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Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic drugs 	Interventions of interest are: <ul style="list-style-type: none"> Radiofrequency ablation or cryoablation 	Comparators of interest are: <ul style="list-style-type: none"> Medication management 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Symptoms Morbid events Quality of life
Individuals: <ul style="list-style-type: none"> With symptomatic atrial fibrillation and congestive heart failure who have failed rate control and antiarrhythmic drugs 	Interventions of interest are: <ul style="list-style-type: none"> Radiofrequency ablation or cryoablation 	Comparators of interest are: <ul style="list-style-type: none"> Atrioventricular nodal ablation and pacemaker insertion 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Symptoms Morbid events Quality of life
Individuals: <ul style="list-style-type: none"> With recurrent symptomatic paroxysmal atrial fibrillation 	Interventions of interest are: <ul style="list-style-type: none"> Radiofrequency or cryoablation as an initial rhythm-control strategy 	Comparators of interest are: <ul style="list-style-type: none"> Medication management 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Symptoms Morbid events Quality of life

DESCRIPTION

Atrial fibrillation (AF) frequently arises from an abnormal focus at or near the junction of the pulmonary veins and the left atrium, thus leading to the feasibility of more focused ablation techniques directed at these structures. Catheter-based ablation, using radiofrequency ablation (RFA) or cryoablation, is being studied as a treatment option for various types of AF.

SUMMARY OF EVIDENCE

For individuals who have symptomatic paroxysmal or persistent AF who have failed antiarrhythmic drugs who receive RFA or cryoablation, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews. The relevant outcomes are overall survival, symptoms, morbid events, and quality of life (QOL). RCTs comparing RFA with antiarrhythmic medications have reported that freedom from AF is more likely after abla-

tion than after medications. Results of long-term follow-up (5-6 years) after ablation have demonstrated that late recurrences continue in patients who are free of AF at one year. However, most patients who are AF-free at one year remain AF-free at five to six years. Multiple RCTs comparing cryoablation with RFA have found that cryoablation is noninferior to RFA for AF control. RFA and cryoablation differ in their adverse event profiles. For example, cryoablation is associated with higher rates of phrenic nerve paralysis but may permit a shorter procedure time. Given current data, it would be reasonable to consider both RFA and cryoablation effective for catheter ablation of AF foci or pulmonary vein isolation, provided there is a discussion about the risks and benefits of each. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have symptomatic AF and congestive heart failure who have failed rate control and antiarrhythmic drugs who receive RFA or cryoablation, the evidence includes RCTs, and systematic reviews. The relevant outcomes are overall survival, symptoms, morbid events, and QOL. Findings from the RCTs have been supported by other comparative studies, which have reported improvements in AF. It is reasonable to consider both RFA and cryoablation effective for catheter ablation of AF foci or pulmonary vein isolation, provided that there is a discussion about the risks and benefits of each. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have recurrent symptomatic paroxysmal AF who receive RFA or cryoablation as an initial rhythm-control strategy, the evidence includes RCTs, nonrandomized studies, and systematic reviews. The relevant outcomes are overall survival, symptoms, morbid events, and QOL. The most current RCT with adequate follow-up compared pulmonary vein isolation by catheter ablation (using either cryoablation or radiofrequency ablation) to medical therapy. Catheter ablation was not superior to medical therapy for major cardiovascular outcomes but secondary outcomes including AF recurrence favored catheter ablation. QOL measures reported in this RCT favored catheter ablation. Two other RCTs with low-risk of bias compared catheter ablation for pulmonary vein isolation with antiarrhythmic medications. One RCT demonstrated reduced rates of AF recurrence, while the other reported reduced cumulative overall AF burden. Together, these results suggest that, when a rhythm-control strategy is desired, catheter ablation is a reasonable alternative to antiarrhythmic drug therapy. These RCTs comparing ablation with medical therapy were conducted using RFA, it is reasonable to consider both RFA and cryoablation effective for catheter ablation of AF foci or pulmonary vein isolation, provided that there is a discussion about the risks and benefits of each. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

POLICY

Transcatheter radiofrequency ablation or cryoablation to treat atrial fibrillation may be considered **medically necessary** as a treatment for either of the following indications which have failed to respond to adequate trials of antiarrhythmic medications:

- Symptomatic paroxysmal or symptomatic persistent atrial fibrillation; or
- As an alternative to atrioventricular nodal ablation and pacemaker insertion in patients with class II or III congestive heart failure and symptomatic atrial fibrillation.

