Catheter Ablation for Treatment of Atrial Fibrillation

Appendices

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Appendix A. Search Strategy

Database: Ovid MEDLINE(R) without Revisions <1996 to March Week 4 2014>

1	Atrial Fibrillation/ or atrial fibrillation.mp. or afib.mp.
2	1 not (child$ or pediatri$ or infant$ or adolescent$).mp.
3	catheter ablation.mp. or Catheter Ablation/
4	exp Pulsed Radiofrequency Treatment/
5	radiofrequency.mp.
6	cryoablation.mp. or Cryosurgery/
7	cryoballoon.mp. or Balloon Occlusion/
8	("pulmonary vein isolation" or "pvi").mp.
9	or/3-8
10	2 and 9
11	("clinical trial" or "comparative study" or "controlled clinical trial" or "randomized controlled trial").pt.
12	(random$ or control$ or trial$ or cohort or prospective or retrospective).mp.
13	(ae or co or mo).fs.
14	("adverse event$" or "adverse effect$" or safety or harm$).mp.
15	11 or 12
16	13 or 14
17	10 and (15 or 16)
18	limit 17 to yr="2005 -Current"
19	limit 18 to humans
20	limit 19 to english language

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2014>
Search Strategy:

1	Atrial Fibrillation/ or atrial fibrillation.mp. or afib.mp.
2	1 not (child$ or pediatri$ or infant$ or adolescent$).mp.
3	catheter ablation.mp. or Catheter Ablation/
4	exp Pulsed Radiofrequency Treatment/
5	radiofrequency.mp.
6	cryoablation.mp. or Cryosurgery/
7	cryoballoon.mp. or Balloon Occlusion/
8	("pulmonary vein isolation" or "pvi").mp.
9	or/3-8
10	2 and 9
11	limit 10 to yr="2005 -Current"

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 2014>

1	Atrial Fibrillation/ or atrial fibrillation.mp. or afib.mp.
2	1 not (child$ or pediatri$ or infant$ or adolescent$).mp.
3	catheter ablation.mp. or Catheter Ablation/

4	radiofrequency.mp.
5	cryoablation.mp. or Cryosurgery/
6	("pulmonary vein isolation" or "pvi").mp.
7	or/3-6
8	2 and 7

Appendix B. List of Included Studies

1. Andrade JG, Khairy P, Macle L, et al. Incidence and significance of early recurrences of atrial fibrillation after cryoballoon ablation: insights from the multicenter Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) Trial. Circ Arrhythm Electrophysiol. 2014 Feb;7(1):69-75. PMID: 24446022.
2. Baman TS, Jongnarangsin K, Chugh A, et al. Prevalence and predictors of complications of radiofrequency catheter ablation for atrial fibrillation. Journal of Cardiovascular Electrophysiology. 2011;22(6):626-31.
3. Bertaglia E, Zoppo F, Tondo C, et al. Early complications of pulmonary vein catheter ablation for atrial fibrillation: a multicenter prospective registry on procedural safety. Heart Rhythm. 2007 Oct;4(10):1265-71. PMID: 17905330.
4. Blandino A, Toso E, Scaglione M, et al. Long-term efficacy and safety of two different rhythm control strategies in elderly patients with symptomatic persistent atrial fibrillation. Journal of Cardiovascular Electrophysiology. 2013 Jul;24(7):731-8. PMID: 23551460.
5. 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. Journal of Cardiovascular Electrophysiology. 2011 Aug;22(8):839-45. PMID: 21410581.
6. Chierchia GB, Capulzini L, Droogmans S, et al. Pericardial effusion in atrial fibrillation ablation: a comparison between cryoballoon and radiofrequency pulmonary vein isolation. Europace. 2010 Mar;12(3):337-41. PMID: 20056597.
7. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med. 2012 Oct 25;367(17):1587-95. PMID: 23094720.
8. Dagres N, Hindricks G, Kottkamp H, et al. Complications of atrial fibrillation ablation in a high-volume center in 1,000 procedures: still cause for concern? Journal of Cardiovascular Electrophysiology. 2009 Sep;20(9):1014-9. PMID: 19490383.
9. D'Ascenzo F, Corleto A, Biondi-Zoccai G, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. International Journal of Cardiology. 2013 Sep 1;167(5):1984-9.
10. Deshmukh A, Patel NJ, Pant S, et al. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. Circulation. 2013;128(19):2104-12.
11. Forleo GB, Mantica M, De Luca L, et al. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. Journal of Cardiovascular Electrophysiology. 2009 Jan;20(1):22-8. PMID: 18775050.
12. Gibson DN, Di Biase L, Mohanty P, et al. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors.[Erratum appears in Heart Rhythm. 2011 Nov;8(11):1828]. Heart Rhythm. 2011 Sep;8(9):1364-71. PMID: 21354332.
13. Hao SC, Hunter TD, Gunnarsson C, et al. Acute safety outcomes in younger and older patients with atrial fibrillation treated with catheter ablation. J Interv Card Electrophysiol. 2012 Nov;35(2):173-82. PMID: 22714547.
14. Herrera Siklody C, Deneke T, Hocini M, et al. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. Journal of the American College of Cardiology. 2011 Aug 9;58(7):681-8. PMID: 21664090.
15. Hoyt H, Bhonsale A, Chilukuri K, et al. Complications arising from catheter ablation of atrial fibrillation: temporal trends and predictors. Heart Rhythm. 2011 Dec;8(12):1869-74. PMID: 21798230.
16. Hunter RJ, Berriman TJ, Diab I, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol. 2014 Feb;7(1):31-8. PMID: 24382410.

17. 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 Jan;98(1):48-53. PMID: 21930724.

18. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study.[Erratum appears in Circulation. 2009 Sep 8;120(10):e83]. Circulation. 2008 Dec 9;118(24):2498-505. PMID: 19029470.

19. Jones DG, Haldar SK, Hussain W, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. Journal of the American College of Cardiology. 2013;61(18):1894-903. PMID: CN-00907192 NEW.

20. Knecht S, Sticherling C, von Felten S, et al. Long-term comparison of cryoballoon and radiofrequency ablation of paroxysmal atrial fibrillation: a propensity score matched analysis. Int J Cardiol. 2014 Oct 20;176(3):645-50. PMID: 25149399.

21. 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 Sep;96(17):1379-84. PMID: 20801856.

22. Kosiuk J, Kornej J, Bollmann A, et al. Early cerebral thromboembolic complications after radiofrequency catheter ablation of atrial fibrillation: Incidence, characteristics, and risk factors. Heart Rhythm. 2014 Nov;11(11):1934-40. PMID: 25086257.

23. 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 Aug;39(8):657-63. PMID: 19490069.

24. MacDonald MR, Connelly DT, Hawkins NM, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. Heart. 2011 May;97(9):740-7. PMID: 21051458.

25. Mandell J, Amico F, Parekh S, et al. Early experience with the cryoablation balloon procedure for the treatment of atrial fibrillation by an experienced radiofrequency catheter ablation center. J Invasive Cardiol. 2013 Jun;25(6):288-92. PMID: 23735354.

26. Michowitz Y, Rahkovich M, Oral H, et al. Effects of sex on the incidence of cardiac tamponade after catheter ablation of atrial fibrillation: results from a worldwide survey in 34 943 atrial fibrillation ablation procedures. Circ Arrhythm Electrophysiol. 2014 Apr;7(2):274-80. PMID: 24519888.

27. Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). European heart journal. 2013 Oct 17PMID: 24135832.

28. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA. 2014 Feb 19;311(7):692-700. PMID: 24549549.

29. Mugnai G, Chierchia GB, de Asmundis C, et al. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. The American journal of cardiology. 2014 May 1;113(9):1509-13. PMID: 24630388.

30. Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. N Engl J Med. 2006 Mar 2;354(9):934-41. PMID: 16510747.

31. Packer DL, Irwin JM, Champagne J. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front STOP-AF pivotal trial. J Am Coll Cardiol. 2010;55:E3015-6.

32. Pappone C, Augello G, Sala S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. Journal of the American College of Cardiology. 2006 Dec 5;48(11):2340-7. PMID: 17161267.

33. Pappone C, Vicedomini G, Augello G, et al. Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study. Circ. 2011 Dec;4(6):808-14. PMID: 21946315.

34. Perez-Castellano N, Fernandez-Cavazos R, Moreno J, et al. The COR trial: a randomized study with continuous rhythm monitoring to compare the efficacy of cryoenergy and radiofrequency for pulmonary vein isolation. Heart Rhythm. 2014 Jan;11(1):8-14. PMID: 24103221.

35. Piccini JP, Sinner MF, Greiner MA, et al. Outcomes of Medicare beneficiaries undergoing catheter ablation for atrial fibrillation. Circulation. 2012 Oct 30;126(18):2200-7. PMID: 23019293.

36. 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 Mar 1;5(2):171-81. PMID: 22373904.

37. 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 Nov;3(6):615-23. PMID: 20940250.

38. Rossillo A, Bonso A, Themistoclakis S, et al. Role of anticoagulation therapy after pulmonary vein antrum isolation for atrial fibrillation treatment. J Cardiovasc Med (Hagerstown). 2008 Jan;9(1):51-5. PMID: 18268419.

39. Sacher F, Monahan KH, Thomas SP, et al. Phrenic nerve injury after atrial fibrillation catheter ablation: characterization and outcome in a multicenter study. J Am Coll Cardiol. 2006 Jun 20;47(12):2498-503. PMID: 16781380.

40. Sang C-H, Chen K, Pang X-F, et al. Depression, anxiety, and quality of life after catheter ablation in patients with paroxysmal atrial fibrillation. Clin Cardiol. 2013 Jan;36(1):40-5. PMID: 22777577.

41. Schmidt M, Dorwarth U, Andresen D, et al. Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. J Cardiovasc Electrophysiol. 2014 Jan;25(1):1-7. PMID: 24134539.

42. Shah RU, Freeman JV, Shilane D, et al. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. J Am Coll Cardiol. 2012 Jan 10;59(2):143-9. PMID: 22222078.

43. Sonne K, Patel D, Mohanty P, et al. Pulmonary vein antrum isolation, atrioventricular junction ablation, and antiarrhythmic drugs combined with direct current cardioversion: survival rates at 7 years follow-up. J Interv Card Electrophysiol. 2009 Nov;26(2):121-6. PMID: 19789970.

44. Srivatsa UN, Danielsen B, Anderson I, et al. Risk predictors of stroke and mortality after ablation for atrial fibrillation: The California experience 2005-2009. Heart Rhythm. 2014 Nov;11(11):1898-903. PMID: 25048442.

45. Stabile G, Bertaglia E, Senatore G, et al. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). European heart journal. 2006 Jan;27(2):216-21. PMID: 16214831.

46. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA. 2005 Jun 1;293(21):2634-40. PMID: 15928285.

47. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA. 2010 Jan 27;303(4):333-40. PMID: 20103757.

48. Wynn GJ, Das M, Bonnett LJ, et al. Quality-of-life benefits of catheter ablation of persistent atrial fibrillation: a reanalysis of data from the SARA study. Europace. 2014 Jul 15PMID: 25028177.

49. Yu S, Zhao Q, Wu P, et al. Effect of anxiety and depression on the recurrence of paroxysmal atrial fibrillation after circumferential pulmonary vein ablation. Journal of Cardiovascular Electrophysiology. 2012 Nov;23 Suppl 1:S17-23. PMID: 22998234.

50. Zado E, Callans DJ, Riley M, et al. Long-term clinical efficacy and risk of catheter ablation for atrial fibrillation in the elderly. J Cardiovasc Electrophysiol. 2008 Jun;19(6):621-6. PMID: 18462325.

Appendix C. List of Excluded Studies with Rationale[1-53]

1. Al-Khatib SM, Allen LaPointe NM, Chatterjee R, et al. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. [Review]. Ann Intern Med. 2014 Jun 3;160(11):760-73. **Duplicate SR.**
2. Ardagh MW, Pitchford AM, Esson A, et al. Project RED--a successful methodology for improving emergency department performance. N Z Med J. 2011 Oct 14;124(1344):54-63. PMID: 22016164. **Does not address Key Questions.**
3. Bertaglia E, Fassini G, Anselmino M, et al. Comparison of ThermoCool Surround Flow catheter versus ThermoCool catheter in achieving persistent electrical isolation of pulmonary veins: a pilot study. Journal of Cardiovascular Electrophysiology. 2013 Mar;24(3):269-73. PMID: 23210452. **Not a comparison of interest.**
4. Bessiere F, Chevalier P. Pulmonary vein hematoma after atrial fibrillation cryoablation: a new complication. Heart Rhythm. 2013 Sep;10(9):1359. **Wrong study type (case-report).**
5. 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 Nov;8(11):1661-6. PMID: 21699857. **N < 1,000, case-series.**
6. Boho A, Misikova S, Spurny P, et al. Complications of circumferential pulmonary vein isolation using the cryoballoon technique: Incidence and predictors. International Journal of Cardiology. 2014 Feb 1;171(2):217-23. **Case-series, n < 1,000.**
7. Bordignon S, Chun KR, Gunawardene M, et al. Comparison of balloon catheter ablation technologies for pulmonary vein isolation: the laser versus cryo study. Journal of Cardiovascular Electrophysiology. 2013 Sep;24(9):987-94. **Investigational device / not FDA approved.**
8. Brodsky MA. Letter by Brodsky regarding article "Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses". Circ. 2009 Dec;2(6):e44; author reply e5-6. PMID: 20009071. **Not a comparison of interest.**
9. Bunch TJ, May HT, Bair TL, et al. Atrial fibrillation ablation patients have long-term stroke rates similar to patients without atrial fibrillation regardless of CHADS2 score. Heart Rhythm. 2013 Sep;10(9):1272-7. PMID: 23835257. **Wrong comparison, no safety data.**
10. Camm AJ, Breithardt G, Crijns H, et al. Real-life observations of clinical outcomes with rhythm- and rate-control therapies for atrial fibrillation RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). Journal of the American College of Cardiology. 2011 Jul 26;58(5):493-501. PMID: 21777747. **Not an intervention of interest.**
11. Chambers D, Rodgers M, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. J Clin Epidemiol. 2009 Dec;62(12):1253-60.e4. PMID: 19349144. **Not a comparison of interest.**
12. Chang CH, Lin JW, Chiu FC, et al. Effect of radiofrequency catheter ablation for atrial fibrillation on morbidity and mortality: a nationwide cohort study and propensity score analysis. Circ. 2014 Feb;7(1):76-82. **Wrong comparison, no safety data.**
13. Da Costa A, Thevenin J, Roche F, et al. Results from the Loire-Ardeche-Drome-Isere-Puy-de-Dome (LADIP) Trial on Atrial Flutter, a multicentric prospective randomized study comparing amiodarone and radiofrequency ablation after the first episode of symptomatic atrial flutter. Circulation. 2006;114(16):1676-81. PMID: CN-00613280. **Not a population of interest.**
14. De Ponti R, Lumia D, Marazzi R, et al. Left atrial diverticula in patients undergoing atrial fibrillation ablation: morphologic analysis and clinical impact. Journal of Cardiovascular Electrophysiology. 2013 Nov;24(11):1232-9. **Case-series, n < 1,000.**
15. Fasol R, Meinhart J, Binder T. A modified and simplified radiofrequency ablation in patients with mitral valve disease. J Thorac Cardiovasc Surg. 2005 Jan;129(1):215-7. PMID: 15632848. **No outcomes of interest.**

16. Gaita F, Leclercq JF, Schumacher B, et al. Incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation may change according to technology used: comparison of irrigated radiofrequency, multipolar nonirrigated catheter and cryoballoon. Journal of Cardiovascular Electrophysiology. 2011 Sep;22(9):961-8. PMID: 21453372. **Not an outcome of interest.**

17. Giovannib F, Massimo M, Lucia De L, et al. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. Journal of Cardiovascular Electrophysiology. 2009;20(1):22-8. PMID: CN-00866400 NEW. **Same population as a prior included study (Packer, 2013).**

18. Haeusler KG, Koch L, Herm J, et al. 3 Tesla MRI-detected brain lesions after pulmonary vein isolation for atrial fibrillation: results of the MACPAF study. Journal of Cardiovascular Electrophysiology. 2013 Jan;24(1):14-21. PMID: 22913568. **Investigational device / not FDA approved.**

19. Hanley CM, Esberg D, Kowey PR. Ablation versus drugs: what is the best first-line therapy for paroxysmal atrial fibrillation? Antiarrhythmic drugs are outmoded and catheter ablation should be the first-line option for all patients with paroxysmal atrial fibrillation: con. Circ. 2014 Aug;7(4):747-54. **Wrong study type (comment/editorial/review).**

20. Herm J, Fiebach JB, Koch L, et al. Neuropsychological effects of MRI-detected brain lesions after left atrial catheter ablation for atrial fibrillation: long-term results of the MACPAF study. Circ. 2013 Oct;6(5):843-50. PMID: 23989301. **Investigational device / not FDA approved.**

21. Hindricks G, Packer DL. Moving catheter ablation forward from paroxysmal to persistent atrial fibrillation: progress, limitations, and surprises of the SARA trial. European heart journal. 2014 Feb;35(8):482-4. **Wrong study type (comment/editorial/review).**

22. Hussein AA, Wazni OM, Harb S, et al. Radiofrequency ablation of atrial fibrillation in patients with mechanical mitral valve prostheses safety, feasibility, electrophysiologic findings, and outcomes. Journal of the American College of Cardiology. 2011 Aug 2;58(6):596-602. PMID: 21798422. **N < 100 patients.**

23. Jones DG, Wong T. Catheter ablation versus rate control for atrial fibrillation: what have we learnt from the ARC-HF trial?. [Review]. Future Cardiology. 2013 Sep;9(5):599-602. **Wrong study type (comment/editorial/review).**

24. Kaba RA, Cannie D, Ahmed O. RAAFT-2: Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation. Global Cardiology Science and Practice. 2014;2PMID: CN-01002382 NEW. **Wrong study type (review of included study, Morillo).**

25. 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. 2009 Oct;2(5):481-7. PMID: 19843915. **Not a comparison of interest.**

26. Khaykin Y, Wang X, Natale A, et al. Cost comparison of ablation versus antiarrhythmic drugs as first-line therapy for atrial fibrillation: an economic evaluation of the RAAFT pilot study. Journal of Cardiovascular Electrophysiology. 2009 Jan;20(1):7-12. PMID: 18803564. **Not a study type of interest.**

27. Khurram IM, Dewire J, Mager M, et al. Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation. Heart Rhythm. 2013 Dec;10(12):1843-9. **Case-series, n < 1,000.**

28. Kim JB, Cho W-C, Jung SH, et al. Alternative energy sources for surgical treatment of atrial fibrillation in patients undergoing mitral valve surgery: microwave ablation vs cryoablation. J Korean Med Sci. 2010 Oct;25(10):1467-72. PMID: 20890428. **Not a comparison of interest.**

29. Koch L, Haeusler KG, Herm J, et al. Mesh ablator vs. cryoballoon pulmonary vein ablation of symptomatic paroxysmal atrial fibrillation: results of the MACPAF study. Europace. 2012 Oct;14(10):1441-9. PMID: 22523379. **Investigational device / not FDA approved.**

30. Kosiuk J, Nedios S, Kornej J, et al. Impact of left atrial appendage morphology on peri-interventional thromboembolic risk during catheter ablation of atrial fibrillation. Heart Rhythm. 2014;11(9):1522-7. PMID: CN-01002159 NEW. **Case-series, n < 1,000.**

31. Kuhne M, Schaer B, Ammann P, et al. Cryoballoon ablation for pulmonary vein isolation in patients with paroxysmal atrial fibrillation. Swiss Med Wkly. 2010 Apr 17;140(15-16):214-21. PMID: 20407957. **N < 100 patients, observational study.**

32. Li X, Wissner E, Kamioka M, et al. Safety and feasibility of transseptal puncture for atrial fibrillation ablation in patients with atrial septal defect closure devices. Heart Rhythm. 2014 Feb;11(2):330-5. **Case-series, n < 1,000.**

33. Lin YJ, Tai CT, Chang SL, et al. Efficacy of additional ablation of complex fractionated atrial electrograms for catheter ablation of nonparoxysmal atrial fibrillation. Journal of Cardiovascular Electrophysiology. 2009 Jun;20(6):607-15. PMID: CN-00723024 UPDATE. **N < 100 patients, observational study.**

34. Lin Z, Shan ZG, Liao CX, et al. The effect of microwave and bipolar radio-frequency ablation in the surgical treatment of permanent atrial fibrillation during valve surgery. Thorac Cardiovasc Surg. 2011 Dec;59(8):460-4. PMID: 21692021. **Not a comparison of interest.**

35. Linhart M, Bellmann B, Mittmann-Braun E, et al. Comparison of cryoballoon and radiofrequency ablation of pulmonary veins in 40 patients with paroxysmal atrial fibrillation: a case-control study. Journal of Cardiovascular Electrophysiology. 2009 Dec;20(12):1343-8. PMID: 19656254. **N < 100 patients, observational study.**

36. 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. Journal of Interventional Cardiac Electrophysiology. 2008 Dec;23(3):167-73. PMID: 18810622. **Same population as prior included study (Lan, 2009).**

37. Magnani JW, Benjamin EJ. Where do we come from? Where are we going? Adverse outcomes in catheter ablation for atrial fibrillation. Circ. 2014 Apr;7(2):195-7. **Wrong study type (comment/editorial/review).**

38. Malmborg H, Lonnerholm S, Blomstrom P, et al. Ablation of atrial fibrillation with cryoballoon or duty-cycled radiofrequency pulmonary vein ablation catheter: a randomized controlled study comparing the clinical outcome and safety; the AF-COR study. Europace. 2013 Nov;15(11):1567-73. PMID: 23703361. Wrong intervention (phased RFA). **Investigational device/ not FDA approved.**

39. Marrouche NF, Guenther J, Segerson NM, et al. Randomized comparison between open irrigation technology and intracardiac-echo-guided energy delivery for pulmonary vein antrum isolation: procedural parameters, outcomes, and the effect on esophageal injury. Journal of Cardiovascular Electrophysiology. 2007 Jun;18(6):583-8. PMID: 17490437. **Not a study type of interest.**

40. Martin F, Jan C, Renata N, et al. Pulmonary vein isolation using segmental versus electroanatomical circumferential ablation for paroxysmal atrial fibrillation: over 3-year results of a prospective randomized study. Journal of Interventional Cardiac Electrophysiology. 2008;22(1):13-21. PMID: CN-00873182 NEW. **Not a study type of interest.**

41. Metzner A, Wissner E, Schoonderwoerd B, et al. The influence of varying energy settings on efficacy and safety of endoscopic pulmonary vein isolation. Heart Rhythm. 2012 Sep;9(9):1380-5. PMID: 22472520. **Not a study type of interest.**

42. Neumann T, Kuniss M, Conradi G, et al. MEDAFI-Trial (Micro-embolization during ablation of atrial fibrillation): comparison of pulmonary vein isolation using cryoballoon technique vs. radiofrequency energy. Europace. 2011 Jan;13(1):37-44. PMID: 20829189. **N < 100 patients, observational study.**

43. Phan K, Xie A, La Meir M, et al. Surgical ablation for treatment of atrial fibrillation in cardiac surgery: a cumulative meta-analysis of randomised controlled trials. [Review]. Heart. 2014 May;100(9):722-30. **Wrong intervention (surgical ablation), SR.**

44. Piccini JP, Stevens SR, Lokhnygina Y, et al. Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. Journal of the American College of Cardiology. 2013 May;61(19):1998-2006. PMID: CN-00877029 NEW. **No outcomes of interest.**

45. Richter B, Gwechenberger M, Socas A, et al. Frequency of recurrence of atrial fibrillation within 48 hours after ablation and its impact on long-term outcome. American Journal of Cardiology. 2008 Mar 15;101(6):843-7. PMID: 18328850. **Not an intervention of interest.**

46. Roberts A. Atrial fibrillation: Catheter ablation as a first-line AF therapy: the RAAFT-2 trial. Nature Reviews Cardiology. 2014 Apr;11(4):188. **Wrong study type (comment/editorial/review).**

47. Sauren LD, Van Belle Y, De Roy L, et al. Transcranial measurement of cerebral microembolic signals during endocardial pulmonary vein isolation: comparison of three different ablation techniques. Journal of Cardiovascular Electrophysiology. 2009 Oct;20(10):1102-7. PMID: 19549035. **N < 100 patients, observational study.**

48. Schmidt B, Gunawardene M, Krieg D, et al. A prospective randomized single-center study on the risk of asymptomatic cerebral lesions comparing irrigated radiofrequency current ablation with the cryoballoon and the laser balloon. Journal of Cardiovascular Electrophysiology. 2013 Aug;24(8):869-74. PMID: 23601001. **No outcomes of interest.**

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Appendix D. Sample Data Extraction Forms

Key Questions Addressed

Publications

Design:

1. Study design (RCT, prospective nonrandomized trial, retrospective nonrandomized trial)
2. Direct funding source
3. Conflict(s) of interest (CoI)
4. Country
5. Number of centers
6. Study objective
7. Inclusion Criteria
8. Exclusion criteria
9. Enrollment period (MM/YYYY – MM/YYYY)
10. Number of patients approached/considered
11. Number of patients eligible
12. Number of patients enrolled
13. Complete follow-up % (n/N)
14. Length follow-up
15. 100% of patients have the following: (Paroxysmal AF, Persistent AF, Permanent AF, Previously failed rate or rhythm control medical therapy, Medicare population, Women, Race/ethnicity, heart failure, hypertension, coronary artery disease, diabetes, kidney disease, hypertrophic cardiomyopathy, thyroid disease, pulmonary disease, obstructive sleep apnea, enlarged left atrium, other heart disease, high risk for stroke or bleeding events, stroke risk categories, history of prior stroke, obesity, atrial fibrosis, other)
16. Comments

Arms

Arm Details:

1. Number of patients enrolled
2. Number of patients treated
3. Number of patients who completed follow-up
4. Was treatment a first or second-line therapy?
5. Ablation: approach(es) (% (n/N))
6. Goal of the isolation/ablation procedure
7. Ablation successful (% (n/N))
8. Ablation: catheter tip details
9. Ablation: max energy (W)
10. Ablation: max temp (°C)
11. Ablation: total procedural time (min)
12. Ablation: total fluoroscopy time (min)
13. Ablation: mapping details
14. Was intracardiac echocardiography used?

