • Started prior to discharge and continued for 3 months (amiodarone) AAD characteristics: • "continued medical treatment for rate control", but no other info given Other important characteristics: • If patient remained in AF following ablation, internal cardioversion was performed to restore sinus rhythm.	Inclusion: • Male or female, 18-80 years • New York Heart Association functional class II – IV symptoms despite optimal heart failure treatment for at least 3 months • Ejection fraction <35% • Persistent AF • No contraindication to cardiovascular MRI Exclusion: • Paroxysmal AF • QRS duration >150 ms or QRS 120-150 with evidence of mechanical cardiac dysynchrony • Any contraindication to oral anticoagulant drugs • Primary valvular disease or acute myocarditis as the cause of heart failure • Coronary revascularisation within the preceding 6 months • Pregnancy and expected cardiac transplantation within 6 months	Follow-up: • 6 months • 93% f/u Outcomes: • Freedom from recurrence • LVEF (primary outcome) • Radionuclide LVEF • RVEF • 6 min walk distance • QoL (SF-36 physical component) • QoL(SF- 36 mental component) • QoL (KCCQ) • QoL (MLHFQ) • Adverse events Subgroup analysis? • Yes (patients in sinus rhythm vs those in AF at study end- post hoc analysis) Blanking period? • 3 months

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
Oral (2006)*[9] USA and Italy Funding: Ellen and Robert Thompson Fibrillarion Research Fund Other conflict of interest includes Ablation Frontier, Biosense Webster, St. Jude Medical, Guidant, and Medtronic	RCT CoE II	• N = 146 • Age (mean): 56 years • Male: 65% • Paroxysmal AF: 0% • Symptom duration: 4.5 years (mean) • CHF: NR • LAD (mean): 4.5 cm • LVEF (mean): 55%	Intervention groups: • PVI: n = 77 • AAD (amiodarone): n = 69 RFA characteristics: • Circumferential PV and additional lines ablation with transient concurrent anti-arrhythmics • PVI? Yes • Isolation (% success, patients): not determined (100% inferred) • Definition of isolation: Local electrogram amplitude 0.2 mV or less • Other ablation? Encircling lesions of PVs; Roof line; Mitral isthmus line; Cavotricuspid line (in 55 patients at discretion of operators) • Checked inducibility? No • Catheter tip: 8 mm (Navistar) • Energy, watts: 70 • Max temp: 55°C • Total ablation time (min): 37 (only for the circumferential PV ablation) Post-RFA anti-arrhythmics: • Transient AAD • Amiodarone 200 per day (3 months) • Most patients also received cardioversion at 6 weeks • NOTE: 53 patients (77%) underwent RFA after relapse	Inclusion: • Chronic AF: defined as AF that had been present for more than 6 months without intervening spontaneous episodes of sinus rhythm and that recurred within one week after cardioversion. Exclusion: • Age < 18 or > 70 years • Left atrial diameter > 55 mm • Left ventricular ejection fraction < 30% • Contraindication to amiodarone therapy or anticoagulation with warfarin • Presence of a mechanical prosthetic valve • History of a cerebrovascular accident • Presence of left atrial thrombus on transesophageal echocardiography • Prior attempt at catheter or surgical ablation for AF	Follow-up: • 12 months • 100% f/u Outcomes: • Maintaining sinus rhythm • Re-intervention • LAD size • LVEF • Adverse events (PV stenosis, cardiac tamponade, stroke, esophageal perforation, peripheral vascular complications, 30-day mortality, atypical atrial flutter, sick sinus syndrome, pneumonia) Subgroup analysis? • No subgroup analysis Blanking period? • No blanking period

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			AAD characteristics: • Transient AAD • Amiodarone 200 per day (6 months) • Most patients also received cardioversion at 6 weeks; second cardioversion permitted within three months after first • If recurrent AF developed more than 3 months after first cardioversion, patients could either resume amiodarone therapy or undergo CPVA (53 patients (77%) underwent RFA after relapse)		
Pappone (2006/2011)*[10, 11] Italy Funding: Arrhythmology Department, San Raffaele University Hospital (Italy); note that Dr. Pappone has advisory board appointments at Johnson & Johnson, St. Jude Medical, Medtronic Inc., Boston Scientific Co., and Biotronik SE.	RCT CoE II	• N = 198 • Age (mean): 56 years • Male: 67% • Paroxysmal AF: 100% • Symptom duration: 6 years (median or mean?) • CHF: NR • LAD (mean): 3.9 cm • LVEF (mean): 61%	Intervention groups: • CPVA: n = 99 • AADs: n = 99 RFA characteristics: • CPVA • PVI? Yes • Isolation (% success, patients): assessed completeness across mitral isthmus lines as previously described (?) • Definition of isolation: previously described (?) • Other ablation? CPVA (including roof and mitral line) + cavotricuspid isthmus ablation (right sided empiric atrial flutter ablation) • Checked inducibility? No • Catheter tip: 8 mm (n = 50) 3.5 mm irrigated (n = 49) • Energy, watts: For 8 mm catheter pts: 60-100 For 3.5 mm catheter pts: 25-40 • Max temp: For 8 mm catheter pts: 50-65°C For 3.5 mm catheter pts: 35-40°C	Inclusion: • Paroxysmal AF with failed AADs • > 18 years or < 70 years • Creatine < 1.5 mg/dL • AF history > 6 months • AF > 2 episodes/month in the last 6 months Exclusion: • LAD > 65 mm • LVEF < 35% • CHF > NYHA class II • Prior amiodarone, flecainide, or solatol • Prior catheter or surgical ablation • AF secondary to transient or correctable abnormality • Intra-artial thrombus • Tumor precluding catheter insertion • Contraindication to beta-blocking therapy • Rheumatic mitral valve disease	Follow-up: • 12 months (2006) (100% f/u) • 48 months (2011) (95% f/u) Outcomes: • Freedom from recurrence (including asymptomatic AF) • QoL (all SF-36 scores) • Re-admission • Adverse events (stroke, small pericardial effusion, pro-arrhythmia, thyroid dysfunction, sexual dysfunction, permanent drug withdrawal secondary to adverse events) Subgroup analysis? • Age • Gender • AF duration • LVEF

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			• Total ablation time (min): 35 Post-RFA anti-arrhythmics: • 6 weeks AAD characteristics: • One or two of the following, as tolerated and at the maximum tolerated dose: • Flecainide: initial dose of 100 mg every 12 hours • Solatol: initial dose of 80 mg every 8 hours • Amiodarone: initial loading of 600 mg/day for first week, 400 mg/day for 2nd week, then daily maintenacnce dose of 200 mg/day • Patients could be considered for crossover to CPVA after 2 unsuccessful trials of AAD	• Unstable angina or acute prior myocardial infarction (< 6 months) • WPW Syndrome • Renal or hepatic failure • Implanted device (pacemaker or cardioverter-defibrillator) • Need for antiarrhythmic therapy for arrhythmias other than AF • Contraindication to antiarrhythmic drug therapy or anticoagulation with warfarin • History of cerebrovascular accident • Prior attempt at catheter or surgical ablation for AF	• Left atrial size • Structural heart disease Blanking period? • Blanking period of 6 days
Stabile (2006)*[12] Italy Funding: Biosense-Webster, Italy	RCT CoE II	• N = 137 • Age (mean): 62 years • Male: 57% • Paroxysmal AF: 67% • Symptom duration: 6.1 years (mean) • CHF: NR • LAD (mean): 4.6 cm • LVEF (mean): 58%	Intervention groups: • CPVA: n = 68 • AAD: n = 69 RFA characteristics: • Circumferential PV and additional lines ablation with continuous concurrent anti-arrhythmics • PVI? Yes • Isolation (% success, patients): not determined (100% implied) • Definition of isolation: low peak-to-peak bipolar potentials (<0.1 mV) inside the lesion by local electrogram analysis and voltage maps • Other ablation? Circumferential lines around each PV; Mitral isthmus line; Cavotricuspid isthmus line (if conduction in this region was detected)	Inclusion: • Paroxysmal or permanent AF (see below for definitions) intolerant of AADs or refractory to two or more anti-arrhythmics • Paroxysmal AF defined as occurrence in previous 6 months of one or more episode of AF/month, each lasting more than 60 minutes but less than 7 days, all episodes terminating spontaneously • Permanent AF defined as occurrence in previous 12 months of 2 or more	Follow-up: • 12 months • 97% f/u Outcomes: • Atrial arrhythmia-free survival (including asymptomatic AF) • Re-admission • Adverse events (PV stenosis, cardiac tamponade, stroke, esophageal perforation, peripheral vascular complications, 30-day mortality, transient phrenic paralysis, AAD-related

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			• Checked inducibility? No • Catheter tip: 8 mm (in first 17 patients only) 3.5 mm cooled (remaining patients) • Energy, watts: For 8 mm catheter: 100 For 3.5 mm catheter: 50 (for each, half of the energy was used when ablation performed in posterior wall) • Max temp: For 8 mm catheter: 60°C For 3.5 mm catheter: 45°C • Total ablation time (min): NR <u>Post-RFA anti-arrhythmics</u>: • Amiodarone (if amiodarone not tolerated, a class IC antiarrhythmic drug was administered) <u>AAD characteristics:</u> • Continuous anti-arrhythmics (preferentially amiodarone (if amiodarone not tolerated, a class IC antiarrhythmic drug was administered))	episodes of AF, each lasting more than 7 days before being terminated pharmacologically or by electrical cardioversion, or lasting less than 7 days but necessitating early cardioversion owing to intolerable symtpoms or hemodynamic compromise, with sinus rhythm maintained for 60 minutes or more after termination <u>Exclusion</u>: • Age < 18 or > 80 years • Permanent AF (AF, the sole rhythm for last 12 months) • AF secondary to transient or correctable abnormality (including electrolyte imbalance, trauma, recent surgery, infection, toxic ingestion, and endocrinopathy) • Peristence of AF episodes triggered by another uniform arrhythmia (i.e. atrial flutter or atrial tachycardia) despite previous SVT ablation • Intra-atrial thrombus, tumor, or other abnormality precluding catheter insertion • WPW syndrome • Heart failure with NYHA class II or IV or EF ≤ 35% • Unstable angina or	complications, coronary artery disease, cancer, sudden death) <u>Subgroup analysis?</u> • No relevant subgroup analysis (tip size only, which is excluded from our analysis) <u>Blanking period?</u> • Blanking period of 1 month

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
				acute myocardial infarction within 3 months • Cardiac revascularization or other cardiac surgery within 6 months or with prior atrial surger • Renal failure requiring dialysis, or hepatic failure • Implanted device (pacemaker or cardioverter debrillator) • Left atrial diameter > 60 mm	
Wazni (2005)*[13] Germany, Italy Funding: "Supported in part by an unrestricted educational grant from Acuson, a division of Siemens Medical Solutions", which did not participate in any part of the study.	RCT CoE II	• N = 70 • Age (mean): 54 years • Male (%): NR • Paroxysmal AF: 96% • Symptom duration: 0.4 years (mean) • CHF: NR • LAD (mean): NR • LVEF (mean): 54%	Intervention groups: • PVI: n = 33 • AAD: n = 37 RFA characteristics: • PVI? Yes (first line therapy) • Isolation (% success, patients): 100% • Definition of isolation: no PV potential or electrical dissociation • Other ablation? None • Checked inducibility? No • Catheter tip: 8 mm • Energy, watts: NR • Max temp: NR • Total ablation time (min): NR • Warfarin initiated in all patients and maintained ≥ 3 months (continued if AF recurrence, or ≥ 50% PV narrowing) Post-RFA anti-arrhythmics: • Time NR AAD characteristics: • AAD (first line therapy), drug choice up to physician • Recommended regimen: flecainide (100-1500 mg) twice daily, propafenone (225-300 mg) 3 times	Inclusion: • Monthly symptomatic AF ≥ 3 months Exclusion: • < 18 years or > 75 years • History of AF ablation • History of open heart surgery • History of AAD use • Contraindication to long-term anticoagulants • Atrial flutter	Follow-up: • 12 months • 96% f/u Outcomes: • AF recurrence (included asymptomatic) • Hospitalization • Thromboembolic events • PV stenosis • QoL (SF-36 physical functioning subscale) • QoL (SF-36 mental health subscale) • Adverse events (PV stenosis, stroke, bleeding) Subgroup analysis? • No subgroup analysis Blanking period? • Blanking period of 2 months

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			daily, and solatol (120-160 mg) twice daily • Warfarin initiated in all patients and maintained throughout the study		
Wilber (2010)*[1] United States, Europe, Canada, and Latin America <u>Funding</u>: Biosense Webster	RCT CoE II	• N = 167 • Age (mean): 55.7 years • Male: 66.5 % • Paroxysmal AF: NR • Symptom duration: mean 5.7 years • CHF: NR • LAD (mean): RFA: 40.0 mm; AAD: 40.5 mm • LVEF (mean): RFA: 62.3%; AAD: 62.7%	<u>Intervention groups:</u> • RFA (cPVI): n = 106 • AAD: n = 61 <u>RFA characteristics:</u> • PVI? Yes • Isolation (% success, patients): NR • Definition of isolation: absence of entrance block confirmed in all PVs at end of procedure • Other ablation? Left atrial linear lesions, ablation at sites with electrogram fractionation, and cavotricuspid isthmus ablation. • Checked inducibility? No • Catheter tip: NR • Energy, watts: NR • Max temp: NR • Total ablation time (min): NR <u>Post-RFA anti-arrhythmics</u>: • NR <u>AAD characteristics:</u> • Previously unused AAD (class I or class III) • Choice of drug was at discretion of investigator • Potential drugs included dofetilide, flecainide, propafernone, sotalol, or quinidine. • Amiodarone was not administered. • 36 patients had protocol determined treatment failures and underwent an ablation procedure during evaluation period. <u>Other important characteristics:</u> • If treatment failed after	<u>Inclusion</u>: • At least 3 symptomatic AF episodes within the 6 months before randomization • No response to at least 1 AAD (class I, class III, atrioventricular nodal blocker). <u>Exclusion</u>: • AF of more than 30 days in duration • < 18 years of age • An ejection fraction of less than 40% previous ablation for AF • Left atrial thrombosis • Amiodarone therapy in the previous 6 months • New York Heart association class II (marked limitation in activity due to symptoms) or IV (severe limitations). • Myocardial infarction within the previous 2 months • Coronary artery bypass graft procedure in the previous 6 months • Thromboembolic event in previous 12 months • Severe pulmonary disease • Prior valvular cardiac surgical procedure • Implanted cardioverter-	<u>Follow-up:</u> • 9 months • % f/u NR (at the most it was90.4%, but the actual follow-up was not clear and could not be determined from the reported results). <u>Outcomes</u>: • Freedom from recurrence (primary outcome) • QoL (SF-36 physical summary scores) • QoL (SF-36 mental summary scores) • QoL (Symptom frequency- AF Symptom Frequency and Severity Checklist) • QoL (Symptom severity- AF Symptom Frequency and Severity Checklist) • Adverse events <u>Subgroup analysis?</u> • No subgroup analysis <u>Blanking period?</u> • Ablation group: 3 months • AAD group: 14 day dose titration period

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			90 days, patients in the AAD group were allowed to crossover and undergo ablation. • Repeat ablation was performed in 13 patients within 80 days of initial ablation procedure.	defibrillator • Contraindication to antiarrhythmic or anticoagulation medications • Life expectancy of less than 12 months • Left atrial size of at least 50 mm in parasternal long axis view.	
Lan (2009)[14] China, Germany Funding: Grant from Health Research Foundation (Health bureau of Chongqing); authors stated no relationships with MSD and Sanofi-Synthelabo; and that they receive no honoraria or consulting fees from Biosense Webster.	Pro-spective cohort CoE III	• N = 240 • Age (mean): 59.0 years • Male: 79.3 % • Paroxysmal AF: 100% • Symptom duration: mean 2.62 years • CHF: NR • LAD (mean): 34.7 mm • LVEF (mean): 65.8%	Intervention groups: • RFA; n = 120 • AAD: n = 120 RFA characteristics: • PVI? One group (n = 60) underwent cPVA, another group (n = 60), underwent sPVI. • Isolation (% success, patients): • Definition of isolation: Disappearance or dissociation of the distal local pulmonary vein potentials during sinus or paced rhythm throughout the ostial circumference. • Other ablation? • Checked inducibility? • Catheter tip: • Energy, watts: • Max temp: x°C • Total ablation time (min): CPVA: 74 ± 18 min; SPVA: 44 ± 19 Post-RFA anti-arrhythmics: • For patients with AF storm after ablation, 600 mg/day amiodarone was administered in the first two weeks, followed by 400 mg/day amiodarone up to 1 month. AAD characteristics: • Amiodaraone alone: 60 patients; amiodarone plus losartan: 60 patients • Amiodraone: 600 mg per day for first week, 400 mg per day for the second week, and 200	Inclusion: • AF attack at 1 times monthly • Symptoms such as palpitations, chest distress during occurence of AF • New York Heart Association Class I and left ventricular ejection fraction of ≥ 55% • No structural heart disease and blood pressure of ≤ 165/95 mmHG in hypertensive patients Exclusion: • Refractory to amiodarone in the past • Left atrium size of more than 45 mm • Hyperthyrodism or electrolyte disturbance, pulmonary, or hepatic disease and/or contraindications to treatment with amiodarone, significant impairment of renal function, metral regurgitation • QT interval ≥ 480 ms in the absense of bundle-brance block • Bracycardia ≤ 55 bpm while the	Follow-up: • 12 months • 100% f/u Outcomes: • Freedom from recurrence (primary outcome) • LAD • LVED (reported in this study as LVDd) • LVEF • Adverse events Subgroup analysis? • Yes (indicate what) or No subgroup analysis Blanking period? • Blanking period of 1 month

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			mg per day thereafter. • Losartan: 50 mg/day for first 2 weeks. If no hypotension occurred, the dose was increased to 100 mg per day thereafter. If patients could not tolerate losartan 100 mg or had blood pressure < 90/55, the dose was reduced to 50, and intensive follow-up was conducted until blood pressure increased to 110/60.	patient was awake • Significant alternations of the atrioventricular conduction, sick sinus syndrome, or any other medical condition that, in the opinion of the investigators, made the patient inappropriate for the study.	
Pappone, Augello (2003)*[15] Italy Funding: NR	Pro-spective cohort LoE III	• N = 1171 • Age (mean): 65 years • Male: 58 % • Paroxysmal AF: 70% • Symptom duration: mean 4.6 years • CHF: NR • LAD (mean): 4.6 cm • LVEF (mean): 54%	Intervention groups: • RFA (cPVI): n = 589 • AAD: n = 582 RFA characteristics: • PVI? Yes • Isolation (% success, patients): NR (100% inferred) • Definition of isolation: Elimination of PV ostial potentials and absence of discrete electrical activity inside the lesion during pacing outside the ablation line, or voltage abatement inside and around the encircled areas • Other ablation? NR • Checked inducibility? No • Catheter tip: NR • Energy, watts: NR • Max temp: NR • Total ablation time (min): 59 Post-RFA anti-arrhythmics: • 3 mo (only 115 patients (20%) who had in-hospital Afib and/or needed DC cardioversion after the procedure were prescribed) AAD characteristics: • AADs given throughout the follow-up period • In patients with	Inclusion: • Two or more previous ineffective trials with antiarrhythmic drugs • More than 2 AF-related hospital admissions during the 2 years before entering the study • Two or more years of AAD treatment Exclusion: • Contraindication to anticoagulation • New York Heart Association functional class IV • Myocardial infarction or cardiac surgery within the past three moths • Sick sinus syndrome or atrioventricular conduction disturbances without an artificial pacemaker • Ventricular tachyarrhythmias • Thyroid dysfunction • Unsuccessful cardioversion to SR by drugs and/or electroshock	Follow-up: • Mean 30 months • 98.4% f/u Outcomes: • AF-free survival • Congestive heart failure • Stroke • Overall survival • Adverse event-free survival • Arrhythmia burden • SF-36 physical component summary score • SF-36 mental component summary score Subgroup analysis? • LAD > 4.5 cm • Reduced encircled ablation area • Recurrent Afib • Non-recurrence • Recurrent Afib • Non-recurrence Blanking period? • No blanking period (follow-up began at discharge)