Transcatheter radiofrequency ablation or cryoablation to treat atrial fibrillation may be considered **medically necessary** as an initial treatment for patients with recurrent symptomatic paroxysmal atrial fibrillation (more than one episode, with four or fewer episodes in the previous six months) in whom a rhythm-control strategy is desired.

Repeat radiofrequency ablation or cryoablation may be considered **medically necessary** in patients with recurrence of atrial fibrillation and/or development of atrial flutter following the initial procedure. (See Policy Guidelines)

Transcatheter radiofrequency ablation or cryoablation to treat atrial fibrillation is considered **investigational** as a treatment for cases of atrial fibrillation that do not meet the criteria outlined above.

POLICY GUIDELINES

Transcatheter treatment of AF may include pulmonary vein isolation and/or focal ablation.

There is no single procedure for catheter ablation. Electrical isolation of the pulmonary vein musculature (pulmonary vein isolation) is the cornerstone of most AF ablation procedures, but additional ablation sites may be included during the initial ablation. Potential additional ablation procedures include: creation of linear lesions within the left atrium; ablation of focal triggers outside the pulmonary veins; ablation of areas with complex fractionated atrial electrograms; and ablation of left atrial ganglionated plexi. The specific ablation sites may be determined by electroanatomic mapping to identify additional sites of excitation. As a result, sites may vary from patient to patient, even if they are treated by the same physician. Patients with long-standing persistent AF may need more extensive ablation. Similarly, repeat ablation procedures for recurrent AF generally involve more extensive ablation than do initial procedures.

As many as 30% of patients will require a follow-up (repeat) procedure due to recurrence of AF or to development of atrial flutter. In most of the published studies, success rates have been based on having as many as three separate procedures, although these repeat procedures may be more limited in scope than the initial procedure.

BACKGROUND

ATRIAL FIBRILLATION

AF is the most common cardiac arrhythmia, with an estimated prevalence of 0.4% of the population, increasing with age. The underlying mechanism of AF involves the interplay between electrical triggering events and the myocardial substrate that permits propagation and maintenance of the aberrant electrical circuit. The most common focal trigger of AF appears to be located within the cardiac muscle that extends into the pulmonary veins.

AF can be subdivided into three types: paroxysmal, persistent, and permanent. AF accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances. Symptoms of AF (e.g., palpitations, decreased exercise tolerance, dyspnea) are primarily related to poorly controlled or irregular heart rate. The loss of atrioventricular synchrony results in a decreased cardiac output, which can be significant in patients with compromised cardiac function. Also, patients with AF are at higher risk for stroke, with anticoagulation typically recommended. AF is also associated with other cardiac conditions, such as valvular heart disease, heart failure, hypertension, and diabetes. Although episodes of AF can be converted to normal sinus rhythm using pharmacologic or electroshock conversion, the natural history of AF is that of recurrence, thought to be related to fibrillation-induced anatomic and electrical remodeling of the atria.

Treatment strategies can be broadly subdivided into rate control, in which only the ventricular rate is controlled, and the atria are allowed to fibrillate, or rhythm control, in which there is an attempt to reestablish and maintain normal sinus rhythm. Rhythm control has long been considered an important treatment goal for management of AF, although its primacy has recently been challenged by the results of several randomized trials report-

ing that pharmacologically maintained rhythm control offered no improvement in mortality or cardiovascular morbidity compared with rate control.