15. Pre-procedural imaging details
16. Re-ablation
17. Ablation: other details
18. Rhythm or rate control meds: general info and duration
19. Rhythm or rate control meds: drug (dosage) (% (n/N))
20. Cardioversion performed?
21. Anticoagulant(s): drug (dosage) (usage period)
22. Blanking period used?
23. Action if AF recurred (specify length of time after initiation of initial treatment)
24. Was crossover permitted?
25. Other intervention details
26. Comments

Baselines:

1. Which population does this study describe? (general, medicare)
2. Age (mean +/- SD)
3. Male: n/N (%)
4. Race/ethnic group(s) (% (n/N))
5. Atrial fibrillation (paroxysmal AF, persistent AF, permanent AF)
6. Duration of symptoms (mean +/- SD)
7. Echocardiographic parameters
8. Comorbidities (% (n/N))

Outcomes

1. Outcome title
2. Type (continuous, categorical, other)
3. Units
4. Follow-up time points
5. Subgroups
6. Outcome description
7. Notes

Outcome Details

Results

1. Varied based on outcome

Adverse Events

2. Title
3. Description
4. n/N (%)
5. follow-up

Quality:

1. Randomization sequence (RCTs only)
2. Allocation concealment (RCTs only)

3. Intention to treat (RCTs only)
4. Blinded outcome assessment
5. Patients blinded to treatment received
6. Attrition acceptable and comparable between groups
7. Controlled for confounding (RCTs only)
8. Controlled for confounding (nonrandomized comparative studies)
9. Full reporting on prespecified outcomes
10. Quality Guideline used
11. Current overall rating
12. Notes on this rating

Appendix E. Evidence Tables

Table E1. Demographics of Included RCTs Comparing Radiofrequency Catheter Ablation versus Medical Therapy in Patients with Paroxysmal Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Cosedis Nielsen, 2012[54] Denmark, Finland, Sweden, Germany	• RCT • Fair Quality • Multicenter (# of sites NR) • AADs used only in medical treatment group • 100% 1st line therapy	N = 294 70.1% male Age = 55 years RFA: n = 146 68.5% male Age = 56 ± 9 years Med: n =148 71.6% male Age = 54 ± 10 years Special Population: No	Left atrial diameter: • RFA: 40 ± 6 mm (echocardiography) • Med: 40 ± 5 mm (echocardiography) AF Duration: NR	FU: 93.5% (275/294); 3, 6, 12, 18, 24 mo Blanking period: 3 months % Crossover: • RFA: n = 13 (9%); circumstances NR; timing NR ("by 24 months") • Med: n = 54 (37%); if antiarrhythmic drug therapy failed (i.e. recurrent AF); first ablation procedure at a mean of 8.7 ± 6.5 months after inclusion in the study	Ablation: • Circumferential PVI (%NR) • Roof of the atrium (%NR) • Cavotricuspid and mitral isthmuses (optional) (%NR) • AADs NR after the blanking period Medical Therapy: • Flecainide 200 mg/day or Propafenone 600 mg/day 89.7% (131/146) • Amiodarone 200 mg/day or Sotalol 160 mg/day 10.3% (15/146) Mapping: • Electroanatomical mapping (CARTO, Biosense Webster)

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Jais, 2008[55] Canada, USA, France	• RCT • Fair quality • Multicenter (4 sites) • AADs used only in medical treatment group • 100% 2nd line therapy	N = 112 83.9% male Age = 51.1 years RFA: n = 53 84.9% male Age = 49.7 ± 10.7 years Med: n = 59 83.1% male Age = 52.4 ± 11.4 years Special Population: No	Left atrial diameter: • RFA: 39.5 ± 5.6 mm (transthoracic echocardiography) • Med: 40.0 ± 5.7 mm (transthoracic echocardiography) • Total: 39.8 ± 5.6 mm (transthoracic echocardiography) AF Duration: (median and IQR) • RFA: 4.0 (1.0 - 12.0) hours • Med: 6.0 (2.0 - 15.0) hours • Total: 5.5 (1.0 - 12.0) hours	FU: 95.5% (107/112); 3, 6, 12 mo Blanking period: 90 days % Crossover: • RFA: 9.4% (5/53); permitted after 3 months in case of failure (recurrent AF lasting >3 minutes and occurring after the stabilization period) • Med: 62.7% (37/59); permitted after 3 months in case of failure (recurrent AF lasting >3 minutes and occurring after the stabilization period)	Ablation: • Left PVI 100% (53/53) • Right PVI 100% (53/53) • Right inferior vein isolation 100% (53/53) • Cavotricuspid isthmus 64.2% (34/53) • Roof of the left atrium 17% (9/53) • Mitral isthmus 30.2% (16/53) • Foci from nonvenous structures 22.6% (12/53) • AADs NR Medical Therapy (drugs administered either alone or in combination): • Amiodarone (loading dose of 600 mg/d for 21 days followed by 200 mg/d was recommended, with an increase to 300 mg daily if required) (%NR) • Quinidine (%NR) • Disopyramide (%NR) • Flecainide (%NR) • Propafenone (%NR) • Cibenzoline (%NR) • Dofetilide (%NR) • Sotalol (%NR) Mapping: • After transseptal access to the left atrium, isolation of all 4 pulmonary veins was performed using circumferential applications of radiofrequency energy and verified with a circular mapping catheter (Lasso Catheter, Biosense Webster, Inc, Diamond Bar, Calif)
Morillo (2014)[56] USA, Canada, Germany, Czech Republic, Italy	• RCT • Fair quality • Multicenter (16 sites) • AADs used only in medical treatment group • 100% 1st line therapy	N = 127 75.6% male Age = 53.3 years RFA: n = 66 77.3% male Age = 56.3 ± 9.3 years Med: n = 61 73.8% male Age = 54.3 ± 11.7 years Special Population: No	Left atrial diameter: • RFA: 40 mm ± 5 mm (mode NR) • Med: 43 cm ± 5 mm (mode NR) AF Duration: • RFA: 47.4 ± 97.9 (IQR: 5.0 - 40.0) episodes in the past 6 months • Med: 33.0 ± 48.7 (IQR: 4.0 - 40.0) episodes in the past 6 months	FU: 82.7% (105/127); 12, 24 mo Blanking period; 90 days % Crossover: • RFA: 9.1% (6/66), circumstances NR • Med: 42.6% (26/61); If treatment had failed, defined as drug discontinuation due to intolerance, adverse events, or inefficacy (i.e. recurrence of documented AF or any atrial tachyarrhythmias lasting >30 seconds)	Ablation: • Circumferential PVI 98.5% (65/66) • PVI + cavotricuspid isthmus (%NR) • PVI + CFAE (%NR) • PVI+ roof line (%NR) • Beta-blockers 60.6% (at baseline) • Calcium channel blockers 21.2% (at baseline) • AADs NR Medical Therapy: • Flecainide 175.8 ± 50.9 mg/d; 69% • Propafenone 487.7 ± 122.4 mg/d; 25% • Beta-blockers 59% (at baseline) • Calcium channel blockers 21.3% (at baseline) Mapping: • Nonfluroscopic mapping systems were used in 86% of patients

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Pappone (2006)[57] Italy	• RCT • Fair Quality • Single center • AADs used only in medical treatment group • 100% 2nd line therapy	N = 198 67.2% male Age = 56 years RFA: n = 99 69.7% male Age = 55 ± 10 years Med: n = 99 64.6% male Age = 57 ± 10 years Special Population: No	Left atrial diameter: • RFA: 40 ± 6 mm (mode NR) • Med: 38 ± 6 mm (mode NR) AF Duration: • RFA: 6 ± 4 (episodes/ mo); 6 ± 4 years • Med: 6 ± 6 (episodes/ mo); 6 ± 6 years • Total: 3.4 (episodes/ mo); 6 ± 5 years	FU: 100% (198/198); 12 mo Blanking period: 6 weeks % Crossover: • RFA: 5/99 (5.1%) Recurrence of symptomatic AF (documented by transtelephonic ECG monitoring), crossover > 6 weeks after first ablation (80% (4/5) flecainide; 20% (1/5) sotalol) • Med: 42/99 (42.4%) Recurrence of symptomatic or asymptomatic AF (documented by transtelephonic ECG monitoring), after 2 trials of medical therapy, patients could be considered for crossover to ablation (> 3 months after blanking period).	Ablation: • Circumferential PVI 100% (99/99) • PVI + cavotricuspid isthmus 100% (99/99) • AAD usage NR Medical Therapy: • Amiodarone, initial loading dose: 600 mg/day for the first week, 400 mg/day in the second week, then maintenance dose 200 mg/day, (single drug: 54.1% (33/61), in combination: 45.9% (28/61)) • Flecainide, initial dose: 100 mg/12 hrs (%NR) • Sotalol, initial dose: 80 mg/8 hrs (%NR); Mapping: • CARTO (Biosense-Webster, Diamond Bar, California) • NavX (Endocardial Solutions Inc., St. Paul, Minnesota)
Pappone (2011)[58] Italy	• RCT • Fair Quality • Single Center • AADs used only in medical treatment group • 100% 2nd line therapy	N = 198 67.2% male Age = 56 years RFA: n = 99 69.7% male Age = 55 ± 10 years Med: n = 99 64.6% male Age = 57 ± 10 years Special Population: No	Left atrial diameter: • RFA: 40 ± 6 mm (mode NR) • Med: 38 ± 6 mm (mode NR) AF Duration: • RFA: 6 ± 4 years • Med: 6 ± 6 years	FU: 95% (188/198); 4 years Blanking Period: 6 weeks % Crossover: • RFA: NR • Med: 87/99 (87.9%) by 4 years f/u; After intolerance, serious side effects, or failure of AADs in different classes and/or combination or after symptomatic and sustained episodes of arrhythmia recurrences (> 12 hours)	Ablation: • PVI + mitral isthmus and between contralateral superior veins (%NR) • AADs NR Medical Therapy: • Flecainide (initial dosage of 100 mg every 12 hours, maximum tolerable dosage 300mg/day); • Sotalol (initial dose of 80 mg every 8 hours, maximum tolerable dosage 320 mg/day) • Amiodarone (initial loading of 600 mg/d for the first week, 400 mg/d for the next week, after which a daily maintenance dose of 200 mg a day was given) Mapping: • 3D-electoanatomic mapping systems (CARTO (Biosense-Webster, Diamond Bar, California) • NavX (Endocardial Solutions Inc., St. Paul, Minnesota))

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Wazni (2005)[59] Italy & Germany	• RCT • Fair Quality • Multicenter (3 sites • AADs used only in medical treatment group • 100% 1st line therapy	N = 70 % male NR Age = 53.5 years RFA: n = 33 % male NR Age = 53 ± 8 years Med: n =37 % male NR Age = 54 ± 8 years Special Population: No	Left atrial diameter: • RFA: 41 ± 8 mm (mode NR) • Med: 42 ± 7 mm (mode NR) AF Duration: • RFA:5 ± 2 months • Med: 5 ± 2.5 months	FU: 67/70 (95.7%); 6, 12 mo Blanking period: Initial 2 mo after enrollment % Crossover: • RFA: after 1 year, 3.1%(1/32) started antiarrhythmic drugs to maintain sinus rhythm • Med: after 1 year, 51.4% (18/35) patients underwent ablation because of recurrent AF	Ablation: • PVI of all 4 veins 100% (33/33) • AADs NR Medical Therapy: • Flecainide (100-150mg twice per day) • Propafenone (225-300mg three times per day) • Sotalol (120-160mg twice per day) Mapping: • Multipolar mapping catheter to record right atrial and coronary sinus electrocardiograms
Wilber (2010)[60] USA, Canada, "Latin America", Europe (NR)	• RCT • Fair Quality • Multicenter (9 sites) • AADs used only in medical treatment group • 100% 2nd line therapy	N = 158 66.5% male Age = 55.7 RFA: n = 103 68.9% male Age = 55.5 (95% CI: 53.7-57.3) years Med: n = 56 62.3% male Age = 56.1 (95% CI: 52.9-59.4) years Special Population: No	Left atrial diameter: • RFA: mean (SD) 40.0 (38.9-41.1) mm (mode NR) • Med: mean (SD) 40.5 (39.0-41.9) mm (mode NR) AF Duration: • RFA: median (IQR) 5.4 (4.3-6.5) years • Med: median (IQR) 6.2 (4.6-7.9) years	FU: NR; 3, 12 mo Blanking Period: RFA: 3 months Med: 14 days % Crossover: • RFA: n = 5; circumstances NR • Med: n = 36 (mean time 3.9 (95% CI, 3.1-4.6) months from the onset of the effectiveness evaluation period); after 90 days of therapy if the treatment failed	Ablation: • PVI 100% (103/103) • PVI + cavotricuspid isthmus 35.9% (37/103) • PVI + superior vena cava 16.5% (17/103) • PVI + other left/ right atrial foci 16.5% (17/103) • PVI + at least 1 left atrial linear lesion (including mitral isthmus and roof lines) 22.3% (23/103) • Use of AADs NR Medical Therapy: • Flecainide 36% (20/56) • Propafenone 41% (23/56) • Sotalol 20% (11/56) • Dofetilide 4% (2/56) • Dosages NR Mapping: • Carto Navigation System (Biosense Webster)

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; CFAE = Complex fractionated atrial electrograms; CI = Confidence Interval; ECG = Electrocardiography; FU = Followup; IQR = Interquartile range; NR = Not reported; PVI = Pulmonary Vein Isolation; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SD = Standard deviation.

Table E2. Demographics of Included RCTs Comparing Radiofrequency Catheter Ablation versus Medical Therapy in Patients with Persistent Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Hunter (2014)[61]	• RCT (CAMTAF Trial) • Fair quality • Single center • AADs used in both treatment groups • 100% 1st line therapy	N = 50 96% male Age = 57.4 years RFA: n = 26 96.1% male Age = 55 ± 12 years Med: n = 24 95.8% male Age = 60 ± 10 years Special Population: Yes, 100% patients have had heart failure	Left atrial diameter: • RFA: 5.2 ± 1.1 cm (mode NR) • Med: 5.0 ± 1.0 cm (mode NR) AF Duration: • RFA: 24 (17 – 33) months (median, IQR) • Med: 24 (12 – 48) months (median, IQR)	FU: 96% (48/50); 6 mo, ablation only 12 mo Blanking period: RFA: 3 mo Med: NR % Crossover: NR	Ablation: • Pulmonary veins isolated by wide area circumferential ablation, with lesions placed 1 to 2 cm outside pulmonary vein to isolate them as ipsilateral pairs 96.1% (25/26) • Linear lesions added at mitral isthmus and roof if patients remained in AF (%NR) • Cavotricuspid isthmus line added only in patients with history of typical right atrial flutter (%NR) • If AF organized into atrial tachycardia, was mapped and ablated (%NR) • If sinus rhythm not restored following these lesions, patient was cardioverted with DC shock (%NR) • Heparin (dose NR) 96.1% (25/26) • AADs (type, dose NR) not stopped during procedure 96.1% (25/26) • Same “baseline” drugs as medical therapy 96.1%(25/26) Medical Therapy: • Beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers (dose NR) 92% (23/24) • Spironolactone (if NYHA class ≥ III and LV EF < 35%), some patients (%NR) • Warfarin with a target international normalized ration of 2 – 3 (dose NR) 92% (23/24) Mapping: • 3-dimensional mapping system either Carto (Biosense Webster Inc, Diamond Bar, CA) or Ensite NavX (St Jude Medical, Minneapolis, MN), with computerized tomography or MRI image integration

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
MacDonald (2011)[62] Scotland	• RCT • Fair Quality • Multicenter (6 sites) • AADs used in both treatment groups • 100% 1st line therapy	N = 41 78% male Age = 63.3 years RFA: n = 22 77% male Age = 62.3 ± 6.7 years Med: n = 19 79% male Age = 64.4 ± 8.3 years Special Population: Yes, 100% patients have had heart failure	Left atrial diameter: • RFA: NR • Med: NR AF Duration: • RFA: 44 ± 36.5 months • Med: 64 ± 47.6 months	FU: 92.7% (38/41); 6 mo Blanking period: RFA: 3 mo Med: NR % Crossover: NR	Ablation: • Electrical isolation of all four pulmonary veins, with an additional adjoining roof line and further ablation at sites of CFAEs 100% (21/21) • Additional atrial flutter ablation 9.5% (2/21) • Amiodarone (dosage NR) 100% (21/21) • Same “baseline” drugs as medical therapy Medical Therapy: • Digoxin (dosage NR) (number of patients who received drug for heart rate > 80 bpm, NR) • Baseline: • Digoxin (dosage NR) 47% (9/19) • Aldosterone antagonist (dosage NR) 16% (3/19) • Beta blocker (dosage NR) 95% (18/19) • Angiotensin-converting enzyme or angiotensin II receptor blocker (dosage NR) 95% (18/19) Mapping: • Pulmonary vein and left atrial anatomy was delineated with pulmonary venous angiography and three-dimensional reconstruction of the left atrium using Nav-X mapping system (St Jude Medical, Minnesota, USA) • Pulmonary vein recordings were performed with a duodecapolar variable-diameter circular mapping catheter (Lasso (Biosense Webster, California, USA) or Inquiry Optima (St Jude Medical))
Mont (2014)[63] Spain	• RCT • Fair Quality • Multicenter (8 sites) • AADs used in both treatment groups • 100% 2nd line therapy	N = 146 77.4% male Age = 55 years RFA: n = 93 77.5% male Age = 55 ± 9 years Med: n = 48 77.0% male Age = 55 ± 9 years Special Population: No	Left atrial diameter: • RFA: 41.3 ± 4.6 mm (electroanatomic mapping system (CARTO)) • Med: 42.7 ± 5.1 mm (electroanatomic mapping system (CARTO)) AF Duration: • RFA: NR • Med: NR	FU: 98% (143/146); 6, 12 mo Blanking Period: 3 mo % Crossover: • RFA: 35.7% (35/98), to relieve symptoms of paroxysmal AF or undocumented palpitations; crossovers considered those patients who received medical therapy BEFORE reaching the primary endpoint (12 months) • Med: 0/48 (0%); 23 patients (47.9%) underwent ablation AFTER reaching the primary endpoint (12 months)	Ablation: • PVI 100% (93/93) • PVI + cavotricuspid isthmus 2% (2/93) • PVI + mitral isthmus line 3.1% (3/93) • PVI+ roof line 23.4% (23/93) • PVI + CFAE 8.1% (8/93) • All patients received AADs (Amiodarone, “class Ic, or another class III drug”) Medical Therapy: • Amiodarone • Flecainide plus diltiazem or beta-blockers Mapping: • A 3D map was constructed using an electroanatomic mapping system (CARTO, Biosense Webster, Diamond Bar, CA, USA or NAVX, St Jude Corporation, St Paul, MN, USA)

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Oral (2006)[64] USA, Italy	• RCT • Multicenter (2 sites) • AADs used only in medical treatment group • 100% 2nd line therapy	N = 146 88% male Age = 56.4 years RFA: n = 77 87% male Age = 55 ± 9 years Med Tx: n = 69 90% male Age = 58 ± 8 years Special Population: No	Left atrial diameter: • RFA: 45 ± 6 mm (mode NR) • Med: 45 ± 5 (mode NR) AF Duration: • RFA: 5 ± 4 years • Med Tx: 4 ± 4 years	FU: 100% (146/146), 12 months Blanking Period: NR % Crossover: • RFA: 0% (0/77) withdrew consent • Med Tx: 77% (53/69) crossed over a mean of 128 ± 57 days after the first cardioversion n	Ablation: • PVI: 100% (77/77) • PVI + cavotricuspid isthmus: 71% (55/77)
Jones (2013)[65] UK	• RCT • Fair Quality • Multicenter (2 sites) • AADs used only in medical treatment group • Both 1st and 2nd line therapy	N = 52 87% male Age = 63 RFA: n = 26 81% male Age = 64 ± 10 years Med: n = 26 92% male Age = 62 ± 9 years Special Population: 100% of patients have had heart failure	Left atrial diameter: • RFA: 50 ± 6 mm (m-mode) • Med: 46 ± 7 mm (m-mode) AF Duration: • RFA: 51 ± 39 months (time since AF dx); 23 ± 22 months (duration of continuous AF) • Med: 51 ± 76 months (time since AF dx); 24 ± 29 months (duration of continuous AF)	FU: 96% (50/52); 3, 6, 12 months Blanking period: RFA: 2 months Med: none % Crossover: • RFA: circumstances NR; 1 w/drew consent and continued existing therapy • Med: circumstances NR; 1 had ablation at 4 mos	Ablation (performed in a stepwise manner): • PVI (%NR) • Linear ablation to the left atrial roof and mitral isthmus (%NR) • Left atrial CFAE (%NR) • No AADs after blanking period Medical therapy: • Beta-blockers and/ or digoxin (dosage NR); goal was mean HR ≤80 bpm resting and ≤110 bpm after 6 minute walk Mapping: • NavX mapping system with an AFoucsII catheter (St. Jude Medical) .

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; CFAE = Complex fractionated atrial electrograms; CI = Confidence Interval; ECG = Electrocardiography; FU = Followup; IQR = Interquartile range; NR = Not reported; PVI = Pulmonary Vein Isolation; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SD = Standard deviation.

Table E3. Demographics of Included RCTs Comparing Radiofrequency Catheter Ablation versus Medical Therapy in Patients with Paroxysmal or Persistent Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Forleo (2009)[66] Italy	• RCT • Fair Quality • Multicenter (3 sites) • AADs used only in medical treatment group • 100% 2nd line therapy	N = 70 61% male Age = 64 RFA: n = 35 57.1% male Age = 63.2 ± 8.6 Med: n = 35 65.7% male Age = 64.8 ± 6.5 Special Population: Yes, 100% of patients have diabetes	AF Duration: • RFA: 41 (18-66) months (median, IQR) • Med: 36 (17-55) months (median, IQR) Left atrial diameter: • RFA: 44.3 ± 5.6 mm (mode NR) • Med: 45.2 ± 5.2 mm (mode NR)	FU: 100% (70/70); 2, 4, 6, 8, 10, 12 months Blanking Period: 5 weeks % Crossover: Not permitted	Ablation: • Circumferential PVI 100% (35/35) • Bidirectional cavotricuspid isthmus block 100% (35/35) • Mitral isthmus 23% (8/35) • Roofline ablation 9% (3/35) • AADs NR Medical Therapy: • Class IC 77% (27/35) • Sotalol 9% (3/35) • Amiodarone 63% (22/35) • Calcium channel antagonist (details NR) 17% (6/35) Mapping: • Nonfluoroscopic mapping (NavX mapping system (Endocaridal Solution Inc.) with the CARTO system (Biosense Webster))
Stabile (2006)[67] Italy	• RCT • Good Quality • Multicenter (# of sites NR) • AADs used in both treatment groups • 100% 2nd line therapy	N = 137 59.1% male Age = 62.3 years RFA: n = 68 54.4% male Age = 62.2 ± 9 years Med: n = 69 63.8% male Age = 62.3 ± 10 years Special Population: No	Left atrial diameter: • RFA: 46 ± 5 mm (mode NR) • Med: 45.4 ± 5.5 mm (mode NR) AF Duration • RFA: 5.1 ± 3.9 years • Med: 7.1 ± 5.9 years	FU: 97.1% (133/137); 13 mo Blanking Period: 1 month % Crossover: • RFA: NR • Med: 57.1% (36/63) AF relapses 3 months after AF recurrence	Ablation: • PVI + mitral isthmus, cavo-tricuspid isthmus, and circumferential PV ablation 100% (68/68), of these patients 13 patients had already undergone cavo-tricuspid ablations, only 55 of those procedures were completed during these trials • All patients received AADs (see medical therapy) Medical Therapy: • Amiodarone 209 ± 49 mg • Flecainide 191 ± 28 mg • Propafenone 750 ± 126 mg • Sotalol 184 ± 54 mg • Disopyramide (dosage NR) • Ace-inhibitors or angiotensin receptor blockers (dosage NR) • Verapamil or diltiazem (dosage NR) • Beta blockers (dosage NR) • Statins (dosage NR) Mapping: • Real-time 3D left atrium maps were reconstructed using a nonfluoroscopic navigation system (CARTO, Biosense-Webster Inc., Diamond Bar, California). Maps were acquired during pacing from the coronary sinus

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; CFAE = Complex fractionated atrial electrograms; CI = Confidence Interval; ECG = Electrocardiography; FU = Followup; IQR = Interquartile range; NR = Not reported; PVI = Pulmonary Vein Isolation; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SD = Standard deviation.

