



**TITLE:** Radiofrequency Ablation for Drug Refractory Symptomatic Paroxysmal Atrial Fibrillation

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## **RADIOFREQUENCY ABLATION FOR DRUG REFRACTORY SYMPTOMATIC PAROXYSMAL ATRIAL FIBRILLATION**

*A Technology Assessment*

### **INTRODUCTION**

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for radiofrequency ablation for the treatment of drug-refractory symptomatic paroxysmal atrial fibrillation. This topic is being reviewed now because of the recently published results of a large multicenter study comparing antiarrhythmic drug therapy with radiofrequency catheter ablation (RFA) in patients with drug resistant paroxysmal atrial fibrillation<sup>1</sup> (Attachment 1).

### **BACKGROUND**

Atrial fibrillation (AF) is the most common sustained atrial arrhythmia, is more common in men and the prevalence increases with increasing age<sup>2</sup>. AF can be paroxysmal (episodes terminate in less than seven days), persistent (more than seven days) or chronic (more than a year). AF can cause significant symptoms including palpitations, shortness of breath and fatigue. In addition, AF is associated with a fivefold increased risk of stroke as well as an increased risk of mortality.

The two goals of therapy of AF are reducing the risk of stroke and alleviation of symptoms. Stroke reduction requires anticoagulation with warfarin for most individuals. Treatment of the symptoms of AF includes strategies to convert the patient back to normal sinus rhythm or strategies to control the rate of the AF. Although there was no overall mortality difference, some randomized trials of rate versus rhythm control have suggested a trend toward reduced mortality in patients who are treated with rate control<sup>3-5</sup>. There were no differences in functional status or quality of life.

Maintenance of sinus rhythm has typically been achieved with electrical cardioversion or with antiarrhythmic drugs. Antiarrhythmic drugs can sometimes have limited efficacy and also can have significant side effects which limit their long term use.



Because of the limitations of antiarrhythmic drugs, nonpharmacologic approaches to the maintenance of sinus rhythm have been explored. These nonpharmacologic approaches include surgery or RFA.

The initiation of AF requires both a trigger either within or near the atria and a susceptible substrate within the atria<sup>6</sup>. Ablation procedures for preventing recurrent AF are directed towards 1) elimination of the triggers of AF which is done by disrupting the conduction of electrical activity between the tissues that contain the arrhythmogenic triggers (usually the pulmonary veins (PV)) and the atrial myocardium or 2) modifying the atrial substrate responsible for maintaining AF.

The triggers in paroxysmal AF and chronic AF appear to be different, which makes paroxysmal AF a better potential target for RFA. In paroxysmal AF, ectopic beats commonly come from muscle fibers that extend from the left atrium (LA) to the PV. These ectopic foci can be localized to the PV in about 90% of people with paroxysmal AF. Most patients only have one or two foci, making them easier targets for ablation. The majority of the foci are from 2-4 cm inside the PV and the remaining foci are usually in the right or LA. Ablation attempts have typically targeted the foci in the PV<sup>7-9</sup>.

In contrast, in chronic AF, there tend to be multiple ectopic sites throughout the atria. Since RFA procedures often focus on isolation of the PV, these procedures are less efficacious in patients with chronic AF<sup>10</sup>.

Challenges with RFA have included difficulties in isolating the ectopic focus, PV stenosis. Because of difficulties in isolating the ectopic foci in the PV, some newer approaches have aimed to isolate all four PVs from the body of the atrium<sup>7</sup>.

Isolation of the PV ectopic foci is complicated and requires complex imaging and mapping techniques. A tool often used during PV isolation is a three dimensional, nonfluoroscopic catheter based, electroanatomic mapping system. The CARTO mapping system has a magnetic field



emitter and sensor and can create a replica of the anatomy of the cardiac chamber where the focus of tachycardia is located, allowing anatomy based transmural linear ablations<sup>11-13</sup>. Another system is called the NavX system which uses electrical localization signals at different frequencies to detect catheters and to generate ablation lesions. After the ectopic foci are localized, then RFA is performed to ablate them.

In conclusion, RFA has been proposed as a treatment alternative for AF refractory to antiarrhythmic drug therapy (ADT). It has the theoretic advantage of avoiding long term drug side effects. Thus, the question is how does it compare to ADT for the treatment of drug refractory paroxysmal AF?

**TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies**

The NaviStar ThermoCool Catheter and EZ Steer ThermoCool NAV Catheter (Biosense Webster Inc., Diamond Bar, CA) received Pre-market Approval (PMA) on February 6, 2009. These catheters are indicated for use in drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional electroanatomic mapping system.

The CARTO family of Navigation Systems for use with this device has received FDA clearance as substantially equivalent through the 510(k) process.

**TA criterion 1 is met.**

**TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.**

The Medline database, Cochrane clinical trials database, Cochrane reviews database and Database of Abstracts of Reviews of Effects (DARE) were searched using the key words atrial fibrillation or paroxysmal atrial fibrillation and also with the term radiofrequency ablation or catheter

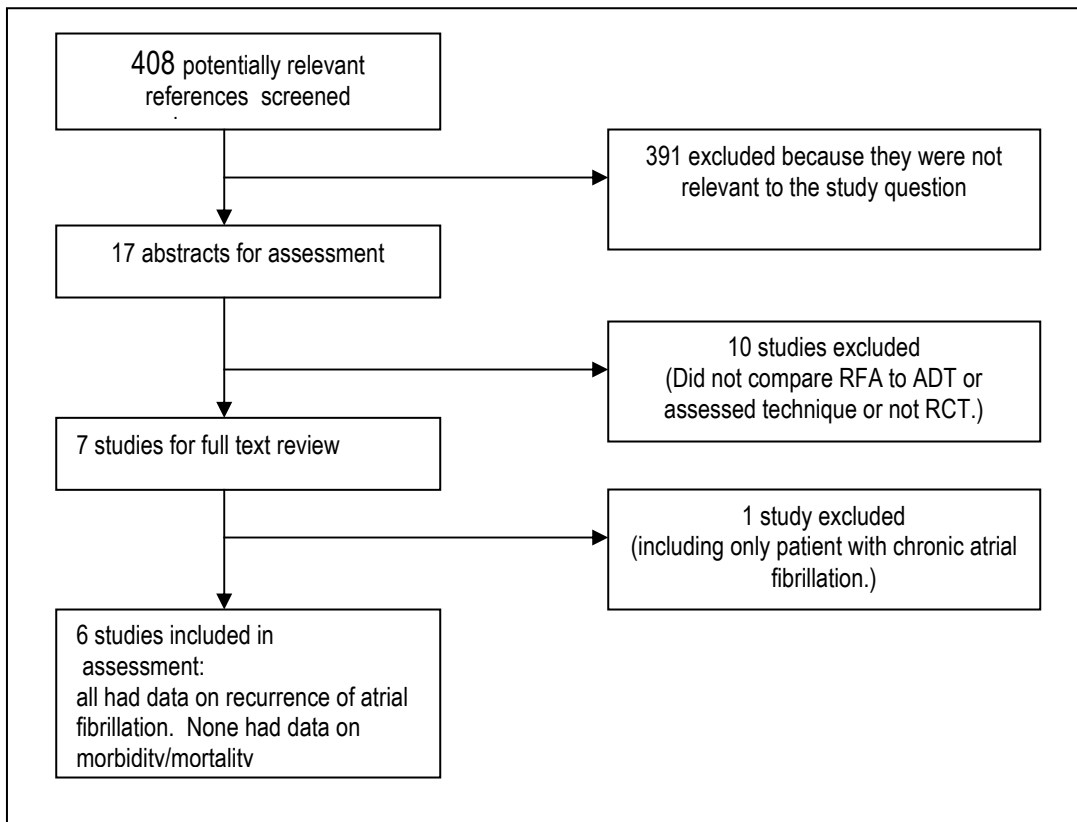
ablation. The search was performed for the period from 1966 to March, 2010. The bibliographies of systematic reviews and key articles were manually searched for additional references and references were requested from the device manufacturer. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

Inclusion criteria:

- Study had to compare RFA with ADT in patients with PAF
- Study had to be a randomized trial
- Study had to measure clinical outcomes
- Included only humans
- Published in English as a peer reviewed article

Studies were excluded if they only focused on non-clinical outcomes. They were also excluded if they were retrospective and/or if they were case series.