However, rhythm control is not curative. A variety of ablative procedures have been investigated as potentially curative approaches, or as modifiers of the arrhythmia so that drug therapy becomes more effective. Ablative approaches focus on the interruption of the electrical pathways that contribute to AF through modifying the arrhythmia triggers and/or the myocardial substrate that maintains the aberrant rhythm. The maze procedure, an open surgical procedure often combined with other cardiac surgeries (e.g., valve repair), is an ablative treatment that involves sequential atriotomy incisions designed to create electrical barriers that prevent the maintenance of AF. Because of the highly invasive nature of this procedure, it is currently, mainly reserved for patients undergoing open heart surgery for other reasons (e.g., valve repair, coronary artery bypass grafting).

Catheter Ablation for AF

Radiofrequency ablation using a percutaneous catheter-based approach is widely used to treat a variety of supraventricular arrhythmias, in which intracardiac mapping identifies a discrete arrhythmogenic focus that is the target of ablation. The situation is more complex for AF because there may be no single arrhythmogenic focus. AF most frequently arises from an abnormal focus at or near the junction of the pulmonary veins and the left atrium, thus leading to the feasibility of more focused, percutaneous ablation techniques. Strategies that have emerged for focal ablation within the pulmonary veins originally involved segmental ostial ablation guided by pulmonary vein potential (electrical approach) but currently more typically involve circumferential pulmonary vein ablation (anatomic approach). Circumferential pulmonary vein ablation using radiofrequency energy is the most common approach at present.

Research into specific ablation and pulmonary vein isolation techniques is ongoing.

Use of current radiofrequency catheters for AF has a steep learning curve because they require extensive guiding to multiple ablation points. The procedure can also be done using cryoablation technology. One of the potential advantages of cryoablation is that cryoablation catheters have a circular or shaped endpoint, permitting a “one-shot” ablation.

Repeat Procedures

Repeat procedures following initial radiofrequency ablation are commonly performed if AF recurs or if atrial flutter develops post procedure. The need for repeat procedures may, in part, depend on the clinical characteristics of the patient (e.g., age, persistent vs. paroxysmal AF, atrial dilatation), and the type of ablation initially performed. Repeat procedures are generally more limited in scope than the initial procedure. Additional clinical factors associated with the need for a second procedure include the length of AF, permanent AF, left atrial size, and left ventricular ejection fraction.

REGULATORY STATUS

In February 2009, the NaviStar® ThermoCool® Irrigated Deflectable Diagnostic/Ablation Catheter and EZ Steer ThermoCool NAV Catheter (Biosense Webster) received expanded approval by the U.S. Food and Drug Administration (FDA) through the premarket approval process for radiofrequency ablation to treat drug refractory recurrent symptomatic paroxysmal AF. FDA product code: OAD.

Devices using laser or cryoablation techniques for substrate ablation have been approved by the FDA through the premarket approval process for AF (FDA product code: OAE). They include:

- Arctic Front™ Cardiac CryoAblation Catheter and CryoConsole (Medtronic) in 2010.
- TactiCath™ Quartz Catheter and TactiSysQuartz® Equipment (St. Jude Medical) in 2014.

- HeartLight® Endoscopic Ablation System (Cardiofocus) in 2016.
- The Freezor™ Xtra Catheter (Medtronic) in 2016.

