

## Indications For AF Ablation: Before Or After The Failure Of Antiarrhythmic Drug Therapy?

Akira Kimata, MD, Yoko Ito, MD, Kentaro Yoshida, MD

*Division of Cardiovascular Medicine, Ibaraki Prefectural Central Hospital, Kasama, Japan.*

### Abstract

Catheter ablation of atrial fibrillation (AF) is considered to be better than anti-arrhythmic drug therapy in terms of maintaining sinus rhythm, and therefore, it has rapidly evolved to become a commonly performed procedure in major hospitals throughout the world. However, on the basis of the evidence currently available, we support the current guidelines recommending antiarrhythmic drugs as a first-line treatment in most patients with AF except younger patients with symptomatic paroxysmal AF with no evidence of structural heart disease, given the risk of fatal complications associated with the ablation procedure. We would like to emphasize that center volume and individual procedure experience are significant determinants of procedure-related complications. As another effect of AF ablation, preventing atrial remodeling and progression to persistent AF is also noteworthy. Further long-term data is needed to answer the question of whether ablation can prevent or delay the advance of structural remodeling and improve life prognosis, particularly in younger patients.

### Introduction

Currently, there are two approaches to the treatment of atrial fibrillation (AF), rhythm-control and rate-control therapy. In the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study, no differences were found between the two approaches in terms of survival benefit.<sup>1</sup> The J-RHYTHM (Japanese Rhythm Management Trial for Atrial Fibrillation) study, mainly conducted in Japan, also reported no significant differences in mortality, incidence of cerebral infarction, and rate of hospitalization between the two approaches.<sup>2</sup> However, a sub-analysis showed that prognosis was better in the patients who achieved stable maintenance of sinus rhythm, and the results suggested that any beneficial antiarrhythmic effects of antiarrhythmic drugs (AADs) are offset by their adverse effects.

In contrast, many studies have reported that catheter ablation is better than AAD therapy in terms of maintaining sinus rhythm.<sup>3-6</sup> Therefore, AF ablation has evolved rapidly to become a commonly performed procedure in many major hospitals throughout the world. The 2007 HRS/EHRA/ESC expert consensus statement recommended that the primary indication for catheter ablation of AF is the presence of symptomatic AF, refractory or intolerant to at least one Class I or III AAD.<sup>7</sup> Recently, several new sets of data have been published that compare catheter ablation to AAD therapy as a

first-line rhythm control intervention.<sup>8,9</sup> Accordingly, the 2012 HRS/EHRA/ESC expert consensus statement recommended that catheter ablation as a class IIa indication is reasonable for the treatment of symptomatic paroxysmal AF prior to initiation of antiarrhythmic drug therapy with a Class I or III antiarrhythmic agent.<sup>10</sup> Here, we explore the reasonable indications for AF ablation. When should we consider AF ablation, before or after the failure of AAD therapy?

### AF Ablation After The Failure Of AAD Therapy

In rhythm-control therapy, long-term maintenance of sinus rhythm by AADs is usually difficult. The J-RHYTHM study was a randomized, multicenter comparison of rate control vs rhythm control in Japanese patients with paroxysmal AF. A total of 823 Japanese patients were enrolled. In this study, sinus rhythm was observed on periodic ECG recordings in 73% of the patients in the rhythm control group treated with AADs at 3 years.<sup>2</sup> Komatsu et al reported that only 39% of patients to whom rhythm control was applied had no recurrence of AF during 4 years of follow-up.<sup>11</sup> Contrastingly, many publications show that catheter ablation is effective therapy for patients with paroxysmal AF who have recurrent episodes resistant to AAD therapy. Representative randomized controlled trials (RCTs) are shown in Table 1.<sup>3-5</sup> These RCTs demonstrate that AF ablation of paroxysmal AF is associated with significantly better rhythm control compared with further attempts at AAD therapy in patients who previously failed one or more AADs. However, evidence regarding the effectiveness of AF ablation is reported in institutions performing a large number of procedures. One meta-analysis shows that the success rate of AF ablation varies widely from 10% to 90%.<sup>6</sup> The guidelines of the Japanese Circulation Society determined that catheter ablation is a class I indication for patients with drug-resistant symptomatic paroxysmal AF only when it is undertaken in

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**Corresponding Author:**  
Kentaro Yoshida, MD  
Division of Cardiovascular Medicine,  
Ibaraki Prefectural Central Hospital  
6528 Koibuchi,  
Kasama, Ibaraki 309-1793, Japan.