Table E4. Demographics of Included Observational Studies Comparing Radiofrequency Catheter Ablation versus Medical Therapy in Patients with Paroxysmal Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Lan (2009)[68]* China	• Prospective, comparative observational • Fair quality • Single center • AADs used only in medical treatment • 100% 2nd line therapy	N = 240 65% male Age = 59.0 years RFA: n = 120 66% male Age = 59.5 years Med: n = 120 64% male Age = 58.5 years Special Population: No	Left atrial diameter: • RFA: 34.66 mm (transthoracic echocardiogram; LA anteroposterior diameter was measured at end-systole on the M-mode image obtained from the parasternal long-axis view) • Med: 34.69 mm (transthoracic echocardiogram; LA anteroposterior diameter was measured at end-systole on the M-mode image obtained from the parasternal long-axis view) AF Duration: RFA: 2.63 years Med: 2.61 years	FU: %NR (n's NR); 3, 6, 9, 12 mo Blanking period: 1 month % Crossover: NR	Ablation: • CPVA 50% (60/120) • SPVI 50% (60/120) Medical Therapy: • Amiodarone (60/120), dosage 600 mg day for the first week, 400 mg day for the second week and 200 mg day thereafter • Amiodarone (same dosage as above) + losartan (60/120), 50 mg day for the first 2 weeks, See article for more dosage details Mapping: • NR
Sang (2013)[69] China	• Prospective, comparative observational • Fair quality • Single center • AADs used in both treatment groups • 100% 2nd line therapy	N = 175 68.1% male Age = 56.6 years RFA: n = 85 67.1% male Age = 55.9 ± 6.1 years Med: n = 90 69.1% male Age = 57.2 ± 5.4 years Special Population: LVEF <35%	Left atrial diameter: RFA: 39.0 ± 5.9 mm (mode NR) Med: 38.6 ± 6.2 mm (mode NR) AF duration: RFA: 90.1 ± 90.1 months Med: 86.9 ± 90.8 months	FU: 94.9% (166/175); 3, 6, 9, 12 mo Blanking Period: RFA: 3 months Med: NR % Crossover: NR	Ablation: • Modified Brockenbrough technique; Circumferential isolation of the right pulmonary vein (PV) antrum (PVA) was performed first, followed by isolation of the left PVA (%NR) • If there were neither contraindications nor intolerance, patients would receive AADs for 2 months after ablation and then discontinue them if no AF recurred, dosage NR, Prior to ablation all AADs except for amiodarone were discontinued in patients for ≥5 half-lives Medical Therapy: • Amiodarone 60.7% (51/84) • Propafenone 38.1% (32/84) • Sotalol 19% (16.84) • ≥2 AADs 16.7% (14/84) • Dosage NR Mapping: • Catheter guided by electroanatomic mapping system (CARTO XP, Biosense-Webster), PV isolation was sometimes confirmed with a circular mapping catheter (Lasso; Biosense-Webster)

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Yu (2012)[70] China	• Retrospective, comparative observational • Poor quality • Single center • AADs used in both treatment groups • 100% 2nd line therapy	N = 210 50.8% male Age = 55 years RFA: n = 98 50% male Age = 55.2 ± 6.5 years Med: n = 112 52% male Age = 54.9 ± 7 years Special Population: None	Left atrial diameter: RFA: 31.7 ± 1.9 mm (echocardiography) Med: 32 ± mm (echocardiography) AF duration: RFA: 2.4 ± 0.1 years Med: 2.3 ± 0.1 years	FU: 94.8% (199/210); 12 months Blanking period: RFA: 3 months Med: NR % Crossover: NR	Ablation • Circumferential PVI 100% (97/97) • All patients were discharged on previously ineffective AADs, and stopped after a blanking period of 3 months • Beta-blocker 27.8% (24/97) • Amiodarone 86% (84/97) • ACEI 81.4% (79/97) • ARB 8.3% (8/97) Medical Therapy • Beta-blocker 29.4% (30/102) • Amiodarone 89.2% (91/102) • ACEI 81.4% (83/102) • ARB 10.8% (11/102) • Digitalis 2% (2/102) Mapping • 3D left atrial maps and pulmonary vein profiles were reconstructed through a transseptal route using a nonfluoroscopic electrogeometric mapping system (CARTO, Biosense-Webster, Diamond Bar, CA, USA)

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; AMIO = amiodarone; CFAE = Complex fractionated atrial electrograms; CI = Confidence Interval; CPVA = circumferential pulmonary vein ablation; ECG = Electrocardiography; FU = Followup; IQR = Interquartile range; LO = losartan; NR = Not reported; PVI = Pulmonary Vein Isolation; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SD = Standard deviation; SPVI = segmental pulmonary vein isolation.
*Lan 2009: Age, AF duration, LA size, were calculated using a weighted mean of the two subgroups of each treatment group.

Table E5. Demographics of Included Observational Studies Comparing Radiofrequency Catheter Ablation versus Medical Therapy in Patients with Persistent Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Blandino (2013)[71] Italy	• Prospective, comparative observational • Fair quality • Number of centers NR • AADs used in both treatment groups • 100% 2nd line therapy	N = 412 72% male Age = 75.6 years RFA: n = 153 71% male Age = 75 ± 5 years Med: n = 259 72% male Age = 76 ± 6 years Special Population: Medicare population	Left Atrial diameter: RFA: 47 ± 5 mm (Doppler transthoracic echocardiography (TTE)) Med: 47 ± 6 mm (Doppler transthoracic echocardiography (TTE)) AF Duration: RFA: 6 ± 4 months Med: 6 ±4 months	FU: 100% (412/412); patients followed every 6 months after 12 month FU Mean: 60 ± 17 months Blanking period: RFA: "for group A patients, a 3-month blanking period was considered" Med: NR % Crossover: RFA: AF/AT recurrence; rate control approach 5.9% (9/153), ECV and continuation of previous AAD therapy 3.3% (5/153) Med: AF/AT recurrence; 1.9% (5/259)	Ablation • PVI + cavotricuspid isthmus100% (153/153) • Linear lesions interconnecting the upper PV ostia (roof line) and the left inferior PV with the mitral annulus (left isthmus line) 60% (92/153); only performed in cases of AF persistence despite PVI • AADs at the beginning of FU (patients continued the same regimen received before the procedure for at least 3 months): • Amiodarone 42% (64/153); dosage: 194 ± 42 mg • Flecainide 23% (35/153); dosage: 226 ± 20 mg • Propafenone 14% (22/153); dosage: 638 ± 125 mg • Sotalol 21% (32/153); dosage: 167 ± 32 mg Medical Therapy* • Amiodarone 45% (117/259); dosage: 233 ± 74 mg • Flecainide 22% (57/153); dosage: 253 ± 38 mg • Propafenone 21% (31/256); dosage: 665 ± 73 mg • Sotalol 21% (54/259); dosage: 194 ± 47 mg Mapping • 3D reconstruction of the left atrium was performed using the electroanatomic mapping system (Carto, Biosense Webster)

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; AMIO = amiodarone; CFAE = Complex fractionated atrial electrograms; CI = Confidence Interval; CPVA = circumferential pulmonary vein ablation; ECG = Electrocardiography; FU = Followup; IQR = Interquartile range; LO = losartan; NR = Not reported; PVI = Pulmonary Vein Isolation; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SD = Standard deviation; SPVI = segmental pulmonary vein isolation.

*Blandino: in patients without heart disease and severe left ventricular hypertrophy, IC class AAD were the first choice. In patients with coronary heart disease and normal left ventricular ejection fraction (LVEF), sotalol was preferred; in patients with severe LV hypertrophy or heart failure amiodarone was the preferred drug. No specific regimen was established, although physicians were encouraged to comply with published guidelines. When amiodarone was prescribed, a loading dose of 600 mg/d for 21 days followed by 200 mg/d was recommended.

Table E6. Demographics of Included Observational Studies Comparing Radiofrequency Catheter Ablation versus Medical Therapy in Patients with Paroxysmal or Persistent Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Reynolds (2012)[72]	• Retrospective comparative observational • From matched cohort administrative database (MarketScan Research Database, Thomson Reuters) • AF type NR • 100% 2nd line	N = 1602 61.7% male Age = ≥65 yrs: 48.2 (386) RFA: n = 801 60.9% male Age = NR Med: n = 801 62.5% male Age = NR Special Population: No	Left atrial diameter: NR AF Duration: NR	FU: 100%; 27 mo (mean) Blanking period: NR % Crossover: NR	Ablation: • PVI + superior vena cava 100% (85/85) Medical Therapy: • Rate control medications such as beta-blockers, nondihydropyridine calcium channel blockers, and digoxin (%NR) • AADs 100% • Warfarin (%NR) Mapping: NR
Rossillo (2008)[73] Italy	• Retrospective, comparative observational • Poor quality • Single center • AADs used only in medical treatment • 2nd line therapy for RFA group, NR for Med group	N = 170 84.7% male Age = 62 years RFA: n = 85 84% male Age = 62 ± 7.6 years Med: n = 85 84% male Age = 62 ± 7.6 years Special Population: No	Left atrial diameter: RFA: 44 ± 6 mm (mode NR) Med: 42 ± 7 mm (mode NR) AF Duration: RFA: 8 years, range (1-24) Med: NR	FU: %Nr (n's NR); 3 mo Mean: 16 ± 7 mo Blanking period: RFA: 8 weeks Med: NR % Crossover: NR	Ablation: • PVI + superior vena cavae 100% (85/85) • No AADs used unless recurrence developed Medical Therapy: • "All patients were pretreated with antiarrhythmic drug therapy to avoid early recurrences of atrial arrhythmias after electrical cardioversion" Mapping: • Mapping of the left atrium and pulmonary veins was carried out after approaching the left atrium via transseptal puncture

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Sonne (2009)[74] USA	• Retrospective, comparative observational • Poor Quality • AADs used in both treatment groups • 100% 2nd line therapy	N = 351 68.4% male Age = years RFA: n = 146 67.8% male Age = 67.2 ± 8 years Med: n = 205 68.8% male Age = 66.7 ± 7.7 years Special Population: Medicare population	Left atrial diameter: RFA:55 ± 8.7 (echocardiography) Med: 56 ± 8.7 (echocardiography) AF Duration: NR	FU: 89.4% (314/351) Mean: 69 ± 27 mo Blanking period: NR % Crossover: Crossover not permitted	Ablation • Pulmonary vein antrum isolation 100% (146/146) • Beta-blocker 32% (46/146) • Calcium channel blocker 18% (27/146) • ACE-inhibitor/ARB (7% (40/146) • Digoxin 13% (19/146) • Amiodarone 3% (4/146) • Sotalol 10% (15/146) • Dofetilide 8% (11/146) • Flecainide 4% (5/146) • Propafenone 3% (4/146) • Other AADs 3% (5/146) • Dosages NR Medical Therapy • Beta-blocker 32% (65/205) • Calcium channel blocker 6% (12/205) • ACE-inhibitor/ARB 21% (43/205) • Digoxin 16% (33/205) • Amiodarone 14% (29/205) • Sotalol 6% (13/205) • Dofetilide 1% (3/205) • Flecainide 3% (6/205) • Propafenone 1% (3/205) • Other AADs 0.4% (1/205) • Dosages NR Mapping • NR

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; AMIO = amiodarone; CFAE = Complex fractionated atrial electrograms; CI = Confidence Interval; CPVA = circumferential pulmonary vein ablation; ECG = Electrocardiography; FU = Followup; IQR = Interquartile range; LO = losartan; NR = Not reported; PVI = Pulmonary Vein Isolation; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SD = Standard deviation; SPVI = segmental pulmonary vein isolation.

Table E7. Study Characteristics of RCTs Comparing Radiofrequency Catheter Ablation versus Medical Therapy in Patients with Paroxysmal Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Cosedis Nielsen (2012)[54] Denmark, Finland, Sweden, Germany	• RCT • Fair Quality • Multicenter (# of sites NR) • AADs used only in medical treatment group • 100% 1st line therapy	• At least two episodes of symptomatic atrial fibrillation within the preceding 6 months • No episode of atrial fibrillation that was longer than 7 days (without spontaneous termination or cardioversion)	• Age of more than 70 years • Previous or ongoing treatment with class IC or class III antiarrhythmic drugs • Contraindication to both class IC and class III agents • Previous ablation for atrial fibrillation • Left atrial diameter of more than 50 mm • Left ventricular ejection fraction of less than 40% • Contraindication to oral anticoagulation therapy • Moderate-to-severe mitral valve disease • Severe heart failure (NYHA functional class III to IV at the time of enrollment) • Expected surgery for structural heart disease • Secondary atrial fibrillation (due to cardiac surgery, infection, or hyperthyroidism)	Primary • SF-36: mental component summary, physical component summary • Mortality (all cause) (timing of occurrence NR) • Mortality (cardiovascular) (timing of occurrence NR) • Transient ischemic attack (timing of occurrence NR) • Hospitalization/readmission for cardiovascular events (including AF) • Congestive heart failure • Myocardial infarction (timing of occurrence NR) • Ventricular tachycardia and implantation of an ICD Secondary • Freedom from recurrence (AF only) • Freedom from symptomatic recurrence (AF only) • Repeat ablation for AF • Repeat ablation for any arrhythmia (or cause NR) • Time to recurrent AF • Drug therapy: Bradycardia • Atrial flutter or atrial tachycardia • AF burden • Cumulative burden of symptomatic AF Adverse events: various	• Funding: Biosense Webster (unrestricted grant) and Danish Heart Foundation (unrestricted grant); Finnish Foundation for Cardiovascular Research (grant) • COI: multiple authors report conflict of interest

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Jais (2008)[55] Canada, USA, France	• RCT • Fair Quality • Multicenter (4 sites) • AADs used only in medical treatment group • 100% 2nd line therapy	• Patients >18 years of age who were capable of providing informed consent • Symptomatic, documented paroxysmal AF over a span of ≥6 months • At least 2 episodes during the preceding month.	• Contraindications to >2 AADs in different classes or to oral anticoagulants • Prior AF ablation • Intracardiac thrombus • AF from a potentially reversible cause • Pregnancy • Contraindication to the discontinuation of oral anticoagulation	Primary • AF burden • SF-36: physical component summary and mental component summary • Stress test: exercise duration, heart rate at rest, maximum heart rate, maximum workload, METS • Symptom checklist: frequency scale, severity scale • Mortality (all cause) (time of occurrence NR) • Mortality (cardiovascular) (time of occurrence NR) • Myocardial infarction (time of occurrence NR) Secondary • Freedom from recurrence (AF lasting ≥ 3 minutes and documented by ECG or reported by the patients as AF (even in the absence of ECG confirmation)) • Repeat ablation for any arrhythmia (or cause NR) • Reduced medication use • LA size • LV size • Left ventricular ejection fraction (LVEF) • Maintenance of sinus rhythm Adverse events: various	• Funding: Biosense Webster, Inc., 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 • COI: multiple authors report conflicts of interest

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Morillo (2014)[56] USA, Canada, Germany, Czech Republic, Italy	• RCT • Fair Quality • Multicenter (16 sites) • AADs used only in medical treatment group • 100% 1st line therapy	• Older than 18 and no older than 75 years • Symptomatic with recurrent paroxysmal AF lasting more than 30 seconds (≤4 episodes within the prior 6 months) • Experienced at least 1 episode that was documented by surface ECG, 6 months before randomization • No previous antiarrhythmic drug treatment	• Documented left ventricular ejection fraction of < 40% • Left atrial diameter larger than 5.5 cm • Moderate to severe left ventricular hypertrophy (wall thickness >1.5 cm), valvular disease, coronary artery disease, or postcardiac surgery within 6 months • Undergone a left heart ablation procedure, either by surgery or by radiofrequency catheter ablation for AF • Complete contraindication for the use of heparin, warfarin, or both	Primary • Mortality (all cause) (timing of occurrence NR) • Stroke (any type) (timing of occurrence NR) • Mortality (cardiovascular) (timing of occurrence NR) • Total number of any atrial tachyarrhythmia episodes • Time to second ablation • EQ5D: visual analog score, tariff score, and anxiety or depression Secondary • Freedom from symptomatic AF lasting >30 seconds • Freedom from recurrence of symptomatic or asymptomatic atrial tachyarrhythmia (AF, atrial flutter, atrial tachycardia) lasting > 30 seconds • Freedom from symptomatic atrial tachyarrthythmia recurrence lasting >30 seconds • Repeat ablation for any arrhythmia (or cause NR) • Drug therapy: Bradycardia • Atrial flutter • Arrhythmia (drug related) Adverse effects: various	• Funding: Biosense Webster (unrestricted research grant) and Population Health Research Institute at McMaster University • COI: Multiple authors received grants and/or consulting fees from one or more of the following: Biosense Webster, Boston Scientific, Medtronic, St Jude Medical, Biotronik, Boehringer Ingelheim, Merck

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Pappone (2006)[57] Italy	• RCT • Fair Quality • Single center • AADs used only in medical treatment group • 100% 2nd line therapy	• Age >18 or <70 years old • Creatinine concentration < 1.5 mg/dl • History of AF >6 months • AF burden >2 episodes/month in the last 6 months before enrollment (quantified by review of patient charts)	• AF secondary to transient or correctable abnormality • Intra-atrial thrombus or tumor precluding catheter insertion • LA diameter >65 mm • Left ventricular ejection fraction ≤35% • Symptoms of heart failure greater than New York Heart Association functional class II • Prior drug therapy with amiodarone, flecainide, and sotalol • Contraindication to beta-blocking therapy • Patients with rheumatic mitral valve disease • Unstable angina or acute or prior myocardial infarction (< 6 months) • Wolff-Parkinson-White syndrome • Renal or hepatic failure • Implanted device (pacemaker or cardioverter-defibrillator) • Need for antiarrhythmic therapy for arrhythmias other than AF • Contraindication to drug therapy or anticoagulation with warfarin • History of a cerebrovascular accident • Prior attempt at catheter or surgical ablation for AF	Primary • None Secondary • Hospitalization. Readmission for cardiovascular events (including AF) • Repeat ablation for AF • Freedom from any recurrence (Atrial tachyarrhythmias (including both AF and atrial tachycardia) beyond the first 6 weeks after the ablation) • LA size • Maintenance of sinus rhythm • Atrial flutter • Hyperthyroidism (related to drug therapy) Adverse events: various	• Funding: NR • COI: NR
Pappone (2011)[58] Italy	• RCT • Fair Quality • Single Center • AADs used only in medical treatment group • 100% 2nd line therapy	• Age >18 or <70 years • AF history >6 months • AF burden >2 episodes per month in the last 6 months as assessed by daily transtelephonic monitoring.	• Persistent AF • LA diameter >65 mm • LVEF ≤35% • Heart failure symptoms • New York Heart Association functional class II • Residents outside of Italy	Primary: • Transient ischemic attack after 30d • Progression of paroxysmal to persistent AF • SF-36: physical functioning, role limitations physical, bodily pain, general health, vitality, social functioning, role limitations emotional, mental health, physical component summary, mental component summary Secondary: • Freedom from recurrence (Atrial tachyarrhythmias (including both AF and atrial tachycardia) beyond the first 6 weeks after the ablation documented by Holter monitoring • Hospitalization/readmission for cardiovascular events (including AF) • Repeat ablation for any arrhythmia (or cause NR) • Arrhythmia (drug related) Adverse events: various	• Funding: Arrhythmology Department at San Raffaele University Hospital • COI: Dr. Pappone reports multiple conflicts of interest

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Wazni (2005)[59] Italy & Germany	• RCT • Fair Quality • Multicenter (3 sites • AADs used only in medical treatment group • 100% 1st line therapy	• Ages 18 to 75 years • Experienced monthly symptomatic AF episodes for ≥3 months • Not been treated with antiarrhythmic drugs	• Ages <18 or >75 years • Previous history of atrial flutter or AF ablation • Previous history of open-heart surgery • Previous treatment with antiarrhythmic drugs • Contraindication to long-term anticoagulation treatment	Primary • SF-36: general health, physical functioning, role limitations physical, bodily pain, mental health, social functioning, role limitations emotional, vitality • Stroke (Any Type) (timing of occurrence NR) • Transient ischemic attack (timing of occurrence NR) • Mortality (all-cause) (timing of occurrence NR) • Mortality (cardiovascular) (timing of occurrence NR) Secondary • Number and duration of episodes • Ventricular rate • Freedom from recurrence (Symptomatic or asymptomatic AF only lasting > 15 seconds during Holter or event monitoring in the 1-year followup period) • Repeat ablation for AF • Hospitalization (cause NR) • Medication use (dosage and/ or frequency) • Incidence of Bradycardia Adverse events: various	• Funding: unrestricted educational grant from Acuson, a division of Siemens Medical Solutions • COI: NR

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Wilber (2010)[60] USA, Canada, "Latin America," Europe (NR)	• RCT • Fair Quality • Multicenter (9 sites) • AADs used only in medical treatment group • 100% 2nd line therapy	• At least 3 symptomatic AF episodes (≥1 episode verified by ECG) within the 6 months before randomization • Not responding to at least 1 antiarrhythmic drug (class I, class III, or atrioventricular nodal blocker)	• Patients with AF of more than 30 days duration • Age younger than 18 years • Ejection fraction of less than 40% • Previous ablation for AF • Documented left atrial thrombus • Amiodarone therapy in the previous 6 months • New York Heart Association class II (marked limitation in activity due to symptoms) or IV (sever limitations) • Myocardial infarction within the previous 2 months • Coronary artery bypass graft procedure in the previous 6 months • Thromboembolic event in the previous 12 months • Severe pulmonary disease • Prior valvular cardiac surgical procedure • Presence of an implanted cardioverter-defibrillator • Contraindication to antiarrhythmic or anticoagulation medications • Life expectancy <12 months • Left atrial size of at least 50 mm in the parasternal long axis view	Primary • Mortality (all-cause) after 30d • Myocardial infarction after 30d • Mortality (cardiovascular) after 30d • SF-36: Mental component summary and physical component summary • Symptom checklist: frequency scale and severity scale Secondary • Freedom from symptomatic recurrence (Symptomatic or asymptomatic AF only lasting >15 seconds during Holter or event monitoring in the 1-year followup period) • Freedom from protocol defined treatment failure Adverse events: various	• Funding: Biosense Webster • COI: Multiple authors received grants and/or consulting fees from various industries (e.g. Biosense Webster, Boston Scientific, Medtronic, St Jude Medical, Johnson & Johnson, etc.)

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; COI = conflict of interest; ECG = Electrocardiography; EF = Ejection Fraction; FU = Followup; ICD = International Classification of Diseases; LA = Left Atrium; LV = Left ventricle; LVEF = Left ventricular ejection fraction; METs = Metabolic equivalents of task; NR = Not reported; NYHA = New York Heart Association; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SF-36 = Short Form-36; QoL = Quality of Life.