**Figure 1:** Selection of studies for inclusion in review



A total of 408 potentially relevant articles were identified. 391 were excluded for not addressing the research question. A total of 17 abstracts were evaluated. 11 were excluded. Reasons for exclusion included not being a randomized controlled trial (RCT), comparing techniques of RFA rather than comparing RFA with ADT, comparing RFA and ADT with ADT alone, or not reporting clinical outcomes. Of these six randomized trials of RFA compared with ADT, evaluated clinical outcomes and are included in this review.

Details of the six randomized trials and the outcomes measured are described in Table 1. Although the outcomes varied among the trials, typical outcomes included the percentage of individuals remaining free from atrial arrhythmias or the time to recurrence of atrial tachyarrhythmia. No studies have assessed the impact of catheter ablation on the important outcomes of mortality, stroke, heart failure or progression of paroxysmal AF to more persistent forms.

**Table 1:** Study Characteristics of Randomized Controlled Trials of RFA for the Treatment of Drug Resistant Atrial Fibrillation

	<b>N</b>	<b>Inclusion criteria</b>	<b>Intervention</b>	<b>Outcome</b>
Wilber, 2010 <sup>1</sup>	167	3 AF episodes in 6 months and failure to respond to at least one antiarrhythmic drug	RFA with pulmonary vein isolation (PVI) vs. ADT	Time to protocol defined treatment failure
Wazni, 2005 <sup>14</sup>	70	Monthly symptomatic episodes of AF for at least 3 months; no prior treatment with ADT	RFA with PVI or ADT	Recurrence of AF, hospitalization, Quality of life (QOL)
Stabile, 2005 <sup>15</sup>	137	Paroxysmal or persistent AF; 2 or more drugs have failed	RFA with Cavo tricuspid and left inferior PV mitral isthmus ablation plus	Absence of recurrence of atrial arrhythmia lasting >30 seconds during one year

			circumferential PV ablation vs. ADT	follow-up
Pappone, 2006 <sup>16</sup>	198	Paroxysmal AF and failed ADT	Circumferential PV ablation vs. ADT	Freedom from recurrent atrial tachyarrhythmias
Jais, 2008 <sup>17</sup>	112	Paroxysmal AF resistant to at least one drug	RFA with PVI vs. ADT	Absence of recurrence of AF between months 3 and 12 after up to 3 ablation procedures
Krittayaphong, 2003 <sup>18</sup>	30	Paroxysmal or persistent AF refractory to medication	RFA vs. amiodarone	Freedom from atrial fibrillation at 1 year follow-up

Level of Evidence: 1

TA Criterion 2 is met

**TA Criteria 3: The technology must improve net health outcomes**

All six of the clinical trials have compared RFA to ADT. In only one of the trials had ADT not been previously tried<sup>14</sup>. In the other four trials, failure of at least one antiarrhythmic drug was an entry criterion. All studies assessed the impact of treatment in patients with PAF, although one study<sup>18</sup> included both patients with PAF and with chronic AF.

All six of the studies assessed some clinically relevant outcomes. Outcomes typically included the percentage of individuals remaining free from atrial tachyarrhythmias, time to recurrence of AF or hospitalizations. No studies to date have assessed the outcomes of mortality, stroke risk, heart failure or progression of paroxysmal AF to more persistent forms.

Although several of the studies were done in multiple centers, all were relatively small, ranging from 30-198 participants each. Follow-up in each of the studies ranged from nine months to a year.

**Table 2:** Outcomes of Randomized Controlled Trials of RFA for the Treatment of Drug Resistant Atrial Fibrillation

Study	Mean Age (treatment and control)	Length of follow-up	Main Outcomes
Wilber, 2010 <sup>1</sup>	55.7	9 months	66% of RFA group vs. 16% of ADT group free of treatment failure
Wazni, 2005 <sup>14</sup>	54	12 months	63% of ADT vs. 13% of RFA with recurrent AF (P<0.001) Hospitalization: 54% ADT vs. 9% RFA (p<0.001)
Stabile, 2005 <sup>15</sup>	62	12 months	91% (ADT) vs. 44% RFA with atrial arrhythmia recurrence
Pappone, 2006 <sup>16</sup>	56	1 year	93% RFA vs. 35% ADT Atrial tachyarrhythmia (AT) free
Jais, 2008 <sup>17</sup>	51	1 year	89% RFA vs. 23% ADT had no AF recurrence
Krittayaphong, 2003 <sup>18</sup>	52	1 year	78.6% of those in the ablation group were free from AF at one year vs. 40% in the amiodarone group; p=0.018

### Potential Benefits

In all six of the studies, clinical outcomes were improved in the individuals who received RFA compared with those who received ADT. However, the follow-up in all the studies was relatively short. Typically, patients were followed for only one year.