**Table 1:** Catheter ablation for patients with paroxysmal AF who have recurrent episodes of AAD therapy

Study	Patients (n)	Study design	Patient characteristics	Primary endpoint	Follow-up (months)	Outcome
Jaïs P <i>Circulation</i> , 2008 <sup>5</sup>	112	Multi-center RCT	Paroxysmal AF resistant to at least 1 AAD	Recurrence of AF	12	89% vs 23% (AF ablation vs AADs therapy) had no recurrence of AF ( $p < 0.0001$ )
Calò P <i>JACC</i> , 2006 <sup>13</sup>	198	Single center RCT	Paroxysmal AF failed ADD therapy	Recurrence of AF/AT	12	86% vs 22% (AF ablation vs AADs therapy) had no recurrence of AF ( $p < 0.01$ )
Wilbur DJ <i>JAMA</i> , 2010 <sup>3</sup>	167	Multi-center RCT	Paroxysmal AF not responding to at least 1 AAD	Freedom from protocol-defined treatment failure, which included documented symptomatic paroxysmal AF	9	66% vs 16% (AF ablation vs AADs therapy) remained free from protocol-defined treatment failure ( $p < 0.001$ )

AAD, anti-arrhythmic drug; AF, atrial fibrillation; AT, atrial tachycardia; RCT, randomized controlled trial.

institutions performing a minimum of 50 ablation procedures for AF annually.<sup>12</sup>

### AF Ablation Before The Failure Of AAD Therapy

Previous studies showed that AF ablation was a second-line rhythm control therapy for patients undergoing recurrent episodes of AAD therapy, but in recent years, two sets of data supporting AF ablation as a first-line therapy have become available. One is the MANTRA-PAF (Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) trial that randomly assigned 294 patients with paroxysmal AF and no history of antiarrhythmic drug use to an initial treatment strategy of either radiofrequency catheter ablation or therapy with class IC or class III AADs.<sup>8</sup> At 24 months, the burden of AF was significantly lower in the AF ablation group versus the AAD group (9% vs. 18%;  $P = 0.007$ ), and more patients in the ablation group were free from symptomatic AF (93% vs. 84%,  $P = 0.01$ ). However, in terms of the cumulative burden of AF, there were no significant differences between the AF ablation versus AAD group (13% vs. 19%,  $P = 0.10$ ). One death due to a procedure-related stroke and three cases of cardiac tamponade occurred in the ablation group. RAAFT II (Radiofrequency Ablation for Atrial Fibrillation Trial) is another trial that compared AF ablation with AAD therapy as the first-line therapy in treating patients with paroxysmal AF.<sup>9</sup> This clinical trial involved 127 treatment-naïve patients with paroxysmal AF who were randomized to receive either AF ablation or AAD therapy. Recurrence of any atrial tachyarrhythmia was significantly lower in the AF ablation group versus the AAD group (54.5% vs. 72.1%;  $P = 0.02$ ). No deaths or strokes were reported in either group, whereas 4 cases of cardiac tamponade were reported in the ablation group.

Both studies have the same limitation in that the findings are limited to younger patients with paroxysmal AF who have little or no evidence of structural heart disease or other comorbidities. These research results suggest some advantages of ablation therapy as a first-line therapy for selected patients, but further investigations are needed to clarify the superiority of catheter ablation with regard to its effectiveness, efficiency, and safety.

### AF Ablation For Persistent AF

The 2012 HRS/EHRA/ESC expert consensus statement recommended as a class IIa indication that AF ablation of persistent AF is reasonable for the treatment of symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication. In long-standing persistent AF, which is defined as continuous AF of one year or more in duration, AF ablation may be considered as a class IIb indication.<sup>10</sup> Catheter ablation of persistent AF is usually more complex than that of paroxysmal AF. Pulmonary vein ablation

alone is not sufficiently effective, and pulmonary vein ablation in combination with complex fractionated atrial electrogram ablation or linear ablation is expected to be effective in 47% to 95% of patients.<sup>13-20</sup> A previous study reported that maintenance of sinus rhythm was associated with a shorter duration of continuous AF, a longer surface ECG AF cycle length, and a smaller left atrium.<sup>21</sup> According to recent data, persistent AF can be terminated and potentially cured by catheter ablation, but the optimal selection of patients for AF ablation of persistent AF is still unclear. Because of unknown mechanisms of persistent AF, the lack of a standardized ablation strategy, and its limited effectiveness and efficiency, catheter ablation is currently not recommended as a first-line therapy in patients with persistent AF.