Also, numerous catheter ablation systems have been approved by the FDA for other ablation therapy for arrhythmias such as supraventricular tachycardia, atrial flutter, and ventricular tachycardia. FDA product code: LPB.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Lee MA, Weachter R, Pollak S, et al. The effect of atrial pacing therapies on atrial tachyarrhythmia burden and frequency: results of a randomized trial in patients with bradycardia and atrial tachyarrhythmias. *J Am Coll Cardiol.* Jun 4 2003;41(11):1926-1932. PMID 12798559.
2. Kay GN, Ellenbogen KA, Giudici M, et al. The Ablate and Pace Trial: a prospective study of catheter ablation of the AV conduction system and permanent pacemaker implantation for treatment of atrial fibrillation. APT Investigators. *J Interv Card Electrophysiol.* Jun 1998;2(2):121-135. PMID 9870004.
3. Falk RH. Management of atrial fibrillation--radical reform or modest modification? *N Engl J Med.* Dec 5 2002;347(23):1883-1884. PMID 12466514.
4. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med.* Dec 5 2002;347(23):1834-1840. PMID 12466507.
5. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* Dec 5 2002;347(23):1825-1833. PMID 12466506.
6. Gupta A, Perera T, Ganesan A, et al. Complications of catheter ablation of atrial fibrillation: a systematic review. *Circ Arrhythm Electrophysiol.* Dec 1 2013;6(6):1082-1088. PMID 24243785.
7. Shemin RJ, Cox JL, Gillinov AM, et al. Guidelines for reporting data and outcomes for the surgical treatment of atrial fibrillation. *Ann Thorac Surg.* Mar 2007;83(3):1225-1230. PMID 17307507.
8. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol.* Aug 15 2006;48(4):854-906. PMID 16904574.
9. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Catheter ablation of the pulmonary veins as a treatment for atrial fibrillation. *TEC Assessments.* 2008;Volume 23:Tab 11.
10. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation.* Dec 9 2008;118(24):2498-2505. PMID 19029470.

11. Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med*. Oct 23 2008;359(17):1778-1785. PMID 18946063.
12. Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med*. Mar 2 2006;354(9):934-941. PMID 16510747.
13. 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. *J Am Coll Cardiol*. Dec 5 2006;48(11):2340-2347. PMID 17161267.
14. 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). *Eur Heart J*. Jan 2006;27(2):216-221. PMID 16214831.
15. 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*. Jun 1 2005;293(21):2634-2640. PMID 15928285.
16. Nyong J, Amit G, Adler AJ, et al. Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation. *Cochrane Database Syst Rev*. Nov 22 2016;11:CD012088. PMID 27871122.
17. 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. *J Cardiovasc Electrophysiol*. Jan 2009;20(1):22-28. PMID 18775050.
18. 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). *Eur Heart J*. Feb 2014;35(8):501-507. PMID 24135832.
19. Shi LZ, Heng R, Liu SM, et al. Effect of catheter ablation versus antiarrhythmic drugs on atrial fibrillation: A meta-analysis of randomized controlled trials. *Exp Ther Med*. Aug 2015;10(2):816-822. PMID 26622399.
20. Chen HS, Wen JM, Wu SN, et al. Catheter ablation for paroxysmal and persistent atrial fibrillation. *Cochrane Database Syst Rev*. Apr 18 2012;4(4):CD007101. PMID 22513945.
21. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc*. Apr 2013;2(2):e004549. PMID 23537812.
22. Noheria A, Kumar A, Wylie JV, Jr., et al. Catheter ablation vs. antiarrhythmic drug therapy for atrial fibrillation: a systematic review. *Arch Intern Med*. Mar 24 2008;168(6):581-586. PMID 18362249.
23. Gjesdal K, Vist GE, Bugge E, et al. Curative ablation for atrial fibrillation: a systematic review. *Scand Cardiovasc J*. Feb 2008;42(1):3-8. PMID 18273730.
24. Nair GM, Nery PB, Diwakaramenon S, et al. A systematic review of randomized trials comparing radiofrequency ablation with antiarrhythmic medications in patients with atrial fibrillation. *J Cardiovasc Electrophysiol*. Feb 2009;20(2):138-144. PMID 18775040.
25. Zhuang Y, Yong YH, Chen ML. Updating the evidence for the effect of radiofrequency catheter ablation on left atrial volume and function in patients with atrial fibrillation: a meta-analysis. *JRSM Open*. Mar 2014;5(3):2054270414521185. PMID 25057380.
26. 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*. Jan 27 2010;303(4):333-340. PMID 20103757.
27. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. Feb 1 2018;378(5):417-427. PMID 29385358.
28. Hussein AA, Saliba WI, Martin DO, et al. Natural history and long-term outcomes of ablated atrial fibrillation. *Circ Arrhythm Electrophysiol*. Jun 2011;4(3):271-278. PMID 21493959.
29. Teunissen C, Kassenberg W, van der Heijden JF, et al. Five-year efficacy of pulmonary vein antrum isolation as a primary ablation strategy for atrial fibrillation: a single-centre cohort study. *Europace*. Sep 2016;18(9):1335-1342. PMID 26838694.