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			intermittent AF, AADs were initiated during sinus rhythm • Patients with non-self terminating or chronic AF underwent AAD therapy and if necessary electrical cardioversion. • Used in accordance with published guidelines and could be stopped at physician's discretion if SR had been maintained for at least 3 months. • "RFA" group had less favorable patient profiles than "medical" group: longer duration of AFib (5.5 years vs. 3.6 years, p<0.001) and more AADs tried (3.1 vs. 2.3, P<0.001). Other important characteristics: • NR		
Rossillo (2008)*[16] Italy Funding: NR	Retro-spective cohort CoE III	• N = 170 • Age (mean): 62 years • Male: 84 % • Paroxysmal AF: 15.9% • Symptom duration: mean for RFA group 8 years • CHF: RFA: 72%; AAD: 76% • LAD (mean): RFA: 4.4; AAD: 4.2 • LVEF (mean): RFA: 58%; AAD: 56	Intervention groups: • RFA (PVI): n = 85 • AAD: n = 85 RFA characteristics: • PVI? Yes • Isolation (% success, patients): 100%, 170/170 patients • Definition of isolation: All 4 pulmonary veins were disconnected • Other ablation? SVC isolation: 72 patients • Checked inducibility? No • Catheter tip: 8 mm tip catheter (Biosense-Webster) • Energy, watts: Energy was controlled by progressively increasing power until scattered microbubbles were observed by ICE • Max temp: NR • Total ablation time	Inclusion: • PVI group: consecutive patients who were referred for ablation of symptomatic drug-refractory AF • AAD: age-, sex- and heart disease-matched patients with persistent AF who underwent electrical cardioversion between May 2002 and July 2003. Exclusion: • NR	Follow-up: • 15 ± 7 months • % f/u NR Outcomes: • Stable sinus rhythm Subgroup analysis? • Yes (indicate what) or No subgroup analysis Blanking period? • Blanking period of 8 weeks

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			(min): NR Post-RFA anti-arrhythmics: • PVI group: no patients received anti-arrhythmic drugs unless arrhythmic recurrences developed during follow-up • Controls: all patients were pre-treated with anti-arrhythmic drug, and the treatment was continued or stopped during follow-up according to the referring physician's indications. 29 (34%) patients stopped anti-arrhythmic drug Rx at least 1 month after electrical cardiov ersion. AAD characteristics: • Pre-treatment with AAD therapy • Electrical cardioversion performed • After cardioversion, AAD therapy was continued OR stopped according to the referring physician's indications. Other important characteristics: • 19% vs. 6% (PVI vs. AAD) were low risk for stroke (i.e. age<65, no HTN, DM, CHF or previous CVA), p<0.01		
Sonne (2009)[17] Countries NR Funding: NR	Retro-spective cohort CoE III	• N = 351 • Age (mean): 66.9 years • Male: 68.4% • Paroxysmal AF: 25.6% • Symptom duration: NR • CHF: NR • LAD (mean): 5.6 cm	Intervention groups: • RFA (PVAI) n = 146 • AAD: n = 205 RFA characteristics: • PVI? Yes • Isolation (% success, patients): NR • Definition of isolation: NR • Other ablation? NR • Checked inducibility? No	Inclusion: • Patients were included the RFA group: if they had PVAI and no prior or subsequent ablative or surgical treatment for AF such as AVJA or Cox-Maze procedure. Patients were considered for PVAI if they had	Follow-up: • Mean 69 months • 82% f/u Outcomes: • Survival rate Subgroup analysis? • No subgroup analysis Blanking period?

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
		• LVEF (mean): NR	• Catheter tip: NR • Energy, watts: NR • Max temp: NR • Total ablation time (min): NR <u>Post-RFA anti-arrhythmics</u>: • NR <u>AAD characteristics:</u> • All patients received direct current cardioversion; most received multiple cardioversions. • AAD treatment varied. <u>Other important characteristics:</u> • Appears to have been a retrospective analysis of a database that was prospectively generated.	symptomatic AF refractory to ≥ 1 AADs. • Patients were included in the AAD group: if they had pharmacological therapy combined with DCC and no prior or subsequent ablative or surgical treatment for AF. The majority of patients had multiple DCCVs. <u>Exclusion</u>: • NR	• No blanking period
Cryoablation versus AADs (anti-arrhythmic drugs)					
STOP AF Pivotal Trial- from Arctic Front Cardiac CryoAblation System: FDA SSED (P100010) (2010)[18] USA, Canada <u>Funding</u>: Medtronic	RCT within FDA SSED for P100010 CoE II	• N = 245 • Age (mean): 56.6 years • Male: 77.1 % • Paroxysmal AF: NR • Symptom duration: NR • CHF: NR • LAD (mean): 40.5 mm • LVEF (mean): 60.2% • NYHA Class I (mean): 93.5% • NYHA class II (mean): 6.5%	<u>Intervention groups:</u> • Cryo (PVI): n = 163 • AADs: n = 82 <u>RFA characteristics:</u> • PVI? Yes • Isolation (% success, patients): >95% • Definition of isolation: NR • Other ablation? NR • Checked inducibility? No • Catheter tip: NR • Energy, watts: NR • Max temp (°C): NR • Total ablation time (min): NR <u>Post-RFA anti-arrhythmics</u>: • NR <u>AAD characteristics:</u> • Flecanide, propafenone, or solatol • Were allowed one crossover cryoablation	<u>Inclusion</u>: • Diagonosis of paroxysmal atrial fibrillation AND • 2 or more episodes of AF during the 2 months prior to the start date, at least 1 of which must be documented with a tracing. • ≥ 18 and ≤ 75 years of age • Documented failure of one or more primary AF drugs for effectiveness • Clinically eligible to follow the standard AAD treatment procedure for both groups, control or experimental. • Willing to comply with AAD treatment regardless of	<u>Follow-up:</u> • 12 months • 93% f/u <u>Outcomes</u>: • Chronic Treatment Failure (recurrence following-blanking period) • Treatment Success (acute procedural success (for ablation pts) <u>and</u> freedom from chronic treatment failure) • AAD -free treatment success • Treatment success with AADs • AAD usage • QoL (SF-36

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			treatment only after they demonstrated chronic treatment failure. • 65 patients crossed over and underwent cryoablation. <u>Other important characteristics:</u> • 31 patients in Cryo group underwent reablation.	randomization and TTM procedures for full 12 month f/u period. <u>Exclusion</u>: • Any previous left atrial ablation except permissible retreatment subjects • Any previous LA surgery • Anteroposterior LA diameter > 5.0 cm by TTE during the 3 month interval preceding the consent date • Presence of any cardiac valve prosthesis • Clinically significant mitral valve regurgitation or stenosis • Any treatment with amiodarone during the 3 month interval preceding the consent date • Previous failure of all three primary AF drugs for either effectiveness or intolerance • Predicted need for use of any of the primary AF drugs or secondary AF drugs listed in Appendix One for "pill in pocket" therapy or any other use for any condition during the 12 month study follow up period, other that for treatment of documented recurrent AF • Any cardioversion (drug or electric) for AF during the 3 month interval	subscales) • Symptoms • Stroke • Death • Adverse events (cryoablation procedure related events, pulmonary vein stenosis, phrenic nerve palsy, major AF events (including freedom from such events), serious adverse events <u>Subgroup analysis?</u> • No subgroup analysis <u>Blanking period?</u> • Blanking period of 90 days

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
				preceding the consent date • More than two cardioversions (drug or electric) for AF within the 2 years preceding the conset date • Myocardial infarction, PCI/PTCA or coronary artery stenting during the 3 month interval preceding the consent date • Unstable angina • Any cardiac surgery during the 3 month interval preceding the consent date • NYHA class III or IV congestive heart failure • Left ventricular ejection fraction < 40% by TTE during the 3 month interval preceding the conset date • Type to or type III atrioventricular block • Presence of a permanent pacemaker, biventricular pacemaker, atrial defibrillator or any type of implantable cardiac defibrillator (with or without biventricular pacing function). • Any cerebral ischemic event (stroke or TIAs) during the 6 month interval preceding the consent date.	

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
PVI versus Cox-Maze					

Stulak (2011)[19]
 	
USA
 	
Funding: NR
	Retro-spective cohort
	
	CoE III
		• N = 289
		• Age (median): 54 years
		• Male: 70.2 %
		
		• Paroxysmal AF: 70.6% "intermittent" AF
		
		• Symptom duration: 4.1 years
		
		• CHF: NR
		• LAD (mean): 4.0 cm
		• LVEF (mean): 64%
			Intervention groups:
			• RFA: n = 194
			• Cox-Maze procedure: n = 97
			
			NOTE. 9% (17/192) of Ablation patients received right-sided ablation. This mapping guided ablation of the right atrium was given if no contractions came from the PV.
			
			RFA characteristics:
			• PVI? Yes, 3 ablation techniques were used:
			  • Invasive catheter mapping and focal RFA of premature atrial contractions arising from a pulmonary vein. If no premature atrial beats arose from the pulmonary vein, mapping guided ablation was applied to the right atrium.
			  • Invasive catheter mapping and segmental circumferential ablation of one or more pulmonary veins.
			  • Invasive catheter mapping and wide area circumferential ablation of right and left pulmonary veins with a circular catheter electrode.
			• Isolation (% success, patients): NR
			
			• Definition of isolation: NR
			• Other ablation? In many
				Inclusion:
				• Patients who underwent biatrial cut-and-sew Cox-Maze procedure for lone AF were matched 1:2 according to age, sex and type of AF, with patients who underwent catheter abaltion for AF during the same time period.
				
				Exclusion:
				• Patients who underwent accessory pathway ablation, ventricular arrhythmia ablation, or atrioventricular node ablation with permanet pacemaker
					Follow-up:
					• RFA: median 3.1 years
					• 96% f/u
					• Cox-Maze: median 5.6 years
					• 90% f/u
					
					Outcomes:
					• Freedom from AF
					• Freedom from AF without AADs
					• Use of AADs
					• Use of Warfarin
					• Adverse events
					
					Subgroup analysis?
					• No subgroup analysis
					
					Blanking period?
					• Blanking period of 3 months

Investigator (year) Country, Funding	Study design CoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			cases "touch up" ablation lesions were required and linear ablation lines in the left atrium were greated. • Checked inducibility? No • Catheter tip: NR • Energy, watts: NR • Max temp: NR • Total ablation time (min): NR <u>Post-RFA anti-arrhythmics</u>: • AADs were administered, but details NR <u>Cox-Maze characteristics:</u> • Cut-and-sew Cox-Maze III procedure done using cardiopulmonary bybass at normothermia or moderate hypothermia. Right atrial incisions performed before aortic cross-clamping and left atrial incisions performed after cardiac arrest with cold blood cardioplegia. • During follow up 6 patients underwent a catheter ablation, and no patient required more than one procedure. <u>Other important characteristics:</u> • During follow up, 41 patients required a second ablation, and 8 of these 41 required a third ablation.		

AAD: antiarrhythmic drug; ADT: antiarrhythmic drug treatment; AF: atrial fibrillation; cPVI: circumferential PVI; CHF: chronic heart failure; CPVA: circumferential pulmonary vein ablation; DM: diabetes mellitus; DM2: diabetes mellitus type 2; IQR: interquartile range; KCCQ: Kansas City Cardiomyopathy Questionnaire; LAD: left atrial dimension; LoE: level of evidence; LPV: left pulmonary veins; LVED: left ventricular end-diastolic dimension/ left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; MLHFQ: Minnesota Living with Heart Failure Questionnaire; N: number of patients; NR: not reported; NS: not statistically significant ($P \geq .05$); NYHA: New York Heart Association; PV: pulmonary vein; PVI: pulmonary vein isolation; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein; SD: standard deviation; WPW: Wolff-Parkinson-White

*Data abstraction accepted and used from the 2009 AHRQ HTA[28] (except LoE and AAD treatment information, which was not in the AHRQ evidence tables).

Table F2. Atrial flutter study characteristics

Investigator (year) Country, Funding	Study design LoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
RFA versus AADs (anti-arrhythmic drugs)					
Da Costa (2006)[20] France Funding Ministère français de la Santé (Projet Hospitalier de Recherche Clinique 2002)	RCT CoE II	• N = 104 • Age (mean): 78.5 years • Male: 80.8 % • 61.5% patients had structural heart disease • Paroxysmal atrial flutter: NR • Symptom duration: NR • CHF: NR • LAD (mean): 43 mm • LVEF (mean): 55%	Intervention groups: • RFA: n = 52 • AAD: n = 52 Ablation characteristics: • Target site: NR • Successful ablation (% success, patients): 100% • Definition of successful ablation: Complete bidirectional isthmus block • Other ablation? NR • Checked inducibility? NR • Catheter tip: 8 mm or irrigated 5 mm • Energy, watts: 70 W or 40 W • Max temp (°C): 60 °C or 45° - 50° C • Total ablation time (min): 12.8 ± 13minutes Post-RFA anti-arrhythmics: • NR AAD characteristics: • AAD + cardioversion • Patients were randomly assigned to electric intracardiac cardioversion . If intracardiac stimulation failed, then an external or internal cardioversion was applied • 400 mg of amiodarone was given daily for 4 weeks and 7 days before sinus rhythm restoration. After this loading period, the dosage was lowered to 200 mg. • At least 72 hours before and for 4 weeks after cardioversion, patients received acenocoumarol. • Patients with recurrence	Inclusion: • ≥ 70 of age • First documented episode of symptomatic AFL without previous antiarrhythmic treatment • An ECG documenting typical AFL • Isthmus participation in the arrhythmic circuit as demonstrated by entrainment maneuvers • Informed patient consent obtained Exclusion: • Absence of informed consent • Amiodarone contraindication • Age <70 years • Previous antiarrhythmic treatment for AFL • AFL recurrence • Inability to catheterize (vena caval clip) • Poorly tolerated AFL including 1/1 AFL • Contraindication of anticoagu —lation therapy • Patients with New York Heart Association class IV heart failure • Current or previous treatment with amiodarone • A corrected QT interval of > 480 ms	Follow-up: • 18 months • 99% f/u Outcomes: • Recurrence of atrial flutter • Occurrence of clinically significant atrial flutter (lasting > 10 minutes) • Occurrence of atrial fibrillation • Adverse events Subgroup analysis? • Previous episode of AF Blanking period? • No blanking period

Investigator (year) Country, Funding	Study design LoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			were treated with RFA <u>Other important characteristics:</u> • 2 patients in RFA group required a second ablation; only one patient underwent the procedure.	or an uncorrected QT interval of > 500 ms in the absence of bundle brance block • Bradycardia defined as a rate of < 50 beats per minute for a period of > 1 minute while the patient was awake or second- or third-degree atrioventricular block • Any condition that would make survival for 1 year unlikely	

Table F3. Supraventricular tachyarrhythmia study characteristics

Investigator (year) Country, Funding	Study design LoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
D'Este (2007)[21] Country: Italy <u>Funding</u> NR	Pro-spective cohort study CoE III	• N = 93 • Age (mean): 33.5 years • Male: 28% • Symptom duration: mean 3.7 – 7.1 years • CHF: NR • LAD (mean): NR • LVEF (mean): NR • Typical AVNRT:NR • Atypical AVNRT: NR	<u>Intervention groups:</u> • RFA : n = 18 • AAD: n = 24 • No (or little) AAD: n = 38 <u>Ablation characteristics:</u> • Target site: NR • Successful ablation (% success, patients): NR • Definition of successful ablation: NR • Other ablation? NR • Checked inducibility? NR • Catheter tip: NR • Energy, watts: NR • Max temp (°C): NR • Total ablation time (min): NR <u>Post-RFA anti-arrhythmics</u>: • NR <u>AAD characteristics:</u> • The drugs used were propafenone (n = 7), verapamil (n = 7), flecainide (n = 3), sotalol (n = 2), diltiazem (n = 2), atenolol (n = 1) or a combination therapy (n = 2). <u>Other important characteristics:</u> • A third group (n = 38) was given no, or only brief (few months), use of AADs.	<u>Inclusion</u>: • AVNRT, defined as a supraventricular tachycardia with a ventriculo-atrial interval < 70 ms during induced or spontaneous tachycardia, accompanied by a double nodal pathway. • Symptomatic and documented and inducible episodes of tachycardia • Double nodal pathway was defined as a sudden jump in the PQ interval greater than 50 ms for brief reduction (10 ms) in the coupling interval during programmed atrial stimulation. <u>Exclusion</u>: • NR	<u>Follow-up:</u> • Mean 13.2 (11.4 – 16.1) years • 86% f/u <u>Outcomes</u>: • Absence of symptoms <u>Subgroup analysis?</u> • No subgroup analysis <u>Blanking period?</u> • No blanking period

Investigator (year) Country, Funding	Study design LoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
Kimman (1999)[22] Countries: Netherlands, USA <u>Funding</u> NR	Pro-spective cohort CoE III	• N = 146 • Age (mean): 44.1 years • Male: 27 % • Symptom duration: mean 13.9 years • CHF: NR • LAD (mean): NR • LVEF (mean): NR • Typical AVNRT: 134 patients • Atypical AVNRT: 12 patients	<u>Intervention groups:</u> • RFA: n = 120 • Surgical (perinodal dissection): n = 26 <u>Ablation characteristics:</u> • Target site: Atrioventricular node modification: • Selective fast pathway ablation (n = 40) • Selective slow pathway ablation (n = 47) • Combined slow and fast pathway ablation (n= 33) done if initially the slow (or fast) pathway was initially chosen and was not successful after more than 20 RF applications, then the opposite pathway (fast (or (slow)) was ablated. • Successful ablation (% success, patients): Fast pathway: 90%; slow pathway: 98%; combined slow and fast pathway: 82% • Definition of successful ablation: Fast pathway: AVNRT was no longer inducible or when a 30% prolongation of the PR interval or an inadvertent second- or third-degree AV block occurred. Slow pathway: non-inducibility of AVNRT with preserved atrioventricular node conduction. • Other ablation? no • Checked inducibility? Yes • Catheter tip: 4 mm • Energy, watts: 7 – 50 W • Max temp (°C): NR • Total ablation time (min): 65.1 min <u>Post-RFA anti-arrhythmics</u>: • NR	<u>Inclusion</u>: • AVNRT <u>Exclusion</u>: • NR	<u>Follow-up:</u> • ≥ 12 months • 100% f/u <u>Outcomes</u>: • Freedom from recurrence • Late recurrence rate • Adverse events <u>Subgroup analysis?</u> • No subgroup analysis <u>Blanking period?</u> • No blanking period