Table E8. Study Characteristics of RCTs Comparing Radiofrequency Catheter Ablation Versus Medical Therapy in Patients with Persistent Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Hunter (2014)[61] United Kingdom	• RCT (CAMTAF Trial) • Fair quality • Single center • AADs used in both treatment groups • 100% 1st line therapy	• Patients ≥18 years • Persistent AF • Symptomatic HF (New York Heart Association functional class II – IV) • LV systolic dysfunction (ejection fraction <50%) • <80 bpm resting heart rate • <110 bpm heart rate upon moderate exertion as assessed on ambulatory monitoring and exercise testing	• HF with suspected reversible cause • Previous left atrial ablation • Any contraindications to catheter ablation • Paroxysmal AF • Symptoms clearly attributable to AF rather than HF i.e., palpitations or dizziness that might mandate a rhythm control strategy • Any event during the past 6 months that might continue to effect on LV function, or a realistic expectation of these occurring within the next year	Primary • Intracranial hemorrhage • Peak oxygen consumption (VO2) • New York Heart Association (NYHA) score • Minnesota Living with Heart Failure Questionnaire (MLHFQ) Secondary • Freedom from recurrence • Reablation Adverse events • Stroke • Tamponade • Intracranial hemorrhage* • Cardiac death*	• Funding: British Heart Foundation grant (PG/08/130) • COI: the authors indicate no conflict of interest
MacDonald (2011)[62] Scotland	• RCT • Fair Quality • Multicenter (6 sites) • AADs used in both treatment groups • 100% 1st line therapy	• Patients ages 18-80 years • New York Heart Association functional class II-IV symptoms despite optimal heart failure treatment for ≥3 months • Ejection fraction ≤35% measured by radionuclide ventriculography • Persistent AF • No contraindication to cardiovascular MRI	• Paroxysmal AF • QRS duration >150ms (or QRS 120-150 with evidence of mechanical cardiac dysynchrony) • Any contraindication to oral anticoagulant drugs • Primary vascular disease or acute myocarditis as the cause of heart failure • Coronary revascularization within the preceding 6 months • Pregnancy • Expected cardiac transplantation within 6 months	Primary • SF-36: mental component summary and physical component summary • 6-minute walk distance • Kansas City Cardiomyopathy Questionnaire (KCCQ) • Minnesota Living with Heart Failure Questionnaire (MLHFQ) Secondary • LA size • Left ventricular end-systolic volume • Left ventricular end-diastolic volume • Maintenance of sinus rhythm • Repeat ablation for AF • Left and right ventricular ejection fraction (LVEF & RVEF) Adverse events: various	• Funding: Chief Scientist Office, Scotland (grant number CZB4475) • COI: the authors indicate no conflict of interest

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Mont (2014)[63] Spain	• RCT • Fair Quality • Multicenter (8 sites) • AADs used in both treatment groups • 100% 2nd line therapy	• Patients with symptomatic persistent atrial fibrillation (greater than 7 or less than 7 days requiring electrical or pharmacological cardioversion) • Refractory to at least one class I or class III antiarrhythmic drug were recruited.	• Age <18 or >70 years, • Long-standing persistent AF (greater than 1 year of continuous AF) • First episode of AF • Hyper- or hypothyroidism • Hypertrophic cardiomyopathy • Implanted pacemaker or defibrillator • Moderate or severe mitral disease or mitral prosthesis • Left ventricular ejection fraction less than 30 percent • Left atrial diameter greater than 50mm • Prior ablation procedure • Contraindication for oral anticoagulation • Left atrial thrombus • Active infection or sepsis • Pregnancy • Unstable angina • Acute myocardial infarction during previous 3 months • Life expectation <12 months • Current participation in another clinical trial • Mental disease or inability to give informed consent • Disease contraindicating ablation or AAD therapy	Primary • Mortality (all-cause) (timing of occurrence NR) • Mortality (cardiovascular) (timing of occurrence NR) • Transient ischemic attack (timing of occurrence NR) • Stroke (any type) (timing of occurrence NR) • AF-QoL (physical domain, global score, sexual domain, psychological domain) • Cardioversions (2 or more) Secondary • Freedom from recurrence (AF or flutter lasting ≥30 seconds after a 3-month blanking period) • Hospitalization/ readmission for cardiovascular events (including AF) • Repeat ablation for AF • Repeat ablation for any arrhythmia (or cause NR) Adverse events: various	• Funding: Unrestricted grant from Medtronic and Biosense Webster, and a grant from Hospital Clinic (premi de Fi de Residencia Emili Letang). • COI: The authors report no conflict of interest

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Oral (2006)[64] USA, Italy	• RCT • Fair Quality • Multicenter (2 sites) • AADs used only in medical treatment groups • 100% 2nd line therapy	• Patients with chronic atrial fibrillation defined as atrial fibrillation that had been present for more than six months without intervening spontaneous episodes of sinus rhythm and that recurred within one week after cardioversion.	• Age <18 or >70 yr • Left atrial diameter >55 mm • Left ventricular ejection fraction <30 percent • 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 atrial fibrillation	Primary: • Mortality (all-cause) after 30d Secondary: • Freedom from recurrence (Symptomatic or asymptomatic AF only lasting >15 seconds during Holter or event monitoring in the 1-year followup period) • Repeat ablation for any arrhythmia (or cause NR) • Repeat ablation for AF • Freedom from Bradyarrhythmia (sick sinus syndrome) Adverse events: various	• Funding: The Ellen and Robert Thompson Atrial Fibrillation Research Fund (Ann Arbor, Mich.) • COI: Drs. Oral and Morady are founders of Ablation Frontiers, report being major stockholders in Ablation Frontiers, and report having served as consultants to Ablation Frontiers and Biosense Webster. Dr. Pappone reports having received grant support from Biosense Webster, St. Jude Medical, Guidant, and Medtronic and having served as a consultant to Biosense Webster. Dr. Chugh reports having received lecture fees from Biosense Webster.

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Jones (2013)[65] UK	• RCT • Fair Quality • Multicenter (2 sites) • AADs used only in medical treatment group • Both 1st and 2nd line therapy	• 18 to 80 years of age • Persistent AF (>7 days) • Symptomatic HF (New York Heart Association functional class II to IV) on optimal HF therapy • Left ventricular ejection fraction (EF) ≤35%	• Cardiovascular implantable electronic device insertion or cerebrovascular event within 6 months • Coronary revascularization or atrioventricular nodal ablation within 3 months • Reversible causes of AF or HF including thyroid dysfunction, alcohol, primary valvular disease, or recent major surgery • Prior heart transplant or on urgent transplant waiting list; pregnancy • Active malignancy • Severe renal impairment • Single chamber pacemaker and atrioventricular block • Contraindications to general anesthesia or oral anticoagulation	Primary: • Peak oxygen consumption (VO2) • Minnesota Living with heart Failure Questionnaire (MLHVQ) • 6-minute walk distance • Mortality (cardiovascular) after 30d • Mortality (all cause) after 30d Secondary: • Repeat ablation for AF • Repeat ablation for any arrhythmia (or cause NR) • Freedom from recurrence (Atrial arrhythmia (assessed by ECG) lasting >30 seconds, occuring during the post-blanking period)) • Biomarker: brain (or B-type) natriuretic peptide • Left ventricular ejection fraction (LVEF) • Left atrial size • Single procedure success • Multi-procedure success • Mean arrhythmia-free survival time • Maintenance of sinus rhythm • Mean time to first atrial arrhythmia recurrence Adverse events: various	• Funding: National Institute for Health Research cardiovascular Biomedical Research Unit • COI: multiple authors report conflict of interest

AAD = antiarrhythmic drugs; AF = Atrial Fibrillation; AF-QoL domain = Atrial Fibrillation Quality of Life Domain; COI = conflict of interest; ECG = Electrocardiography; EF = Ejection Fraction; FU = Followup; HF = heart failure; ICD = International Classification of Diseases; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = Left Atrium; LV = Left ventricle; LVEF = Left ventricular ejection fraction; METs = Metabolic equivalents of task; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NR = Not reported; NYHA = New York Heart Association; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; RVEF = right ventricular ejection fraction; SF-36 = Short Form-36; VO2 = oxygen consumption; QoL = Quality of Life.
*These results only reported for the medical group.

Table E9. Study Characteristics of RCTs Comparing Radiofrequency Catheter Ablation Versus Medical Therapy in Patients with Paroxysmal or Persistent Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Forleo (2009)[66] Italy	• RCT • Fair Quality • Multicenter (3 sites) • AADs used only in medical treatment group • 100% 2nd line therapy	• Diabetes mellitus type 2 patients • Symptomatic paroxysmal or persistent AF for at least 6 months • Refractory to at least one class 1-3 antiarrhythmic drugs	• Age <18 or >75 years • Prior cardiac surgery • History of previous ablation for AF • Ejection fraction ≤30% • Left atrial size >55mm • Absence of informed patient consent • Any condition that would make survival for 1 year unlikely.	Primary: • SF-36: general health, social and physical functioning, bodily pain, role limitations emotional, mental health, vitality, role limitations physical • Transient ischemic attack (timing of occurrence NR) • Stroke (any type) (timing of occurrence NR) Secondary: • Freedom from recurrence (Any ECG confirmed episode of AF or atypical atrial flutter lasting 30 seconds, occurring between 5 weeks and 12 months) • Hospitalization (cause NR) Adverse events: various	• Funding: NR • COI: Last author receives lecture fees from St. Jude Medical and serves on the advisory board of Biosense-Webster

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Stabile (2006)[67] Italy	• RCT • Good Quality • Multicenter (# of sites NR) • AADs used in both treatment groups • 100% 2nd line therapy	• Patients with paroxysmal (occurrence, in the previous 6 months, of one or more episodes of AF a month, each lasting > 60 min but < 7 days, with all episodes terminating spontaneously) or persistent (occurrence, in the previous 12 months, of two or more episodes of AF, each lasting > 7 days before being terminated pharmacologically or by electrical cardioversion, or lasting < 7 days but necessitating early cardioversion owing to intolerable symptoms or haemodynamic compromise, with sinus rhythm maintained for 60 min or more after termination) AF who were intolerant of antiarrhythmic drugs or in whom two or more antiarrhythmic drug regimens had failed. • First diagnosis of AF had been made at least 6 months before enrollment.	• Age <18 or >80 years • Permanent AF (AF was the sole rhythm for the last 12 months) • AF secondary to a transient or correctable abnormality, including electrolyte imbalance, trauma, recent surgery, infection, toxic ingestion, and endocrinopathy • Persistence of AF episodes triggered by another uniform arrhythmia (i.e. atrial flutter or atrial tachycardia) despite previous supraventricular tachycardia ablation • Intra-atrial thrombus, tumour, or other abnormality precluding catheter insertion • Wolff–Parkinson–White syndrome • Heart failure with NYHA class III or IV or EF ≤35% • Unstable angina or acute myocardial infarction within 3 months • Cardiac revascularization or other cardiac surgery within 6 months or with prior atrial surgery • Renal failure requiring dialysis, or hepatic failure • An implanted device (pacemaker or cardioverter-defibrillator). • Left atrial diameter > 60 mm	Primary: • Mortality (all-cause) (timing of occurrence NR) • Transient ischemic attack (timing of occurrence NR) Secondary: • Freedom from recurrence (At least one occurrence of atrial arrhythmia (flutter or fibrillation) lasting > 30 seconds, in the 1 year followup period, after the 1-month blanking period) • Hospitalization (cause NR) Adverse events: various	• Funding: The trial was partly supported by Biosense-Webster, Italy. • COI: Authors report that there are no conflicts of interest besides their received finding.

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; COI = conflict of interest; ECG = Electrocardiography; EF = Ejection Fraction; FU = Followup; ICD = International Classification of Diseases; LA = Left Atrium; LV = Left ventricle; LVEF = Left ventricular ejection fraction; METs = Metabolic equivalents of task; NR = Not reported; NYHA = New York Heart Association; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SF-36 = Short Form-36; QoL = Quality of Life.

Table E10. Study Characteristics of Observational Studies Comparing Radiofrequency Catheter Ablation Versus Medical Therapy in Patients with Paroxysmal Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Lan (2009)[68] China	• Prospective, comparative observational • Fair quality • Single center • 100% 2nd line therapy	• Frequency of AF attack is at least one times monthly, which was documented by Holter or 12-lead ECG • Presence of obvious symptoms of palpitations, chest distress during occurrence of AF • New York Heart Association Class I and left ventricular ejection fraction (LVEF) >/= 55%(measured by transthoracic echocardiogram) • No structural heart diseases and blood pressure </= 165／95 mmHg in hypertensive patients	• Patients refractory to amiodarone in the past • Left atrium (LA) size more than 45 mm • Hyperthyroidism or electrolyte disturbance, pulmonary, or hepatic disease and／or contraindications to treatment with amiodarone, significant impairment of renal function, mitral regurgitation • QT interval ‡ 480 ms in the absence of bundle branch block • Bradycardia £ 55 bpm while the patient was awake • Significant alternations of the atrioventricular conduction, sick sinus syndrome, or any other medical condition that, in the opinion of the investigators, could make the patient inappropriate for the study	Primary • Blood pressure (diastolic) • Blood pressure (systolic) Secondary • LA size • Freedom from recurrence (AF >30 seconds) Adverse events: various	• Funding: grant from Health Research Foundation (Health bureau of Chongqing) • COI: the authors indicate no conflict of interest
Sang (2013)[69] China	• Prospective, comparative observational • Fair quality • Single center • 100% 2nd line therapy	• Patients with symptomatic paroxysmal AF	• Age <18 years • Contraindication to anticoagulation • Previous nonpharmacological interventions for AF • New York Heart Association functional class III or IV • Myocardial infarction • Cardiac surgery or transient ischemic attack/stroke within the previous 6 months • Malignancy of any type, and presence of an implanted cardioverter defibrillator	Primary • Zung Self-Rating Anxiety Scale (SAS) – total score • Zung Self-Rting Depression Scale (SDS) – total score • SF-36: mental component summary (MCS) and physical component summary (PCS) • Thromboembolic events Secondary • Repeat ablation for AF • Freedom from recurrence (any symptomatic episodes of documented atrial tachyarrhythmias lasting ≥30 seconds, as well as any episode of asymptomatic atrial tachyarrhythmias lasting ≥10 minutes on 24-hour ambulatory Holter recordings) • Maintenance of sinus rhythm Adverse events: various	• Funding: government, and the National Science Foundation Council of China (No. 30971239 and No. 81070147) and the Beijing Natural Science Foundation (No. 7101004) • COI: the authors indicate no conflict of interest

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Yu (2012)[70] China	• Retrospective, comparative observational • Poor quality • Single center • 100% 2ns line therapy	• NR	• History of myocardial infarction in the last 12 months • Cardiac surgery • Congenital heart disease • Pericardial disease • History of cancer • Tuberculosis • Hyperthyroidism or hypothyroidism • Rheumatism • Decompensated liver cirrhosis • Serum creatinine level >2 mg/dL	Primary • Zung Self-Rating Anxiety Scale (SAS) – total score, normalized score • Zung Self-Rating Depression Scale (SDS) – total score, normalized score • SF-36: bodily pain, general health, mental health, physical functioning, role limitations emotional, role limitations physical, social functioning, vitality Secondary • Freedom from recurrence (AF >30 seconds) Adverse events: NR	• Funding: NR • COI: the authors report no conflict of interest

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; COI = conflict of interest; ECG = Electrocardiography; EF = Ejection Fraction; FU = Followup; ICD = International Classification of Diseases; LA = Left Atrium; LV = Left ventricle; LVEF = Left ventricular ejection fraction; METs = Metabolic equivalents of task; NR = Not reported; NYHA = New York Heart Association; nonRCT = Nonrandomized Controlled Trial; RFA = Radiofrequency Ablation; SF-36 = Short Form-36; QoL = Quality of Life.

Table E11. Study Characteristics of Observational Studies Comparing Radiofrequency Catheter Ablation Versus Medical Therapy in Patients with Persistent Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Blandino (2013)[71] Italy	• Prospective, comparative observational • Fair quality • Number of centers NR • 100% 2nd line therapy	• Patients aged 70 or greater • Persistent and symptomatic AF • AF refractory to at least one antiarrhythmic medication • At least one episode of AF documented by ECG or Holter monitoring within 12 months of study enrollment • Continuous anticoagulation with target international normalized ratio (INR) of 2–3 for at least 4 weeks before the procedure • Written informed consent to participate in the study	• Paroxysmal and longstanding persistent AF • Previous AF ablation procedure • Cardiac surgical procedure in the previous 6 months • Documented left atrial (LA) thrombus • INR < 2 at admission and in the last 4 weeks before the procedure • New York Heart Association (NYHA) class III or IV • Acute myocardial infarction within the previous 2 months • Severe pulmonary disease • Contraindications to antiarrhythmic or anticoagulation medications • inability to give written informed consent	Primary • Mortality (cardiovascular) after 30d • Stroke/ TIA (undefined) after 30d • Myocardial infarction after 30d • Peripheral embolism after 30d • Congestive heart failure • SF-36: bodily pain, general health, mental health, physical functioning, role limitations emotional, role limitations physical, social functioning, vitality Secondary • Repeat ablation for any arrhythmia (or cause NR) • Maintenance of sinus rhythm • Freedom from recurrence (any episode of AF or atrial tachycardia lasting >30 seconds documented by an ECG) Adverse events: various	• Funding: NR • COI: Dr. Blandino's fellowship was sponsored by Biosense-Webster

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; COI = conflict of interest; ECG = Electrocardiography; EF = Ejection Fraction; FU = Followup; ICD = International Classification of Diseases; LA = Left Atrium; LV = Left ventricle; LVEF = Left ventricular ejection fraction; METs = Metabolic equivalents of task; NR = Not reported; NYHA = New York Heart Association; nonRCT = Nonrandomized Controlled Trial; RFA = Radiofrequency Ablation; SF-36 = Short Form-36; QoL = Quality of Life.

Table E12. Study Characteristics of Observational Studies Comparing Radiofrequency Catheter Ablation Versus Medical Therapy in Patients with Paroxysmal or Persistent Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Reynolds (2012)[72] USA	• Retrospective comparative observational • From matched cohort administrative database (MarketScan Research Database, Thomson Reuters) • AF type NR • 100% 2nd line	• In patient or outpatient visit with both a recorded diagnosis of AF (ICD-9 code 427.31) and a documented catheter ablation procedure (ICD-9 code 37.34 or CPT code 93651)	• Code designating a pacemaker or implantable cardioverter defibrillator implantation • Record of any cardiac ablation procedure before the first procedure meeting inclusion requirements • Procedure code for open (surgical) ablation procedure or atriventricular junction ablation at the same visit	Primary • Stroke/TIA • Heart failure hospitalization Secondary • Medication use Adverse events: NR	• Funding: Biosense Webster, Inc, Diamond Bar, CA • COI: Multiple authors report funding and/or paid consulting and/or employment from Biosense Webster, Inc; Sanofi Adventis, St Jude Medical; Medtronic, Inc; and S^2 Statistical Solutions, Inc.
Rossillo (2008)[73] Italy	• Retrospective, comparative observational • Poor quality • Single center • 2nd line therapy for RFA group, NR for Med group	• NR	• NR	Primary • Stroke (any type) after 30d • Mortality (all cause) after 30d Secondary • Freedom from recurrence (Symptomatic or asymptomatic AF) • Freedom from recurrence (any arrhythmia) Adverse events: various	• Funding: NR • COI: NR
Sonne (2009)[74] USA	• Retrospective, comparative observational • Poor Quality • Single center • 100% 2nd line therapy	Ablation • PVAI • No prior or subsequent ablative or surgical treatment for AF such as AV node junction ablation or Cox–Maze procedure • Symptomatic AF refractory to ≥1 AADs Medical Therapy • Had pharmacologic therapy combined with DCC • No prior or subsequent ablative or surgical treatment for AF such as AV node junction ablation, PVI, or maze procedure • Majority of patients had multiple DCCVs (Did not report criteria for AVJA since it's excluded)	• NR	Primary • Mortality (all cause) (timing of occurrence NR) • Mortality (cardiovascular) (timing of occurrence NR) • Congestive heart failure • Myocardial infarction (timing of occurrence NR) • Stroke (any type) (timing of occurrence NR) Secondary • Freedom from recurrence (AF that persists 8 weeks after ablation) Adverse effects: various	• Funding: NR • COI: NR

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; AV = Atrioventricular; AVJA = atrioventricular junctional ablation; COI = conflict of interest; DCC = direct current cardioversion; ECG = Electrocardiography; EF = Ejection Fraction; FU = Followup; ICD = International Classification of Diseases; LA = Left Atrium; LV = Left ventricle; LVEF = Left ventricular ejection fraction; METs = Metabolic equivalents of task; NR = Not reported; NYHA = New York Heart Association; nonRCT = Nonrandomized Controlled Trial; PVI = pulmonary vein isolation; RFA = Radiofrequency Ablation; SF-36 = Short Form-36; QoL = Quality of Life.

Table E13. Demographics of Included RCTs Comparing Cryoballoon Ablation with Medical Therapy in Patients with Paroxysmal/Early Persistent Atrial Fibrillation

Author (year)	Study Design (Quality rating)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Packer (2013)[75] Andrade (2014) US Canada	• RCT (STOP-AF trial) • Fair quality • Multicenter (26 sites) • 2nd line therapy	N = 245 77.1% male Age = 57 ± 9 years Cryo: n = 163 76.7% male Age = 57 ± 9 years Medical: n = 82 78% male Age = 56 ± 9 years Special Population: None	Left Atrial diameter: Cryo: 40 ± 5 mm Med: 41 ± 6 mm AF Duration: NR No. AF episodes in prior 2 months Cryo: 24 ± 42 Med: 21 ± 32	FU: 12 months 98.8% (242/245) Cryo: 100% (163/163) Med: 96.3% (79/82) Blanking period: Cryo: 90 days Med: 90 days % Crossover: Cryo: NR Med: 79.3% (65/82)	Cryoballoon Ablation: • PV isolation of the four major PV's 97.6% (159/163) • PVI achieved with the balloon catheter alone in 83% (135/163) • Additional catheter based focal cryoablation in one or more PVs for 16.6% (27/163) • Left common PV isolation 100% (21/21) • Right middle PVs 76.9% (10/13) • Cavotricuspid isthmus ablation with bidirectional block achieved in 97% (64/66) • 74.2% (121/163) patients received AADs after cryoballoon ablation, but these drugs were discontinued after the blanking period. At the end of 12 months, 26% of patients were taking AADs. Medical Therapy (dosages according to 2006 AHA/ACC guidelines): • Flecainide 65% • Propafenone 57% • Sotalol 44% Mapping: • Pacing and a circular mapping catheter used to assess entrance and/or exit blockage after a 30 min waiting period

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; COI = conflict of interest; ECG = Electrocardiography; EF = Ejection Fraction; FU = Followup; ICD = International Classification of Diseases; LA = Left Atrium; LV = Left ventricle; LVEF = Left ventricular ejection fraction; METs = Metabolic equivalents of task; NR = Not reported; NYHA = New York Heart Association; nonRCT = Nonrandomized Controlled Trial; RFA = Radiofrequency Ablation; SF-36 = Short Form-36; QoL = Quality of Life.

Table E14. Study Characteristics of Included RCTs Comparing Cryoballoon Ablation with Medical Therapy in Patients with Paroxysmal/Early Persistent Atrial Fibrillation.

Author (year)	Study Design (Quality rating)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Packer (2013)[75] Andrade (2014) US Canada	• RCT (STOP-AF trial) • Fair quality • Multicenter (26 sites) • 2nd line therapy	• Patients with more than 2 episodes of paroxysmal atrial fibrillation in the 2 months prior to randomization • Treatment failure of least one membrane-active drug	• Left atrium (LA) >5.0 cm • Left ventricular ejection fraction <40% • New York Heart Association functional class III or IV congestive heart failure • Coronary artery disease warranting intervention • Stroke or transient ischemic attack within 6 months • Previous LA ablation or surgery for AF • A prosthetic heart valve • Amiodarone therapy in the preceding 3 months • More than 2 cardioversions within 2 years • Have an implantable rhythm device	Primary • Myocardial infarction after 30d • Mortality (cardiovascular) after 30d Secondary • Freedom from recurrence (any detectable AF after the blanking period) • Freedom from protocol defined treatment failure • Symptom reduction Adverse events: various	• Funding: funded by Medtronic, Inc. (which purchased Cryocath over the course of the study). • COI: various

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; COI = conflict of interest; ECG = Electrocardiography; EF = Ejection Fraction; FU = Followup; ICD = International Classification of Diseases; LA = Left Atrium; LV = Left ventricle; LVEF = Left ventricular ejection fraction; METs = Metabolic equivalents of task; NR = Not reported; NYHA = New York Heart Association; nonRCT = Nonrandomized Controlled Trial; RFA = Radiofrequency Ablation; SF-36 = Short Form-36; QoL = Quality of Life.