30. 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*. Sep 2013;10(9):1272-1277. PMID 23835257.
31. Weerasooriya R, Khairy P, Litalien J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol*. Jan 11 2011;57(2):160-166. PMID 21211687.
32. Tzou WS, Marchlinski FE, Zado ES, et al. Long-term outcome after successful catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol*. Jun 1 2010;3(3):237-242. PMID 20335557.
33. Bertaglia E, Tondo C, De Simone A, et al. Does catheter ablation cure atrial fibrillation? Single-procedure outcome of drug-refractory atrial fibrillation ablation: a 6-year multicentre experience. *Europace*. Feb 2010;12(2):181-187. PMID 19887458.
34. Sawhney N, Anousheh R, Chen WC, et al. Five-year outcomes after segmental pulmonary vein isolation for paroxysmal atrial fibrillation. *Am J Cardiol*. Aug 1 2009;104(3):366-372. PMID 19616669.
35. Anselmino M, Grossi S, Scaglione M, et al. Long-term results of transcatheter atrial fibrillation ablation in patients with impaired left ventricular systolic function. *J Cardiovasc Electrophysiol*. Jan 2013;24(1):24-32. PMID 23140485.
36. Takigawa M, Takahashi A, Kuwahara T, et al. Long-term follow-up after catheter ablation of paroxysmal atrial fibrillation: the incidence of recurrence and progression of atrial fibrillation. *Circ Arrhythm Electrophysiol*. Apr 2014;7(2):267-273. PMID 24610740.
37. 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*. Feb 2014;7(1):31-38. PMID 24382410.
38. Lellouche N, Jais P, Nault I, et al. Early recurrences after atrial fibrillation ablation: prognostic value and effect of early reablation. *J Cardiovasc Electrophysiol*. Jun 2008;19(6):599-605. PMID 18462321.
39. Pokushalov E, Romanov A, De Melis M, et al. Progression of atrial fibrillation after a failed initial ablation procedure in patients with paroxysmal atrial fibrillation: a randomized comparison of drug therapy versus reablation. *Circ Arrhythm Electrophysiol*. Aug 2013;6(4):754-760. PMID 23748210.
40. Packer DL, Kowal RC, Wheelan KR, et al. 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*. Apr 23 2013;61(16):1713-1723. PMID 23500312.
41. Su W, Orme GJ, Hoyt R, et al. Retrospective review of Arctic Front Advance Cryoballoon Ablation: a multicenter examination of second-generation cryoballoon (RADICOOOL trial). *J Interv Card Electrophysiol*. Apr 2018;51(3):199-204. PMID 29478173.
42. Vogt J, Heintze J, Gutleben KJ, et al. Long-term outcomes after cryoballoon pulmonary vein isolation: results from a prospective study in 605 patients. *J Am Coll Cardiol*. Apr 23 2013;61(16):1707-1712. PMID 23199518.
43. Neumann T, Wojcik M, Berkowitsch A, et al. Cryoballoon ablation of paroxysmal atrial fibrillation: 5-year outcome after single procedure and predictors of success. *Europace*. Aug 2013;15(8):1143-1149. PMID 23419659.
44. Boho A, Misikova S, Spurny P, et al. A long-term evaluation of cryoballoon ablation in 205 atrial fibrillation patients: a single center experience. *Wien Klin Wochenschr*. Oct 2015;127(19-20):779-785. PMID 26142169.
45. Davies AJ, Jackson N, Barlow M, et al. Long term follow-up of pulmonary vein isolation using cryoballoon ablation. *Heart Lung Circ*. Mar 2016;25(3):290-295. PMID 26621109.
46. 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*. Feb 2014;7(1):69-75. PMID 24446022.
47. Dagues 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? *J Cardiovasc Electrophysiol*. Sep 2009;20(9):1014-1019. PMID 19490383.
48. Cappato R, Calkins H, Chen SA, et al. Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation. *J Am Coll Cardiol*. May 12 2009;53(19):1798-1803. PMID 19422987.