Investigator (year) Country, Funding	Study design LoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			Surgical characteristics: • Skeletonization • Exposure of AV node using normothermic cardiopulmonary bypass • AV node dissected from surrounding tissue to separate superficial and posterior atrial inputs while deep inputs were left intact. • AV nodal conduction monitored through the operation. • Successful result (% success, patients): 96% • Definition of successful result: non-inducibility of AVNRT during electrophysiological testing prior to closure. • 2 patients underwent RFA, while 1 patient had 3 successive ablations. Other important characteristics: • 22 repeat ablations were performed, 4 patients required a third ablation, and 1 required a fourth.		
Lin (1998)[23] Countries: Taiwan, USA Funding NR	Pro-spective cohort CoE III	• N = 27 • Age (mean): 42 (range, 14 – 74) years • Male: 70% • Symptom duration: ≥1 year (mean NR) • CHF: NR • LAD (mean): NR • LVEF (mean): NR • No patients had accessory pathways, atrial flutter/fibrillation or ventricular tachycardia.	Intervention groups: • RFA : n = 16 • No treatment: n = 11 Ablation characteristics: • Target site: slow pathways • Successful ablation (% success, patients): 100% • Definition of successful ablation: elimination of slow pathway conduction, demonstrated by the disappearance of dual AV node pathways and AV node echo beats. • Other ablation? NR • Checked inducibility? NR • Catheter tip: 4 mm	Inclusion: • AVNRT • Spontaneous, electrocardio-graphically documented paroxysmal SVT with the presence of dual AV node pathways but without inducible tachycardia Exclusion: • NR	Follow-up: • 23 ± 13 (range, 1 - 54) months • % f/u NR Outcomes: • Freedom from recurrence • Adverse events Subgroup analysis? • No subgroup analysis Blanking period? NR

Investigator (year) Country, Funding	Study design LoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			• Energy: 500 Hz • Max temp (°C): NR • Total ablation time (min): NR <u>Post-RFA anti-arrhythmics</u>: • NR <u>Control group characteristics:</u> • No treatment described • Patients refused ablation <u>Other important characteristics:</u> NR		
Natale (1993)[24] Country: Canada <u>Funding</u> Heart and Stroke Foundation of Ontario, Toronto, Canada.	Retro-spective cohort CoE III	• N = 96 • Age (mean): 36.4 years • Male: 18% • Symptom duration: NR • CHF: NR • LAD (mean): NR • LVEF (mean): NR	<u>Intervention groups:</u> • RFA: n = 43 • Surgical (perinodal dissection): n = 53 <u>Ablation characteristics:</u> • Target site: AV node modification (not complete ablation) via anterior approach (fast pathway: n = 15); or posterior approach (slow pathway: n = 28) • Successful ablation (% success, patients): Fast pathway: 93%; Slow pathway: 96% • Definition of successful ablation: Fast pathway: PR (not defined) prolongation or an impedance rise were observed, and marked prolongation of ventriculoatrial refractoriness or block. Slow pathway: elimination of the slow pathway as evaluated by atrial extrastimuli or incremental atrial pacing. • Other ablation? NR • Checked inducibility? Yes • Catheter tip: NR • Energy, watts: 20 – 30 W • Max temp (°C): NR	<u>Inclusion</u>: • AVNRT <u>Exclusion</u>: • NR	<u>Follow-up:</u> • Mean 8.2 – 38 months • 100 % f/u <u>Outcomes</u>: • Freedom from recurrence • Adverse events <u>Subgroup analysis?</u> • No subgroup analysis <u>Blanking period?</u> • No blanking period

Investigator (year) Country, Funding	Study design LoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			• Total ablation time (min): NR Post-RFA anti-arrhythmics: • NR		
			Surgical characteristics: • Aim of surgery: to interrupt all inputs to the AV node except the "deep", left atrial input by perinodal dissection ("skeletonization"). • AV node exposed using normothermic cardiopulmonary bypass. • Guided by anatomical landmarks • Definition of successful result: Loss of dual pathway physiology • Successful result (% success, patients): 92% Other important characteristics: • NR		
Pappone, Santinelli (2003)[25] Countries: USA, Italy Funding NR	RCT CoE II	• N = 72 • Age (median): 22-23 years • Male: 42 % • Symptom duration: NR • CHF: NR • LAD (mean): NR • LVEF (mean): NR	Intervention groups: • RFA: n = 37 • Control (no treatment): n = 35 Ablation characteristics: • Target site: Left free wall, right free wall, posteroseptal, or anteroseptal • Successful ablation (% success, patients): 100% • Definition of successful ablation: Conduction in the accessory pathways could not be induced 30 minutes after ablation, either with or without isoproterenol infusion. • Other ablation? NR • Checked inducibility? Yes • Catheter tip: • Energy, watts: 30 – 50 W • Max temp (°C): 65 °C • Total ablation time (min):	Inclusion: • Wolff-Parkinson-White (WPW) syndrome • Ventricular preexitation documented by 12-lead electrocardiography and the absence of arrhythmia related symptoms. Exclusion: • Participation in other investigational protocols. • ≤ 13 years of age • Pregnancy • Concomitant medical conditions	Follow-up: • 60 months • 95% f/u Outcomes: • Freedom from recurrence Subgroup analysis? • No subgroup analysis Blanking period? • No blanking period

Investigator (year) Country, Funding	Study design LoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			Post-RFA anti-arrhythmics: • No AADs were given AAD characteristics: • Location of single accessory pathways: left free wall: 36%; right free wall: 42%; posteroseptal: 17%; anteroseptal: 4% • Location of multiple accessory pathways: left free wall and posteroseptal: 36%; left free wall and right free wall: 27%; right free wall and posteroseptal: 36%		
			Other important characteristics: • For ablation group: location of single accessory pathways: left free wall: 50%; right free wall: 38%; posteroseptal: 8%; anteroseptal: 4% • For ablation group: location of multiple accessory pathways: left free wall and posteroseptal: 31%; left free wall and right free wall: 39%; right free wall and posteroseptal: 31%		
Goldberg (2002)[26] Country: USA Funding NR	Pro-spective cohort CoE III	• N = 95 • Age (mean): 50.5 years* • Male: 30%* • Symptom duration: 38 months • CHF: NR • LAD (mean): NR • LVEF (mean): NR	Intervention groups: • RFA: n = 39 • AAD: n = 44 Ablation characteristics: • First-line therapy • Target site: NR • Successful ablation (% success, patients): 100% • Definition of successful ablation: NR • Other ablation? NR • Checked inducibility? NR • Catheter tip: NR • Energy, watts: NR	Inclusion: • Newly diagnosed paroxysmal SVT, including AVNRT (67%), AVRT (28%), atrial tachycardia (5%) Exclusion: • NR	Follow-up: • 60 months • 87 % f/u Outcomes: • Successful operation • SF-36 • Adverse events Subgroup analysis? • No subgroup analysis

Investigator (year) Country, Funding	Study design LoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			• Max temp (°C): NR • Total ablation time (min): NR Post-RFA anti-arrhythmics: • NR AAD characteristics: • First-line therapy • 22 patients underwent RFA between first and fifth year • 15 patients were treated with 1 drug. • The average number of medications used was 1.49 Other important characteristics: • NR		Blanking period? • No blanking period
Weerasooriya (1994)[27] Country: Australia Funding National Health and Medical Research Council of Australia, National Heart Foundation of Australia and Royal Perth Hospital Medical Research Foundation	Retro-spective cohort CoE III	• N = 52 • Age (mean): 38.2 years • Male: 56% • Symptom duration: NR • CHF: NR • LAD (mean): NR • LVEF (mean): NR	Intervention groups: • RFA: n = 20 • Surgical (division of accessory pathways): n = 20 • AAD: n = 12 Ablation characteristics: • Target site: Left parietal region, right parietal region, anteroseptal region, posteroseptal region • Successful ablation (% success, patients): 90%, 18/20 patients • Definition of successful ablation: Abolishment of accessory pathway conduction • Other ablation? No • Checked inducibility? NR • Catheter tip: 4 mm • Energy, watts: NR • Max temp (°C): NR • Total ablation time (min): NR Post-RFA anti-arrhythmics: • One patient is on long term AAD therapy	Inclusion: • Patients with accessory pathways who underwent an invasive electrophysiology study for symptomatic supraventricular tachycardia. Exclusion: • NR	Follow-up: • Mean 8.4 – 58 months • % f/u NR Outcomes: • Freedom from recurrence • Hospitalization • Adverse events Subgroup analysis? • No subgroup analysis Blanking period? • No blanking period

Investigator (year) Country, Funding	Study design LoE	Patient demographics	Intervention(s)	Inclusion/exclusion	Follow-up duration (% followed) Outcomes reported
			following 2 failed ablation attempts. <u>AAD characteristics:</u> • Accessory pathway located in left parietal region for 9 patients, anteroseptal region in one patient, and posteroseptal region in 2 patients. • Drugs administered were flecainide (five patients) verapamil (two patients), sotalol (two patients), propranolol (two patients), and procainamide (one patient).		
			<u>Surgical Characteristics:</u> • Aim of surgery: division of accessory pathways. • 17 left sided pathways and 5 posteroseptal pathways. 2 patients had 2 accessory pathways. • Definition of successful result: Loss of accessory pathways conduction • Successful result (% success, patients): 100%, 20/20 patients • 2 patients required 2 procedures. <u>Other important characteristics:</u> • For ablation group, location of single accessory pathway: left parietal region: 11 patients; right parietal region: 1 patient; anteroseptal region: 1 patient; posteroseptal region: 6 patients In ablation group, three patients underwent two procedures.		

AAD: antiarrhythmic drug; AV: atrioventricular; AVNRT: atrioventricular nodal reentry tachycardia; CHF: chronic heart failure; CoE: class of evidence; LAD: left atrial dimension; LVEF: left ventricular ejection fraction; N: number of patients; NR: not reported; RFA: radiofrequency ablation; SVT: supraventricular tachycardia; WPW: Wolff-Parkinson-White

* data reported after loss to f/u

Table F4. Radiofrequency catheter ablation compared with cryoablation: RCT characteristics

Investigator (year) Country, CoE	Patient demographics	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Atrial fibrillation					
No RCTs identified for inclusion					
Atrial flutter					
Collins (2006)[29] Australia CoE II	• N = 32 (four pts excluded after randomization due to diagnosis of atypical atrial flutter, atrial fibrillation (AF) , or need for general anaesthsia) • Age (mean): 65 years • Male: 71% • Typical atrial flutter Symptom duration: 32 months (mean)	• Freedom from arrythmia recurrence (atrial flutter or AF) 14 (9-19) months	• RF ablation (n = 15) • Cryoablation (n = 13)	93% (14/15) 85% (11/13)	NR
Kuniss (2009)[30] Germany CoE II	• N = 191 (ten pts excluded after randomization due to diagnosis of atypical atrial flutter) • Age (mean): 66 years • Male: 73% • Typical atrial flutter • Symptom duration: 4 (range, 1-18) months	• Persistent bidirectional conduction block 3 months	• RF ablation (n = 91) • Cryoablation (n = 90)	85% (51/60 who complied with invasive f/u testing) 66% (42/64 who complied with invasive f/u testing)	.014
Malmborg (2009)[31] Sweden CoE II	• N = 40 • Age (mean): 59 years • Male: 88% • Typical atrial flutter • Symptom duration: NR	• Freedom from recurrence of atrial flutter 15 (6-23) months	• RF ablation (n = 20) • Cryoablation (n = 20)	85% (17/20) 80% (16/20)	.45

Investigator (year) Country, CoE	Patient demographics	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Thornton (2008)[32] The Netherlands CoE II	• N = 62 • Age (mean): 56 years • Male: 89% • Typical atrial flutter ± atrial fibrillation (76% of patients had history of atrial fibrillation) • Symptom duration: NR	• Freedom from recurrence of arrhythmia (after successful procedure) 4.6 (3-13.7) months	• RF ablation (n = 30) • Cryoablation (n = 32)	33% (10/30) 31% (10/32)	NS
SVTs					
Deisenhofer (2010)[33] Germany CoE II	• N = 509 • Age (mean): 50.8 years • Male: 34.4% • Inducible AVNRT (slow-fast in 98% of patients) • Symptom duration: NR	• Freedom from documented arrhythmia recurrence 6 months	• RF ablation (slow pathway) • Cryoablation (slow pathway)	95.6% (238/249) 90.7% (223/246)	.029
Kardos (2007)[34] Hungary CoE II	• N = 30 • Age (median): 35 years • Male: 33% • AVNRT: 57% (17/30) • AVRT: 43% (13/30) • Symptom duration: NR	• Freedom from indcuible arrhythmia recurrence 12 months	• RF ablation (n = 17) • Cryoablation (using ice mapping) (n = 13)	71% 77%	NS
Kimman (2006)[35] The Netherlands CoE II	• N = 63 • Age (mean): 48 years • Male: 38% • AVNRT • Symptom duration: NR	• Freedom from palpitations (patient-reported) 12 months	• RF ablation (slow pathway) (n = 33) • Cryoablation (slow pathway) (using ice mapping) (n = 30)	70% 57%	NR

Investigator (year) Country, CoE	Patient demographics	Outcome (follow-up duration)	Interventions	Results	P-value between groups
Zrenner (2004)[36] Germany CoE II	• N = 200 • Age (mean): 51 years • Male: 38% • AVNRT • Symptom duration: NR	• Freedom from AVNRT recurrence (details NR) mean 8 months	• RF ablation (slow pathway) (n = 100)	99%	NR
			• Cryoablation (slow pathway) (n = 100)	92%	
		• Procedural success, and freedom from AVNRT recurrence and permanent complete AV block* (details NR) mean 8 months	• RF ablation (slow pathway) (n = 100)	97%	.03
			• Cryoablation (slow pathway) (n = 100)	89%	

*no patient experienced permanent complete AV block.

Table F5. Approaches to radiofrequency catheter ablation in patients with atrial fibrillation: study characteristics

Investigator (year) Country	Study design CoE	Patient demographics	Intervention(s)	Follow-up duration (% followed)
PVI versus WACA				
Arentz (2007)[37]* Germany	RCT CoE II	• N = 110 • Age (mean): 56 years • Male: 75% • Paroxysmal AF: 61% • Symptom duration: 5.5 years • LAD (mean): 4.0 cm • LVEF (mean): NR	Intervention groups: • PVI (ostia): n = 55 • WACA: n = 55	Follow-up: • 15 months • 100% f/u
Oral (2003)[38]* US	RCT CoE II	• N = 80 • Age (mean): 52 years • Male: 78% • Paroxysmal AF: 100% • Symptom duration: 7 years • LAD (mean): 4.0 cm • LVEF (mean): 56%	Intervention groups: • PVI (ostia): n = 55 • WACA + MIL + posterior line: n = 40	Follow-up: • 15 months • 100% f/u
Nilsson (2006)[39]* Denmark	RCT CoE II	• N = 80 • Age (mean): 56 years • Male: 71% • Paroxysmal AF: 51% • Symptom duration: 4.1 years • LAD (mean): NR • LVEF (mean): NR	Intervention groups: • PVI (ostia): n = 54 • WACA: n = 46	Follow-up: • 12 months • % f/u NR
Karch (2005)[40]* Germany	RCT CoE II	• N = 100 • Age (mean): 60 years • Male: 64% • Paroxysmal AF: 89% • Symptom duration: 4.5 years • LAD (mean): 4.7 cm • LVEF (mean): 63%	Intervention groups: • PVI (ostia): n = 50 • WACA: n = 50	Follow-up: • 6 months • 100% f/u

Investigator (year) Country	Study design CoE	Patient demographics	Intervention(s)	Follow-up duration (% followed)
Liu, Long (2006)[41]* China	RCT CoE II	• N = 110 • Age (mean): 60 years • Male: 64% • Paroxysmal AF: 100% • Symptom duration: 5 years • LAD (mean): 3.8 cm • LVEF (mean): 64%	Intervention groups: • Stepwise PVI (add roof line if inducible, then add MIL if inducible): n = 55 • WACA: n = 55	Follow-up: • 3-9 months • % f/u NR
PVI versus PVI with additional left-sided ablation lines				
Willems (2006)[42]* Germany	RCT CoE II	• N = 62 • Age (mean): 59 years • Male: NR • Paroxysmal AF: 0% • Symptom duration: 6 years • LAD (mean): 4.8 cm • LVEF (mean): ≥ 40%	Intervention groups: • PVI (antrum) + cavotricuspid isthmus ablation: n = 30 • PVI (antrum) + cavotricuspid isthmus ablation + left atrial linear lines: n = 32	Follow-up: • 7 months • 100% f/u
Pappone (2004)[43]* Italy	RCT CoE I	• N = 560 • Age (mean): 56 years • Male: 52% • Paroxysmal AF: 63% • Symptom duration: 7.2 years • LAD (mean): 4.0 cm • LVEF (mean): NR	Intervention groups: • WACA: n = 280 • WACA + posterior left atrial lines + mitral isthmus line: n = 280	Follow-up: • 12 months • 100% f/u
Fassini (2005)[44]* Italy	RCT CoE II	• N = 187 • Age (mean): 55 years • Male: 80% • Paroxysmal AF: 67% • Symptom duration: NR • LAD (mean): 4.3 cm • LVEF (mean): 56%	Intervention groups: • PVI: n = 92 • PVI + mitral isthmus line: n = 95	Follow-up: • 12 months • 100% f/u
Haissaguerre (2004)[45]* France	RCT CoE II	• N = 70 • Age (mean): 53 years • Male: 74% • Paroxysmal AF: NR • Symptom duration: 5.1 years	Intervention groups: • PVI + cavotricuspid isthmus ablation: n = 35 • PVI + cavotricuspid isthmus ablation + MIL: n = 35	Follow-up: • 7 months • 100% f/u

Investigator (year) Country	Study design CoE	Patient demographics	Intervention(s)	Follow-up duration (% followed)
		• LAD (mean): 4.3 cm • LVEF (mean): 67%		
Sheikh (2006)[46]* USA	RCT CoE II	• N = 100 • Age (mean): 59 years • Male: 63% • Paroxysmal AF: 100% • Symptom duration: NR • LAD (mean): 4.1 cm • LVEF (mean): 54%	<u>Intervention groups:</u> • PVI (ostia): n = 50 • PVI + superior PV line + LIPV to MV annulus line: n = 50	<u>Follow-up:</u> • 9 months • 100% f/u
Hocini (2005)[47]* France	RCT CoE II	• N = 90 • Age (mean): 55 years • Male: 79% • Paroxysmal AF: 100% • Symptom duration: 5.25 years • LAD (mean): 4.1 cm • LVEF (mean): 67%	<u>Intervention groups:</u> • PVI (antrum) + cavotricuspid isthmus ablation: n = 45 • PVI + superior PV line + LIPV to MV annulus line: n = 45	<u>Follow-up:</u> • 14 months • 100% f/u
Gaita (2008)[48] Italy	RCT CoE II	• N = 204 • Age (mean): 51 years • Male: 71% • Paroxysmal AF: 67% • Symptom duration: 1.9 years • LAD (mean): NR • LVEF (mean): NR	<u>Intervention groups:</u> • PVI: n = 67 • PVI + left linear lesions: n = 137	<u>Follow-up:</u> • 12-36 months • % f/u NR
Mikhaylov (2010)[49] Russia, Netherlands	RCT CoE II	• N = 34 • Age (mean): 55 years • Male: 79% • Paroxysmal AF: 0% • Symptom duration: 5.2 years • LAD (mean): 4.5 cm • LVEF (mean): NR	<u>Intervention groups:</u> • PVI: n = 17 • PVI + LA: n = 17	<u>Follow-up:</u> • 13 months • 100% f/u