Table E15. Demographics of Included RCTs and Comparative Observational Studies Comparing Ablation with Different Energy Sources in Patients with Paroxysmal Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Perez-Castellano (2014)[76] Spain	• RCT (COR Trial) • Fair quality • Single center • 100% 2nd line therapy	N = 50 78% male Age = 57 years RFA: n = 25 88% male Age = 56 (40 – 61) years (median, IQR) Cryo: n = 25 68% male Age = 58 (45 – 62) years (median, IQR) Special Population: Refractory to AADs (Class I or III)	Left atrial diameter: RFA: 42 (38 – 45) mm (median, IQR) (parastemal long-axis echocardiographic view) Cryo: 42 (39 – 47) mm (median, IQR) (paratemal long-axis echocardiographic view) AF Duration: NR	FU: NR; 12 mo Blanking period: 3 mo % crossover: NR	RFA Ablation: • Ostial PVI 100% • Right inferior PV (1% each group) • Bidirectional block (83% cryo, 100% RFA) • Cavotricuspid isthmus ablation (4% cryo, 5% RFA) • Systemic anticoagulation with intravenous heparin • AADs could be prescribed temporarily within a 3-month blanking period, which were discontinued after end of blanking period Cryoballoon Ablation: • The cryoballoon was positioned in the targeted PV (or PVs) where 2 consecutive 300-second applications were delivered • Systemic anticoagulation with intravenous heparin (dose NR) • AADs could be prescribed temporarily within a 3-month blanking period, which were discontinued after end of blanking period • Touch-up: cavotricuspid isthmus ablation 4% Mapping: • RFA: CARTO electroanatomical mapping system (Biosense Webster, Tirat-Hacarmel, Israel) • Selective PV angiograms were obtained through a 6-F angled pigtail catheter (Supertorque Plus, Cordis Corp, Miami, FL) • Cryo: 15-mm-diameter circular decapolar catheter (Lasso, Biosense Webster Inc, Diamond Bar, CA)

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Chierchia (2010)[77] Belgium	• Prospective, comparative observational • Poor quality • Single center • 100% 2nd line therapy	N = 133 79% male Age = 56 years RFA: n = 87 79% male Age = 56 ± 9 years Cryo: n = 46 78% male Age = 56 ± 11 years Special Population: No	Left atrial diameter: RFA: 42 ± 5 mm (transthoracic examination) Cryo: 41 ± 5 mm (transthoracic examination) AF Duration: RFA: 3.2 ± 1.7 years Cryo: 3.3 ± 1.9 years	FU: 100% (133/133); 24 hours of the procedure Blanking period: NR % crossover: NR	RFA Ablation: • Circumferential PVI with no additional lines 100% • No usage of AADs Cryoballoon Ablation: • The cryoballoon was positioned in the PV ostium of each vein with a minimum of two applications lasting for 5 minutes each %NR (n's NR) • No usage of AADs • Touch-up: no touch ups performed Mapping: • Cryo: A circular mapping catheter (Lasso, Biosense Webster, Inc., Diamond Bar, CA, USA) was advanced in each PV ostium to obtain baseline electrical information of the PVs and the left atrium • RFA: electroanatomical mapping (Carto, Biosense Webster, Diamond Bar, CA, USA)
Knecht (2014)[78] Switzerland	• Prospective comparative observational (BEAT-AF-PVI cohort study) • Fair quality • Multicenter (2 sites) • 2nd line therapy	N = 142 54% male Age = 58.2 years RFA: n = 71 77.5% male Age = 57.8 ± 11.2 years Cryo: n = 71 74.7% male Age = 58.6 ± 10.6 years Special Population: No	Left atrial diameter: RFA: 39.2 ± 5.3 mm, median 39 mm (mode NR) Cryo: 39.5 ± 6.0 mm, median 40 mm (mode NR) AF duration: RFA: 57 ± 70 months, median 36 months Cryo: 67 ± 70 months, median 52 months	FU: %NR; mean followup 28 mo Blanking period: 3 mos % crossover: 28.1% (20/71) patients	RFA Ablation: • Acute PCI 100% • AADs discontinued after procedure Cryoballoon Ablation: • A freezing cycle with a standard duration of 300 s was started after PV occlusion was demonstrated by contrast ejection Cryoballoon + RFA Ablation: • If ablation using CB alone was not effective in isolating PV after up to a max of 4 applications, PVI was completed as described above 28.1% (20/71)† • AADs discontinued after procedure Mapping: • Cryo: Circumferential mapping catheter (manufacturer NR) • RFA: 3D-mapping system and a 3.5 mm open irrigated-tip catheter (manufacturer NR)

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Mugnai (2014)[79] Belgium, Italy	• Retrospective, comparative observational • Poor quality • Single center • 2nd line therapy	N = 396 70.5% male Age = 57.8 years <u>RFA:</u> n = 260 69.6% male Age = 58.3 ± 8.7 (30 – 77, 60) (median IQR, mean) <u>Cryo:</u> n = 136 72.1% male Age = 57 ± 13.3 (15 – 78, 56) <u>Special Population:</u> No	<u>Left atrial diameter:</u> RFA: 42.8 ± 5.7 (42.6) mm (median) Cryo: 41.8 ± 6.8 (42) mm (median) <u>AF duration:</u> RFA: 25.4 ± 37.1 (10) months (median) Cryo: 25.1 ± 24 (10.5) months (median)	<u>FU:=</u> %NR; 23 ± 13.4 mo, median 27 mo <u>Blanking period:</u> 3 mo <u>% crossover:</u> NR	<u>RFA Ablation:</u> • PVI 100% • Contiguous focal lesions were created at a distance of >5 mm from the ostia of PVs resulting in circumferential lines around ipsilateral PVs • Each application lasted a maximum of 60 seconds • AADs administered for 2 months after procedure and stopped if patient was free of AF relapse (dose NR) • Oral anticoagulants started day after procedure and continued for 3 months (dose NR) • Low molecular weight heparin started upon patient discharge and stopped when target international normalized ration of 2 – 3 was reached (dose NR) <u>Cryoballoon Ablation:</u> • PVI 100% • CB was advanced over to the left atrium, inflated, and positioned in the PV ostium of each vein • Minimum of 2 applications lasting 5 minutes each • AADs administered for 2 months after procedure and stopped if patient was free of AF relapse (dose NR) • Oral anticoagulants started day after procedure and continued for 3 months (dose NR) • Low molecular weight heparin started upon patient discharge and stopped when target international normalized ration of 2 – 3 was reached (dose NR) • Touch-up: Focal touch-up with either a focal-tip cryocatheter (Freezor Max; CryoCath Technologies Inc., Montreal, Quebec, Canada) or an irrigated-tip RF catheter (NaviStar ThermoCool; Biosense Webster Inc.) (3.7%, 5/136)
Mugnai (2014)[79] Belgium, Italy Continued					<u>Mapping:</u> • RFA: Circumferential mapping catheter (Lasso; Biosense Webster, Inc., Diamond Bar, CA) was positioned into proximal portion of the PV ostium, whereupon an electroanatomic map of the left atrium was performed with a nonfluoroscopic navigation system (CARTO; Biosense Webster Inc.) • Cryo: NR

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Schmidt (2014)[80] Germany	• Prospective, comparative observational • Poor quality • Multicenter (55 sites) • 1st and 2nd line therapy (% NR)	N = 3775 63% men Age = 63 years (median) <u>RFA:</u> n = 2870 62.7% men Age = 73 years (median) <u>Cryo:</u> n = 905 64.3% male Age = 63 years (median) <u>Special Population:</u> No	<u>Left atrial diameter:</u> NR <u>AF duration:</u> NR*	<u>FU:</u> 100%, periprocedural <u>Blanking period:</u> NR <u>% crossover:</u> NR	<u>RFA Ablation:</u> • PVI (100%) • 56.2% of patients received AADs at time of hospital discharge • Class III AADs: 20.6% • Class I AADs: 33.1% • Class IV AADs: 3% • Anticoagulated using phenprocoumon aiming an INR of 2 – 3 at least 3 months after procedure (dose NR) 90.5% • Antithrombotic agents (dose NR) 11.9% • Low molecular weight heparin (dose NR) 67.1% <u>Cryoballoon Ablation:</u> • PVI (100%) • 48% patients received AADs at time of hospital discharge • Class II AADs: 21.3% • Class I AADs: 25.1% • Class IV AADs: 0.6% • Anticoagulated using phenoprocoumon aiming an INR of 2 – 3 at least 3 months after procedure (dose NR) 85% • Antithrombotic agents (dose NR) 11.9% • Low molecular weight heparin (dose NR) 54.1% • Touch-up: Additional touch-up freezes with a conventional cryocatheter (Freezor MAX, CryoCath, Medtronic) or an RF catheter could be performed if deemed necessary: touchup focal cryoablation was reported in 10.6% of patients <u>Mapping:</u> • Electroanatomic mapping system (CARTO, Biosense Webster, Diamond Bar, CA or NavX, St. Jude Medical, St. Paul, MN); Conventional mapping (28.5% of patients, device NR), 3D electroanatomical mapping (71.2% of patients)

3D = 3 dimensional; AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; CB = cryoballoon; CFAE = Complex fractionated atrial electrograms; CI = Confidence Interval; ECG = Electrocardiography; FU = Followup; IQR = Interquartile range; INR = International Normalized Ratio; NR = Not reported; PVI = Pulmonary Vein Isolation; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SD = Standard deviation.

*Percentage of patients with palpitations, palpitations monthly, and a severity and atrial fibrillation (SAF) scale are reported in supplementary tables in SRDR.

† Authors report propensity score matched subgroup analysis in those patients who received cryoballoon only (n = 51) versus RFA only (n = 51)

Table E16. Demographics of Included RCTs or Comparative Observational Studies Comparing Ablation with Different Energy Sources in Patients with Paroxysmal or Persistent Atrial Fibrillation

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Herrera Siklody (2012)[81] Germany, France	• RCT • Poor quality • Single center • 2nd line therapy	N = 60 80% male Age = 56.5 years RFA: n = 30 76.7% male Age = 56 ± 10 years Cryo: n = 30 83.3% male Age = 57 ± 8 years Special Population: 100% drug-resistant symptomatic AF	Left atrial diameter: RFA: 40.4 ± 5.5 mm Cryo: 41.4 ± 4.3 mm AF duration: RFA: 5.6 ± 4.2 years Cryo: 4.2 ± 2.7 years	FU: 12 mo (median) Blanking period: 3 mo % crossover: NR	RFA: • Circumferential PVI of both ipsilateral veins %NR • Oral anticoagulation was stopped 2 days prior to intervention • AAD treatment suspended day of procedure, restarted the following day, and stopped after 2 months Cryo: • Balloon was inflated in front of each PV ostium and advanced to achieve PV occlusion %NR • Each PV frozen twice over 5 minutes • Oral anticoagulation was stopped 2 days prior to intervention • AAD treatment suspended day of procedure, restarted the following day, and stopped after 2 months • Electrical isolation was completed with focal applications 33% (10/30) in the cryoballoon group Mapping • RFA: Circular mapping catheter (Optima, St. Jude Medical) • Cryo: Circular mapping catheter (Optima, St. Jude Medical)

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Kojodjojo (2010)[82] United Kingdom	• Retrospective, comparative observational • Poor quality • Single center • 2nd line therapy	N = 143 76% male Age = 58 years RFA: n = 53 77% male Age = 59.3 ± 9.7 years Cryo: n = 90* 75% male Age = 57.3 ± 9.4 years Special Population: No	Left atrial diameter: RFA: 41.6 ± 5.4 mm (mean) Cryo: 39.6 ± 7.1 mm (mean) AF duration: RFA: 6.0 ± 4.8 years Cryo: 5.6 ± 4.1 years	FU: RFA: % NR, 15.6 ± 7.4 mo Cryo: % NR, 14.9 ± 7.7 mo* Blanking period: 3 mo % crossover: NR	RFA: • Circumferential antral ablation (PVI alone) 15% • If typical AF detected before or during procedure, cavotricuspid isthmus ablation performed 11.3% (6/53) • AADs except amiodarone stopped at least 5 half lives before treatment • Warfarin stopped 5 days prior to procedure with briding tinzaparin (175 IU/kg) %NR • Anticoagulation was continued for at least 3 months Cryo: • Cryoballoon ablation alone 40% • PVI + ostial focal cryoablation 60% • Two 5 min cryoballoon applications were applied to each PV (100%) • AADs except amiodarone stopped at least 5 half lives before treatment • Warfarin stopped 5 days prior to procedure with briding tinzaparin (175 IU/kg) (%NR) • Anticoagulation was continued for at least 3 months • Touch-up: PVI + cavotricuspid isthmus ablation with RFA catheter 23% Mapping • RFA: Either fluoroscopy or a three-dimensional mapping system (Carto, Biosense Webster, USA); electroanatomical mapping system 96.2% (51/53) • Cryo: Curvilenear mapping catheter (Inquiry Optima, St. Jude Medical OR Lasso, Biosense Webster, Diamond Bar, CA) % NR

Author (year)	Study Design (Study Quality)	Demographics	Patient Characteristics	Followup Blanking Period % Crossover	Interventions
Mandell (2013)[83] New York	• Retrospective, comparative observational • Poor quality • Single center • Both 1st and 2nd line therapy	N = 124 66.1% male Age = 60.7 years RFA: n = 62 74.2% male Age = 60.4 ± 8.4 years Cryo: n = 62 58.1% male Age = 61 ± 8.8 years Special Population: No	Left atrial diameter: RFA: 25.0% dilated (mode NR) Cryo: 23.4% dilated (mode NR) AF Duration: NR	FU: 100% (124/124); No followup, just periprocedural Blanking period: None used % Crossover: RFA: NR Cryo: 25.8% (16/62) patients received RF to treat right-sided isthmus dependent atrial flutter; 3.2% (2/62) patients had concomitant RF left-sided lines created	RFA Ablation: • PVI only 79% (49/62) • PVI + cavotricuspid isthmus for atrial flutter 9.7% (6/62) • PVI + supraventricular tachycardia 1.6% (1/62) • PVI + superior vena cavae 3.2% (2/62) • PVI + lines 1.6% (1/62) • PVI + cavotricuspid isthmus for atrial flutter + lines 1.6% (1/62) • CFE only 1.6% (1/62) • PVI + CFE 1.6% (1/62) • Most patients who were on warfarin therapy underwent the procedure on therapeutic anticoagulation • Patients not on therapy and in sinus rhythm were started on therapeutic anticoagulation after the procedure Cryoballoon Ablation: • PVI only 75.8% (47/62) • PVI + cavotricuspid isthmus for atrial flutter 21% (13/62) • PVI + lines 3.2% (2/62) • Most patients who were on warfarin therapy underwent the procedure on therapeutic anticoagulation • Patients not on therapy and in sinus rhythm were started on therapeutic anticoagulation after the procedure Mapping: • Imaging was performed with intracardiac echocardiography (to assist with the transeptal punctures and monitor for pericardial effusion), single-plane fixed fluoroscopy, and nonfluoroscopic three-dimensional electroanatomical imaging (Ensite NavX; St. Jude Medical) in all patients

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; CFAE = Complex fractionated atrial electrograms; CI = Confidence Interval; ECG = Electrocardiography; FU = Followup; IQR = Interquartile range; NR = Not reported; PVI = Pulmonary Vein Isolation; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SD = Standard deviation.
*The study reports two different n's and followups for the cryoballoon ablation group.

Table E17. Study Characteristics of Included RCTs or Comparative Observational Studies Comparing Ablation with Different Energy Sources in Patients with Paroxysmal Atrial Fibrillation

Author (year)	Study Design (Quality rating)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Perez-Castellano (2014)[76]	• RCT (COR Trial) • Fair quality • Single center • 100% 2nd line therapy	• Symptomatic paraoxysmal AF (>2 episodes in the last 6 months) • Refractory to 1 or more antiarrhythmic drugs (class I or III) • Anatomic pattern consisting of 4 single PVs	• Ages <18 or >75 years • Prior AF ablation • Prio cardiac surgery • Moderate to severe valvular heart disease • Anteroposterior diameter of the left atrium >50 mm (parasternal long-axis view) • Hyperthyroidism • Intracardiac thrombus • Contraindications for anticoagulant therapy • Concomitant acute illness • Pregnancy • Unavailability for followup at center for at least 1 year	Primary • NR Secondary • Freedom from recurrence • Reablation • Atrial flutter • AF burden Adverse events: various	• Funding: NR • COI: NR
Chierchia (2010)[77] Belgium	• Prospective nonRCT • Poor quality • Single center • 100% 2nd line therapy	• Frequent occurrence of recurrent episodes of AF • Self-terminating within 7 days • Developing in spite of treatment with at least two antiarrhythmic drugs.	• NR	Primary • NR Secondary • NR Adverse events: various	• Funding: NR • COI: the authors report no conflict of interest
Knecht (2014)[78] Switzerland	• Prospective comparative observational (BEAT-AF-PVI cohort study) • Fair quality • Multicenter (2 sites) • 2nd line therapy	• Paroxysmal AF undergoing PVI	• Persistent or permanent AF • History of previous left atrial procedure (surgical or percutaneous) • Use of magnetic navigation system	Primary • NR Secondary • Freedom from recurrence Adverse events: NR	• Funding: Grants from the Basel University, the "Freiwillige Akademische Gesellschaft" (FAG) Basel, the University Hospital Basel, Bayer, Daiichi-Sankyo, and Sanofi-Aventis. Author D. Conen was supported by a grant of the Swiss National Science Foundation (PP00P3_1331681) • COI: Multiple authors reported conflicts of interest
Mugnai (2014)[79] Belgium, Italy	• Retrospective, comparative observational • Poor quality • Single center • 2nd line therapy	• Documented symptomatic paroxysmal AF	• Repeat procedures for recurrent AF after index procedure • (Previous?) first-line ablation treatment • Acute complications disrupting procedure continuation • Persistent AF	Primary • TIA • Death Secondary • Freedom from AF without AADs Adverse events: various	• Funding: NR • COI: Multiple authors reported conflicts of interest

Author (year)	Study Design (Quality rating)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Schmidt (2014)[80] Germany	• Retrospective, comparative observational • Poor quality • Multicenter (55 sites) • 1st and 2nd line therapy (% NR)	• Symptomatic paroxysmal AF, defined as AF lasting <6 days with spontaneous termination • Underwent PV ablation	• NR	Primary • NR Secondary • NR Adverse events: various	• Funding: Unrestricted grant from foundation Stiftung Institut fur Herzinfarkt-forschung Ludwigshafen, Germany • COI: Multiple authors reported conflicts of interest

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; AV = atrioventricular; CFAE = Complex fractionated atrial electrograms; CI = Confidence Interval; ECG = Electrocardiography; FU = Followup; IQR = Interquartile range; MACCE = major adverse cardiac and cerebrovascular event; NR = Not reported; PVI = Pulmonary Vein Isolation; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SD = Standard deviation.

Table E18. Study Characteristics of Included RCTs or Comparative Observational Studies Comparing Ablation with Different Energy Sources in a Mixed Population

Author (year)	Study Design (Quality rating)	Inclusion Criteria	Exclusion Criteria	Outcomes	Funding
Herrera Siklody (2012)[81] Germany, France	• RCT • Poor quality • Single center • 2nd line therapy	• Highly symptomatic, drug-refractory paroxysmal or persistent episodes of AF	• Long persistent AF (>12 months) • Left atrial diameter >55 mm • Intracardiac thrombi determined by TEE • MI or cardiac surgery in the previous 3 months • Previous ablation for AF	Primary • NR Secondary • Freedom from recurrence • reablation • atrial flutter • biomarkers Adverse events: various	• Funding: Study received financial support from CryoCath • COI: Multiple authors report conflicts of interest
Kojodjojo (2010)[82] United Kingdom	• Retrospective, comparative observational • Poor quality • Single center • 2nd line therapy	• Symptomatic, medically refractory AF • Paroxysmal AF or early persistent AF • Undergoing first AF procedure	• NR	Primary NR Secondary • Freedom from recurrence • Reablation Adverse events: various	• Funding: British Heart Foundation; Dr. Kojodjojo is funded by British Heart Foundation Travel Fellowship (FS/09/047) • COI: The authors report no conflict of interest
Mandell (2013)[83] New York	• Retrospective nonRCT • Poor quality • Single center • Both 1st and 2nd line therapy	• Symptomatic atrial fibrillation • Failed or couldn't tolerate antiarrhythmic drug therapy	• No RF-only ablations since the introduction of cryoballoon ablation were included.	Primary • None Secondary • Freedom from protocol defined treatment failure Adverse events: various	• Funding: NR • COI: The authors report no conflict of interest

AF = Atrial Fibrillation; AAD = antiarrhythmic drugs; CFAE = Complex fractionated atrial electrograms; CI = Confidence Interval; ECG = Electrocardiography; FU = Followup; IQR = Interquartile range; NR = Not reported; PVI = Pulmonary Vein Isolation; RCT = Randomized Controlled Trial; RFA = Radiofrequency Ablation; SD = Standard deviation; TEE = Transesophogeal Echocardiography

Appendix F. Quality Assessment of Included Studies

Table F1. Study Quality Ratings of Included RCTs Comparing Radiofrequency Catheter Ablation Versus Medical Therapy in Patients with Paroxysmal or Persistent Atrial Fibrillation

Methodological Principle	Forleo (2009)[66]	Hunter (2014)[61]	Jais (2008)[55]	Jones (2013)[65]	MacDonald (2011)[62]	Mont (2014)[63]	Morillo (2014)[56]	Cosedis Nielsen (2012)[54]	Oral (2006)[64]	Pappone (2011/2006)[57, 58]	Stabile (2006)[67]	Wazni (2005)[59]	Wilber (2010)[60]
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 blinded outcome assessment		✓			✓	✓		✓	✓	✓	✓		✓
Patients blinded to treatment received													
Attrition (≤ 20% overall; ≤ 10% difference between groups)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Controlling for possible confounding†	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓
Full reporting on prespecified outcomes	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓
Overall Quality Rating	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Fair**	**Good**	**Fair**	**Fair**

*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

Table F2. Study Quality Ratings of Included Observational Studies Comparing Radiofrequency Catheter Ablation Versus Medical Therapy in Patients with Paroxysmal or Persistent Atrial Fibrillation

Methodological Principle	Blandino (2013)[71]	Lan (2009)[68]	Reynolds (2012)[72]	Rossillo (2008)[73]	Sang (2013)[69]	Sonne (2009)[74]	Yu (2012)[70]
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 blinded outcome assessment							
Patients blinded to treatment received							
Attrition (≤ 20% overall; ≤ 10% difference between groups)	✓				✓		✓
Controlling for possible confounding†	✓	✓	✓	✓	✓	✓	✓
Full reporting on prespecified outcomes	✓	✓	✓	✓			✓
Overall Quality Rating	**Fair**	**Fair**	**Fair**	**Poor**	**Fair**	**Poor**	**Poor**

*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

Table F3. Study Quality Ratings of the Included RCT Comparing Cryoballoon Ablation with Medical Therapy with a Mixed Population of Patients with Atrial Fibrillation

Methodological Principle	Packer (2013)[75]
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 blinded outcome assessment	✓
Patients blinded to treatment received	
Attrition (≤ 20% overall; ≤ 10% difference between groups)	✓
Controlling for possible confounding†	✓
Full reporting on prespecified outcomes	✓
Overall Quality Rating	**Fair**

*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

Table F4. Study Quality Ratings of Included RCTs Comparing Radiofrequency Catheter Ablation with Cryoballoon Ablation in Patients with Paroxysmal or Persistent Atrial Fibrillation

Methodological Principle	Herrera Siklody (2012)[81]	Perez Castellano (2014)[76]
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 blinded outcome assessment		✓
Patients blinded to treatment received		
Attrition (≤ 20% overall; ≤ 10% difference between groups)		✓
Controlling for possible confounding†	✓	✓
Full reporting on prespecified outcomes	✓	✓
Overall Quality Rating	**Poor**	**Fair**

*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

Table F5. Study Quality Ratings of Included Observational Studies Comparing Radiofrequency Catheter Ablation with Cryoballoon Ablation in Patients with Paroxysmal or Persistent Atrial Fibrillation

Methodological Principle	Chierchia (2010)[77]	Mandell (2013)[83]	Knecht (2014)[78]	Kojodjojo (2010)[82]	Mugnai (2014)[79]	Schmidt (2014)[80]
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 blinded outcome assessment						
Patients blinded to treatment received						
Attrition (≤ 20% overall; ≤ 10% difference between groups)	✓	✓				✓
Controlling for possible confounding†	✓		✓		✓	
Full reporting on prespecified outcomes	✓	✓	✓	✓		
Overall Quality Rating	**Fair**	**Poor**	**Fair**	**Poor**	**Poor**	**Poor**

*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

Studies rated "good" will be considered to have the least risk of bias, and their results will be considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated "fair" will be susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated "poor" will have significant flaws that imply biases of various types that may invalidate the results. They will have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies will be least as likely to reflect flaws in the study design as the true difference between the compared interventions. We will not exclude studies rated as being poor in quality *a priori*, but poor-quality studies will be considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present.