49. 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. *J Cardiovasc Electrophysiol*. Jan 2013;24(1):14-21. PMID 22913568.
50. 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 Arrhythm Electrophysiol*. Oct 2013;6(5):843-850. PMID 23989301.
51. Waldo AL, Wilber DJ, Marchlinski FE, et al. Safety of the open-irrigated ablation catheter for radiofrequency ablation: safety analysis from six clinical studies. *Pacing Clin Electrophysiol*. Sep 2012;35(9):1081-1089. PMID 22817524.
52. Shah RU, Freeman JV, Shilane D, et al. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. *J Am Coll Cardiol*. Jan 10 2012;59(2):143-149. PMID 22222078.
53. Ellis ER, Culler SD, Simon AW, et al. Trends in utilization and complications of catheter ablation for atrial fibrillation in Medicare beneficiaries. *Heart Rhythm*. Sep 2009;6(9):1267-1273. PMID 19716081.
54. Reddy VY, Dukkipati SR, Neuzil P, et al. Randomized, controlled trial of the safety and effectiveness of a contact force-sensing irrigated catheter for ablation of paroxysmal atrial fibrillation: results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study. *Circulation*. Sep 8 2015; 132(10):907-915. PMID 26260733.
55. Nakamura K, Naito S, Sasaki T, et al. Randomized comparison of contact force-guided versus conventional circumferential pulmonary vein isolation of atrial fibrillation: prevalence, characteristics, and predictors of electrical reconnections and clinical outcomes. *J Interv Card Electrophysiol*. Dec 2015;44(3):235-245. PMID 26387117.
56. Afzal MR, Chatta J, Samanta A, et al. Use of contact force sensing technology during radiofrequency ablation reduces recurrence of atrial fibrillation: A systematic review and meta-analysis. *Heart Rhythm*. Sep 2015; 12(9):1990-1996. PMID 26091856.
57. Zhu M, Zhou X, Cai H, et al. Catheter ablation versus medical rate control for persistent atrial fibrillation in patients with heart failure: A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. Jul 2016;95(30):e4377. PMID 27472728.
58. Anselmino M, Matta M, Castagno D, et al. Catheter ablation of atrial fibrillation in chronic heart failure: state-of-the-art and future perspectives. *Europace*. May 2016;18(5):638-647. PMID 26857188.
59. Vaidya K, Arnott C, Russell A, et al. Pulmonary vein isolation compared to rate control in patients with atrial fibrillation: a systematic review and meta-analysis. *Heart Lung Circ*. Aug 2015;24(8):744-752. PMID 25890871.
60. 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. *J Am Coll Cardiol*. May 7 2013;61(18):1894-1903. PMID 23500267.
61. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs. antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA*. 2019; Epub ahead of print.
62. Mark DB, Anstrom KJ, Sheng S, et al. Effect of catheter ablation vs. medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA*. 2019; Epub ahead of print.
63. Blomström-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of catheter ablation vs. antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. *JAMA*. 2019; Epub ahead of print.
64. Hakalahti A, Biancari F, Nielsen JC, et al. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. *Europace*. Mar 2015; 17(3):370-378. PMID 25643988.
65. 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*. Feb 19 2014;311(7):692-700. PMID 24549549.

66. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. Oct 25 2012;367(17):1587-1595. PMID 23094720.
67. Nielsen JC, Johannessen A, Raatikainen P, et al. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. *Heart*. Mar 2017;103(5):368-376. PMID 27566295.
68. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. *Heart Rhythm*. Apr 2012;9(4):632-696 e621. PMID 22386883.
69. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace*. Jan 1 2018;20(1):e1-e160. PMID 29016840.
70. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. Dec 02 2014;64(21):e1-76. PMID 24685669.