Investigator (year) Country	Study design CoE	Patient demographics	Intervention(s)	Follow-up duration (% followed)
Sawhney (2010)[50] USA	RCT CoE II	• N = 67 • Age (mean): 57 years • Male: 73% • Paroxysmal AF: 100% • Symptom duration: 5.6 years • LAD (mean): 3.6 cm • LVEF (mean): 61%	Intervention groups: • Segmental PVI: n = 33 • Circumferential PVI + left atrial linear ablation: n = 33	Follow-up: • 16 ± 6 months • 100% f/u
Mun (2012)[51] South Korea	RCT CoE II	• N = 156 • Age (mean): 56 years • Male: 76% • Paroxysmal AF: 100% • Symptom duration: NR • LAD (mean): 4.0 cm • LVEF (mean): 64%	Intervention groups: • Circumferential PVI: n = 52 • Circumferential PVI + left atrial roof line: n = 52 • Circumferential PVI + PostBox Ablation: n = 52	Follow-up: • 15 ± 5 months • 100% f/u
PVI versus PVI with additional right-sided ablation lines				
Wazni (2003)[52]***** USA, Germany, Italy	RCT CoE II	• N = 108 • Age (mean): 55 years • Male: 81% • Paroxysmal AF: 59% • Symptom duration: 5.5 years • LAD (mean): 4.2 cm • LVEF (mean): 53%	Intervention groups: • PVI (ostia-antrum): n = 59 • PVI (ostia-antrum) + CTI: n = 49	Follow-up: • > 8 months • 100% f/u
Wang (2008)[53]***** China	RCT CoE II	• N = 106 • Age (mean): 66 years • Male: 55% • Paroxysmal AF: 100% • Symptom duration: 3.6 years • LAD (mean): 3.7 cm • LVEF (mean): 54%	Intervention groups: • WACA: n = 54 • WACA + SVC: n = 52	Follow-up: • 12 months • 100% f/u
Corrado (2010)[54] USA, Italy	RCT CoE II	• N = 320 • Age (mean): 56 years • Male: 74% • Paroxysmal AF: 46%	Intervention groups: • PVI (antrum): n = 160 • PVI (antrum) + SVC: n = 134	Follow-up: • 12 months • 92% f/u

Investigator (year) Country	Study design CoE	Patient demographics	Intervention(s)	Follow-up duration (% followed)
		• Symptom duration: 6.8 years • LAD (mean): 4.6 cm • LVEF (mean): 53%		
Pontoppidan (2012)[55] Denmark	RCT CoE II	• N = 149 • Age (mean): 56 years • Male: 71% • Paroxysmal AF: 54% • Symptom duration: 4.3 years • LAD (mean): 4.7 cm • LVEF (mean): 62%	Intervention groups: • Circumferential PV ablation: n = 73 • Circumferential PV ablation + cavotricuspid isthmus block: n = 73	Follow-up: • 12 months • 96% f/u
PVI versus Complex Fractionated Electrogram (CFE) ± PVI				
Chen (2011)[56] China	RCT CoE II	• N = 118 • Age (mean): 56 years • Male: 67% • Paroxysmal AF: 100% • Symptom duration: 4.34 years • LAD (mean): 3.5 cm • LVEF (mean): 65%	Intervention groups: • PVI (antrum): n = 60 • CFE ablation: n = 58	Follow-up: • 22 ± 6 months • 99% f/u
Deisenhofer (2009)[57] Germany	RCT CoE II	• N = 98 • Age (mean): 57 years • Male: 76% • Paroxysmal AF: 100% • Symptom duration: 4 years • LAD (mean): 4.4 cm • LVEF (mean): NR	Intervention groups: • PVI: n = 46 • PVI + CFE: n = 48	Follow-up: • 19 ± 8 months • 96% f/u
Di Biase (2009)[58] USA, Italy, China, Egypt, Canada, Singapore	RCT CoE II	• N = 103 • Age (mean): 58 years • Male: 82% • Paroxysmal AF: 100% • Symptom duration: 5.2 years • LAD (mean): 4.3 cm • LVEF (mean): 55%	Intervention groups: • PVI (antrum): n =35 • CFE: n = 34 • PVI (antrum) + CFE: n = 34	Follow-up: • 12 months • 100% f/u

Investigator (year) Country	Study design CoE	Patient demographics	Intervention(s)	Follow-up duration (% followed)
Elayi (2008)[59] France, Italy, USA, Canada, Singapore, Egypt, China	RCT CoE II	• N = 144 • Age (mean): 59 years • Male: 66% • Paroxysmal AF: 0% • Symptom duration: 2.4 years • LAD (mean): 4.5 cm • LVEF (mean): 54%	Intervention groups: • Circumferential PVI (antrum): n = 47 • PVI (antrum): n = 48 • CFE + PVI (antrum): n = 49	Follow-up: • 16 months • 100% f/u
Elayi (2011)[60] USA, Italy	RCT CoE II	• N = 98 • Age (mean): 62 years • Male: 81% • Paroxysmal AF: 0% • Symptom duration: 8.6 years • LAD (mean): 4.8 cm • LVEF (mean): 56%	Intervention groups: • PVI (antrum): n = 48 • CFE + PVI (antrum): n = 50	Follow-up: • 17 ± 5 months • 100% f/u
Estner (2011)[61] Germany	RCT CoE II	• N = 116 • Age (mean): 58 years • Male: 74% • Paroxysmal AF: 0% • Symptom duration: 6.6 years • LAD (mean): 4.8 cm • LVEF (mean): NR	Intervention groups: • Circumferential PVI + additional lines ("linear ablation") n = 59 • CFE + PVI ("spot ablation"): n = 57	Follow-up: • 12 - 23 months • 100% f/u
Verma (2010)[62] Canada, Italy, Norway, Spain	RCT CoE II	• N = 101 • Age (mean): 57 years • Male: 74% • Paroxysmal AF: 64% • Symptom duration: 7 years • LAD (mean): 4.2 cm • LVEF (mean): 62%	Intervention groups: • PVI: n = 32 • CFE: n = 34 • PVI + CFE: n = 34	Follow-up: • 12 - 23 months • 99% f/u
Miscellaneous comparisons				
Liu, Dong (2006)[63]* China	RCT CoE II	• N = 100 • Age (mean): 57 years • Male: 69% • Paroxysmal AF: 75% • Symptom duration: 6.7 years	Intervention groups: • WACA, then closing gaps in pts with residual PV conduction (aggressive): n = 50 • WACA, then PVI inside circular lines in pts with residual PV conduction (modified): n = 50	Follow-up: • 13 months • 100% f/u

Investigator (year) Country	Study design CoE	Patient demographics	Intervention(s)	Follow-up duration (% followed)
		• LAD (mean): 3.9 cm • LVEF (mean): 65%		
Oral (2004)[64]* USA	RCT CoE II	• N = 60 • Age (mean): 55 years • Male: 83% • Paroxysmal AF: 100% • Symptom duration: 7 years • LAD (mean): 4.3 cm • LVEF (mean): 59%	Intervention groups: • WACA + posterior LA lines + MIL: n = 30 • WACA + posterior LA lines + MIL + additional lines: n = 30	Follow-up: • 6 months • 100% f/u
Oral (2005)[65]* USA	RCT CoE II	• N = 80 • Age (mean): 54 years • Male: 84% • Paroxysmal AF: 0% • Symptom duration: 4.5 years • LAD (mean): 4.8 cm • LVEF (mean): 53%	Intervention groups: • WACA + posterior LA (or roof line) + MIL + ablation of amplitude >0.2 mv within the circles but outside the PV: n = 40 • non-encircling LA roof, septum, anterior wall, mitral isthmus and annulus lines: n = 40	Follow-up: • 10 months • 100% f/u
Kim (2010)[66] South Korea	RCT CoE II	• N = 102 • Age (mean): 53 years • Male: 80% • Paroxysmal AF: 100% • Symptom duration: 4.4 years • LAD (mean): 4.0 cm • LVEF (mean): 55%	Intervention groups: • Wide area circumferential PV ablation: n = 49 • Wide area circumferential PV ablation with PVI and ablation of residual potentials: n = 53	Follow-up: • 23 ± 8 months • 85% f/u
Tamborero (2009)[67] Spain	RCT CoE II	• N = 120 • Age (mean): 53 years • Male: 77% • Paroxysmal AF: 60% • Symptom duration: 5.3 years • LAD (mean): 4.1 cm • LVEF (mean): 60%	Intervention groups: • Circumferential PVAI + linear lesions along the left atrial roof: n = 60 • Circumferential PVAI left atrial posterior wall isolation: n = 60	Follow-up: • 10 ± 4 months • 100% f/u
Chilukuri (2011)[68] USA	RCT CoE II	• N = 30 • Age (mean): 60 years • Male: 62% • Paroxysmal AF: 79%	Intervention groups: • PVI: n = 13 • Box isolation: n = 16	Follow-up: • 10 ± 2 months • 97% f/u

Investigator (year) Country	Study design CoE	Patient demographics	Intervention(s)	Follow-up duration (% followed)
		• Symptom duration: NR • LAD (mean): 4.2 cm • LVEF (mean): 60%		
Mun (2012)[51] South Korea	See above for study details			
Gavin (2012)[69] Australia	RCT CoE II	• N = 42 • Age (mean): 68 years • Male: 71% • Paroxysmal AF: 100% • Symptom duration: 1.5 years • LAD (mean): 4.1 cm • LVEF (mean): 64%	Intervention groups: • PVI (antrum): n = 22 • PVI (antrum) + coronary sinus: n = 20	Follow-up: • 18 months • 100% f/u
Katritsis (2011)[70] Greece, USA, UK	RCT CoE II	• N = 67 • Age (mean): 54 years • Male: 76% • Paroxysmal AF: 100% • Symptom duration: 1.5 years • LAD (mean): 4.1 cm • LVEF (mean): 56%	Intervention groups: • PVI: n = 33 • PVI + autonomic ganglia modification: n = 34	Follow-up: • 12 months • 100% f/u
Pokushalov (2009)[71] Russia, Greece	RCT CoE II	• N = 80 • Age (mean): 53 years • Male: 83% • Paroxysmal AF: 100% • Symptom duration: 6 years • LAD (mean): 4.9 cm • LVEF (mean): 58%	Intervention groups: • Selective GP ablation: n = 40 • Anatomic GP ablation: n = 40	Follow-up: • 13 ± 2 months • 100% f/u

AAD: antiarrythmic drug treatment; AF: atrial fibrillation; AFL: atrial flutter; AT: atrial tachycardia; CFE: complex fractionated electrogram; CPVA: circumferential pulmonary vein ablation CTI: cavo tricuspid isthmus; GP: ganglionated plexi; LA: left atrium; LIPV: left inferior pulmonary vein; MIL: mitral isthmus line; MV: mitral valve; NR: not reported; PV: pulmonary vein; PVI: pulmonary vein isolation; SR: sinus rhythm; SVC: superior vena cava; WACA: wide area circumferential ablation

*Data abstraction accepted and used from the 2009 AHRQ HTA[28] (except LoE and AAD treatment information, which was not in the AHRQ evidence tables).

Table F6. Adverse events: RCTs and cohort studies comparing pulmonary vein isolation (PVI) with anti-arrhythmic drugs (AADs) in patients with AF

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Forleo (2009)[5] N = 70	12 months (100%)	Access-site hematoma	RF cPVI (n = 35)	3% (1/35) (required prolongation of hospitalization, no transfusion, no sequelae)	
			AADs (n = 35)	NR	
		Procedure-related thromboembolic events	RF cPVI (n = 35)	0% (0/35)	--
			AADs (n = 35)	0% (0/35)	
		Hospitalizations	RF cPVI (n = 35)	9% (3/35)	
			AADs (n = 35)	34% (12/35)	.01
		Bleeding rate	RF cPVI (n = 35)	6% (2/35)	
			AADs (n = 35)	6% (2/35)	NS
		AAD-related adverse events	RF cPVI (n = 35)	3% (1/35)	
			AADs (n = 35)	17% (6/35)	NS
Jais (2008)*[6] N = 112	12 months (96%)	Treatment-related death	RF cPVI (n = 53)	0% (0/53)	--
			AADs (n = 59)	0% (0/59)	
		Cardiac tamponade (both required pericardiocentesis, had favorable outcome)	RF cPVI (n = 53)	2% (1/53)	
			AADs (n = 59)	2% (1/59)	NR
		Groin hematoma (both had favorable outcome)	RF cPVI (n = 53)	2% (1/53)	
			AADs (n = 59)	2% (1/59)	NR
		Pulmonary vein stenosis (required dilatation and stent implantation, uneventful course thereafter)	RF cPVI (n = 53)	2% (1/53)	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
			AADs (n = 59)	0% (0/59)	NR
		Hyperthyroidism	RF cPVI (n = 53)	0% (0/53)	
			AADs (n = 59)	2% (1/59)	NR
Krittayaphong (2003)*[7] N = 30	12 months (93%)	Treatment-related cerebral infarction	RF cPVI (n = 15)	7% (1/15) (occurred immediately after procedure)	NR
			AADs ± cardioversion (n = 15)	NR	
		Groin hematoma	RF cPVI (n = 15)	7% (1/15) (minor)	
			AADs ± cardioversion (n = 15)	NR	NR
		AAD-related side effects	RF cPVI (n = 15)	21% (3/15) (GI side effects (n = 2), sinus node dysfunction (1))	
			AADs ± cardioversion (n = 15)	47% (7/15) (GI side effects (n = 6), corneal microdeposit (n = 2), hypothyroidism (n = 2), abnormal liver function test (n = 2), hyperthyroidism (n = 1), sinus node dysfunction (1))	NR
MacDonald (2011)[8] N = 41	6 months (93%)	Treatment-related stroke	RF cPVI (n = 22)	5% (1/22) (6 days post-ablation; patient then withdrew)	
			AADs (n = 19)	NR	
		Cardiac tamponade	RF cPVI (n = 22)	9% (2/22) (occurred during ablation procedure, underwent emergency pericardiocentesis and had no long-term complications)	
			AADs (n = 19)	NR	
		Worsening heart failure	RF cPVI (n = 22)	14% (3/22) (occurred within a few days of the procedure)	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
			AADs (n = 19)	NR	
		Pulmonary vein stenosis	RF cPVI (n = 22)	0% (0/22)	
			AADs (n = 19)	0% (0/19)	
Oral (2006)*[9] N = 146	12 months (100%)		RF cPVI (n = 77)	"No complications in either group."	
			AADs (n = 69)		
Pappone (2006/2011)*[10, 11] N = 198	12 months (2006) (100%) 48 months (2011) (95%)	Femoral hematoma	RF cPVI (n = 99)	3% (3/99) (treated conventionally, no long-term sequelae)	
			AADs (n = 99)	NR	
		Transient ischmic attack	RF cPVI (n = 99)	1% (1/99) (occurred shortly after the procedure; treated conventionally, no long-term sequelae)	
			AADs (n = 99)	NR	
		Pericardial effusion	RF cPVI (n = 99)	1% (1/99) (not due to cardiac perforation, did not require pericardiocentesis; treated conventionally, no long-term sequelae)	
			AADs (n = 99)	NR	
		Acute pulmonary edema	RF cPVI (n = 99)	NR	
			AADs (n = 99)	4% (4/99) (these patients had all progressed to permanent AF and had not yet received ablation, all had other comorbidities, treated with rate control	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
				medication)	
		Procedure-related complications	RF cPVI (n = 99)	"No procedure-related late complications were observed." (2011 paper)	
			AADs (n = 99)	NR	
		Sexual dysfunction	RF cPVI (n = 99)	NR	
			AADs (n = 99)	11% (11/99) (or 11/31 of pts taking sotalol))	
		QRS duration increase	RF cPVI (n = 99)	NR	
			AADs (n = 99)	11% (11/99) (or 11/82 of pts taking flecainide)	
		Bradyarrhythmia	RF cPVI (n = 99)	NR	
			AADs (n = 99)	15% (15/99) (or 15/61 pts taking amiodarone, symptomatic, no medical intervention required)	
		Thyrotoxicosis	RF cPVI (n = 99)	NR	
			AADs (n = 99)	19% (19/99) (or 19/61 pts taking amiodarone, subclinical) In 7 pts, this "amiodarone-induced thyroid dysfunction was difficult to manage long-term."	
		Hepatitis	RF cPVI (n = 99)	NR	
			AADs (n = 99)	1% (1/99) (or 1/61 pts taking amiodarone)	
		"Visual or dermatologic events"	RF cPVI (n = 99)	NR	
			AADs (n = 99)	2% (2/99) (or 2/61 of pts taking amiodarone)	
		Hospitalization (cardiovascular causes) (includes repeat	RF cPVI (n = 99)	61 events (n = NR)	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
		procedure or crossover to ablation)			
			AADs (n = 99)	325 events (n = NR)	NR
Stabile (2006)*[12] N = 137	12 months (97%)	Treatment-related stroke	RF cPVI (n = 68)	1% (1/68) (occurred during left atrium ablation, died of brain hemorrhage 9 mos later)	
			AADs (n = 69)	NR	
		Transient ischemic attack	RF cPVI (n = 68)	NR	
			AADs (n = 69)	1% (1/69)	
		Treatment-related transient phrenic paralysis	RF cPVI (n = 68)	1% (1/68)	
			AADs (n = 69)	NR	
		Treatment-related pericardial effusion	RF cPVI (n = 68)	1% (1/68) (required pericardiocentesis)	
			AADs (n = 69)	NR	
		Cancer	RF cPVI (n = 68)	NR	
			AADs (n = 69)	3% (2/68)	
		Hospitalizations (median number per patient)	RF cPVI (n = 68)	1 (1-2)	
			AADs (n = 69)	2 (1-2)	.34
		Percutaneous coronary angioplasty	RF cPVI (n = 68)	1% (1/68) (3 months post-ablation)	
			AADs (n = 69)	NR	
Wazni (2005)*[13] N = 70	12 months	Thromboembolic events (defined as transient ischemic attacks, stroke, deep vein thrombosis, or pulmonary embolism)	RF PVI (first-line therapy) (n = 33)	0% (0/33)	
			AADs (first-line therapy) (n = 37)	0% (0/37)	
		Hospitalizations (2 months)	RF PVI (first-line therapy) (n = 33)	0% (0/33)	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
			AADs (first-line therapy) (n = 37)	54% (20/37) (26 hospitalizations for direct current cardioversion and medication adjustment after AF recurrence)	NR
		Hospitalizations (12 months)	RF PVI (first-line therapy) (n = 33)	9% (3/33)	< .001
			AADs (first-line therapy) (n = 37)	54% (19/37)	
		Bleeding	RF PVI (first-line therapy) (n = 33)	6% (2/33)	.60
			AADs (first-line therapy) (n = 37)	3% (1/37)	
		Bradycardia	RF PVI (first-line therapy) (n = 33)	0% (0/33)	.20
			AADs (first-line therapy) (n = 37)	9% (3/37)	
		Pulmonary vein stenosis	RF PVI (first-line therapy) (n = 33)	6% (2/33) (mild (n = 1); moderate (n = 1); severe (n = 0)	NR
			AADs (first-line therapy) (n = 37)	0% (0/37)	
Wilber (2010)*[1] N = 167	30 days % f/u NR	Pericardial effusion	RF cPVI (n = 106)	1% (1/106)	NR
			AADs (n = 61)	0% (0/61)	
		Pulmonary edema	RF cPVI (n = 106)	1% (1/106)	NR
			AADs (n = 61)	0% (0/61)	
		Pneumonia	RF cPVI (n = 106)	1% (1/106)	NR
			AADs (n = 61)	0% (0/61)	
		Vascular complication	RF cPVI (n = 106)	1% (1/106)	NR
			AADs (n = 61)	0% (0/61)	
		Heart failure	RF cPVI (n = 106)	1% (1/106)	NR
			AADs (n = 61)	0% (0/61)	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
		Life-threatening arrhythmia	RF cPVI (n = 106)	0% (0/106)	NR
			AADs (n = 61)	3% (2/61)	
		Disabling drug intolerance (considered major adverse event)	RF cPVI (n = 106)	0% (0/106)	NR
			AADs (n = 61)	5% (2/61)	
STOP AF Pivotal Trial (2010)[18] N = 245	12 months (93%)	Hematoma (groin)	Cryo cPVI (n = 163)	0.6% (1/163) (recovered)	NR
			AADs (n = 82)	n/a	
		Pericardial effusion / cardiac tamponade	Cryo cPVI (n = 163)	0.6% (1/163) (procedure related, recovered)	NR
			AADs (n = 82)	1% (1/82) (not drug related, recovered)	
		Occlusion to left interior pulmonary vein	Cryo cPVI (n = 163)	0.6% (1/163) (sequelae)	
			AADs (n = 82)	n/a	
		Deep vein thrombosis	Cryo cPVI (n = 163)	1.2% (2/163) (not procedure related, recovered)	
			AADs (n = 82)	NR	
		Pulmonary embolus	Cryo cPVI (n = 163)	0.6% (1/163) (not procedure or device related, recovered)	
			AADs (n = 82)	n/a	
		Procedure-related embolic pneumonia (including stroke)	Cryo cPVI (n = 163)	0% (0/163)	NR
			AADs (n = 82)	n/a	
		Procedure-related arrhythmias	Cryo cPVI (n = 163)	0.6% (1/163)	NR
			AADs (n = 82)	n/a	
		Phrenic nerve palsy	Cryo cPVI (n = 163)	Procedure-related injury: 0% (0/163) Total: 12/3% (20/163)	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
				(first-ablation pts); 10% (3/31) (reablation pts)	
			AADs (n = 82)	Total: 7% (6/82) (all patients had crossed over and rec'd cryoablation)	
		Procedure-related death	Cryo cPVI (n = 163)	0% (0/163)	
			AADs (n = 82)	n/a	
		Pulmonary vein stenosis	Cryo cPVI (n = 163)	Procedure-related: 1.2% (2/163) (classified this way due to significant symptoms and disability) Total: 3.1% (5/163)	
			AADs (n = 82)	2% (2/84) (both patients had crossed over and rec'd cryoablation)	
		Hospitalization (cardiac-related causes)	Cryo cPVI (n = 163)	1.8% (3/163)	
			AADs (n = 82)	7% (6/82)	.064
		Systemic embolization (not stroke)	Cryo cPVI (n = 163)	0% (0/163)	
			AADs (n = 82)	0% (0/82)	--
		Hemorrhagic event (not stroke)	Cryo cPVI (n = 163)	1.2% (2/163)	
			AADs (n = 82)	2% (2/82)	**.603**
		AAD initiation (after initial treatment in AAD group), adjustment, or complication	Cryo cPVI (n = 163)	0.6% (1/163)	
			AADs (n = 82)	5% (4/82)	.044
		"Serious Adverse Events"*	Cryo cPVI (n = 163)	12.3% (20/163)	
			AADs (n = 82)	15% (12/82)	.688
		Worsening AF	Cryo cPVI (n = 163)	2.5% (4/163)	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
			AADs (n = 82)	2% (2/82)	NR
		Pneumonia	Cryo cPVI (n = 163)	2.5% (4/163)	
			AADs (n = 82)	2% (2/82)	NR
		Acute renal failure	Cryo cPVI (n = 163)	NR	
			AADs (n = 82)	1% (1/82)	NR
		Cardiac arrest	Cryo cPVI (n = 163)	1.2% (2/163) (myocardial infarction)	
			AADs (n = 82)	1% (1/82) (cardiopulmonary arrest)	NR
		Atrial appendage thrombus	Cryo cPVI (n = 163)	NR	
			AADs (n = 82)	1% (1/82)	NR
		30-day mortality	Cryo cPVI (n = 163)	0% (0/163)	
			AADs (n = 82)	0% (0/82)	
Lan (2009)[14] N = 240 Prospective	12 months (100%)	Treatment-related complications†	RF circumferential OR segmental PVI (n = 120)	5.8% (7/120)	
			AAD (n = 120)	9.2% (11/120)	NS
		Pulmonary vein stenosis	RF circumferential OR segmental PVI (n = 120)	1.7% (2/120) (moderate to severe)	
			AAD (n = 120)	NR	
		Cerebral embolism	RF circumferential OR segmental PVI (n = 120)	1.7% (2/120) (led to transient retrograde amnesia)	
			AAD (n = 120)	NR	