In the recently published study, the second largest to date, 167 patients who had not responded to at least one antiarrhythmic drug and who had at least three episodes of AF in the prior six months were randomized to either catheter ablation or ADT<sup>1</sup>. Exclusion criteria included AF of more than 30 days, ejection fraction (EF) EF <40%, New York Heart Association (NYHA) Class III or IV, recent myocardial infarction (MI), coronary artery bypass graft surgery (CABG) done in the past six months, thromboembolic event in the prior 12 months, contraindication to anticoagulation, a history of valvular cardiac surgery, LA size of at least 50 mm and a life expectancy of <12 months. Those randomized to the catheter ablation group were treated with the NaviStar ThermoCool Irrigated Tip Catheter and the Carto Navigation System was used to map and document the frequency of the radiofrequency lesions. The main outcome was time to protocol defined treatment failure. Treatment failure included documented symptomatic paroxysmal AF during the effectiveness evaluation period, the requirement for a repeat ablation after day 80 in the RFA group, absence of entrance block confirmed in all PVs or changes in the post procedure drug regimen required. In the ADT group, an adverse event requiring discontinuation of the assigned drug was also considered a treatment failure. Major treatment related adverse events were also assessed.

Overall, participants were young- the average was 55, and they had AF for an average of 5.7 years and had previously tried an average of 1.3 antiarrhythmic drugs. At the end of nine months, 66% of patients in the catheter ablation group remained free from protocol defined treatment failure, in contrast to only 16% of those in the ADT group (HR 0.30: 95% C.I. 0.19, 0.47; p<0.001). Similarly, 70% of the patients treated by catheter ablation were free of symptomatic recurrent atrial arrhythmia versus 19% of patients treated with ADT (HR 0.24: 95% C.I.: 0.15, 0.39. p<0.001) at 9 month follow-up.

In the one RCT that assessed RFA as first line treatment, 70 patients were randomized to receive RFA versus ADT<sup>14</sup>. Recurrence of symptomatic AF was significantly lower in the RFA group at one year follow-up (63% in ADT vs. 13% in RFA p, 0.001). In addition, hospitalization during one year follow-up occurred in 54% of patients in the ADT group compared with 9% of individuals in the RFA group (P<0.001).



The other trials comparing RFA with ADT have included similar young populations without significant structural heart disease, with an average age ranging from 50-63 and have all followed patients for one year. In those studies, 79-93% of patients have remained free of atrial arrhythmias at one year follow-up compared with 23-44% of controls<sup>15-17</sup>. These studies did not assess the impact of treatment on stroke or mortality, nor did they assess freedom from atrial arrhythmias at more than one year.

### **Potential Harms**

In the Wilber trial<sup>1</sup>, thirty day major treatment related adverse events occurred in five (4.9%) patients in the catheter ablation group and five (8.8%) patients in the ADT group. The events in the catheter ablation group were pericardial effusion, pulmonary edema, pneumonia, vascular complication and heart failure, whereas those in the ADT group were life threatening arrhythmias (2) and drug intolerance requiring discontinuation of the drug (3).

A commonly reported adverse effect in studies of RFA is PV stenosis (although it is often asymptomatic). In a recent meta-analysis of the comparative effectiveness of RFA for the treatment of AF, asymptomatic PV stenosis has been estimated to occur in 0-19% of studies, whereas symptomatic PV stenosis requiring interventions occurred in less than 1% of individuals. Cardiac tamponade was reported in 0-5% of participants (median 1%), and may require pericardiocentesis or even surgery but is rarely fatal. Stroke occurs in 1% of patients. Atrioesophageal fistulas have also been reported rarely<sup>19</sup> (Attachment 2).

### **Summary**

In summary, in patients with frequent paroxysmal AF who are relatively young and otherwise relatively healthy, ablation leads to significantly better outcomes at 9-12 month follow-up than does ADT. The complication rate is relatively low when measured at one year follow-up. What remains



unknown are the long term effects- both positive and negative- of catheter ablation. In addition, because the participants were young and relatively healthy, the effect of catheter ablation in older adults with more comorbidities is not known.