### Atrial Remodeling And Progression From Paroxysmal To Persistent AF

Epidemiological studies have shown that paroxysmal AF naturally progresses toward persistent/permanent AF at an estimated rate of 15% to 30% over a 1- to 3-year period.<sup>22-24</sup> Data derived from a Japanese hospital-based cohort ( $n = 19,994$ ) also revealed that AF progression occurred in 115 patients (6.0%/year) despite the use of class Ia/Ic drugs.<sup>25</sup> Although most of these studies focused on the maintenance of sinus rhythm by ablation as a therapeutic goal, we believe it is also important especially for young patients that ablation can prevent progression from paroxysmal to persistent AF. Ouyang et al reported the long-term data on clinical outcome after pulmonary vein isolation in 161 patients with paroxysmal AF and noted that progression toward persistent AF after PVI was observed in only 4 patients (2.4%) over a 5-year follow-up period.<sup>26</sup> More recently, a study that evaluated 1220 patients with symptomatic paroxysmal AF who underwent catheter ablation found that the rate of progression from paroxysmal to persistent AF was very low (0.3%/year) during a median follow-up period of 48 months.<sup>27</sup> Compared with paroxysmal AF, persistent AF is likely to increase the incidence of death, heart failure, and stroke.<sup>28</sup> Persistence of AF may induce atrial structural remodeling and impair LA mechanical function. Although further study is needed to determine the actual benefit of preventing progression toward persistent AF, this result achieved by ablation would appear to favorably affect the prognosis of young patients with paroxysmal AF by suppressing the progression of atrial structural remodeling.

### Risk Of Stroke After AF Ablation

The possible life-long requirement for oral anticoagulation is a very important consideration for a number of patients with AF. Evidence has emphasized that long-term oral anticoagulation based on the risk for stroke should be continued regardless of whether sinus rhythm

**Table 2: Causes and proportions of death in 32,569 patients from 162 centers**

Cause of death	Intraoperative (n)	Postoperative (n)	Total (n)	Proportion (%)
Early death (within 30 days from procedure)				
Tamponade with subsequent cardiac arrest	5	2	7	21.8
Atrio-esophageal fistula	0	5	5	15.6
Peripheral embolism				
Stroke	2	1	3	9.4
Myocardial infarction	1	0	1	3.1
Massive pneumonia	0	2	2	6.3
Extrapericardial pulmonary vein perforation	1	0	1	3.1
Irreversible torsades de pointes	1	0	1	3.1
Septicemia (3 weeks after procedure)	0	1	1	3.1
Sudden respiratory arrest	1	0	1	3.1
Acute pulmonary vein occlusion of both lateral veins	0	1	1	3.1
Hemothorax	0	1	1	3.1
Anaphylaxis	1	0	1	3.1
Late death (after 30 days from procedure)				
Complications from prior perioperative events				
Stroke			2	6.3
Tracheal compression from subclavian hematoma			1	3.1
Acute respiratory distress syndrome			1	3.1
Esophageal perforation from intraoperative TEE probe			1	3.1
Acutely precipitated events				
Tamponade with subsequent cardiac arrest in prior stroke			1	3.1
Intracranial bleeding under oral anticoagulation therapy for prior stroke			1	3.1

TEE, transesophageal echocardiography

is maintained by AAD because asymptomatic and undetected recurrence of AF is common even in patients on rhythm-control treatment.<sup>1</sup> AF ablation is more effective in maintaining sinus rhythm than is AAD therapy, and thus the incidence of stroke is expected to drop for patients with successful AF ablation. Several observational studies actually showed that the risk of stroke was low (0.2-3%) in patients who discontinued systemic anticoagulation several months following AF ablation.<sup>29-31</sup> If oral anticoagulant can be discontinued after AF ablation, it would be a great advantage over AAD therapy, and ablation therapy could be applied even to asymptomatic patients. However, asymptomatic AF is also common after AF ablation, and there have been no large-scale, randomized, controlled and prospective trials to give us a clear answer to the question of whether to continue oral anticoagulation post AF ablation. As a result, current guidelines recommend that anticoagulation should be continued indefinitely after ablation in patients with a high risk for stroke and especially in those who are 75 years of age or older or have had a prior stroke.

### Complications Of AF Ablation

AF ablation is one of the most complex interventional electrophysiologic procedures performed. It is therefore to be expected that the risk associated with AF ablation is higher than that for ablation of most other cardiac arrhythmias. In a recent survey, death was reported in 32 (0.1%) of 32,569 patients undergoing 45,115 AF ablation procedures.<sup>32</sup> The most frequent cause of death was cardiac tamponade, accounting for 25% of the deaths. Stroke was responsible for 16% and atrio-esophageal fistula also for 16% of the deaths (Table