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
		Torsades de pointes	RF circumferential OR segmental PVI (n = 120)	0% (0/120)	
			AAD (n = 120)	0% (0/120)	--
Pappone (2003)[15] N = 1171 Prospective	mean 30 months (98.4%)	NR	RF cPVI (n = 589)	NR	
			AAD ± cardioversion (n = 582)	NR	
Rossillo (2008)[16] N = 170 Retrospective	15 ± 7 months (% f/u NR)	Stroke	RF PVI (n = 85)	1% (1/85) (occurred just after electrical cardioversion, outcome NR)	
			AAD + cardioversion (n = 85)	1% (1/85) (occurred < 30 days after starting treatment, fatal)	NR
		Pulmonary vein stenosis	RF PVI (n = 85)	7% (6/85) (moderate; asymptomatic)	
			AAD + cardioversion (n = 85)	NR	
		Perfusion defects	RF PVI (n = 85)	0% (0/85)	
			AAD + cardioversion (n = 85)	NR	
		Iatrogenic atrial flutter	RF PVI (n = 85)	8% (7/85)	
			AAD + cardioversion (n = 85)	NR	
Sonne (2009)[17] N = 351 Retrospective	mean 69 months (82%)	Adverse events	RF PVI (n = 146)	NR	
			AAD + cardioversion (n = 205)	NR	

* Serious adverse events included (each event occurred in one patient unless noted): (See next page.)

- Cryo cPVI group: worsening AF (n = 4), recurrent rapid AF, worsening atrial flutter (n = 2), myocardial infarction (n = 2), multiple organ failure, interstitial pneumonitis, pneumonia (n = 4), pericardial effusion (tamponade), acute pyelonephritis secondary to vesical catheter, occlusion to left interior pulmonary vein, hematoma from left groin, cardiopulmonary decompensation, deep vein thrombosis (n = 2), physical deconditioning secondary to procedural complications and immobilization, iletis, focal hemorrhage of ileum secondary to warfarin induced coagulopathy, *E.coli* bacteremia, pulmonary vein stenosis, right lung blebs with persistent air leak, Wegener's granulomatosis, pulmonary embolus, abdominal wall hemorrhage, sepsis-induced hypotensis, subarachnoid hypotension, and acute exacerbation of asthma.
- AAD group: worsening AF (n = 2), worsening atrial flutter (drug-related), pericardial effusion, cardiopulmonary arrest with resuscitation, cardiac tamponade, acute renal failure, gastrointestinal bleeding, AF, appendicitis, right diaphragm paresis (drug-related), non-bacterial meningitis, left atrial appendage thrombus, right wrist heparin lock insertion site infection

† Details on the majority of ablation-related complications and treatment-related complications were not provided per treatment group, but included: sinus bradycardia, hypotension, significant QT prolongation, hyperthyroidism, hypothyroidism and heaptic deterioration, pericardial tamponade requiring pericardiocentesis, moderate to severe pulmonary vein stenosis, and cerebral embolism leading to transient retrograde amnesia.

Table F7. Adverse events: Cohort studies comparing pulmonary vein isolation (PVI) with Cox-Maze surgery in patients with AF

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
Stulak (2011)[19] N = 289 Retrospective	RFA: 3.1 yrs (median) Cox-Maze: 5.6 yrs (median) (*P* < .001) (92%)	Myocardial infarction	RF PVI (n = 194)	NR	
			Cox-Maze Surgery (n = 97)	1% (1/97) (< 30 days; nonfatal)	
		Renal failure	RF PVI (n = 194)	NR	
			Cox-Maze Surgery ***(n = 97)***	1% (1/97) (< 30 days; nonfatal)	
		Respiratory failure	RF PVI (n = 194)	NR	
			Cox-Maze Surgery (n = 97)	1% (1/97) (< 30 days; nonfatal)	
		Permanent pacemaker placement	RF PVI (n = 194)	7.3% (14/194) <u>< 30 days:</u> 2.6% (5/194) (sinus node dysfunction) <u>≥ 30 days:</u> 4.6% (9/194) (after AV node ablation (n = 5), sinus node dysfunction (n = 3), tachycardia-bradycardia (n = 1))	
			Cox-Maze Surgery (n = 97)	9% (9/97) <u>< 30 days:</u> 7% (7/97) (sick sinus syndrome) <u>≥ 30 days:</u> 2% (2/97) (following AV node ablation for recurrent AF)	.55

Investigator (year) Country, CoE	Follow-up duration	Adverse event	Interventions	Results	P-value between groups
		Pulmonary vein stenosis (≥ 50%)	RF PVI (n = 194)	9.8% (19/194) (intervention required in 14 patients, including 18 balloon angioplasties and 11 stenting procedures)	
			Cox-Maze Surgery (n = 97)	NR	
		Pericardial effusion	RF PVI (n = 194)	4.6% (9/194) (required pericardiocentesis) (acute tamponade developed in 4 patients, 1 required surgical exploration)	
			Cox-Maze Surgery (n = 97)	NR	
		Access complications	RF PVI (n = 194)	3.1% (6/194) (groin hematoma (n = 2); femoral arterial pseudoaneurysm (n = 2), femoral arteriovenous fistula (n = 2))	
			Cox-Maze Surgery (n = 97)	NR	

Table F8. Adverse events: Prospective case series evaluating safety of PVI in at least 1000 patients with AF

Investigator (year)	Follow-up	Intervention	N	Results
Procedure-related mortality				
Baman 2011[72]	NR	RF PVI (antrum)	1295	0% (0/1295)
Bertaglia 2007[73]	30 days	RF PVI	1011	0% (0/1011)
Dagres 2009[74]	NR	RF PVI	1000	0% (0/1000)
Hunter 2012[75]	30 days	PVI	1273	0.1% (2/1273)
Procedure-related thromboembolic complications				
Baman 2011[72]	NR	RF PVI (antrum)	1295	0.31% (4/1295)
Bertaglia 2007[73]	30 days	RF PVI	1011	0.49% (5/1011)
Dagres 2009[74]	NR	RF PVI	1000	0.40% (4/1000)
Di Biase 2010[76]	Peri-procedural	RF PVI (antrum)	6454	0.40% (26/6454)
Hunter 2012[75]	30 days	PVI	1273	0.7% (9/1273)
Patel 2010[77]	Peri-procedural	RF PVI (antrum)	3060	0.85% (26/3060)
Procedure-related heart failure				
(No studies reporting)				
Pericardial effusion or cardiac tamponade				
Baman 2011[72]	NR	RF PVI (antrum)	1295	1.54% (20/1295)
Bertaglia 2007[73]	30 days	RF PVI	1011	1.38% (14/1011)
Dagres 2009[74]	NR	RF PVI	1000	1.30% (13/1000)
Di Biase 2010[76]	Peri-procedural	RF PVI (antrum)	6454	0.53% (34/6454)
Hunter 2012[75]	30 days	PVI	1273	0.2% (3/1273)
Pulmonary vein stenosis				
Baman 2011[72]	NR	RF PVI (antrum)	1295	0.08% (1/1295)
Bertaglia 2007[73]	30 days	RF PVI	1011	0.40% (4/1011)
Dagres 2009[74]	NR	RF PVI	1000	0.10% (1/1000)
Hunter 2012[75]	30 days	PVI	1273	0.1% (2/1273)
Atrioesophageal fistula				
Baman 2011[72]	NR	RF PVI (antrum)	1295	0% (0/1295)
Bertaglia 2007[73]	30 days	RF PVI	1011	0.30% (3/1011)
Dagres 2009[74]	NR	RF PVI	1000	0.20% (2/1000)
Deep vein thrombosis				
Baman 2011[72]	NR	RF PVI (antrum)	1295	0.08% (1/1295)
Dagres 2009[74]	NR	RF PVI	1000	0.10% (1/1000)
Hunter 2012[75]	30 days	PVI	1273	0.08% (1/1273)
Peripheral vascular complications				
Baman 2011[72]	NR	RF PVI (antrum)	1295	2.32% (30/1295)
Bertaglia 2007[73]	30 days	RF PVI	1011	0.99% (10/1011)

Investigator (year)	Follow-up	Intervention	N	Results
Dagres 2009[74]	NR	RF PVI	1000	1.00% (10/1000)
Hunter 2012[75]	30 days	PVI	1273	2.1-2.2% (28*/1273)
Radiation exposure				
(No studies reporting)				

*approximated

Table F9. Adverse events: Prospective case series evaluating esophageal lesions following PVI in at least 100 patients with AF

Investigator (year)	Follow-up	Intervention	N	Results
Esophageal lesions				
Halm 2010[78]	1-4 days	Left atrial PVI (antrum)	185	14.6% (27/185)
Martinek 2009[79]	24 hours	RF Left atrial PVI	175	2.9% (5/175)
Martinek 2010[80]	24 hours	RF Left atrial PVI	267	2.2% (6/267)
Yamasaki 2011[81]	48 hours	RF Left atrial PVI	104	9.6% (10/104)

Table F10. Adverse events: RCT comparing radiofrequency ablation with conversion to sinus rhythm in patients with atrial flutter

Investigator (year) Country, CoE	Follow-up duration	Outcome	Interventions	Results	P-value between groups
Da Costa (2006)[20] N = 104	18 months (mean, 13 ± 6 months) (99%)	Treatment-related mortality	RF ablation (n = 52)	0% (0/52)	
			Conversion to sinus rhythm (n = 51)	0% (0/51)	
		Treatment-related complications	RF ablation (n = 52)	0% (0/52)	.03
			Conversion to sinus rhythm (n = 51)	10% (5/51)	
		Hypothyroidism (treatment-related)	RF ablation (n = 52)	0% (0/52)	
			Conversion to sinus rhythm (n = 51)	4% (2/51)	
		Hyperthyroidism (treatment-related)	RF ablation (n = 52)	0% (0/52)	
			Conversion to sinus rhythm (n = 51)	2% (1/51)	
		Symptomatic sick sinus syndrome (treatment-related)	RF ablation (n = 52)	0% (0/52)	
			Conversion to sinus rhythm (n = 51)	4% (2/51)	

Table F11. Adverse events: Prospective case series evaluating safety of catheter ablation in at least 100 patients with atrial flutter

Investigator (year)	Follow-up	Intervention	N	Results
Procedure-related mortality				
Calkins 2004[82]	9 months	RF ablation	150	0% (0/150)
Feld 2004[83]	6 months	RF ablation	169	0% (0/169)
Marijon 2009[84]	1 month	RF ablation	632	0% (0/632)
O'Hara 2007[85]	1-3 months	RF ablation	377	0% (0/377)
Scheinman 2000[86]	NR	RF ablation	477	0% (0/477)
Procedure-related thromboembolic complications				
Calkins 2004[82]	9 months	RF ablation	150	0% (0/150)
Feld 2004[83]	6 months	RF ablation	169	1.8% (3/169)
Gronefeld 2003	Periprocedural	RF ablation	201	0% (0/201)
O'Hara 2007[85]	1-3 months	RF ablation	377	0% (0/377)
Procedure-related heart failure				
(No studies reporting)				
Pericardial effusion or cardiac tamponade				
Calkins 2004[82]	Periprocedural	RF ablation	150	0.7% (1/150)
O'Hara 2007[85]	1-3 months	RF ablation	377	0% (0/377)
Scheinman 2000[86]	NR	RF ablation	477	0.21% (1/477)
Pulmonary vein stenosis				
(No studies reporting)				
Atrioesophageal fistula				
(No studies reporting)				
Deep vein thrombosis				
Feld 2004[83]	6 months	RF ablation	169	0.6% (1/169)
O'Hara 2007[85]	1-3 months	RF ablation	377	0.3% (1/377)
Scheinman 2000[86]	NR	RF ablation	477	0.2% (1/477)
Peripheral vascular complications				
Calkins 2004[82]	Periprocedural	RF ablation	150	0.7% (1/150)
Feld 2004[83]	6 months	RF ablation	169	0.6% (1/169)
O'Hara 2007[85]	1-3 months	RF ablation	377	0.5% (2/377)
Scheinman 2000[86]	NR	RF ablation	477	0.6% (3/477)
Radiation exposure				
(No studies reporting)				

Table F12. Adverse events: Cohort studies comparing catheter ablation with anti-arrhythmic drugs (AADs) in patients with AVNRT

Investigator (year) Country, CoE	Follow-up duration	Outcome	Interventions	Results	P-value between groups
D'Este (2007)[21] N = 93 Prospective	13.2 years (mean) (11.4 – 16.1 years) (86%)	No info on complications was reported	RF ablation (n = 18)† (performed 1-8 yrs after baseline)		
			Chronic AADs (n = 24)†		
			Brief (or no) AAD: (n = 38)† (3/38 pts rec'd no treatment, remaining patients received AADs for a few months)		

Table F13. Adverse events: Cohort studies comparing catheter ablation with open perinodal dissection surgery in patients with AVNRT