Appendix G. Strength of Evidence Tables

Table G1. Strength of evidence for KQ1: What is the comparative efficacy and effectiveness of AF catheter ablation on long- (>12 months) term outcomes in the general adult and Medicare populations? Consider (a) Catheter ablation versus medical therapy: Radiofrequency ablation (RFA) versus medical therapy

Long-term (>12 months) Efficacy and Effectiveness, KQ 1a: RFA Versus Medical Therapy	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause) >30 days							
Paroxysmal AF							
RCTs	2 RCTs (N = 408)	medium	direct	unknown	imprecise	undetected	Low
Observational	None	-	-	-	-	-	Insufficient
Persistent AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational (Medicare population)	1 (N = 412)	medium	direct	unknown	imprecise	undetected	Insufficient*
Mixed population							
RCTs	None	-	-	-	-	-	Insufficient
Observational (general population)	1 (N = 170)	medium	direct	consistent	imprecise	undetected	Insufficient*
Observational (Medicare population)	1 (N = 351)	high	direct	unknown	imprecise	undetected	Insufficient*
Stroke >30 days							
Paroxysmal AF							
RCTs	1 (N = 127)	medium	direct	unknown	imprecise	undetected	Insufficient*
Observational	None	-	-	-	-	-	Insufficient
Persistent AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational (Medicare population)	1 (N = 412)	medium	direct	unknown	imprecise	undetected	Insufficient*
Mixed population							
RCTs	None	-	-	-	-	-	Insufficient
Observational	1 (N = 170)	medium	direct	consistent	imprecise	undetected	Insufficient*
Observational (Medicare population)	1 (N = 351)	high	direct	unknown	imprecise	undetected	Insufficient*
MI >30 days							
Paroxysmal AF							
RCTs	1 (N = 294)	medium	direct	unknown	imprecise	undetected	Insufficient*
Observational	None	-	-	-	-	-	Insufficient
Persistent AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational (Medicare population)	1 (N = 412)	medium	direct	unknown	imprecise	undetected	Insufficient*
Mixed population							
RCTs	None	-	-	-	-	-	Insufficient
Observational (Medicare population)	1 (N = 351)	medium	direct	unknown	imprecise	undetected	Insufficient*

Long-term (>12 months) Efficacy and Effectiveness, KQ 1a: RFA Versus Medical Therapy	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Congestive Heart Failure							
Paroxysmal							
RCTs	1 (N = 294)	medium	direct	unknown	imprecise	undetected	Insufficient*
Persistent AF							
Observational (Medicare population)	1 (N = 412)	medium	direct	unknown	imprecise	undetected	Insufficient*
Mixed AF							
Observational (Medicare population)	1 (N = 351)	high	direct	unknown	imprecise	undetected	Insufficient*
Health Related Quality of Life: SF-36							
Mental Component Score							
Paroxysmal AF							
RCTs	1 (N = 294) at 24 months; 1 (N = 198) at 48 months	medium	direct	consistent	imprecise	undetected	Insufficient*
Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient
Physical Component Score							
Paroxysmal AF							
RCTs	1 (N = 294) at 24 months; 1 (N = 198) at 48 months	medium	direct	consistent	precise	undetected	Insufficient*
Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient
Other HRQOL Measures							
Minnesota Living with Heart Failure Questionnaire							
Persistent AF (CHF patients)							
RCTs	1 (N = 52) at 12 months	medium	direct	unknown	imprecise	undetected	Insufficient
Observational studies	None	-	-	-	-	-	Insufficient
Paroxysmal AF, Mixed population	None	-	-	-	-	-	Insufficient
Freedom from recurrence (any arrhythmia)							
Paroxysmal AF							
RCTs	3 (N = 619)	medium	indirect	consistent	precise	undetected	Moderate
Persistent AF	None	-	-	-	-	-	Insufficient
Mixed population							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	1 (N = 85 in RFA arm)	high	indirect	unknown	imprecise	suspected	Insufficient*

Long-term (>12 months) Efficacy and Effectiveness, KQ 1a: RFA Versus Medical Therapy	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Maintenance of sinus rhythm							
Paroxysmal	None	-	-	-	-	-	Insufficient
Persistent							
RCTs	None	-	-	-	-	-	Insufficient
Observational (Medicare population)	1 (N = 412)	high	indirect	unknown	precise	undetected	Insufficient*
Mixed population							
RCTs	None	-	-	-	-	-	Insufficient
Observational	1 (N = 170)	high	indirect	unknown	imprecise	suspected	Insufficient*
Reablation (any arrhythmia)							
Paroxysmal							
RCTs	4 (N = 337)	medium	indirect	inconsistent	imprecise	undetected	Low
Observational	None	-	-	-	-	-	Insufficient
Persistent							
RCTs	None	-	-	-	-	-	Insufficient
Observational (Medicare population)	1 (N = 153 ablation group only)	medium	direct	unknown	imprecise	undetected	Insufficient*

AAD = Antiarrhythmic drug; AF = atrial fibrillation; CHF = chronic heart failure; KQ = Key Question; MLHFQ = Minnesota living with heart failure questionnaire; RCT = randomized controlled trial; RFA = radiofrequency catheter ablation.

*Conclusions are not possible secondary to study limitations (i.e. methodology), small sample sizes resulting in low precision of estimates and/or limited data from single studies.

Table G2. Key findings and strength of evidence for Key Question (KQ) 1: What is the comparative efficacy and effectiveness of AF catheter ablation on short- (≤12 months) term outcomes in the general adult and Medicare populations? Consider (a) Catheter ablation versus medical therapy: radiofrequency ablation (RFA) versus medical therapy

Short-term (≤12 months) Efficacy and Effectiveness, KQ 1a: RFA Versus Medical Therapy	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause) >30 days							
All RCTs (regardless of AF type)	7 (N = 814)	medium	direct	inconsistent	imprecise	undetected	Low
Paroxysmal AF							
RCTs	3 (N = 333)	medium	direct	inconsistent	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Persistent AF							
RCTs	3 (N = 344)	medium	direct	consistent	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Mixed population							
RCTs	1 (N = 137)	low	direct	unknown	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Stroke >30 days							
All RCTs (regardless of AF type)							
Paroxysmal AF							
RCTs	1 (N = 67)	medium	direct	unknown	imprecise	undetected	Insufficient*
Observational studies	None	-	-	-	-	-	Insufficient
Persistent AF							
RCTs	1 (N = 146)	medium	direct	unknown	imprecise	undetected	Insufficient*
Observational studies	None	-	-	-	-	-	Insufficient
Mixed population							
RCTs	1 (N = 70) (Diabetic patients)	medium	direct	unknown	imprecise	undetected	Insufficient*
Observational studies	None	-	-	-	-	-	Insufficient
Myocardial infarction >30 days							
Paroxysmal AF							
RCTs	2 (N = 270)	medium	direct	unknown	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient
Congestive heart failure							
Paroxysmal AF, Persistent AF and Mixed population	None	-	-	-	-	-	Insufficient
Health related quality of life (HRQOL): SF- 36							
Mental Component Score							

Short-term (≤12 months) Efficacy and Effectiveness, KQ 1a: RFA Versus Medical Therapy	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Paroxysmal AF							
RCTs	2 (N = 406)	medium	direct	consistent	imprecise	undetected	Insufficient*
Observational studies	1 (N = 166)	medium	direct	unknown	imprecise	undetected	Insufficient*
Persistent AF							
RCTs	1 (N = 41) at 6 months	medium	direct	unknown	imprecise	undetected	Insufficient*
Observational studies	None	-	-	-	-	-	Insufficient
Physical Component Score							
Paroxysmal AF							
RCTs	2 (N = 406)	medium	direct	consistent	imprecise	undetected	Insufficient*
Observational studies	1 (N = 166)	medium	direct	unknown	imprecise	undetected	Insufficient*
Persistent AF							
RCTs	1 (N = 41) at 6 months (heart failure)	medium	direct	unknown	imprecise	undetected	Insufficient*
Observational studies	None	-	-	-	-	-	Insufficient
Mixed population	None	-	-	-	-	-	Insufficient
Other HROQL Measures							
Minnesota Living with Heart Failure Questionnaire							
Persistent AF							
RCTs	3 (N = 141) (Heart failure)	medium	direct	unknown	imprecise	undetected	Insufficient
Observational studies	None	-	-	-	-	-	Insufficient
Paroxysmal AF, Mixed population	None	-	-	-	-	-	Insufficient
EuroQOL-5D and Symptom Check List							
Paroxysmal AF							
RCTs	1 (N = 127) EQ5D; 1 (N = 112) Symptom Check List	medium	direct	unknown	imprecise	undetected	Insufficient*
Observational studies	None	-	-	-	-	-	Insufficient
Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient
AFQOL and KCCQ							
Persistent AF							
RCTs	1 (N = 146)	medium	direct	consistent	imprecise	undetected	Insufficient*

Short-term (≤12 months) Efficacy and Effectiveness, KQ 1a: RFA Versus Medical Therapy	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	AF-QOL; 1 (N = 127) KCCQ						
Observational studies	None	-	-	-	-	-	Insufficient
Paroxysmal AF, Mixed population	None	-	-	-	-	-	Insufficient
Zung Self-Rating Anxiety Scale (SAS)							
Paroxysmal AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	2 (N = 365)	medium	direct	consistent	imprecise	undetected	Insufficient*
Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient
Zung Self-Rating Depression Scale (SDS)							
Paroxysmal AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	2 (N = 365)	medium	direct	consistent	imprecise	undetected	Insufficient*
Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient
Freedom from recurrence (any arrhythmia)							
All RCTs (regardless of AF type)	9 (N = 1089)	medium	indirect	consistent	precise	undetected	Moderate
Paroxysmal AF							
RCTs	4 (N = 538)	medium	indirect	consistent	precise	undetected	Moderate
Observational	2 (N = 322)	medium	indirect	inconsistent	imprecise	undetected	Insufficient
Persistent AF							
RCTs	3 (N = 344)	medium	indirect	inconsistent	imprecise	undetected	Low
Observational	None	-	-	-	-	-	Insufficient
Mixed Population							
RCTs	2 (N = 207)	medium	indirect	consistent	imprecise	undetected	Low
Maintenance of sinus rhythm							
Paroxysmal AF							
RCTs	2 (N = 310)	medium	indirect	inconsistent	precise	undetected	Low
Observational studies	2 (N = 385)	high	indirect	unknown	imprecise	undetected	Insufficient*
Persistent AF							
RCTs	2 (N = 93)	medium	indirect	consistent	imprecise	undetected	Low
Reablation (post-blanking period)							
All RCTs (regardless of AF type)	8 (N = 430) (ablation group only)	medium	indirect	inconsistent	imprecise	undetected	Low
Paroxysmal AF							
RCTs	3 (N = 184) (ablation	medium	indirect	inconsistent	imprecise	undetected	Low

Short-term (≤12 months) Efficacy and Effectiveness, KQ 1a: RFA Versus Medical Therapy	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
	group only)						
Observational studies	1 (N = 82) (ablation group only)	-	-	-	-	-	Insufficient
Persistent AF							
RCTs	5 (N = 246) (ablation group only)	medium	indirect	inconsistent	imprecise	undetected	Low
(patients with heart failure)	3 RCTs (N = 71) (ablation group only)	medium	indirect	inconsistent	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Mixed population	None	-	-	-	-	-	Insufficient

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency catheter ablation.

*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

Table G3. Key findings and strength of evidence for Key Question 1: What is the comparative efficacy and effectiveness of AF catheter ablation on short- (≤12 months) term outcomes in the general adult and Medicare populations? Consider (a) Catheter ablation versus medical therapy: Cryoballoon ablation versus medical therapy

Short-Term (≤12 months) Efficacy, KQ 1a: Cryoballoon ablation Versus Medical Therapy	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
All outcomes are for the same RCT in a mixed population							
Mortality (all cause) >30 days							
Paroxysmal AF, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed Population							
RCTs	1 (N = 245)	medium	direct	unknown	imprecise	undetected	Insufficient*
Stroke >30 days							
Paroxysmal AF, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed Population							
RCTs	1 (N = 245)	medium	direct	unknown	imprecise	undetected	Insufficient*
MI >30 days							
Paroxysmal AF, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed Population							
RCTs	1 (N = 245)	medium	direct	unknown	imprecise	undetected	Insufficient*
Congestive Heart Failure							
Paroxysmal AF, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed Population							
RCTs	1 (N = 245)	medium	direct	unknown	imprecise	undetected	Insufficient*
Health Related Quality of Life							
Paroxysmal AF, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed Population							
RCTs	1 (N = 245)	medium	direct	unknown	imprecise	undetected	Insufficient*
Freedom From Protocol-Defined Treatment Failure							
Paroxysmal AF, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed Population							
RCTs	1 (N=245)	medium	direct	unknown	precise	undetected	Low†
Maintenance of Sinus Rhythm	None	-	-	-	-	-	Insufficient

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency catheter ablation.

*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

†Upgraded for a large effect size.

Table G4. Key findings and strength of evidence for Key Question 1: Long-term (>12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with RFA for AF

Long-Term (> 12 months) Efficacy, KQ 1a: Cryoballoon ablation RFA	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality (all cause) > 30 days							
Paroxysmal AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational	1 (N = 396)	medium	direct	unknown	imprecise	undetected	Insufficient*
Persistent AF, Mixed Population	None	-	-	-	-	-	Insufficient
Freedom from AF Recurrence							
Paroxysmal AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational	2 (N = 538)	medium	direct	consistent	imprecise	undetected	Insufficient*
Persistent AF	None	-	-	-	-	-	Insufficient
Mixed Population							
RCTs	None	-	-	-	-	-	Insufficient
Observational							
Reablation							
Paroxysmal, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed Population							
RCTs	None	-	-	-	-	-	Insufficient
Observational	1 (N = 177)	medium	direct	unknown	imprecise	undetected	Insufficient*

AF = atrial fibrillation; KQ = Key Question; RFA = radiofrequency ablation.
*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

Table G5. Key findings and strength of evidence for Key Question 1: Short-term (≤12 months) efficacy and effectiveness outcomes comparing cryoballoon ablation with RFA for AF

Short-Term (≤ 12 months) Efficacy, KQ 1a: Cryoballoon ablation RFA	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Freedom from AF Recurrence							
Paroxysmal AF							
RCTs	1 (N = 50)	medium	indirect	unknown	imprecise	undetected	Insufficient*
Observational studies	1 (N=177)	medium	direct	unknown	imprecise	undetected	Insufficient*
Persistent AF	None	-	-	-	-	-	Insufficient
Mixed Population							
RCTs	1 (N =60)	medium	indirect	unknown	imprecise	undetected	Insufficient*
Observational studies	None	-	-	-	-	-	Insufficient
Reablation							
Paroxysmal AF							
RCTs	1 (N = 50)	medium	indirect	unknown	imprecise	undetected	Insufficient*
Observational studies	None	-	-	-	-	-	Insufficient
Persistent AF	None	-	-	-	-	-	Insufficient
Mixed							
RCTs	1 (N =60)	medium	indirect	unknown	imprecise	undetected	Insufficient*
Observational studies	None	-	-	-	-	-	Insufficient

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency ablation.

*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

Table G6. Key findings and strength of evidence for Key Question 1: What is the comparative efficacy and effectiveness of AF catheter ablation on long- (>12 months) term outcomes in the general adult and Medicare populations? Consider (a) Comparison of energy sources: Cryoballoon ablation versus RFA

Long-term (>12 months) Efficacy, KQ 1a: Cryoballoon ablation versus RFA	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SoE grade
Mortality (all cause) >30 days							
Paroxysmal AF							
Observational studies	1 (N=396)	Medium	Direct	Unknown	imprecise	undetected	Insufficient*
Persistent AF, Mixed Population	None	-	-	-	-	-	Insufficient
Freedom From AF Recurrence							
Paroxysmal AF	None	-	-	-	-	-	Insufficient
Observational studies	2 (N=498)	Medium	Direct	consistent	imprecise	undetected	Insufficient*
Persistent AF, Mixed Population	None	-	-	-	-	-	Insufficient
Reablation							
Paroxysmal AF, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed Population							
Observational studies	1 (N= 177)	Medium	Direct	Unknown	imprecise	undetected	Insufficient*

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency catheter ablation.
*Conclusions are not possible secondary to study limitations, small sample sizes resulting in low precision of estimates and/or limited data from single studies.

Table G7. Key findings and strength of evidence for KQ 2: What are the comparative short- and long-term complications and harms (e.g., periprocedural or device-related harms) associated with AF catheter ablation in the general adult and Medicare populations? Consider (a) Catheter ablation versus medical therapy: radiofrequency ablation (RFA) versus medical therapy.

Safety, KQ 2a: RFA Versus Medical Therapy	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality <30 days							
All RCTs (regardless of AF type)	5 (N = 761)	medium	direct	consistent	imprecise	undetected	Low
Paroxysmal AF							
RCTs	3 (N = 570)	medium	direct	consistent	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Persistent AF							
RCTs	2 (N = 191)	medium	direct	unknown	imprecise	undetected	Low
Observational (Medicare population)	1 (N = 412)	low	direct	unknown	imprecise	undetected	Insufficient*
Stroke <30 days							
All RCTs (regardless of AF type)	8 (N = 919)	medium	direct	consistent	imprecise	undetected	Low
Paroxysmal AF							
RCTs	3 (N = 481)	medium	direct	consistent	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Persistent AF							
RCTs	2 (N = 181)	medium	direct	consistent	imprecise	undetected	Low
Observational (Medicare population)	1 (N = 412)	low	direct	unknown	imprecise	undetected	Insufficient*
Mixed population							
RCTs	2 (N = 207)	medium	direct	consistent	imprecise	undetected	Low
Observational studies	1 (N = 166)	high	direct	unknown	imprecise	undetected	Insufficient*
AF <3 months							
Paroxysmal AF							
RCTs	2 (N = 183)	medium	direct	consistent	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Persistent AF							
RCTs	2 (N = 196)	medium	direct	consistent	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Mixed population							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	1 (N = 85)	high	direct	unknown	imprecise	suspected	Insufficient*
Cardiac Tamponade†							
Paroxysmal AF							
RCTs	4 (N = 512)	medium	direct	consistent	imprecise	undetected	Low
Observational studies	1 (N = 85)	medium	direct	unknown	imprecise	undetected	Insufficient*
Persistent AF							
RCTs	3 (N = 73)	medium	direct	consistent	imprecise	undetected	Insufficient*
Observational (Medicare population)	1 (N = 158)	low	direct	unknown	imprecise	undetected	Insufficient*

Safety, KQ 2a: RFA Versus Medical Therapy	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Pericardial Effusion[†]							
All RCTs (regardless of AF type)	5 (N = 772)	medium	direct	consistent	imprecise	undetected	Low
Paroxysmal AF							
RCTs	3 (N = 519)	medium	direct	consistent	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Persistent AF							
RCTs	1 (N = 116)	medium	direct	unknown	imprecise	undetected	Insufficient[*]
Observational (Medicare population)	1 (N = 158)	low	direct	unknown	imprecise	undetected	Insufficient*
Mixed population							
RCTs	1 (N = 137)	low	direct	unknown	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Pulmonary vein stenosis[†]							
Paroxysmal AF							
RCTs	5 (N = 433)	medium	direct	consistent	imprecise	undetected	Low
Observational studies	1 (N = 85)						Insufficient*
Persistent AF							
RCTs	2 (N = 137)	medium	direct	consistent	imprecise	undetected	Low
Observational (Medicare population)	1 (N = 158)	low	direct	unknown	imprecise	undetected	Insufficient*
Mixed population							
RCTs	1 (N = 137)	low	direct	unknown	imprecise	undetected	Low
Observational studies	1 (N = 85)						Insufficient*
Drug intolerance requiring discontinuation							
Paroxysmal							
RCTs	2 (N = 155 medical therapy patients)	medium	direct	consistent	imprecise	undetected	Low
Observational studies	None	-	-	-	-	-	Insufficient
Persistent							
RCTs	None	-	-	-	-	-	Insufficient
Observational (Medicare population)	1 (N = 412)	medium	direct	unknown	imprecise	undetected	Insufficient[*]
Mixed population							
RCTs	1 (N = 70)	medium	direct	unknown	imprecise	undetected	Insufficient[*]
Observational studies	None	-	-	-	-	-	Insufficient

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency catheter ablation.

[*] Conclusions are not possible secondary to study limitations, small sample sizes or sparse data resulting in low precision of estimates, and/or unknown consistency from single studies.

[†]Ablation-related adverse events were reported for all patients who received ablation, either as randomized or who crossed over from the medical therapy group.

Table G8. Key findings and strength of evidence for Key Question 2: Comparative short-term and long-term complications and harms associated with cryoballoon ablation versus medical therapy for AF

Harms, KQ 2a (one RCT*): Cryoballoon ablation versus Medical Therapy	Number of studies* (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SoE grade
Mortality <30 days							
Paroxysmal, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed population	1 (N = 245)	medium	direct	unknown	imprecise	undetected	Insufficient†
Stroke <30 days							
Paroxysmal, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed population	1 (N = 245)	medium	direct	unknown	imprecise	undetected	Insufficient†
AF <3 months							
Paroxysmal, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed population	1 (N = 163)	medium	direct	unknown	imprecise	undetected	Insufficient†
Cardiac Tamponade‡							
Paroxysmal, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed population	1 (N = 228)	medium	direct	unknown	imprecise	undetected	Insufficient†
Pericardial Effusion‡							
Paroxysmal, Persistent AF, mixed population	None	-	-	-	-	-	Insufficient
Pulmonary Vein Stenosis‡							
Paroxysmal, Persistent AF	None	-	-	-	-	-	Insufficient
Mixed population	1 (N = 228)	medium	direct	unknown	imprecise	undetected	Insufficient†
Drug intolerance requiring discontinuation							
Paroxysmal, Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial.

*Only 1 RCT (no observational studies) was identified for this comparison.

†Conclusions are not possible secondary to study limitations, small sample sizes or sparse data resulting in low precision of estimates, and/or unknown consistency from single studies.

‡Ablation-related adverse events were reported for all patients who received ablation, either as randomized or who crossed over from the medical therapy group.

Table G9. Key findings and strength of evidence for KQ 2: What are the comparative short- and long-term complications and harms (e.g., periprocedural or device-related harms) associated with AF catheter ablation in the general adult and Medicare populations? Consider (b) Comparing ablation using different energy sources: Cryoballoon ablation versus radiofrequency ablation (RFA)

Safety, KQ 2b: Cryoballoon ablation Versus RFA	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Mortality <30 days							
Paroxysmal AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	2 (N = 4171)	high	direct	consistent	precise	undetected	Insufficient*
Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient
Stroke <30 days							
All RCTs (regardless of AF type)	None	-	-	-	-	-	Insufficient
Paroxysmal AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	1 (N = 133)	low	direct	unknown	imprecise	undetected	Insufficient*
Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient
AF <3 months							
Paroxysmal AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	1 (N = 3775)	high	direct	unknown	precise	undetected	Insufficient*
Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient
Cardiac Tamponade†							
Paroxysmal AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	3 (N = 4304)	low	direct	unknown	imprecise	undetected	Insufficient*
Persistent AF, Mixed population	None	-	-	-	-	-	Insufficient
Pericardial Effusion†							
Paroxysmal AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	2 (N = 529)	low	direct	unknown	imprecise	undetected	Insufficient*
Persistent AF	None	-	-	-	-	-	Insufficient
Mixed population							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	1 (N = 267)	high	direct	unknown	imprecise	undetected	Insufficient*
Pulmonary vein stenosis†							
Paroxysmal AF							
RCTs	None	-	-	-	-	-	Insufficient
Observational studies	2 (N = 4171)	high	direct	consistent	precise	undetected	Insufficient
Persistent AF	None	-	-	-	-	-	Insufficient
Mixed population							
RCTs	None	-	-	-	-	-	Insufficient

Safety, KQ 2b: Cryoballoon ablation Versus RFA	Number of Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Grade
Observational studies	1 (N = 124)	high	direct	unknown	imprecise	undetected	Insufficient*

AF = atrial fibrillation; KQ = Key Question; RCT = randomized controlled trial; RFA = radiofrequency catheter ablation.