2). In particular, atrio-esophageal fistula is a very rare but devastating complication because 5 (71.4%) of the 7 reported patients died. In other reports, a total of 14 patients suffered atrio-esophageal fistula, and only 1 patient survived after emergency cardiac and esophageal surgery.<sup>33-37</sup> Fatality rates from cardiac tamponade (2.3%) and stroke (5.1%) are much lower than that from atrio-esophageal fistula, but these complications occur more frequently.<sup>32</sup> Major complications defined as life threatening or that required intervention or prolonged hospitalization are reported in Table 3.<sup>38-42</sup> These complications occurred in 1.4-6% of patients: cardiac tamponade in 0.5-1.3%, stroke in 0.3-1.2%, and vascular complications in 0.95-1.2%. Predictors of complications in AF ablation have been reported by some investigators and include congestive heart failure,<sup>40</sup> elderly patients,<sup>40,41</sup> and female sex.<sup>41</sup> Moreover, complication rates at one high-volume center were higher during the first 100 cases (9%) than during the subsequent 541 cases (4.3%), indicating the salutary effect of institutional or individual operator experience.<sup>41</sup> In a study using data from the California State Inpatient Database, 4156 patients underwent an initial AF ablation in California between 2005 and 2008.<sup>43</sup> Of note, the mean annual volume of AF ablations per hospital was only 15.4 throughout the study period. Recent hospital procedural experience during the preceding 12 months varied from 7.0±4.4 procedures in the lowest quartile to 136.9±27.8 in the highest quartile. Less hospital experience with AF ablation was one of the significant predictors of inpatient complications and all-cause 30-day rehospitalizations. Cardiac tamponade is the most dramatic complication observed during AF ablation and is the leading cause



**Table 3:** Rates of major complications

Author	n	Fatality rate (%)	Major complication (%)	Tamponade (%)	Stroke (%)	Atrio-esophageal fistula (%)
Bertaglia E Heart Rhythm, 2007 <sup>38</sup>	1011	0.0	3.9	0.5	0.4	0.0
Cappato R Circulation, 2005 <sup>39</sup>	8745	0.1	6.0	1.2	0.3 (TIA 0.7%)	0.0
Dagres N J Cardiovasc Electrophysiol, 2009 <sup>40</sup>	1000	0.2	3.9	1.3	0.4	0.2
Spragg DD J Cardiovasc Electrophysiol, 2008 <sup>41</sup>	517	0.0	5.0	1.1	1.2	0.0
Takahashi A Circ J, 2009 <sup>42</sup>	1600	0.0	1.4	0.6	0.3	0.0

of procedure-related mortality. A recent study evaluated 34,943 ablation procedures and found a reciprocal association between the number of procedures performed at a center and the occurrence of tamponade, with a substantially lower risk in high-volume centers.<sup>44</sup> Tamponade was more frequent in women: 16% of the cases of tamponade required surgery, and the rates of tamponade were lower in high-volume centers. Taken together, these results help to verify the universal truth that the rates of procedure-related complications are significantly associated with center volume and procedural experience.

### Risk Of Antiarrhythmic Drug Therapy

Serious adverse events can also occur in AAD therapy. The AFFIRM study demonstrated that adverse events, such as bradycardia, prolongation of the corrected QT interval, and gastrointestinal and pulmonary events, occurred more frequently in the rhythm-control group than in the rate-control group.<sup>1</sup> To maintain sinus rhythm, administration of amiodarone is necessary in many cases, and amiodarone carries a risk of serious noncardiac toxicity.<sup>45</sup> Pulmonary toxicity can be severe and occasionally fatal. The 1-year net risk was 1% for pulmonary toxicity, 0.6% for hepatic toxicity, 0.9% for hyperthyroidism, and 6% for hypothyroidism.<sup>46</sup> Atrial flutter with a 1:1 atrioventricular conduction ratio and Torsade de Pointes are also life-threatening arrhythmias associated with drug therapy. Unlike the “one-off” risk associated with catheter ablation, the risk of these adverse effects with drugs is continuous and potentially life-long and therefore might be underestimated in clinical trials, especially for younger patients.

### Conclusion:

According to the evidence currently available, we support the current guidelines recommending AADs as first-line treatment in most patients with AF, given the risk of fatal complications associated with ablation procedures. However, ablation can be first-line therapy in younger patients with symptomatic paroxysmal AF who have little or no evidence of structural heart disease or other comorbidities. We would emphasize that center volume and individual procedural experience are significant determinants of the rates of procedure-related complications. Therefore, the inclusion in the Japanese guidelines of center volume as a condition for class I indication is reasonable and appropriate. The effect of ablation on preventing the progression of paroxysmal AF to persistent AF as well as on the maintenance of sinus rhythm is noteworthy, and further long-term data is needed to answer the question of whether ablation can prevent or delay structural remodeling and improve prognosis, particularly in younger patients.

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