Investigator (year) Country, CoE	Follow-up duration	Outcome	Interventions	Results	P-value between groups
Kimman (1999)[22] N = 146 Prospective	28 months (mean) (100%)	Persistent 1st degree AV block	RF ablation (n = 120)	30% (36/120)	NR
	53 months (mean) (100%)		Perinodal dissection surgery (n = 26)	8% (2/26)	
	28 months (mean) (100%)	Pacemaker implantation	RF ablation (n = 120)	3.3% (4/120)	
	53 months (mean) (100%)		Perinodal dissection surgery (n = 26)	8% (2/26)	NR
	28 months (mean) (100%)	Pneumothorax	RF ablation (n = 120)	2.5% (3/120)	
	53 months (mean) (100%)		Perinodal dissection surgery (n = 26)	4 % (1/26)	NR
	28 months (mean) (100%)	Occlusion of left anterior descending coronary artery	RF ablation (n = 120)	NR	
	53 months (mean) (100%)		Perinodal dissection surgery (n = 26)	4 % (1/26) (associated with myocardial infarction)	NR

Investigator (year) Country, CoE	Follow-up duration	Outcome	Interventions	Results	P-value between groups
	28 months (mean) (100%)	Myocardial infarction	RF ablation (n = 120)	NR	
	53 months (mean) (100%)		Perinodal dissection surgery (n = 26)	4 % (1/26) (associated with occlusion of left anterior descending coronary artery)	NR
	28 months (mean) (100%)	Pericarditis	RF ablation (n = 120)	1.7% (2/120)	
	53 months (mean) (100%)		Perinodal dissection surgery (n = 26)	NR	NR
	28 months (mean) (100%)	Ischemic cerebral infarction (procedure-related)	RF ablation (n = 120)	0.8% (1/120) (2 hours after procedure, patient fully recovered)	
	53 months (mean) (100%)		Perinodal dissection surgery (n = 26)	NR	NR
Natale (1993)[24] N = 96 Retrospective	10 months (mean) (100%)	AV block requiring pacemaker implantation	RF ablation (n = 43)	2% (1/43)	
	38 months (mean) (100%)		Perinodal dissection surgery (n = 53)	2% (1/53)	

Table F14. Adverse events: Cohort studies comparing catheter ablation with no treatment in patients with AVNRT

Investigator (year) Country, CoE	Follow-up duration	Outcome	Interventions	Results	P-value between groups
Lin (1998)[23] N = 27 Prospective	23 ± 13 (range, 1-54) (% f/u NR)	Procedure-related complications	RF ablation (n = 16)	0% (0/16) (not specifically defined)	
	13 ± 14 months (range, 1-45) (% f/u NR)		No treatment (n = 11)	n/a	

Table F15. Adverse events: Cohort studies comparing catheter ablation with AADs or surgery in patients with AVRT

Investigator (year) Country, CoE	Follow-up duration	Outcome	Interventions	Results	P-value between groups
Weerasooriya (1994)[27] N = 52 Retrospective	8.4 ± 1.6 months	Mitral regurgitation	RF ablation (n = 20)	5% (1/20) (procedure-related; mild)	
	58 months (mean)		Long-term AADs (n = 12)	NR	
	54 ± 15 months		Surgery (n = 20)	NR	
	8.4 ± 1.6 months	Complete heart block	RF ablation (n = 20)	NR	
	58 months (mean)		Long-term AADs (n = 12)	NR	
	54 ± 15 months		Surgery (n = 20)	5% (1/20) (procedure-related; required pacemaker implantation)	
	8.4 ± 1.6 months	Pericardial effusion	RF ablation (n = 20)	NR	
	58 months (mean)		Long-term AADs (n = 12)	NR	
	54 ± 15 months		Surgery (n = 20)	5% (1/20) (procedure-related; required hospitalization)	
	8.4 ± 1.6 months	Pleural effusion	RF ablation (n = 20)	NR	
	58 months (mean)		Long-term AADs (n = 12)	NR	
	54 ± 15 months		Surgery (n = 20)	5% (1/20) (procedure-related; required hospitalization)	

Table F16. Adverse events: RCTs comparing catheter ablation with no treatment in patients with WPW Syndrome

Investigator (year) Country, CoE	Follow-up duration	Outcome	Interventions	Results	P-value between groups
Pappone, Santinelli (2003)[25] N = 76	24 months (median) (9 – 60 months) (95%)	Procedure-related death	RF ablation (n = 38)	0% (0/38)	
			No treatment (n = 38)	0% (0/38)	
		Pneumothorax	RF ablation (n = 38)	5% (2/38) (related to the electrophysiological testing)	
			No treatment (n = 38)	NR	
		Femoral hematoma	RF ablation (n = 38)	3% (1/38) (related to the electrophysiological testing)	
			No treatment (n = 38)	NR	
		Permanent right bundle-branch block	RF ablation (n = 38)	3% (1/38) (caused by ablation; patient had an anteroseptal accessory pathway)	
			No treatment (n = 38)	NR	
		Myocardial infarction	RF ablation (n = 38)	NR	
			No treatment (n = 38)	3% (1/38) (caused by ventricular fibrillation, patient was successfully cardioverted)	

Table F17. Adverse events: Cohort studies comparing catheter ablation with anti-arrhythmic drugs (AADs) in patients with SVT

Investigator (year) Country, CoE	Follow-up duration	Outcome	Interventions	Results	P-value between groups
Goldberg (2002)[26] N = 95 Prospective	1 year (87%) 5 years (87%)	Pericardial effusion/ tamponade	RF ablation (n = 39)	3% (1/39) (required emergency pericardiocentesis, no permanent sequelae)	
			AADs (n = 44)	NR	

Table F18. Adverse events: Prospective case series evaluating safety of catheter ablation in at least 500 patients with supraventricular tachyarrythmia

Investigator (year)	Diagnosis	Follow-up	Intervention	N	Results
Procedure-related mortality					
Bohnen 2011[87]	**SVTs**		**Ablation**	**524**	**0% (0/524)**
Calkins 1999[88]	**SVTs**	**30 days**	**RF ablation**	**1050**	**0.30% (3/1050)**
Hoffman 2011[89]	**AVNRT**	**17 months**	**RF ablation**	**3234**	**0% (0/3234)**
Marijon 2009[84]	**SVTs**	**1 month**	**RF ablation**	**710**	**0% (0/710)**
	AVNRT	1 month	RF ablation	436	0% (0/436)
	Accessory pathways	1 month	RF ablation	202	0% (0/202)
	Atrial tachycardia	1 month	RF ablation	72	0% (0/72)
O'Hara 2007[85]	**SVTs (all)**	**1-3 months**	**RF ablation**	**4373**	**0% (0/4373)**
	AVNRT	1-3 months	RF ablation	2263	0% (0/2263)
	Accessory pathways	1-3 months	RF ablation	1147	0% (0/1147)
	AV node	1-3 months	RF ablation	803	0% (0/803)
	Atrial tachycardia	1-3 months	RF ablation	160	0% (0/160)
Scheinman 2000[86]	**SVTs (all)**	**NR**	**RF ablation**	**2713**	**0.04% (1/2713)**
	AVNRT	NR	RF ablation	1197	0% (0/1197)
	Accessory pathways	NR	RF ablation	654	0% (0/654)
	AV junctional ablation	NR	AV junctional ablation	646	0.15% (1/646) (pacemaker malfunction)
	Atrial tachycardia	NR	RF ablation	216	0% (0/216)
Procedure-related thromboembolic complications					
Bohnen 2011[87]	**SVTs**		**Ablation**	**524**	**0% (0/524)**
Calkins 1999[88]	**SVTs**	**30 days**	**RF ablation**	**1050**	**0.57% (6/1050)**
O'Hara 2007[85]	**SVTs (all)**	**1-3 months**	**RF ablation**	**4373**	**0.07% (3/4373)**
	AVNRT	1-3 months	RF ablation	2263	0.13% (3/2263)
	Accessory pathways	1-3 months	RF ablation	1147	0% (0/1147)
	AV node	1-3 months	RF ablation	803	0% (0/803)
	Atrial tachycardia	1-3 months	RF ablation	160	0% (0/160)
Scheinman 2000[86]	**SVTs (all)**	**NR**	**RF ablation**	**1197**	**0.11 % (2/1851)**
	AVNRT	NR	RF ablation	1197	0.08% (1/1197)
	Accessory pathways	NR	RF ablation	654	0.15% (1/654)
Persistent AV block					
Calkins 1999[88]	**SVTs**	**30 days**	**RF ablation**	**1050**	**1.00% (10/1050)**
Hoffman 2011[89]	**AVNRT**	**17 months**	**RF ablation**	**3234**	**0.37% (12/3234)**
O'Hara 2007[85]	**SVTs (all)**	**1-3 months**	**RF ablation**	**4373**	**0.16% (7/4373)**
	AVNRT	1-3 months	RF ablation	2263	0.22% (5/2263)

Investigator (year)	Diagnosis	Follow-up	Intervention	N	Results
	Accessory pathways	1-3 months	RF ablation	1147	0.17% (2/1147)
	AV node	1-3 months	RF ablation	803	0% (0/803)
	Atrial tachycardia	1-3 months	RF ablation	160	0% (0/160)
Scheinman 2000[86]	**SVTs (all)**	**NR**	**RF ablation**	**1891**	**0.58% (11/1891)**
	AVNRT	NR	RF ablation	1197	0.74% (9/1197)
	Accessory pathways	NR	RF ablation	654	0.15% (1/654)
	Inappropriate sinus tachycardia	NR	RF ablation	40	3% (1/40)
Pericardial effusion or cardiac tamponade					
Bohnen 2011[87]	**SVTs**		**Ablation**	**524**	**0.2% (1/524)**
Calkins 1999[88]	**SVTs**	**30 days**	**RF ablation**	**1050**	**2.86% (30/1050)**
Hoffman 2011[89]	**AVNRT**	**17 months**	**RF ablation**	**3234**	**0.22% (7/3234)**
O'Hara 2007[85]	**SVTs (all)**	**1-3 months**	**RF ablation**	**4373**	**0.21% (9/4373)**
	AVNRT	1-3 months	RF ablation	2263	0.18% (4/2263)
	Accessory pathways	1-3 months	RF ablation	1147	0.26% (3/1147)
	AV node	1-3 months	RF ablation	803	0% (0/803)
	Atrial tachycardia	1-3 months	RF ablation	160	1.3% (2/160)
Scheinman 2000[86]	**SVTs (all)**	**NR**	**RF ablation**	**870**	**1.1% (10/870)**
	Accessory pathways	NR	RF ablation	654	1.22% (8/654)
	Atrial tachycardia	NR	RF ablation	216	0.9% (2/216)
Pulmonary vein stenosis					
(no studies reporting)					
Atrioesophageal fistula					
(no studies reporting)					
Deep vein thrombosis					
Bohnen 2011[87]	**SVTs**	**NR**	**Ablation**	**524**	**0% (0/524)**
O'Hara 2007[85]	**SVTs (all)**	**1-3 months**	**RF ablation**	**4373**	0.02% (1/4373)
	AVNRT	1-3 months	RF ablation	2263	0% (0/2263)
	Accessory pathways	1-3 months	RF ablation	1147	0.09% (1/1147)
	AV node	1-3 months	RF ablation	803	0% (0/803)
	Atrial tachycardia	1-3 months	RF ablation	160	0% (0/160)
Scheinman 2000[86]	AVNRT	NR	RF ablation	1197	0.08% (1/1197)
Peripheral vascular complications					
Bohnen 2011[87]	AV junctional ablation	NR	AV junctional ablation	646	**0.4% (2/524)**
Calkins 1999[88]	**SVTs**	**30 days**	**RF ablation**	**1050**	**3.23% (34/1050)**
Hoffman 2011[89]	**AVNRT**	**17 months**	**RF ablation**	**3234**	**0.56% (18/3234)**
O'Hara 2007[85]	**SVTs (all)**	**1-3 months**	**RF ablation**	**4373**	**0.53% (23/4373)**

Investigator (year)	Diagnosis	Follow-up	Intervention	N	Results
	AVNRT	1-3 months	RF ablation	2263	0.18% (4/2263)
	Accessory pathways	1-3 months	RF ablation	1147	1.22% (14/1147)
	AV node	1-3 months	RF ablation	803	0.5% (4/803)
	Atrial tachycardia	1-3 months	RF ablation	160	0.6% (1/160)
Scheinman 2000[86]	**SVTs (all)**	**NR**	**RF ablation**	**2497**	**0.84% (21/2497)**
	AVNRT	NR	RF ablation	1197	0.50% (6/1197)
	Accessory pathways	NR	RF ablation	654	2.0% (13/654)
	AV junctional ablation	NR	AV junctional ablation	646	0.31% (2/646)
Radiation injury					
Calkins 1999[88]	SVTs	30 days	RF ablation	1050	0.10% (1/1050)

Table F19. Detailed Evidence Tables for Economic Analysis Studies

Author (year) Country Funding QHES score	Population Interventions Methods	Evidence Base and Assumptions	Cost Estimates	Results

Assasi (2010)[90]
 	
Canada
 	
Funding: no direct funding was disclosed; but several authors have had consulting relationships with AF ablation device manufacturer and have helped to develop AF ablation techniques.
 	
QHES: 90
	Population:
	Hypothetical cohorts representing:
	• 65 year-old
	• Male
	• Unsuccessfully treated with AAD
	• CHAD stroke risk score of 2
	
	Interventions:
	• Minimally invasive AF ablation
	• AAD (amiodarone 200mg/day)
	
	Methods:
	• Cost utility analysis
	• Outcome measures:
	  • Quality adjusted life years (QALY)
	  • Incremental cost-effectiveness ratio (ICER)
	• Perspective: Publicly funded health care system
	• Model used: Markov decision analysis
	• Population source: hypothetical cohorts
	• Time horizon: 5 years with 3 month cycles
		• Effectiveness measures: derived from literature review using clinical reviews when possible.
		  ○ Normal Sinus Rhythm with ablation: 76%[36,43]
		  ○ Normal Sinus Rhythm for AAD: 26%[6, 91, 92]
		  ○ Ischemic stroke: 4%[93]
		  ○ Major bleed w/out warfarin: .5%[94]
		  ○ Major bleed w/ warfarin: 1.2%[94]
		  ○ AF reoccurrence post ablation: 3.6%[95]
		  ○ Ablation complications:[96]
		  ▪ Cardiac tamponade: 0.8%
		  ▪ Stroke: 0.3%
		  ▪ Pulmonary vein stenosis: 0.2%
		  ▪ Death: 0.5%[97, 98]
		  ○ AF reoccurrence post AAD: 22%[95]
		• Utility measures: derived from literature review:
		  ○ Age, gender specific, male 65: 0.78 (app 19)
		  ○ Quality of life adjustments:
		  ○ AF ablation complications: -1.0 for 7 days
		  ○ Pulmonary toxicity: -1.0 for 13 days (106)
		  ○ Irreversible Pulmonary toxicity: 0.6[99]
		  ○ In AF health state disutility: 0.046[100]
		  ○ Ischemic stroke: 0.46[101]
		  ○ Hemorrhagic stroke 0.28[101]
			• Cost estimates (in 2004 USD)
			• Ablation: $12,179 /ablation
			• Amiodarone: $433/year
			• Cost of ischemic stroke: $53,576
			• Cost of hemorrhagic stroke: $56,573
			• Cost of gastrointestinal bleed: $6,023
			• Discounted at 5%
				Base-case analysis (5 year time horizon):
				• Expected cost:
				  • Ablation: $21,150
				  • AAD: $12,611
				  • Incremental (ablation – AAD): $8,539
				• Expected QALY:
				  • Ablation: 3.416
				  • AAD: 3.272
				  • Incremental (ablation – AAD): 0.144
				• ICER ($/QALY): $59,194
				
				One-way sensitivity analysis varying age and gender (5 year time horizon):
				• Constant ischemic stroke risk for all ages:
				  • ICER for females:
				  ▪ 55 years old: $57,088
				  ▪ 75 years old: $65,147
				  • ICER for males:
				  ▪ 55 years old: $57,167
				  ▪ 75 years old: $65,129
				• Increasing ischemic stroke risk according to starting age:
				  • ICER for females:
				  ▪ 55 years old: $67,918
				  ▪ 75 years old: $49,363
				  • ICER for males:
				  ▪ 55 years old: $65,672
				  ▪ 75 years old: $55,275
				• Varying $CHADS_2$ index score:
				  • $CHADS_2$=0: $68,822
				  • $CHADS_2$=4: $44,652
				
				One-way uncertainty analysis:
				• 10 year time horizon ICER: $14,273
				• 0% discount rate ICER: $49,308
				• Assuming restoration does not affect stroke risk ICER: $86,129
				• Disutility of AF health state =0.08 ICER: $38,390
				• Disutility of AF health state =0.02 ICER: $101,083
				• Disutility of AF health state =0.0 ICER: $221,831

Author (year) Country Funding QHES score	Population Interventions Methods	Evidence Base and Assumptions	Cost Estimates	Results

				• Probability of being cost effective at following ICER thresholds:
				  • $25,000: 0.03
				  • $50,000: 0.30
				  • $100,000: 0.89
				  • $150,000: 0.98

Chan (2006)[102]
 	
US
 	
Funding: no direct funding was disclosed; but two authors have financial relationships with AF ablation device manufacturer and have helped to develop AF ablation techniques.
 	