* Conclusions are not possible secondary to study limitations, small sample sizes or sparse data resulting in low precision of estimates, and/or unknown consistency from single studies.

†Ablation-related adverse events were reported for all patients who received ablation, either as randomized or who crossed over from the medical therapy group.

Appendix H. Description of Outcomes Measures, Devices, and Ongoing Trials, and Additional Results Tables

Table H1. Descriptions and Scoring Details for Health Related Quality of Life Measures used in Included Studies

HRQOL measure	Description	Scoring
Short-Form (SF-36) General measure	• 36-items, self-administered, constructed to survey health status and quality of life • 8 health domains: limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities because of emotional problems; vitality (energy and fatigue); general health perceptions • Summary Mental and Physical Component score are generated using a proprietary algorithm supplied by the instrument developers	• Likert-type scales (some with 5 or 6 points and others with 2 or 3 points) • Scores are transformed to a range of 0 (worst) to 100 (best)
European Quality of Life-5 Dimensions (EQ5D) General measure	• 25 items, self-administered • 5 categories: anxiety/depression, mobility, pain, self-care, usual activity • Contains an additional category relating to health state today; score on a 0 to 100 VAS scale (not part of the final score)	• Items ranked from 1 to 3 depending on level of disability • Preferential weights are assigned to each health state level to obtain a score of 0 (death) to 1 (optimal health) (societal-based utility score)
Zung Self-Rating Depression Scale (SDS) General measure	• 20 items, self-administered • questions assess psychological and somatic symptoms associated with depression	• All items are 1-4 Likert-type scale • Scores are transformed to a range of 20 (best) to 80 (worst) • Most people with depression score between 50 and 69, while a score of 70 and above indicates severe depression
Zung Self-Rating Anxiety Scale (SAS) General measure	• 20 items, self-administered • 4 groups of manifestations: cognitive, autonomic, motor and central nervous system symptoms	• All items are 1-4 Likert-type scale • Scores are transformed to a range of 20 (best) to 80 (worst) • Most people with anxiety score between 45 and 59, while a score of 60 and above indicates severe or extreme anxiety
Atrial Fibrillation Quality of Life Questionnaire (AF-QOL) Disease-specific measure	• 18 items, self-administered, measures the health-related quality of life in patients with AF • 3 domains: psychological (7 items), physical (8 items), and sexual activity (3 items).	• Scores standardized from 0 (worst) to 100 (best)
Kansas City Cardiomyopathy Questionnaire (KCCQ)	• 23 items, self-administered • 5 categories: physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and	• Scores are transformed to a range of 0 (worst) to 100 (best)

HRQOL measure	Description	Scoring
Disease-specific measure	knowledge, and quality of life	
Minnesota Living with Heart Failure Questionnaire (MLHFQ) Disease-specific measure	• 21 items, self-administered, measures the effects of symptoms, functional limitations, and psychological distress on an individual's quality of life • questions assess the impact of frequent physical symptoms, the effects of heart failure on physical/social functions, and side effects of treatments, hospital stays, and costs of care	• All items are 0-5 Likert-type scale in which a lower score reflects better health status.
Symptom Checklist – Frequency and Severity Scales Disease-specific measure	• 16 items for both scales, self-administered • measures the patient's perception of the frequency and severity of arrhythmia-related symptoms	Frequency Scale • All items are 0-4 Likert-type scale • Scores range from 0 (worst) to 64 (best) Severity Scale • All items are 1-3 Likert-type scale • Scores range from 0 (worst) to 48 (best)

Table H2. SF-36 domain scores from RCTs comparing RF ablation with medical therapy for the treatment of AF

SF-36 domains (mean ± SD)*	AF Type	1st/2nd line therapy	Study	Followup	RF Ablation	Medical Therapy	p-value
Physical functioning	Paroxysmal	1st line	Wazni 2005[59]		n = 32	n = 35	
				Baseline	71 ± 3	69 ± 2	NR
				6 months	97 ± 3	75 ± 7.5	0.001
		2nd line	Pappone 2011[58]		n = 99	n = 99	
				Baseline	69 ± 18	68 ± 21	NS
				48 months	85 ± 12	82 ± 15	NR
	Persistent	1st/2nd line	Hunter 2014		n = 26	n = 24	
				6 months	71%	49.1%	p = 0.007
	Mixed population	2nd line	Forleo 2009[66]		n = 35	n = 35	
			(Diabetes)	Baseline	NR	NR	
				Difference in mean change at 12 months between groups	NR	NR	8.4† <0.05
Role physical	Paroxysmal	1st line	Wazni 2005[59]		n = 32	n = 35	
				Baseline	73 ± 5	51 ± 5	NR
				6 months	71 ± 2	53 ± 3	0.047
		2nd line	Pappone 2011[58]		n = 99	n = 99	
				Baseline	63 ± 19	61 ± 17	NS
				48 months	82 ± 14	80 ± 15	NR
	Persistent	1st/2nd line	Hunter 2014		n = 26	n = 24	
				6 months	67.5%	42.4%	p = 0.004
	Mixed population	2nd line	Forleo 2009[66]		n = 35	n = 35	
			(Diabetes)	Baseline	NR	NR	
				Difference in mean change at 12 months between groups	NR	NR	NS
Bodily pain	Paroxysmal	1st line	Wazni 2005[59]		n = 32	n = 35	
				Baseline	71 ± 3	70 ± 3	NR
				6 months	97 ± 1	90 ± 3	0.004
		2nd line	Pappone 2011[58]		n = 99	n = 99	
				Baseline	68 ± 19	66 ± 24	NS
				48 months	80 ± 17	77 ± 21	NR
	Persistent	1st/2nd line	Hunter 2014		n = 26	n = 24	
					78.8%	57.1%	p = 0.005

SF-36 domains (mean ± SD)*	AF Type	1st/2nd line therapy	Study	Followup	RF Ablation	Medical Therapy	p-value
	Mixed population	2nd line	Forleo 2009[66]		n = 35	n = 35	
			(Diabetes)	Baseline	NR	NR	
				Difference in mean change at 12 months between groups	NR	NR	5.9† <0.05
General health	Paroxysmal	1st line	Wazni 2005[59]		n = 32	n = 35	
				Baseline	57 ± 2	57 ± 2	NR
				6 months	NR‡	68 ± 2	<0.001
		2nd line	Pappone 2011[58]		n = 99	n = 99	
				Baseline	65 ± 17	67 ± 17	NS
				48 months	79 ± 15	77 ± 16	NR
	Persistent	1st/2nd line	Hunter 2014		n = 26	n = 24	
					NR	NR	NS
	Mixed population	2nd line	Forleo 2009[66]		n = 35	n = 35	
			(Diabetes)	Baseline	NR	NR	
				Difference in mean change at 12 months between groups	NR	NR	8.9† <0.05
Vitality	Paroxysmal	1st line	Wazni 2005[59]		n = 32	n = 35	
				Baseline	52 ± 4	51 ± 1	NR
				6 months	65 ± 1	60 ± 2	.21
		2nd line	Pappone 2011[58]		n = 99	n = 99	
				Baseline	56 ± 22	55 ± 18	NS
				48 months	71 ± 23	68 ± 21	NR
	Persistent	1st/2nd line	Hunter 2014		n = 26	n = 24	
					54.3%	36.4%	p = 0.009
	Mixed population	2nd line	Forleo 2009[66]		n = 35	n = 35	
			(Diabetes)	Baseline	NR	NR	
				Difference in mean change at 12 months between groups	NR	NR	NS
Social Functioning	Paroxysmal	1st line	Wazni 2005[59]		n = 32	n = 35	
				Baseline	78 ± 3	76 ± 3	NR
				6 months	93 ± 3	82 ± 2	0.004
		2nd line	Pappone 2011[58]		n = 99	n = 99	
				Baseline	68 ± 22	66 ± 20	NS
				48 months	87 ± 14	86 ± 14	NR

SF-36 domains (mean ± SD)*	AF Type	1st/2nd line therapy	Study	Followup	RF Ablation	Medical Therapy	p-value
	Persistent	1st/2nd line	Hunter 2014		n = 26	n = 24	
					NR	NR	NS
	Mixed population	2nd line	Forleo 2009[66]		n = 35	n = 35	
			(Diabetes)	Baseline	NR	NR	
				Difference in mean change at 12 months between groups	NR	NR	7.7† <0.05
Role emotional	Paroxysmal	1st line	Wazni 2005[59]		n = 32	n = 35	
				Baseline	70 ± 1	70 ± 1	NR
				6 months	76 ± 1	75 ± 1	.90
		2nd line	Pappone 2011[58]		n = 99	n = 99	
				Baseline	70 ± 24	70 ± 22	NS
				48 months	86 ± 18	84 ± 19	NR
	Persistent	1st/2nd line	Hunter 2014		n = 26	n = 24	
					NR	NR	NS
	Mixed population	2nd line	Forleo 2009[66]		n = 35	n = 35	
			(Diabetes)	Baseline	NR	NR	
				Difference in mean change at 12 months between groups	NR	NR	6.8† <0.05
Mental health	Paroxysmal	1st line	Wazni 2005[59]		n = 32	n = 35	
				Baseline	65 ± 4	64 ± 2	NR
				6 months	65 ± 2	68 ± 3	0.62
		2nd line	Pappone 2011[58]		n = 99	n = 99	
				Baseline	66 ± 21	67 ± 19	NS
				48 months	81 ± 17	78 ± 17	NR
	Persistent	1st/2nd line	Hunter 2014		n = 26	n = 24	
					NR	NR	NS
	Mixed population	2nd line	Forleo 2009[66]		n = 35	n = 35	
			(Diabetes)	Baseline	NR	NR	
				Difference in mean change at 12 months between groups	NR	NR	NS

AF = atrial fibrillation; NR = not reported; NS = not significant; RF = radiofrequency; SD = standard deviation; SF-36 = Short Form-36 Questionnaire.
*A higher score reflects better health status.
†Difference in mean change of QoL scores between groups. Favored RF Ablation.
‡Authors report this value as 9 ± 1; however, this appears to be a typo in the article and the correct value cannot be ascertained. The authors report that the improvement in quality of life of patients in the ablation group was significantly better than the improvement in quality of life in the medical group.

Table H3. SF-36 domain scores from comparative observational studies comparing RF ablation with medical therapy for the treatment of AF

SF-36 domains (mean ± SD)*	AF Type†	Study‡	Followup	RF Ablation	Medical Therapy	p-value
Physical functioning	Persistent	Blandino 2013[71]		n = 153	n = 259	
			Baseline	44.2 ± 25.4	58.7 ± 25.2	<0.001
			Change from baseline (mean 60 months)	36.4 ± 33.4	9.9 ± 35.3	<0.001
	Paroxysmal	Yu 2012[70]		n = 97	n = 102	
			Baseline	83.17 ± 12.98	81.29 ± 22.44	NR
			12 months	85.26 ± 11.40	83.10 ± 16.12	NR
Role physical	Persistent	Blandino 2013[71]		n = 153	n = 259	
			Baseline	25.5 ± 37.6	59.0 ± 42.2	<0.001
			Change from baseline (mean 60 months)	61.2 ± 53.4	10.5 ± 53.6	<0.001
	Paroxysmal	Yu 2012[70]		n = 97	n = 102	
			Baseline	54.12 ± 16.72	52.70 ± 8.06	NR
			12 months	63.45 ± 10.10	57.48 ± 8.14	NR
Bodily pain	Persistent	Blandino 2013[71]		n = 153	n = 259	
			Baseline	86.9 ± 18.8	99.3 ± 5.1	<0.001
			Change from baseline (mean 60 months)	0.8 ± 23.8	–1.5 ± 10.3	0.21
	Paroxysmal	Yu 2012[70]		n = 97	n = 102	
			Baseline	92.91 ± 14.20	90.06 ± 14.89	NR
			12 months	95.11 ± 11.13	91.17 ± 10.41	NR
General health	Persistent	Blandino 2013[71]		n = 153	n = 259	
			Baseline	33.6 ± 16.8	57.2 ± 18.1	<0.001
			Change from baseline (mean 60 months)	44.2 ± 26.0	6.1 ± 25.3	<0.001
	Paroxysmal	Yu 2012[70]		n = 97	n = 102	
			Baseline	51.65 ± 12.78	48.06 ± 13.11	NR
			12 months	54.86 ± 9.75	51.58 ± 13.53	NR
Vitality	Persistent	Blandino 2013[71]		n = 153	n = 259	
			Baseline	38.6 ± 18.1	52.0 ± 15.9	<0.001
			Change from baseline (mean 60 months)	37.0 ± 29.8	4.7 ± 23.1	<0.001
	Paroxysmal	Yu 2012[70]		n = 97	n = 102	
			Baseline	66.08 ± 11.57	59.42 ± 14.69	NR
			12 months	73.56 ± 9.74	64.76 ± 10.54	NR
Social Functioning	Persistent	Blandino 2013[71]		n = 153	n = 259	
			Baseline	42.4 ± 19.4	79.8 ± 20.3	<0.001
			Change from baseline (mean 60 months)	38.1 ± 35.1	3.2 ± 22.0	<0.001

SF-36 domains (mean ± SD)*	AF Type†	Study‡	Followup	RF Ablation	Medical Therapy	p-value
Role emotional	Paroxysmal	Yu 2012[70]		n = 97	n = 102	
			Baseline	66.88 ± 15.84	59.47 ± 15.64	NR
			12 months	69.90 ± 16.22	58.00 ± 12.16	NR
	Persistent	Blandino 2013[71]		n = 153	n = 259	
			Baseline	31.2 ± 41.2	81.3 ± 35.2	<0.001
			Change from baseline (mean 60 months)	53.6 ± 49.5	–0.7 ± 36.6	<0.001
Mental health	Paroxysmal	Yu 2012[70]		n = 97	n = 102	
			Baseline	77.32 ± 18.05	69.40 ± 17.20	NR
			12 months	83.96 ± 10.45	73.02 ± 11.29	NR
	Persistent	Blandino 2013[71]		n = 153	n = 259	
			Baseline	45.2 ± 21.2	61.8 ± 14.2	<0.001
			Change from baseline (mean 60 months)	36.7 ± 30.9	3.7 ± 19.5	<0.001
	Paroxysmal	Yu 2012[70]		n = 97	n = 102	
			Baseline	73.15 ± 13.01	67.83 ± 15.89	NR
			12 months	80.21 ± 11.26	69.78 ± 12.77	NR

AF = atrial fibrillation; NR = not reported; RF = radiofrequency.
*A higher score reflects better health status.
†All treatments were a second-line therapy for AF.
‡Blandino et al. 2013 is a Medicare population (age ≥ 75 years). All other studies represent the general adult population.

Table H4. Adverse events for case series evaluating catheter ablation for the treatment of AF

Adverse Event	Number of Studies (N)	Number of Patients	Energy Type	Percent Patients
MAJOR EVENTS (< 30 DAYS)				
Mortality (all cause)	5[84-88]	N = 1000–5947	RF	0%–0.4%
	2[89, 90]	1190–93,801 procedures	RF	0%–0.4% procedures
	4[91-94]	N = 1273–15,423	Mixed	0.1%–0.8%
Stroke (any type)*	6[84, 85, 87, 88, 95, 96]	N = 1000–7217	RF	0.08%–0.71%
	1[90]	1190 procedures	RF	0.8% procedures
	2[93, 94]	4156–6207	Mixed	0.2%–0.6%
Stroke/TIA	2[89, 97]	1506–93,801 procedures	RF	0.4%–1.0% procedures
	2[91, 92]	N = 1273–15,423	Mixed	0.7%–0.8%
Transient ischemic attack	6[84-88, 95]	N = 1000–5947	RF	0.1%–0.6%
	1[90]	1190 procedures	RF	0.3% procedures
	1[93]	N = 4156	Mixed	0.07%
Other embolic events	2[84 , 88]	N = 1294–5947	RF	0.08%–0.7%
Myocardial infarction	1[88]	N = 5947	RF	0.3%
	1[89]	93,801 procedures	RF	0.37% procedures
	1[92]	N = 15,423	Mixed	0.31%
Bleeding (major)/ hemorrhage/ transfusion	1[88]	N = 5947	RF	3.7%
	3[89, 90, 97]	1190–93,801 procedures	RF	0.07%–4.0% procedures
	1[94]	N = 6207	Mixed	2.1%
Other major events	1[91]	N = 1273	Mixed	0.8%
ABLATION-RELATED EVENTS†				
Cardiac tamponade*	4[85-87, 96]	N = 1000–7217	RF	0.6%–1.3%
	1[90]	1190 procedures	RF	1.1% procedures
	3[91, 93, 94]	N = 1273–6207	Mixed	2.5%–6.7%
	1[98]	34,943 procedures	Mixed	0.8% procedures
Cardiac tamponade or pericardial effusion	1[97]	1506 procedures	RF	0.8% procedures
Pericardial effusion or cardiac tamponade requiring pericardiocentesis	1[88]	N = 5947	RF	0.42%
Pericardial effusion	4[84, 85, 88, 99]	N = 1011–5947	RF	0.1%–6.0%
Pericardial effusion or cardiac tamponade requiring pericardiocentesis	1[88]	N = 5947	RF	0.4%
	1[97]	1506 procedures	RF	0.8% procedures
	1[92]	N = 15,423	Mixed	1.7%
Pericardial complications	1[89]	93,801 procedures	RF	1.5% procedures
Pulmonary vein stenosis	4[84, 85, 87, 99]	N = 1000–1380	RF	0%–0.4%
	2[90, 97]	1190–1506 procedures	RF	0.08%–0.4% procedures
	1[91]	N = 1273	Mixed	0.2%

Adverse Event	Number of Studies (N)	Number of Patients	Energy Type	Percent Patients
Hematoma	2[91, 94]	N = 1273–6207	Mixed	2.1%–3.7%
Atrioesophageal fistula	3[84, 87, 99]	N = 1000–1380	RF	0%–0.2%
	2[90, 97]	1190–1506 procedures	RF	0%–0.07% procedures
Arteriovenous fistula	2[85, 87]	N = 1000–1011	RF	0.1%–0.3%
	2[90, 97]	1190–1506 procedures	RF	0.2%–0.7% procedures
Atrioventricular fistula	1[86]	N = 4212	RF	0.2%
Persistent postoperative fistula (not otherwise specified)	1[88]	N = 5947	RF	0.1%
Phrenic nerve paralysis	5[84, 85, 88, 99, 100]	N = 1011–5947	RF	0%–0.5%
	1[90]	1190 procedures	RF	0% procedures
Phrenic nerve injury	1[97]	1506 procedures	RF	0.13% procedures
Heart block	1[85]	N = 1011	RF	0.1%
	1[90]	1190 procedures	RF	0.08% procedures
Perforation at transseptal puncture	1[85]	N = 1011	RF	0.1%
Esophageal perforation	1[86]	N = 4212	RF	0.05%
Endocarditis	1[87]	N = 1000	RF	0.2%
Pneumothorax	2[85, 88]	N = 1011–5947	RF	0.1%–0.3%
	1[89]	93,801 procedures	RF	0.4% procedures
Hemothorax	1[85]	N = 1011	RF	0.1%
	1[90]	1190 procedures	RF	0.2% procedures
Pneumothorax or Hemothorax	1[93]	N = 4156	Mixed	0.1%
Mitral valve injury	1[90]	1190 procedures	RF	0.1% procedures
Iatrogenic cardiac complications	1[89]	93,801 procedures	RF	1.2% procedures
Other iatrogenic respiratory complications	1[89]	93,801 procedures	RF	0.2% procedures
PERIPHERAL VASCULAR COMPLICATIONS				
Hematoma at insertion site	1[99]	N =1380	RF	0.4%
	1[97]	1506 procedures	RF	0.2% procedures
Vascular injury due to access	1[84]	N = 1294	RF	2.4%
	1[91]	N = 1273	Mixed	0.1%
Vascular complication requiring surgical repair	1[89]	93,801 procedures	RF	1.0% procedures
	2[92, 93]	N = 4156–15,423	Mixed	0.5%–2.6%
Retroperitoneal hematoma	1[87]	N = 1000	RF	0.1%
Pseudoaneurysm	2[85, 87]	N = 1000–1011	RF	0.6%–1.0%
	2[90, 97]	1190–1506 procedures	RF	0.6% procedures
OTHER ADVERSE EVENTS				
Postoperative infectious complications	1[89]	93,801 procedures	RF	0.4% procedures
Deep vein thrombosis	2[84, 87]	N = 1000–1294	RF	0.08%–0.1%
	1[97]	1506 procedures	RF	0.07% procedures
Respiratory compromise/failure	2[89, 90]	1190–93,801 procedures	RF	0.4%–0.8% procedures
Aspiration with or without pneumonia	1[87]	N = 1000	RF	0.2%
Pulmonary hypertension	1[99]	N = 1380	RF	1.4%

Adverse Event	Number of Studies (N)	Number of Patients	Energy Type	Percent Patients
Requiring open heart surgery	1[89]	93,801 procedures	RF	0.3% procedures
Hospitalization (all-cause)	1[93]	N = 4156	Mixed	9.4%
Anaphylaxis	1[97]	1506 procedures	RF	0.13% procedures
Radiation burn	1[97]	1506 procedures	RF	0.07% procedures
Air embolism with transient ST changes	1[97]	1506 procedures	RF	0.07% procedures
Fluid overload prolonging hospitalization	1[97]	1506 procedures	RF	0.13% procedures

Mixed: radiofrequency ablation or cryoballoon ablation (not reported separately); RF: radiofrequency ablation only.

*One of the included studies is a meta-analysis of case-series of AF ablation (D'Ascenzo 2013).

†Denominator is the number of patients who underwent the procedure.

Table H5. Table of FDA-Approved Catheter Ablation Devices

Device (PMA #)	Date Approved	Manufacturer
Atrial Fibrillation		
NAVISTAR® THERMOCOOL® and EZ Steer THERMOCOOL® Nav Irrigated Deflectable Diagnostic/Ablation Catheter for Treatment of Paroxysmal Atrial Fibrillation (P030031S011)	2009	Biosense Webster, Inc.
Arctic Front® Cardiac CryoAblation Catheter (P100010) Includes models 2AF232 and 2AF282; Freezor® *MAX* Cardiac CryoAblation Catheter (Models 239F3 and 239F5); CryoConsole (Model 106A2); Manual Retraction Kit (Model 20MRK)	2010	Medtronic Cryocath, LP
Arctic Front Advance™ Cardiac Cryoballoon	2012	Medtronic Cryocath, LP
Atrial Flutter		
NaviStar DS and Celsius DS Diagnostic/Ablation Catheters, Stockert 70 RF Generator and accessories (P010068)	2002	Biosense Webster, Inc.
Blazer II XP™ Cardiac Ablation Catheter, EPT-1000 XP Cardiac Ablation Controller and Accessories (P020025)	2003	Boston Scientific Corporation, Electrophysiology Division
NAVISTAR™ and CELSIUS™ THERMOCOOL® Irrigated Deflectable Diagnostic/Ablation Catheter (P030031)	2004	Biosense Webster, Inc.
IBI Therapy™ Dual 8™ Ablation Catheter and IBI 1500T6 (USA) Cardiac Ablation Generator (P040042)	2005	Irvine Biomedical, Inc.
IBI Therapy™ Cool Path™ Ablation Catheter and IBI 1500T9 RF Generator (P060019)	2007	Irvine Biomedical, Inc.
CryoCor Cryoablation System (CryoBlator Catheters & Model 2020 Console) (P050024)	2007	CryoCor, Inc.
Helios II Ablation Catheter (P050029)	2008	Stereotaxis, Inc.
Therapy Cool Path Duo™ Ablation Catheter, Safire BLU Duo™ Ablation Catheter, and IBI1500T9-CP V1.6 Cardiac Ablation Generator (P110016)	2012	Irvine Biomedical, Inc.
Other indications		
Blazer II™ Cardiac Ablation Catheter, EPT-1000 Cardiac Ablation Controller and Accessories (P920047)	1994	Boston Scientific Corporation, Electrophysiology Division
Atakr™ Radiofrequency Catheter Ablation (RFCA) System (P930029)	1995	Medtronic, Inc.
Webster Diagnostic/Ablation Deflectable Tip Catheter (P950005)	1997	Cordis Corporation
Chilli Cooled RF Ablation System (P980003) Includes Chilli Cooled Ablation Catheter, Standard Curve, and Chilli Cooled Ablation Catheter, Large Curve	1999	Boston Scientific Corporation
Livewire TC® Steerable Electrophysiology Catheter and Accessory Cables (P960016)	1999	Daig Corporation
Stinger™ Ablation Catheter and TempLink™ Extension Cable (P000020**)**	2000	C.R. Bard, Inc., Bard Electrophysiology Division
NAVISTAR™ Diagnostic/Ablation Deflectable Tip Catheter (P990025)	2000	Biosense Webster, Inc.
7F Freezor® Cardiac Cryoablation Catheter and CCT.2 CryoConsole System (P020045)	2003	Medtronic Cryocath, LP
IBI Therapy™ Cardiac Ablation System (P040014)	2005	Irvine Biomedical
NAVISTAR™ THERMOCOOL® Deflectable Diagnostic/Ablation Catheter (P040036)	2006	Biosense Webster, Inc.
FIRMap Catheter™ (K021232)	2013	Topera, Inc.