**TA Criterion 3 is met.**

**TA Criterion 4: The technology must be as beneficial as any of the established alternatives.**

Once a rhythm control strategy has been decided upon, the main alternative to RFA is ADT. Among patients with paroxysmal AF, without prior exposure to ADT, approximately 20-40% of patients treated with either class I drugs or sotalol and 60-70% of patients treated with amiodarone will have no recurrence of AF at one year<sup>3, 20, 21</sup>. Many patients cannot be maintained in sinus rhythm with ADT. Amiodarone, although commonly used for the treatment of atrial fibrillation, is not FDA approved.

Since ADT as the established alternative for rhythm control is not ideal, other options are needed. As described above, several RCTs have compared RFA with ADT although the duration of follow-up was short. In the short term, RFA was actually more beneficial than ADT at preventing recurrent symptomatic AF, however the longer term effects such as the impact on stroke, morbidity and mortality are not known. Other long term unknown effects are the likelihood of atrial arrhythmia recurrence and the possibility of longer term complications. In addition, since the majority of the patients in the trials to date have been relatively young with near intact cardiac function, the impact of RFA on older individuals with more comorbidities is not known.

Although there are no clinical trial data assessing long term outcomes, one prospective study has reported the outcomes of 1,404 patients with AF (728 with paroxysmal AF) treated with RFA by 12 operators at four different institutions. After a median follow-up of 57 months, 77.6% of those with PAF had freedom from AF after a single ablation procedure. Repeat ablation for those who needed it resulted in 92.4% of patients with PAF remaining free from AF at follow-up<sup>22</sup>. Although



these results are promising, there is no comparison group and outcomes other than recurrent AF are not reported. Thus, how RFA compares with established treatments longer term is not known,

The CABANA trial (Catheter-Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) is an ongoing large RCT including 3,000 patients. In this trial ablation (mostly with RFA) will be compared with ADT and the primary endpoint is total mortality. In this trial, patients are enrolled regardless of whether or not they have previously been treated with ADT and thus in this study some patients are receiving catheter ablation as first line treatment. In addition, not all participants have PAF. The pilot results were recently presented at the recent American College of Cardiology meeting. These results showed that it was feasible to continue with the main trial. Participants were older than those in the Wilber study (average age 61.1) and had more comorbidities. In the pilot phase, those in the ablation group had more freedom from symptomatic AF (65% vs. 41%), but recurrence of AF at 12 months was only slightly better in the ablation group compared with medications (66% vs. 72%). Adverse events included transient ischemic attacks (TIAs) in 3.4% of patients and tamponade in 3.4% of patients overall. The study is ongoing and the mortality results are expected to be reported in 2015 or 2016.

In summary, RFA for the treatment of paroxysmal drug refractory AF can lead to a reduction in symptomatic AF and recurrent AF at one year follow-up. However, the impact of RFA on longer term clinical outcomes as well as on stroke and mortality is not currently known.

**TA Criterion 4 is met for individuals with drug refractory PAF healthy hearts and without other significant comorbidities.**

**TA criterion 4 is not met for patients with atrial fibrillation, underlying heart disease and other significant comorbidities.**

**TA Criterion 5: The improvement must be attainable outside the investigational settings.**



An important issue in the multi-center trial by Wilber et al, was that although the ablations were performed at multiple different sites, all of the investigators had performed many RFA procedures. And as described in the discussion section of the manuscript, all had “a considerable amount of expertise in AF ablation. {Wilber, #2}. One prospective study has reported the outcomes of 1,404 patients with AF (728 with paroxysmal AF) treated with RFA by 12 operators at four different institutions. After a median follow-up of 57 months, 77.6% of those with PAF had freedom from AF after a single ablation procedure, suggesting that RFA can be performed in multiple settings. Research on the importance of operator characteristics such as the clinical setting, the number of previous ablation procedures performed is currently limited but potentially important for the future. Evidence focusing on the performance of RFA outside of investigational settings will be important.