QHES: 88
	<u>Population:</u> Hypothetical cohorts representing:
	• 65 year-old patients with low or moderate risk of stroke
	• 55 year-old patients with moderate risk of stroke
	
	<u>Interventions:</u>
	• PVI + left linear lesions
	• AAD (amiodarone)
	• Rate control (digoxin + atenolol)
	
	<u>Methods:</u>
	• Cost utility analysis
	• Outcome measures:
	  • Quality adjusted life years (QALY)
	  • Incremental cost-effectiveness ratio (ICER)
	• Perspective: direct cost
	• Model used: Markov decision analysis
	• Population source: hypothetical cohorts
	• Time horizon: lifetime
		• Effectiveness measures: derived from literature review. The following is a partial list of measures, represents percentage of patients affected annually):
		  ○ Ablation efficacy: 80% [95, 103]
		  ○ Ablation re-do rate: 30%
		  ○ Relapse to AF after successful restoration to sinus rhythm: 2%[104-106]
		  ○ Ablation complications:[95, 103]
		  ▪ Cardiac tamponade: 0.7%
		  ▪ Stroke: 0.8%
		  ▪ Atrio-esophageal fistula: 0.2%
		  ▪ Death: 0.1%
		  ○ AAD cardioversion success: 85%[99, 107-110]
		  ○ AAD mortality: .01%[111, 112]
		  ○ AAD stroke risk: .27%[111]
		  ○ Rate control cardioversion: 38%[113]
		  ○ Rate control reversion to AF: 5%[113]
		  ○ Rate control digitalis toxicity: 1.1%[113, 114]
		  ○ Rate control beta-blocker toxicity: 0.2%[115, 116]
		• Utility measures: derived from literature review
		  ○ Quality of life:
		  ▪ Normal sinus rhythm: 1
		  ▪ Amiodarone: 0.987[99, 115]
		  ▪ Mild stroke/intracranial bleed: 0.76[99, 115, 117, 118]
		  ▪ Moderate stroke/intracranial bleed: 0.39[99, 115, 117, 118]
		  ○ Pulmonary toxicity: 0.6[99] decrement
		  ○ Utility of short-term events: 0.5[99, 112] decrement
		  ○ Telemetry admission: 3[99, 112] days
		  ○ Ablation procedure: 1 days
		  ○ Tamponade: 2[99, 112] weeks
		• Sensitivity analysis: threshold analysis, one-way sensitivity analysis, and multivariate sensitivity analysis using 10,000 trials and assuming normally distributed variables and lognormal for skewed data.
			• Cost estimates (in 2004 USD)
			• Based on Medicare reimbursement, hospital accounting, Red Book for wholesale drug cost, and literature review.
			• Ablation: $16,500 /ablation[119]
			• Amiodarone: $1,200/year[115, 120]
			• Digitalis: $140/year[120]
			• Atenolol: $260/year[120]
			• Discounted at 3%
				<u>Base-case analysis:</u>
				• <u>Moderate risk of stroke (65 years):</u>
				  • PVI + left linear lesions: $52,369; 11.06 QALY
				  • Amiodarone: $43,358; 10.75 QALY
				  • Rate control: $39,391; 10.81 QALY
				  • Incremental Differences: (Ablation – Amiodarone): $9,011; 0.31 QALY (Ablation - Rate control): $12,978; 0.25 QALY
				
				  • ICER with PVI ($/QALY): Amiodarone: $29,068 Rate control: $51,800
				
				• <u>Moderate risk of stroke (55 years):</u>
				  • PVI + left linear lesions: $59,380; 14.26 QALY
				
				  • Amiodarone: $55,795; 13.81 QALY
				  • Rate control: $50,509; 13.95 QALY
				  • Incremental Differences: (Ablation – Amiodarone): $3585; 0.45 QALY (Ablation - Rate control): $8,871; 0.31 QALY
				
				  • ICER with PVI ($/QALY): Amiodarone: $7,966 Rate control: $28,700
				
				• <u>Low risk of stroke (65 years):</u>
				  • PVI + left linear lesions:

Author (year) Country Funding QHES score	Population Interventions Methods	Evidence Base and Assumptions	Cost Estimates	Results
		• Cost effectiveness thresholds: $50,000 and $100,000 per QALY		$43,036; 11.40 QALY • Amiodarone: $38,425; 11.02 QALY • Rate control: $24,540; 11.21 QALY • Incremental Differences: (Ablation – Amiodarone): $4,611; 0.38 QALY (Ablation - Rate control): $18,496; 0.19 QALY • ICER with PVI ($/QALY): Amiodarone: $12,134 Rate control: $98,900 <u>One-way sensitivity analysis (PVI versus rate control):</u> Variables identified based on largest impact on ICER: rate of stroke, discount rate, PVI reversion rate to AF, PVI cost, utility of warfarin therapy, rate of hemorrhage, efficacy of rate control. • The ICER range did not exceed $95,000 per QALY for any of the variables examined in one-way analysis only patients at moderate risk of stroke included in analysis <u>Multivariate sensitivity analysis (PVI versus rate control):</u> Monte Carlo Simulations across ranges of parameter estimates provides likelihood of $/QALY. • <u>Moderate Risk of Stroke (65 years):</u> 22% chance greater than $100K/QALY 40% chance less than$50K/QALY • <u>Moderate Risk of Stroke (55 years):</u> 4% chance greater than $100K/QALY 82% chance less than $50K/QALY
Eckard (2009)[120] Sweden Funding: no direct funding was disclosed. QHES: 84	<u>Population:</u> Hypothetical cohorts representing: • Symptomatic patients with paroxysmal or persistent AF • Not responding well to AAD treatments <u>Interventions:</u> • RF ablation • AAD (amiodarone)	• Effectiveness measures: derived from literature review using clinical review. Percentage of patients affected annually: ○ AF free with at 12 months: ▪ RFA: 78%[95, 121] ▪ AAD: 9.0%[6, 92, 95, 122] ○ Average RFA procedures needed: 1.47 ○ Risk of stroke: 1.5%[123] ○ Rate of AF in AAD: 2.4 (RR) ○ Complication with RFA: 3.0% • Utility measures: derived from literature review:	• Cost estimates (in 2006 USD) • Ablation: $9,860 /ablation • Amiodarone: $1,649/year[124] • Cost of RFA complication: $2,190[103] • Cost of stroke (1yr): $19,180[125] • Cost of stroke (>1yr):	<u>Base-case analysis:</u> • Expected cost: • Ablation: $25,460 • AAD: $30,440 • Incremental (ablation – AAD): $-4,980 • Expected QALY: • Ablation: 9.46 • AAD: 8.68 • Incremental (ablation – AAD): 0.78 QALY • ICER ($/QALY): Dominated (ablation associated with

Author (year) Country Funding QHES score	Population Interventions Methods	Evidence Base and Assumptions	Cost Estimates	Results

	Methods:
	• Cost utility analysis
	• Outcome measures:
	  • Quality adjusted life years (QALY)
	  • Incremental cost-effectiveness ratio (ICER)
	• Perspective: direct cost
	• Model used: Markov decision analysis
	• Population source: hypothetical cohorts
	• Time horizon:
	  • Short-term 12 month to estimate health states
	  • Long-term until death with annual Markov cycles
		○ Quality of life (sources in Swedish lit):
		  ▪ Age < 69: 0.83
		  ▪ Age 70-79: 0.80
		  ▪ Age > 80: 0.74
		• Decrement for AF: 0.1
		• Decrement of stroke: 0.25
			$4,380[125]
			• Discounted at 3%
			• Converted to USD using standard price parities
				less expected costs and more expected QALYs)
				
				One-way sensitivity analysis varying risk of reversion to uncontrolled AF
				• Annual probability of reversion:
				  • 5%
				  ▪ RFA: $34,920; 9.06 QALY
				  ▪ AAD: $30,660; 8.55 QALY
				  ▪ ICER ($/QALY): $8,290
				  • 10%
				  ▪ RFA: $40,160; 8.91 QALY
				  ▪ AAD: $30,660; 8.55 QALY
				  ▪ ICER ($/QALY): $26,460
				  • 15%
				  ▪ RFA: $43,330; 8.81 QALY
				  ▪ AAD: $30,660; 8.55 QALY
				  ▪ ICER ($/QALY): $48,310

Reynolds (2009)[100]
 	
United States
 	
Funded by a grant from The National Institute of Health. Authors report consulting relationship with Biosense Webster and Sanofi-Aventis
 	
QHES: 91
	Population: Hypothetical cohorts representing:
	• Symptomatic patients with paroxysmal AF
	• Refractory to one or more AADs
	• Modeled for cohort of age 60
	• Male
	• Without severe structural heart disease
	• Non-procedural stroke risk same in both arms.
	
	Interventions:
	• RF ablation +AAD
	• AAD alone (amiodarone)
	
	Methods:
	• Cost utility analysis
	• Outcome measures:
	  • Quality adjusted life years (QALY)
	  • Incremental cost-
		• Effectiveness measures: derived from literature review using clinical review. Percentage of patients affected annually:
		  ○ Ablation efficacy: 60%[96, 122, 126]
		  ○ Ablation re-do rate: 25%[95, 126, 127]
		  ○ AAD success post 1st ablation: 30%[95, 126]
		  ○ AAD success post 2nd ablation: 35%
		  ○ Ablation complications:[95, 103]
		  ▪ Cardiac tamponade: 0.8%[73, 96, 103, 126, 128]
		  ▪ Stroke: 0.3%[73, 96, 103, 128]
		  ▪ Pneumothorax: 0.18%[73, 96, 126]
		  ▪ Vascular Access: 1.2%[73, 103, 106, 126]
		  ▪ Death: 0.05%
		  ○ Recur on AAD: 65%[6, 95, 129]
		  ○ AAD toxicity: 10%[106, 130, 131]
		• Utility measures: derived from literature review and transformed SF-36/SF-12 health survey response data.
		  ○ Quality of life in chronic health states:
		  ▪ Well post ablation: 0.79
		  ▪ Well on ADD: 0.79
		  ▪ Rate control/anticoagulation: 0.725
		  ▪ Post procedural major stroke: 0.39[102]
			• Cost estimates (in USD)
			• Ablation: $15,000 /ablation[102, 128]
			• Well on amiodarone: $3,500[106, 132, 133]
			• Rate control/ anticoagulation: $2,800[132, 133]
			• Cost of stroke (1yr): $8,200
			• Cost of tamponade: $7,500
			• Cost of Vascular access: $8,000
			• Telemetry admission: $5,000
			• All costs discounted at 3%
				Base-case analysis:
				• Expected cost:
				  • Ablation: $26,584
				  • AAD: $19,898
				  • Incremental (ablation – AAD): $6,686
				• Expected QALY (over 5 years):
				  • Ablation: 3.51
				  • AAD: 3.38
				  • Incremental (ablation – AAD): 0.23 QALY
				• ICER ($/QALY): $51,431/QALY
				
				Generalizing age and gender risks:
				• Expected QALY (over 5 years):
				  • Ablation: 3.64
				  • AAD: 3.50
				  • Incremental (ablation – AAD): 0.14
				• ICER ($/QALY): $47,333/QALY
				
				One-way sensitivity analysis:
				• Revealed the time horizon, cost of ablation, and utility inputs to be most influential.
				• Time Horizon:

Author (year) Country Funding QHES score	Population Interventions Methods	Evidence Base and Assumptions	Cost Estimates	Results
	effectiveness ratio (ICER) • Perspective: United States health care system • Model used: Markov decision analysis • Population source: hypothetical cohorts • Time horizon: 5 years with 1 month cycles	▪ Post procedural minor stroke: 0.76[102] • Disutility of short-term events: ▪ Non-fatal drug toxicity: 7 days ▪ Telemetry admission: 3 days ▪ Ablation complication: 4 days		• 3 year ICER: $157,000/QALY • 10-year ICER: < $1,000/QALY • Ablation cost increased to $20,000: • ICER ~ $100,000 • Assuming difference in utility levels are larger than 0.04: • ICER < $100,000
Rodgers (2008)[134] United Kingdom Commission by NIHR HTA Programme QHES: 100	<u>Population:</u> Hypothetical cohorts representing: • Primarily patients with paroxysmal AF • Refractory to at least one AAD • Age: 52[135] • 80% male[135] <u>Interventions:</u> • RF catheter ablation (without long term use of AAD) • Long-term AAD alone (amiodarone) <u>Methods:</u> • Cost utility analysis • Outcome measures: • Quality adjusted life years (QALY) • Incremental cost-effectiveness ratio (ICER) • Perspective: UK's NHS and Personal Social Services • Model used: Markov decision analysis • Population source: hypothetical cohorts populated using data from systematic review and synthesis of clinical effectiveness conducted in	• Effectiveness measures: base case results derived solely from RCT evidence. Sensitivity analysis explores other sources. Complications derived from literature review. ○ Ablation efficacy: 84% ○ AAD efficacy: 36% ○ Reoccurrence of AF with ablation: 3.3% ○ Reoccurrence of AF with AAD: 28.8% ○ Risk of stroke based on CHAD score:[93] ▪ CHAD = 0: 1.9% ▪ CHAD = 1: 2.8% ▪ CHAD = 2: 4.0% ▪ CHAD = 3: 5.9% ○ Anticoagulant use: ▪ Warfarin: 64% ▪ Aspirin: 27% ▪ None: 8% ○ Risk of Stoke in AF vs NSR hazard ratio: 1.6 ○ Mortality risk from stroke (RR) ▪ In year 1: 7.4 ▪ Subsequent years: 2.3 ○ Side effects of AADS:[136] ▪ Pulmonary toxicity: • Pulmonary complication: 15% • Irreversible complication: 25% ▪ Major bleed on warfarin: 2.4% ▪ Minor bleed on warfarin: 15% ○ Ablation complications:[103] ▪ Cardiac tamponade: 1.2% ▪ Stroke: 0.28% ▪ PV stenosis: 0.74% ▪ Operative death: 0.05%	• Cost estimates (in 2006 USD) • Converted using purchasing power parities[141] • Ablation: $15,635/ablation • Amiodarone: $51/per year • Cost of stroke (1yr): $15,002 • Cost of tamponade: $1,298 • Cost of PV stenosis $5,127 • Cost of toxicity: $2,385 • Cost of major bleed: $2,505 • Cost of minor bleed: $138 • All costs discounted at 3.5%	<u>Base-case analysis (assumes parameters derived from RCT):</u> • CHAD score = 0: • 5 year QoL measured: ▪ RFA: $40,246; 11.35 QALY ▪ AAD: $22,997; 10.96 QALY ▪ Incremental (RFA – AAD): $17,245; 0.39 QALY ▪ ICER ($/QALY): $44,221 • Life time QoL measured: ▪ RFA: $40,228; 12.37 QALY ▪ AAD: $22,975; 10.98 QALY ▪ Incremental (RFA – AAD): $17,253; 1.39 QALY ▪ ICER ($/QALY): $12,372 • CHAD score = 1: • 5 year QoL measured: ▪ RFA: $41,482; 11.18 QALY ▪ AAD: $24,468; 10.76 QALY ▪ Incremental (RFA – AAD): $17,014; 0.42 QALY ▪ ICER ($/QALY): $40,658 • Life time QoL measured: ▪ RFA: $41,482; 12.14 QALY ▪ AAD: $24,492; 10.77 QALY ▪ Incremental (RFA – AAD): $17,080; 0.37 QALY ▪ ICER ($/QALY): $12,400 • CHAD score = 3: • 5 year QoL measured: ▪ RFA: $45163; 10.67 QALY ▪ AAD: $28869; 10.18 QALY ▪ Incremental (RFA – AAD): $16,294; 0.49 QALY ▪ ICER ($/QALY): $33,201 • Life time QoL measured: ▪ RFA: $45,174; 11.49 QALY

Author (year) Country Funding QHES score	Population Interventions Methods	Evidence Base and Assumptions	Cost Estimates	Results

	same study.
	• Time horizon:
	  • Short-term 12 month to estimate health states and ensures consistency with clinical results.
	  • Long-term over remaining life of the patient using annual Markov cycles.
	  • Separate analysis presented assumes quality of life benefits only last for 5 years.
		• Utility measures: derived from literature review
		  ○ Quality of life adjustments (decrements):
		  ▪ From normal sinus rhythm[137]
		  • Ablation: 0
		  • AADs: 0.019
		  ▪ From AF[138]
		  • Ablation: 0.003
		  • AADs: 0.092
		  ▪ Pulmonary toxicity: 0.03[139]
		  ▪ Decrement for bleeding event and general side effects (days): 1[136]
		  ○ Mild stroke: 0.74[140]
		  • Moderate stroke: 0.38[140]
				▪ AAD: $28,859; 10.19 QALY
				▪ Incremental (RFA – AAD): $16,315; 0.3 QALY
				▪ ICER ($/QALY): $12,607
				
				<u>One-way sensitivity analysis:</u>
				• Source of data:
				  • 5 year QoL measured:
				  ▪ RCT ($/QALY): $40,758
				  ▪ Literature[103] ($/QALY): $40838
				  • Life time year QoL measured:
				  ▪ RCT ($/QALY): $12,513
				  ▪ Literature[103] ($/QALY): $12,454
				• Duration of QoL benefit with ablation:
				  • 10 years:
				  ▪ ($/QALY): $23,542
				  • 15 years:
				  ▪ ($/QALY): $17,909
				  • 20 years:
				  ▪ ($/QALY): $15,128
				• Gender:
				  • 5 year QoL measured:
				  ▪ Male ($/QALY): $40,685
				  ▪ Female ($/QALY): $40,563
				  • Life time year QoL measured:
				  ▪ Male ($/QALY): $12,624
				  ▪ Female ($/QALY): $11,670
				• Age:
				  • 5 year QoL measured:
				  ▪ 50 years ($/QALY): $40,088
				  ▪ 65 years ($/QALY): $46,849
				  • Life time year QoL measured:
				  ▪ 50 ($/QALY): $12,031
				  ▪ 65 ($/QALY): $17,887
				• Reversion back to AF post RFA:
				  • 5 year QoL measured:
				  ▪ 5% ($/QALY): $42,984
				  ▪ 15% ($/QALY): $51,058
				  • Life time year QoL measured:
				  ▪ 5% ($/QALY): $12,749
				  ▪ 15% ($/QALY): $13,871

Author (year) Country Funding QHES score	Population Interventions Methods	Evidence Base and Assumptions	Cost Estimates	Results
SVTs				

Cheng (2000)[119]
 	
United States
 	
Grant support from Agency for Healthcare Research and Quality and from Veterans Affairs Health Services Research and Development Services.
 	
QHES: 88
	Population: [142-162]
	Hypothetical cohorts representing:
	• 70% female
	• 40 years old
	• Symptomatic patients with 4.6 unscheduled visits per year to emergency room or physician's office while receiving drug therapy.
	• Symptomatic for median of 3 years
	• 30% with bypass tract
	• 60% with atrioventricular nodal reentrant tachycardia
	
	Interventions:
	• RF ablation
	• Long-term AAD (amiodarone)
	• Treatment of acute episodes of arrhythmia with antiarrhythmic drugs
	
	Methods:
	• Cost utility analysis
	• Outcome measures:
	  • Quality adjusted life years (QALY)
	  • Incremental cost-effectiveness ratio (ICER)
	• Perspective: Societal
	• Model used: Markov decision analysis
	• Population source: hypothetical cohorts populated using data from systematic review and synthesis of clinical effectiveness conducted in same study.
		• Effectiveness measures: derived from literature review using clinical review. Percentage of patients affected annually: [142-162]
		  ○ Ablation success: 93%
		  ○ AAD efficacy: 60%
		  ○ Reoccurrence of AF with ablation: 8%
		  ○ Rate of major complication RFA: 1.5%
		• Utility measures: quality of life derived from literature review:
		  ○ Receiving episodic drug treatment: 0.828
		  ○ Receiving long-term drug therapy: 0.833
		  ○ Cured by RFA: 0.983
		  ○ Having atrioventricular block: 0.776
		  ○ Disutility (days of health lost):
		  ▪ Unscheduled visit to physician: 0.25 days
		  ▪ Procedural complications: 1 days
			• Cost estimates (in 1999 USD)
			• Sources include Red Book and Current procedural Terminology and a cohort of sample patients
			• Ablation: $8,190/ablation
			• Annual drug prescription: $120
			• All costs discounted at 3%
				Base-case analysis:
				• Expected cost:
				  • Ablation: $61,880
				  • AAD: $89,820
				  • Incremental: (ablation – AAD): -$29,940
				• Expected QALY:
				  • Ablation: 21.66
				  • AAD: 18.56
				  • Incremental: (ablation – AAD): 3.1 QALY
				• ADD is dominated by RFA
				• Cost equivalent after approximately 10 years
				
				One-way sensitivity analysis:
				• QoL with pacemaker = .40:
				  • Result unaffected
				• Doubling rate of atrioventricular nod block:
				  • Total cost of RFA: $62,320
				  • QALY of RFA: 21.64
				
				Multivariate sensitivity analysis:
				• Comparing changes in annual cost of drug therapy and increases in QoL after RFA, authors found RFA dominated AAD with for all cost greater than $250/year and changes in QoL from 0.01 to 0.15.
				• The ICER if AAD costs are $250/year are:
				  • RFA QoL = 0.01: $23,500
				  • RFA QoL = 0.05: $4,000
				  • RFA QoL = 0.1: $2,000
				  • RFA QoL = 0.15: $1,200
				• Simultaneously changing all variables within 95% confidence range resulting in RFA dominated AAD in 93.7% of the simulations.
				