AF: atrial fibrillation; FDA: Food and Drug Administration; PMA: premarket approval number;

Table H6. Catheter details, mapping information and ablation approaches used in included studies

Study	Catheter Used	Mapping	Ablation Approach
RFA vs. Medical Therapy			
Randomized Controlled Trials			
Cosedis Nielsen, 2012	3.5-mm catheter with an irrigated tip (NaviStar ThermoCool, Biosense Webster) or an 8-mm solid-tip catheter (for 15 procedures; NaviStar DS, Biosense Webster).	• Carto®	• Circumferential PVI (%NR) • Roof of the atrium (%NR) • Cavotricuspid and mitral isthmuses (optional) (%NR)
Forleo, 2009	3.5 mm cooled-tip catheter	• NavX‡ with Carto®	• Circumferential PVI 100% (35/35) • Bidirectional cavotricuspid isthmus block 100% (35/35) • Mitral isthmus 23% (8/35) • Roofline ablation 9% (3/35)
Hunter, 2014	Irrigated-tip catheter	• Either Carto® or NavX‡	• Circumferential PVI (%NR) • PVI + lines (%NR) • Cavotricuspid lines (%NR)
Jais, 2008	Either a 3.5- or 5-mm irrigated tip (Thermocool, Biosense Webster; n95) or a 4-mm nonirrigated tip (n13)	• Lasso Circular mapping catheter§	• Left PVI 100% (53/53) • Right PVI 100% (53/53) • Right inferior vein isolation 100% (53/53) • Cavotricuspid isthmus 64.2% (34/53) • Roof of the left atrium 17% (9/53) • Mitral isthmus 30.2% (16/53) • Foci from nonvenous structures 22.6% (12/53)
Jones, 2013	3.5-mm irrigated-tip catheter (ThermoCool, Biosense Webster, Diamond Bar, California)	• NavX‡ mapping system with an AFoucsII catheter	• PVI (%NR) • Linear ablation to the left atrial roof and mitral isthmus (%NR) • Left atrial CFAE (%NR)
MacDonald, 2011	Irrigated tip ablation catheter (ThermoCool, Biosense Webster)	• Pulmonary venous angiography and three-dimensional reconstruction of the left atrium using NavX‡ mapping system • Pulmonary vein recordings were performed with a duodecapolar variable-diameter circular mapping catheter (Lasso§ or Inquiry Optima‡‡)	• PVI with an additional adjoining roof line and further ablation at sites of CFAEs 100% (21/21) • Additional atrial flutter ablation 9.5% (2/21)
Mont, 2013	Cooled-tip catheter	• Carto® or NavX‡	• PVI 100% (93/93) • PVI + cavotricuspid isthmus 2% (2/93) • PVI + mitral isthmus line 3.1% (3/93) • PVI+ roof line 23.4% (23/93) • PVI + CFAE 8.1% (8/93)
Morillo, 2014	Selection of ablation catheter, power and irrigation settings, and use of navigation systems were left to the discretion of the investigator	• Nonfluroscopic mapping systems were used in 86% of patients (no other details)	• Circumferential PVI 98.5% (65/66) • PVI + cavotricuspid isthmus (%NR) • PVI + CFAE (%NR) • PVI+ roof line (%NR)

Study	Catheter Used	Mapping	Ablation Approach
Oral, 2006	Temperature-controlled, quadripolar, deflectable catheter with an 8-mm tip (Navistar, Biosense Webster)	• Carto®	• PVI: 100% (77/77) • PVI + cavotricuspid isthmus: 71% (55/77)
Pappone, 2006; 2011	Either an 8-mm standard catheter (Navi-Star, Biosense-Webster or Livewire TC, St. Jude Medical, St. Paul, Minnesota) or an irrigated tip catheter (3.5-mm Cool-Path, St. Jude Medical or Thermo-Cool Navi-Star, Biosense-Webster)	• Either Carto® or NavX‡	• Circumferential PVI 100% (99/99) • PVI + cavotricuspid isthmus 100% (99/99)
Stabile, 2006	8 mm tip catheter	• Carto®	• PVI + mitral isthmus, cavo-tricuspid isthmus, and circumferential PV ablation 100% (68/68), of these patients 13 patients had already undergone cavo-tricuspid ablations, only 55 of those procedures were completed during these trials
Wazni, 2005	8-mm tip ablation catheter (Biosense Webster, Baldwin Park, Calif, and EP Technologies, Sunnyvale, Calif)	• Multipolar mapping catheter (no other details)	• PVI of all 4 veins 100% (33/33)
Wilber, 2010; Reynolds 2010	NaviStar ThermoCool Irrigated Tip Catheter; (Biosense Webster, Diamond Bar, California)	• Carto®	• PVI 100% (103/103) • PVI + cavotricuspid isthmus 35.9% (37/103) • PVI + superior vena cava 16.5% (17/103) • PVI + other left/ right atrial foci 16.5% (17/103) • PVI + at least 1 left atrial linear lesion (including mitral isthmus and roof lines) 22.3% (23/103)
Comparative Observational Studies			
Blandino, 2013	3.5-mm irrigated tip ablation catheter (Navistar, Biosense Webster, Diamond Bar, CA, USA)	• Carto®	• PVI + cavotricuspid isthmus100% (153/153) • Linear lesions interconnecting the upper PV ostia (roof line) and the left inferior PV with the mitral annulus (left isthmus line) 60% (92/153); only performed in cases of AF persistence despite PVI
Lan, 2009	8-mm tip catheter and/or the cooled 4-mm tip	• NR	• CPVA 50% (60/120) • SPVI 50% (60/120)
Reynolds, 2012	NR	• NR	• PVI + superior vena cava 100% (85/85)
Rossillo, 2008	8mm tip catheter (Biosense-Webster)	• Mapping was carried out (no other details)	• PVI + superior vena cava 100% (85/85)

Study	Catheter Used	Mapping	Ablation Approach
Sang, 2013	3.5-mm cool saline-irrigated ablation catheter (Navi-Star Thermo-Cool; Biosense-Webster Inc., Diamond Bar, CA)	• Carto*, sometimes PV isolation was confirmed with a Lasso circular mapping catheter	• Modified Brockenbrough technique; Circumferential isolation of the right pulmonary vein (PV) antrum (PVA) was performed first, followed by isolation of the left PVA %NR (n's NR)
Sonne, 2009	NR	• NR	• Pulmonary vein antrum isolation 100% (146/146)
Yu, 2012	Navigation catheter	• Carto*	• Circumferential PVI 100% (97/97)
Cryoballoon Ablation vs. Medical			
Randomized Controlled Trials			
Packer, 2013; Andrade, 2014	Cryo: 23- or 28-mm (Medtronic, Inc.) Arctic Front cryoablation balloon catheter	Cryo: • Pacing and a circular mapping catheter used (no other details)	• PVI of the four major PV's 97.6% (159/163) • PVI achieved with the balloon catheter alone in 83% (135/163) • Additional catheter based focal cryoablation in one or more PVs for 16.6% (27/163) • Left common PV isolation 100% (21/21) • Right middle PVs 76.9% (10/13) • Cavotricuspid isthmus ablation with bidirectional block achieved in 97% (64/66)
Cryoballoon Ablation vs. RFA			
Randomized Controlled Trials			
Herrera Siklody, 2012	RFA: • Open irrigated tip catheter (ThermoCool, Biosense Webster, Diamond Bar, CA, USA) Cryoballoon: • ArcticFront balloon (CryoCath, Medtronic, Minneapolis, MN USA) 28-mm balloon, 7 with a 23-mm balloon, and 2 using both sizes • Touch up with 10-mm cryoablation catheter (Freezor MAX, CryoCath, Medtronic)	RFA: • NavX‡ Cryoballoon: • Circular mapping catheter**	• Circumferential PVI of both ipsilateral veins with no further ablation beyond PVI allowed during the index procedure • Electrical isolation was completed with focal applications 33% (10/30) in the cryoballoon group

Study	Catheter Used	Mapping	Ablation Approach
Perez-Castellano, 2014	RFA: • 3.5-mm open-irrigated tip ablation catheter (Navistar ThermoCool, Biosense Webster) Cryoballoon: • Arctic Front cryoablation balloon catheter (23 or 28 mm)	RFA: • Carto[†] • Selective PV angiograms were obtained through a 6-F angled pigtail catheter (Supertorque Plus)[††] Cryoballoon: • Lasso circular decapolar catheter[§]	• PVI (100%) • Right inferior PV (1% each group) • Bidirectional block (83% cryo, 100% RFA) • Cavotricuspid isthmus ablation (4% cryo, 5% RFA)
Comparative Observational Studies			
Chierchia, 2010	RFA: • Open irrigated cool tip 3.5 mm catheter (Navistar, Biosense Webster, Inc.) Cryoballoon: • 28 mm double-walled cryoballoon (Arctic Front, Cryocath, Medtronic)	RFA: • Carto[*] Cryoballoon: • Lasso circular mapping catheter[§]	• Circumferential PVI with no additional lines 100% • No touch-ups performed
Knecht, 2014	RFA: • 3.5 mm open irrigated-tip catheter Cryoballoon: • Arctic Front, Medtronic, Minneapolis, USA, 23-mm or other size	RFA: • Carto3 or CartyXP systems (69%) • NavX system[‡] (31%) Cryoballoon: • Lasso2515 20-pole circumferential mapping catheter[§]	• Acute PVI (100%) • Some cryoballoon patients required RFA to complete PVI (28.2%; 20/71) (authors report propensity score matched subgroup analysis in those patients who received cryoballoon only (n = 51) vs. RFA (n = 51))
Kojodjojo, 2010	RFA: • 4mm cooled tipped catheter (Thermocool, Biosense Webster, USA) • OR 8 mm tipped radiofrequency catheter for cavotricuspid ablation (IBI, St Jude Medical, USA) (60W, 608C) Cryoballoon: • 28 mm cryoablation balloon (Arctic Front, Medtronic, USA) • Any residual LA-PV connections were treated by focal cryoablation (Freezor Max, Medtronic, USA)	RFA: • Either fluoroscopy or Carto[*] Cryoballoon: • Inquiry Optima curvilinear mapping catheter[‡‡] or Lasso[§]	• PVI alone (15% RFA, 40% cryo) • PVI + Ostial focal cryoablaiton (60% cryo) • PVI + Cavotricuspid isthmus ablation with RFA catheter (11% RFA, 23% cryo)

Study	Catheter Used	Mapping	Ablation Approach
Mandell, 2013	RFA: NR Cryoballoon: • Arctic Front Cardiac CryoAblation balloon catheter (Medtronic, Inc)	Imaging was performed in all patients using: • Intracardiac echocardiography (to assist with the transeptal punctures and monitor for pericardial effusion) • single-plane fixed fluoroscopy • NavX‡	RFA: • PVI only 79% (49/62) • PVI + cavotricuspid isthmus for atrial flutter 9.7% (6/62) • PVI + supraventricular tachycardia 1.6% (1/62) • PVI + superior vena cava 3.2% (2/62) • PVI + lines 1.6% (1/62) • PVI + cavotricuspid isthmus for atrial flutter + lines 1.6% (1/62) • CFE only 1.6% (1/62) • PVI + CFE 1.6% (1/62) Cryo: • PVI only 75.8% (47/62) • PVI + cavotricuspid isthmus for atrial flutter 21% (13/62) • PVI + lines 3% (2/62) • Touch-up ablation with RFA 11% (7/62)
Mugnai, 2014	RFA: • Open irrigated cool tip 3.5-mm catheter (NaviStar ThermoCool; Biosense Webster Inc.) Cryoballoon: • A first-generation 28-mm double-walled CB (Arctic Front; Cryocath)	RFA: • Lasso circumferential mapping catheter§ • And Carto* Cryoballoon: • Lasso circular mapping catheter§	• PVI (100%) • Cryo: Focal touch-up with either a focal-tip cryocatheter (Freezor Max; CryoCath Technologies Inc., Montreal, Quebec, Canada) or an irrigated-tip RF catheter (NaviStar ThermoCool; Biosense Webster Inc.) (3.7%, 5/136)
Schmidt, 2014	RFA: • RF Catheter Cryoballoon: • Arctic Front, Medtronic, Minneapolis, MN, USA; 23-mm or 28-mm balloon	RFA: • Fluoroscopy • OR Carto* with or without integration of preprocedural imaging • OR intracardiac echocardiography-guided mapping using a 10-Fr 64 element phased-array ultrasound imaging catheter (AcuNav§§) Cryoballoon: • Conventional mapping (no further details)	• PVI (100%) • Cryo: Additional touch-up freezes with a conventional cryocatheter (Freezor MAX, CryoCath, Medtronic) or an RF catheter could be performed if deemed necessary: touchup focal cryoablation was reported in 10.6% of patients

CB: cryoballoon; CFE: continuous fractionated electrical activity; FU: Followup; NR: not reported; PVI: pulmonary venous isolation; RFA: Radiofrequency Ablation; SVC: superior vena cava; SVT: supraventricular tachycardia

*CARTO (Biosense Webster, Diamond Bar, CA, USA)

†(Biosense Webster, Tirat-Hacarmel, Israel)

‡Ensite NavX (Endocaridal Solutions, St. Jude Medical, St. Paul, MN, USA)

§Lasso Catheter (Biosense Webster, Inc, Diamond Bar, Calif)

**Circular mapping catheter (Optima, St. Jude Medical)

††Supertorque Plus (Cordis Corp, Miami, FL)

‡‡Inquiry Optima (St Jude Medical)

§§AcuNav (Siemens Medical Solution, Malvern, PA, USA)

Table H7. Study definitions of AF Recurrence and study reported techniques for monitoring recurrences

Study	Study Definition of Recurrence	Recurrence Monitoring Technique
RFA vs. Medical Therapy		
Randomized Controlled Trials		
Cosedis Nielsen, 2012[54]	Any AF (not defined further) or symptomatic AF (not defined further)	7-day Holter-monitor recording
Forleo, 2009[66]	Any ECG confirmed episode of AF or atypical atrial flutter lasting 30 seconds	All patients were instructed to regularly assess their pulse and to confirm on electrocardiogram (ECG Holter monitor) any suspected recurrence of arrhythmia.
Hunter, 2014[61]	Documented AF/atrial tachycardia lasting ≥30 seconds	12-lead ECG, and 48-hour ambulatory ECG monitoring at baseline and FU visits
Jais, 2008[55]	AF lasting ≥ 3 minutes and documented by ECG or reported by the patients as AF (even in the absence of ECG confirmation)	12-lead ECG, and 24-hour ambulatory Holter recording at baseline and FU visits
Jones, 2013[65]	Atrial arrhythmia (assessed by ECG) lasting > 30 seconds	ECG rhythm documentation, plus 48-h ambulatory monitoring
MacDonald, 2011[62]	Maintenance of sinus rhythm (not defined further)	12-lead ECG; 24 h ambulatory ECG monitoring at baseline and final study visit
Mont, 2013; Wynn 2014[63, 101]	AF or flutter lasting >24 hours or requiring cardioversion OR AF or flutter lasting ≥30 seconds	12-lead ECG. A 24-h Holter monitor at followup
Morillo, 2014[56]	Symptomatic or asymptomatic atrial tachyarrhythmia (AF, atrial flutter, atrial tachycardia) lasting > 30 seconds OR Symptomatic atrial tachyarrhythmia lasting > 30 seconds OR Symptomatic AF lasting > 30 seconds	Detected by either scheduled or unscheduled electrocardiogram, Holter, transtelephonic monitor, or rhythm strip.
Oral, 2006[64]	AF or atrial flutter >3 seconds, documented by an event monitor (LifeWatch)	Cardiac rhythm was assessed with daily telephonic transmissions
Pappone, 2006; 2011[57, 58]	Atrial tachyarrhythmias (including both AF and atrial tachycardia)	12-lead ECG, 48-h Holter monitoring
Stabile, 2006[67]	At least one occurrence of atrial arrhythmia (flutter or fibrillation) lasting >30 seconds	Multiple ECG and Holter monitoring, and, daily transtelephonic recording of ECGs
Wazni, 2005[59]	Symptomatic or asymptomatic AF only lasting > 15 seconds during Holter or event monitoring	Patients were asked to record when they experienced symptoms and 2 to 3 times daily, even if they were asymptomatic. Additional event recorder monitoring at followup. Patients also monitored with a 24-hour Holter recording at followup. In addition, patients were called by telephone on a monthly basis.
Wilber, 2010; Reynolds 2010[60, 102]	Symptomatic or asymptomatic atrial arrhythmia (AF, atrial tachycardia, or atrial flutter) OR Symptomatic atrial arrhythmia	Holter monitoring at followup and patients were asked to transmit all symptomatic episodes.
Comparative Observational Studies		
Blandino, 2013[71]	AF/AT lasting more than 30 seconds documented by an ECG	ECG and 24-hour Holter monitoring during visits. Between visits, all patients were encouraged to document any symptoms suggestive for AF/atrial tachycardia (AT) recurrence by a 12-lead ECG. Furthermore, routinely every month, a physician performed trans-telephonic monitoring
Lan, 2009[68]	AF (>30 s in duration) documented by 12-lead ECG or Holter	Holter or conventional 12-lead ECG at followup. All patients were followed by telephone and had physical and ECG examinations

Study	Study Definition of Recurrence	Recurrence Monitoring Technique
Reynolds, 2012[72]	NR	NR
Rossillo, 2008[73]	NR	24-h Holter recording during the first 3 months of followup and daily pulse check
Sang, 2013[69]	Any symptomatic episodes of documented atrial tachyarrhythmias lasting ≥30 seconds, as well as any episode of asymptomatic atrial tachyarrhythmias lasting ≥10 minutes	12-lead electrocardiography and 24-hour ambulatory Holter recordings during followup
Sonne, 2009[74]	AF recurrence was defined as AF that persists 8 weeks after ablation	Measured by serial event recorder transmission and/or Holter monitoring; Patients were asked to transmit their rhythm status three times a day and whenever they experienced symptoms consistent with AF
Yu, 2012[70]	The AF recurrence was defined as the first documented AF recurrence >30 seconds	Twelve-lead and 24-hour ambulatory electrocardiograph were measured during followup or as soon as the patients first felt recurrent palpitations, whichever event occurred earlier; Ambulatory electrocardiographic recorders were used to correlate symptoms with arrhythmia recurrence
Cryoballoon Ablation vs. Medical		
Randomized Controlled Trials		
Packer, 2013; Andrade, 2014[75, 103]	AF occurrence (not defined further)	Personal trans-telephonic monitoring (TTM) systems were provided for weekly scheduled transmissions and recordings at the occurrence of arrhythmia symptoms; Twenty-four-hour Holter monitoring was required at 6 and 12 months.
Cryoballoon Ablation vs. RFA		
Randomized Controlled Trials		
Herrera Siklody, 2012[81]	Freedom from AF was defined as no symptoms of AF and no atrial arrhythmias lasting >30 seconds on Holter monitoring after a single procedure	24-hour Holter monitoring, holter monitoring and exercise testing at followup; Patients with symptoms of AF but no documentation on ECG or Holter monitoring were provided with an event monitor for 8 weeks
Perez-Castellano, 2014[76]	Clinical or subclinical AF episode ≥2 minutes	Minutes recorded on ECG, Holter monitor, or ICM
Comparative Observational Studies		
Chierchia, 2010[77]	NR	NR
Knecht, 2014[78]	Episodes of AF (>30 s) or any sustained left atrial tachycardia were counted as recurrences	Physical examination, 12-lead ECG, 24-h Holter monitoring and a 7 day Holter at followup
Kojodjojo, 2010[82]	Recurrence was defined as any documented episode of AF (both symptomatic and asymptomatic) or atrial tachycardia lasting for more than 30 s	Repeated 24 h Holter monitoring and event recorders
Mandell, 2013[83]	NR	NR
Mugnai, 2014[79]	All documented episodes of atrial tachyarrhythmias lasting >30 seconds were considered as recurrence	Physical examinations, electrocardiography, and 24-hour Holter recording performed at followup
Schmidt, 2014[80]	NR	NR

AF: atrial fibrillation; AT: atrial tachycardia; ECG: electrocardiogram; FU: Followup; ICM: implantable cardiac monitor; NR: not reported; RFA: Radiofrequency Ablation; TTM: trans-telephonic monitoring

Table H8. Ongoing clinical trials

Study (Identifier)	Design	Estimated Completion	AF Type	Special Population	Notes
Cryo vs RFA					
Prevention of Atrial Fibrillation by Combined Right Isthmus Ablation and cryoBalloon Pulmonary Vein Isolation in Patients With Typical Atrial Flutter NCT01521988	RCT Line of therapy NR	June 2015	Mixed	None	RFA used in both treatment groups.
A Controlled, Prospective, Non-Inferiority, Parallel-Group, Randomised, Interventional, Open, Blinded Outcome Assessment (PROBE-Design), Multi-centre Trial, Comparing Efficacy and Safety of Isolation of the Pulmonary Veins With a Cryoballoon Catheter Versus a Radiofrequency Ablation With a ThermoCool Catheter in Patients With Paroxysmal Atrial Fibrillation NCT01490814	RCT 2nd line therapy	June 2016	Paroxysmal	None	
Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation: The Effect of Double Short vs. Standard Exposure Cryoablation Duration During Pulmonary Vein Isolation NCT01913522	RCT 2nd line therapy	January 2017	Paroxysmal	None	
Cryo vs Med					
Ablation as First Line Treatment in Paroxysmal Atrial Fibrillation NCT01466842	RCT 1st line therapy	January 2016	Paroxysmal	None	
Catheter Cryoablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation. NCT01803438	RCT 1st line therapy	June 2017	Paroxysmal	None	
RFA vs Med					
Comparison of Treatment of Atrial Fibrillation (AF) Between Surgical Ultrasonic Technology (EPICOR) or Drug Therapy (Cordarone) for Patients With AF Requiring Mitral Valve Surgery NCT01649544	RCT Line of therapy NR	May 2015	Mixed	All patients have mitral valvulopathy requiring surgery	
Comparison of a Rhythm Control Treatment Strategy Versus a Rate Control Strategy in Patients With Permanent or Long-term	RCT Line of therapy NR	July 2015	Mixed	All patients had prior cardiac resynchronization therapy	Med group undergoes EEC in addition to med therapy.

Study (Identifier)	Design	Estimated Completion	AF Type	Special Population	Notes
Persistent Atrial Fibrillation and Heart Failure Treated With Cardiac Resynchronization Therapy - a Pilot Study NCT01850277					Med group has the option to undergo ablation, but is not required of patients.
Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted ICD/CRTD NCT00729911	RCT 2nd line therapy	December 2015	Mixed	All patients have congestive heart failure and an implanted ICD/ CRTD	
Atrial Fibrillation Therapy: A Multi-Center Clinical Study NCT01341353	Non-randomized 1st line therapy	December 2015	"Symptomatic"	None	
Pulmonary Vein Ablation Versus Amiodarone in the Elderly NCT01276093	RCT 1st and 2nd line therapy	June 2016	Paroxysmal	All patients >/= 65 years old	
A Randomized Ablation-based Atrial Fibrillation Rhythm Control Versus Rate Control Trial in Patients With Heart Failure and High Burden Atrial Fibrillation NCT01420393	RCT Line of therapy NR	September 2016	Mixed	All patients have had heart failure	
Catheter Ablation Versus Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation NCT00643188	RCT 1st and 2nd line therapy	August 2019	Mixed	All patients have heart failure and an ICD	
Other					
Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial NCT00911508	RCT 1st line therapy	March 2018	Mixed	None	Either Cryoablation or RFA used in comparison to med.
Atrial Fibrillation Progression Trial NCT01570361	RCT 2nd line therapy	June 2018	Paroxysmal	All patients >/= 60 years old	Either Cryoablation or RFA used in comparison to med.

AF: atrial fibrillation; CRDT: cardiac resynchronization therapy; Cryo: cryoballoon ablation; ICD: Implantable cardiac defibrillator; NR: not reported; RCT: Randomized controlled trial; RFA: Radiofrequency ablation

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