**TA Criterion 5 is met for individuals with drug refractory PAF healthy hearts and without other significant comorbidities.**

**TA Criterion 5 is not met for other patients with atrial fibrillation, underlying heart disease and other significant comorbidities.**

## **Summary**

RFA is proposed as an alternative treatment for paroxysmal atrial fibrillation refractory to drug treatment. Randomized trials comparing RFA to ADT in relatively young healthy individuals have shown that RFA leads to a significant decrease in recurrent atrial fibrillation and symptomatic atrial fibrillation at one year follow-up. However, evidence comparing longer term benefits and harms to other treatments are not available. In particular, there is currently no evidence about the impact of RFA compared with other treatments on stroke or mortality. In addition, the impact of RFA on clinical outcomes in older individuals with more comorbidities is also not known.



## **RECOMMENDATION**

It is recommended that RFA as a treatment for paroxysmal atrial fibrillation refractory to drug therapy meets CTAF TA criteria 1-5 for improvement in health outcomes in relatively young patients without other significant underlying heart disease

It is recommended that RFA as a treatment for paroxysmal atrial fibrillation refractory to drug therapy does not meet CTAF TA criteria 4 or 5 for improvement in health outcomes in older individuals with atrial fibrillation and comorbidities.

**June 2, 2010**

This is the first time CTAF has reviewed this technology.

After hearing expert testimony and discussion, the CTAF panel discussion leader presented an alternative recommendation.

It is recommended that RFA as a treatment for paroxysmal atrial fibrillation refractory to drug therapy meets CTAF criteria 1 through 5 for safety, effectiveness and improvement in health outcomes.

The panel voted twelve in favor and two opposed to this alternate recommendation.



## **RECOMMENDATIONS OF OTHERS**

### **Blue Cross Blue Shield Association (BCBSA)**

In April 2009 the BCBSA Technology Evaluation Center Medical Advisory Panel determined that: “radiofrequency catheter ablation of the pulmonary veins as a treatment for atrial fibrillation meets the TEC criteria for:

- \* patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic medications, as an alternative to continued medical management; and
- \* patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications, as an alternative to AV nodal ablation and pacemaker insertion.

For other patients with atrial fibrillation, including first-line treatment for paroxysmal atrial fibrillation, radiofrequency catheter ablation of the pulmonary veins does not meet the TEC criteria.”

### **Centers for Medicare and Medicaid Services (CMS)**

In October 2009 the CMS MEDCAC met to discuss the topic of Catheter Ablation for the Treatment of Atrial Fibrillation. Neither a National Coverage Decision nor a Local Coverage Decision is currently posted for this technology.

### **California Chapter of the American College of Cardiology (CA ACC)**

The CA ACC provided an opinion in support of this technology.

### **Heart Rhythm Society (HRS)**

The HRS provided an opinion supporting the use of this technology. A representative did attend the meeting to provide testimony.



### **Agency for Healthcare Research and Quality (AHRQ)**

In July 2009 the AHRQ Effective Health Care Program published Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation. This report is available at: <http://effectivehealthcare.ahrq.gov>

### **National Institute for Health and Clinical Excellence (NICE)**

In April 2006 NICE published Percutaneous radiofrequency ablation for atrial fibrillation available at: <http://www.nice.org.uk/nicemedia/live/11194/31461/31461.pdf>.

### **ACC/AHA/ESC**

In 2006 the American College of Cardiology, American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines revised their 2001 Guidelines for the Management of Patients With Atrial Fibrillation. These updated guidelines were developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. The guideline is available at: [http://www.acc.org/qualityandscience/clinical/guidelines/atrial\\_fib/pdfs/AF\\_Full\\_Text.pdf](http://www.acc.org/qualityandscience/clinical/guidelines/atrial_fib/pdfs/AF_Full_Text.pdf). A more recent update was not found.



## ABBREVIATIONS USED IN THIS REPORT

CTAF	California Technology Assessment Forum
RFA	Radiofrequency catheter ablation
AF	Atrial fibrillation
LA	Left atrium
PV	Pulmonary veins
ADT	Antiarrhythmic drug therapy
DARE	Database of Abstracts of Reviews of Effects
RCT	Randomized controlled trials
PVI	Pulmonary vein isolation
QOL	Quality of life
AT	Atrial tachyarrhythmia
EF	Ejection fraction
NYHA	New York Heart Association
MI	Myocardial infarction
CABG	Coronary artery bypass graft surgery
PAF	Paroxysmal atrial fibrillation
CABANA	Catheter-Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation
TIA	Transient ischemic attacks

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