				Best-case vs. worst-case sensitivity analysis:
				• Rate of complication:
				  • Best-case (1/3 original):
				  ▪ RCT: $61,220; 21.71 QALY
				  • Twofold increase:
				  ▪ RCT: $61,680; 21.48 QALY
				  • Threefold increase:

Author (year) Country Funding QHES score	Population Interventions Methods	Evidence Base and Assumptions	Cost Estimates	Results
	• Time horizon: Patient lifetime. With 1 month Markov cycles.			▪ RCT: $61,400; 21.28 QALY
SVTs				
Hogenhuis (1993)[163] United States Supported by grants from the National Library of Medicine and from the John A. Hartford Foundation. QHES: 73	Population: Hypothetical cohorts representing: • Age: 40 years Suffering from Wolf-Parkinson-White Syndrome (WPW) Interventions: • Compared 5 clinical treatments: o Observation o Observation until cardiac arrest dictates medical therapy o Drug therapy o RFA o Surgical ablation Methods: • Cost utility analysis • Outcome measures: • Quality adjusted life years (QALY) • Incremental cost-effectiveness ratio (ICER) • Model used: Markov decision analysis • Population source: hypothetical cohorts • Time horizon: Patient lifetime. Annual Markov cycles.	• Effectiveness measures: derived from literature review using clinical review. Percentage of patients affected annually: o RFA success: 85%[152, 164, 165] o RFA mortality: 0.01%[34,44166, 167] o RFA Inguinal hematoma: 5%[164, 165] o RFA cardiac tamponade: 1%[152, 165-167] o AAD efficacy: 90% o AAD mortality (yearly): 0.02%[106, 168] • Utility measures: derived primarily from expert opinion o Long-term quality of life (lifetime: ▪ Heart block: 0.99 o Short-term quality of life (yearly): ▪ Cardiac arrest episode: 0.85 ▪ Drug side effect: 0.95 ▪ AF episode: 0.9	• Cost estimates (in 1992 USD) • Data estimated by Clinical Cost Manager for hospital specific cost on 13 consecutive patients, ratio of reimbursement to charge for physician costs, average annual costs for others.. • RFA costs: o Hospital: $3,000 o Physician: $1,700 o Vascular surgery: $5,000 o Cardiac tamponade: $600 o Pacemaker: $10,000 • Annual drug prescription: $1,200 • All costs discounted at 5%	Base-case analysis: • Expected cost: • RFA w/ AAD: $6,250 • AAD: $20,250 • Incremental (ablation – AAD): -1$14,000 • Expected QALY: • RFA w/AAD: 17.21 • AAD: 17.18 • Incremental: (ablation – AAD): -0.97 • ICER ($/QALY): AAD dominated by RFA One-way sensitivity analysis: • Showed cost of RFA and rate of incidence of AF in asymptomatic patients to be most sensitive variables.

AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CHAD: ICER: incremental cost-effectiveness ratio; PVI: pulmonary vein isolation; QALY: quality adjusted life years; QHES: quality of health economic studies; RFA: radiofrequency ablation; WPW: Wolf-Parkinson-White syndrome

Appendix G. FDA-Approved Radiofrequency and Cryoablation Devices

Device	Manufacturer	PMA # (supplements)	Approval Date (year)	Catheter Tip Size Irrigation?	Indications and Contraindications
Radiofrequency-based devices					
Blazer II XP Cardiac Ablation System; EPT-1000 Cardiac Ablation Controller	Boston Scientific Corp.	P920047 52 supplements	1994	4 mm – 5 mm NR	NR
ATAKR(TM) RFCA System (includes the RF Ablatr and the RF Marinr Series of RFCA Catheters)	Medtronic, Inc.	P930029 36 supplements	1995	4 mm No	Indications • Interruption of accessory atrioventricular (AV) conduction pathways associated with tachycardia, for the treatment of AV nodal re-entrant tachycardia, and for creation of complete AV block in patients with a difficult to control ventricular response to an atrial arrhythmia. Contraindications • Patients with active systemic infection • Transseptal approach contraindicated in patients with left atrial thrombus or myxoma, or interarterial baffle or patch. • Retrograde transaortic approach contraindicated in patients with aortic valve replacement.
Webster Diag./Ablation Deflectable Tip Catheter	Cordis Corp.	P950005 39 supplements	1997	SSED not found	SSED not found
Chilli Cooled RF Ablation System (Includes Chilli Cooled Ablation Catheter, Standard Curve, and Chilli Cooled Ablation Catheter, Large Curve)	Boston Scientific Corp.	P980003 36 supplements	1999	NR No	Indications • Cardiac electrophysiological mapping • Delivering diagnostic pacing stimuli • Radiofrequency ablation of mappable ventricular tachycardia attributable to ischemic heart disease or cardiomyopathy in patients who have failed drug therapy. Contraindications • Patients with active systemic infection • Patients with a mechanical prosthetic heart valve through which the catheter must pass • Patients with left ventricular thrombus; or with left atrial thrombus or myxoma via the

Device	Manufacturer	PMA # (supplements)	Approval Date (year)	Catheter Tip Size Irrigation?	Indications and Contraindications
					transseptal approach • Patients unable to receive heparin or an acceptable alternative to achieve adequate anticoagulation
Daig LIVEWIRE(R) Cardiac Ablation System	St. Jude Medical	P960016 39 supplements	1999	4 mm No	Indications • Interruption of accessory atrioventricular conduction pathways associated with tachycardia • The treatment of AV nodal re-entrant tachycardia • Creating of complete AV nodal block in patients with difficult to control ventricular response to atrial arrhythmia. Contraindications • Patients with active systemic infection • Via the transseptal approach in patients with left atrial thrombus or myxoma, or interatrial baffle or patch • In patients with aortic valve replacement via the retrograde transaortic approach
Navi-Star Diagnostic/ Ablation Deflectable Tip Catheter	Biosense Webster, Inc.	P990025 34 supplements	2000	4mm	Indications • Interruption of accessory atrioventricular conduction pathways associated with tachycardia, including persistent junctional re-entrant tachycardia and Mahaim fibers • The treatment of AV nodal re-entrant tachycardia • The creation of complete AV nodal block in patients with hard to control ventricular response to atrial arrhythmia. Contraindications • In patients with active systemic infection • Via the transseptal approach in patients with left atrial thrombus or myxoma, or interatrial baffle or patch • Via the retrograde transaortic approach in patients with aortic valve replacement.
Stinger Ablation Catheter; TempLink Extension Cable	C.R. Bard Inc., Bard Electrophysiology Division	P000020 16 supplements	2000	4 mm No	Indications • For treatment of focal endocardial lesions during cardiac ablation procedures for the treatment of arrhythmias • For cardiac electrophysiological

Device	Manufacturer	PMA # (supplements)	Approval Date (year)	Catheter Tip Size Irrigation?	Indications and Contraindications
					mapping and delivering of diagnostic pacing stimuli. Contraindications • In conditions where manipulation of the catheter would be unsafe, for example in the case of intracardiac mural thrombus • Via transseptal approach is contraindicated in patients with left atrial thrombus or myxoma, or interatrial baffle patch. • Via the retrograde transaortic approach in patients with aortic valve replacements
Stockert 70 Radiofrequency Ablation Generator	Biosense Webster, Inc.	P990071 20 supplements	2000	NR No	Indications • In conjunction with a Biosense Webster Diagnostic/Ablation Deflectable Tip catheter for cardiac ablation Contraindications • In patients with active systemic infection • Via the transseptal approach in patients with left atrial thrombus or myxoma, or interatrial baffle or patch • Via the retrograde transaortic approach in patients with aortic valve replacement.
NaviStar DS 8 mm Deflectable Diagnostic/ Ablation Catheter (includes Celsius DS 8 mm Deflectable Diagnostic/ Ablation catheter)	Biosense Webster, Inc.	P010068 30 supplements	2002	8 mm	Indications • For catheter based cardiac electrophysiological mapping (stimulation and recording) • When used with Stocker 70, for treatment of Type 1 atrial flutter in patients 18 years of older Contraindications • In patients with active systemic infection • Via the transseptal approach in patients with left atrial thrombus or myxoma • Via the retrograde approach in patients with aortic valve replacement.
EP Technologies EPT-1000 XP RF Ablation System	Boston Scientific	P020025 37 supplements	2003	8mm – 10mm No	Indications • For treatment of sustained or recurrent type I atrial flutter in patients 18 or older • For use in conjunction with standard and high power catheters for cardiac ablation procedures.

Device	Manufacturer	PMA # (supplements)	Approval Date (year)	Catheter Tip Size Irrigation?	Indications and Contraindications
					Contraindications • Patients with active systemic infection • Via the transseptal approach in patients with left atrial thrombus or myxoma • Via retrograde approach in patients with aortic valve replacement
Biosense Webster NAVISTAR/ CELSIUS THERMO COOL Diagnostic/ Ablation Deflectable Tip Catheters	Biosense Webster, Inc.	P030031 48 supplements	2004	3.5 mm Yes	Indications • Catheter-based cardiac electrophysiological mapping (stimulation and recording) • For treatment of Type I atrial flutter in patients > 18 years of age, when used with the Stockert 70 generator Contraindications • Patients with active systemic infection • If patient has intracardiac mural thrombus or has had a ventriculotomy or atriotomy within the preceding four weeks
IBI Therapy Cardiac Ablation System ERS/ 1500T RF Generator	Irvine Biomedical, Inc.	P040014 19 supplements	2005	4 mm No	Indications • For mapping and for use with compatible RF generator for the interruption of accessory atrioventricular conduction pathways associated with tachycardia, the treatment of AV nodal reentrant tachycardia, or the creation of complete AV nodal block in patients with difficult to control ventricular response to an atrial arrhythmia Contraindications • Not for use in patients with active systemic infection • Not for use via the retrograde transaortic approach in patients with aortic valve replacement • Not for use via the transseptal approach in patients with left atrial thrombus or myxoma, or interatrial baffle or patch
Therapy Dual 8 Cardiac Ablation System	Irvine Biomedical, Inc.	P040042 24 Supplements	2005		Indications • For creating long, linear endocardial lesions during cardiac ablation procedures (mapping, stimulation and ablation) for treatment of typical atrial flutter. Contraindications

Device	Manufacturer	PMA # (supplements)	Approval Date (year)	Catheter Tip Size Irrigation?	Indications and Contraindications
					Patients with active systemic infection • Patients with intracardia mural thrombus or those who have had a ventriculotomy or atriotomy within the preceding four weeks
NAVISTAR THERMOCOOL Deflectable Diagnostic/ Ablation Catheter	Biosense Webster, Inc.	P040036 29 supplements	2006	3.5 mm No	Indications • For treatment of recurrent drug/device refractory sustained monomorphic ventricular tachycardia due to prior myocardial infarction in adults • When used with CARTO EP/XP Navigation System, can be used for catheter-based cardiac electrophysiological mapping Contraindications • If patients has had ventriculotomy or atriotomy within the previous eight weeks, due to increased risk of perforations • In patients with prosthetic valves, as the catheter might damage the prosthesis • In the coronary vasculature, due to the risk of damage to the coronary arteries • In patients with active systemic infection • In patients with myxoma or intracardia thrombus • Via the transseptal approach in patients with interatrial baffle or pitch
Cool Path Ablation Catheter & IBI-1500T9 RF	Irvine Biomedical, Inc.	P060019 23 supplements	2007	4 mm No	Indications • Intended for use with compatible external infusion pump and the IBI 1500T9 Radiofrequency Generator at maximum of 50 watts. • Intended for creating endocardial lesions during cardiac ablation procedures for the treatment of typical atrial flutter. • Intended for use with compatible St. Jude Medical temperature controlled ablation catheters for creating endocardial lesions for treatment of cardiac arrhythmias. • Must be used with compatible external infusion pump. Contraindications • Patients with active systemic infections

Device	Manufacturer	PMA # (supplements)	Approval Date (year)	Catheter Tip Size Irrigation?	Indications and Contraindications
					• Patients with intracardiac dural thrombus or a ventriculotomy or atriotomy within the previous four weeks.
Helios II Ablation Catheter	Stereotaxis, Inc.	P050029 No supplements	2008	4 mm No	Indications • For use in cardiac electrophysiological mapping, delivering diagnostic pacing stimuli, and for the creation of endocardial lesions to treat patients with supraventricular tachycardia • To eliminate atrioventricular reentrant tachycardia in patients with overt or concealed accessory pathways, to eliminate atrioventricular nodal re-entrant tachycardia, and to create complete atrioventricular nodal block in patients with difficult to control ventricular response to atrial fibrillation. • For use with the Biosense Webster Stockert 70 RF Generator via a Biosense Webster cable model C6-Mr10/MSTK-S (6 foot) or C10-MR10/MSTK-S (10 foot). • For use only with the Stereotaxis Magnetic Navigation System (MNS) and is compatible with the Cardiodrive Catheter Contraindications • Not intended for use in the coronary vasculature, other than the coronary sinus • Not for use in patients with active systemic infection • Via the transseptal approach in patients with left atrial thrombosis or myxoma, or interatrial baffle or patch • Via the retrograde transaortic approach in patients with aortic valve replacement.
AtriCure Synergy Ablation System	Atricure, Inc.	P100046 1 supplement	2011	NR No	Indications • For the ablation of cardiac tissue for the treatment of persistent atrial fibrillation or longstanding persistent atrial fibrillation (continuous atrial fibrillation of greater than one year in duration) in patients undergoing concomitant coronary artery bypass grafting and/or valve

Device	Manufacturer	PMA # (supplements)	Approval Date (year)	Catheter Tip Size Irrigation?	Indications and Contraindications
					replacement or repair. Contraindications • Contraceptive coagulation of the fallopian tubes.
Therapy Cool Path Duo/ Safire BLU Duo Ablation Catheter and IBI 1500T9-CP V1.6 Cardiac Ablation Generator	St. Jude Medical, Inc.	P110016 5 supplements	2012	4 mm Yes	Indications • For creating endocardial lesions during cardiac ablation procedures (mapping, stimulation and ablations) for the treatment of typical atrial flutter Contraindications • Patients with active systemic infection • Patients with intracardia mural thrombus or those who have had a ventriculotomy or atriotomy within the preceding four weeks
Cryoablation					
7F Freezor Cardiac Cryoablation Catheter and CCT.2 CryoConsole System	Medtronic Cryocath LP	P020045 45 supplements	2003	4 mm No	Indications • For cryoablation of the conducting tissues of the heart for the treatment of atrioventricular nodal reentrant tachycardia Contraindications • In patients with active systemic infection • In conditions where manipulation of the catheter would be unsafe, such as intracardiac mural thrombus • In patients with cryoglobulinemia
CryoCor Cryoablation System	Boston Scientific Corp.	P050024 1 supplement	2007	6.5 mm No	Indications • For ablation of isthmus-dependent right atrial flutter in patients 18 years of age or older Contraindications • In patients with active systemic infection • In patients with intracardiac mural thrombus or in patients who have had a ventriculotomy or atriotomy within the previous four weeks • In patients with cryoglobulinemia
Arctic Front Cryocatheter System (Includes Freezor MAX Cardiac CryoAblation Catheter)	Medtronic Cryocath LP	P100010 21 supplements	2010	Balloon diameter: 23 mm and 28 mm No	Indications • For treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation • As an adjunctive device in the endocardial treatment of paroxysmal atrial fibrillation in conjunction with Arctic Front Cryocatheter for the following

Device	Manufacturer	PMA # (supplements)	Approval Date (year)	Catheter Tip Size Irrigation?	Indications and Contraindications
					uses: • Gap cryoablation to complete electrical isolation of the pulmonary veins • Cryoablation of focal trigger sites, and • Creation of ablation line between the inferior vena cava and the tricuspid valve <u>Contraindications</u> • Arctic Front Cardiac CryoAblation Catheter is contraindicated in the following circumstances • In the ventricle because of the danger of catheter entrapment in the chordae tendinae • In patients with active systemic infections • In conditions where the manipulation of the catheter within the heart would be unsafe, such as intracardiac mural thrombus • In patients with cryoglobulinemia • In patients with one or more pulmonary vein stents • The Freezor MAX Cardia CryoAblation Catheter is contraindicated in the following circumstances • Active systemic infections • Cryoglobulinemia • In conditions where the manipulation of the catheter within the heart would be unsafe, such as intracardiac mural thrombus

AV: atrioventricular; NR: not reported; RF: radiofrequency; SSED: summary of safety and effectiveness data

Appendix H. Clinical Peer Reviewers

The following have agreed to provide clinical peer review:

Reviewer	Areas of expertise
Ramakota, K. Reddy, M.D Oregon Cardiology, Electrophysiologist; Practicing at: Sacred Heart Medical Center, Eugene, OR Mackenzie-Willamette Hospital, Springfield, OR Good Samaritan Hospital, Corvalis, OR Peacehealth Hospital, Florence, OR	• MD, University of Pennsylvania, Cardiology fellowship, University of Washington • Board Certifications: American Board of Internal Medicine, American Board of Cardiovascular Disease, ABIM Special Certification in Clinical Cardiac Electrophysiology • Formerly Chief of Cardiology and Director of Electrophysiology and Clinical Research Wright Patterson Air Force Base Medical Center, Dayton OH • Over 20 years of research and clinical experience related to cardiac electrophysiology • Organization memberships: North American Society of Pacing and Electrophysiology, American College of Cardiology, Aerospace Medical Associations and Society of Air Force Physicians
Jeanne E. Poole, MD University of Washington, Electrophysiology/ Arrhythmia - Cardiology Practicing at: University of Washington , Seattle, WA Harborview Medical Center, Seattle, WA	• MD, University of Washington; Cardiology Fellowship, University of Washington; Clinical and Electrophysiological Training: University of Washington • Board Certifications: American Board of Internal Medicine, Subspecialty of Electrophysiology • Over 20 years of research and clinical experience related to cardiac electrophysiology • Director of Electrophysiology/Arrhythmia Service – Cardiology, University of Washington • Director of Clinical Cardiac Electrophysiology Fellowship Training Program, University of Washington • Organization memberships: American College of Cardiology, American Heart Association, Washington State Medical Society, Heart Rhythm Society, King County Medical Society
Gerhard H. Muelheims, MD, FACC **NOTE: no review received** Providence Spokane Cardiology Practicing at: Sacred Heart Medical Center, Spokane Deaconess Medical Center, Spokane Holy Family Hospital, Spokane Valley Hospital and Medical Center, Spokane	• MD, Saint Louis University; Cardiology fellowship University of Utah • Board Certifications: American Board of Internal Medicine, American Board of Cardiovascular Disease, ABIM Special Certification in Clinical Cardiac Electrophysiology • Over 20 years of research and clinical experience related to cardiac electrophysiology • Formerly Director of Electrophysiology - Cardiology/Tulsa • Organization memberships: North American Society of Pacing and Electrophysiology, American College of Cardiology, American Heart Association

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