Chapter 23
When Should Ablation Be Considered in the Treatment of Atrial Fibrillation – A Clinician's View

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Abstract Catheter ablation is a relatively recent and evolving modality for the maintenance of sinus rhythm in patients with atrial fibrillation. What its role is in the management of the general patient population with atrial fibrillation remains unclear. In order to understand the role of catheter ablation for treatment of atrial fibrillation, an overview of the problem of atrial fibrillation will be discussed. Management strategies will be considered. The mechanisms of atrial fibrillation along with a history of ablation and a rationale for atrial fibrillation ablation will be presented. Data on the outcomes, efficacy and complications of catheter ablation will be reviewed. Finally, patient selection will be discussed.

Keywords Atrial Fibrillation • Radio-frequency Ablation of Atrial Fibrillation • Pulmonary Vein Isolation • Efficacy of Catheter Ablation of Atrial Fibrillation • RAFFT-2 Trial • SARA Study • Patient Selection for Atrial Fibrillation Ablation

Introduction

Catheter ablation is a relatively recent and evolving modality for the maintenance of sinus rhythm in patients with atrial fibrillation (AF). What its role is in the management of the general population with AF remains unclear. The general population with AF is elderly with multiple comorbidities and concomitant cardiac disorders. Studies demonstrating catheter ablation's superiority over antiarrhythmic drug therapy for maintaining sinus rhythm have involved a significantly younger population with fewer comorbidities and concomitant cardiac disorders than the general

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J.A. Ambrose, A.E. Rodríguez (eds.), *Controversies in Cardiology*,
DOI 10.1007/978-3-319-20415-4_23

population with AF. This chapter discusses the role of catheter ablation in the management of the different presentations of AF in the general population.

Overview of the Problem

AF is the most common significant arrhythmia encountered in clinical practice. The estimated prevalence is 2–2.5 % of the adult population, which is likely an underestimation of the true prevalence [1, 2]. The incidence increases with age. The aging of our population and the increasing prevalence of hypertension, diabetes mellitus, and obesity are leading to its increasing prevalence. The average AF patient is 73 years old and AF is unusual prior to the age of 55 years [2]. Men are slightly more likely than women to develop AF. However, because women live longer than men, there are more women than men with AF. The lifetime risk of developing AF after the age of 40 was found to be approximately 25 % in the Framingham Heart Study [3]. This was confirmed in the Rotterdam Study where the lifetime risk of AF at age 55 years old was 23.8 % in men and 22.2 % in women [4].

Patients with AF have a high likelihood of having significant co-morbidities. In a large population study of 176,891 patients with AF, 87.4 % had hypertension, 43.3 % had diabetes mellitus, 42.1 % had heart failure, 33.8 % had asthma/COPD, and 20.4 % had vascular disease [2]. The average CHA2DS2-VASc was 4.2 making this population at high risk of stroke requiring chronic anticoagulation therapy to decrease thromboembolic events [2].

In order to more specifically classify the overall population with AF, the following classification of AF has been adopted by HRS/EHRA/ECAS in collaboration with the ACC, AHA, APHRS, and STS in 2012 [5]:

- AF Episode – AF documented by ECG monitoring with a duration of ≥30 s., or if <30 s. is present continuously throughout the ECG monitoring.
- Paroxysmal AF – Recurrent AF (≥2 episodes) terminating spontaneously within 7 days or ≤48 h with electrical or medical cardioversion.
- Persistent AF – Continuous AF >7 days or cardioverted after >48 h and ≤12 months.
- Long-standing persistent AF – Continuous AF for >12 months.
- Permanent AF – AF patients where the decision is not to restore or maintain sinus rhythm (NSR) by any means, including catheter or surgical ablation.

Management Strategies

The three strategies related to AF are prevention of thromboembolic events, control of ventricular rate, and maintenance of NSR. Prevention of thromboembolism applies to all types of AF and to all patients. Control of ventricular rate is referred to as "rate control" and maintenance of NSR is "rhythm control". These are the two competing approaches in AF management.

Use of the CHA2DS2-VASc score is the recommended tool to evaluate thromboembolic risk and to aid in the selection of the appropriate therapeutic intervention to reduce the risk of an event by all the major cardiac societies [6] (See Table 23.1). For patients with a CHA2DS2-VASc score of ≥2 oral anticoagulant therapy is recommended. This includes the vast majority with AF. In patients who have undergone catheter ablation, the continuation of long-term oral anticoagulant therapy post-ablation is recommended for all with a CHA2DS2-VASc score of ≥2, irrespective of procedural success [7]. Only patients with a CHA2DS2-VASc score of 0 or possibly 1 should be considered for discontinuation of long-term oral anticoagulation therapy after successful ablation [7].

The role of the competing strategies of rate control versus rhythm control remains an unsettled issue. In the perfect world, most practitioners would opt for rhythm control. The publication of the AFFIRM [8] and RACE [9] trials in 2002 demonstrated that rate control was not inferior to rhythm control with medication and that rate control may be advantageous to rhythm control. As a result, rate control became the preferred strategy in the majority of AF cases. With the advent of catheter ablation of AF the pendulum appears to be shifting back toward rhythm control. However, due to a lack of a well-designed large randomized study related to ablation with long term follow-up and hard clinical end points of morbidity and mortality to establish its clinical benefit, its benefit for rhythm control remains unsettled.

Mechanisms of Atrial Fibrillation

There are two main mechanisms involved in the genesis and maintenance of AF: 1-the multiple wavelet hypothesis with large and small reentrant wavelets, 2- the focal trigger hypothesis with enhanced automaticity of 1 or several rapidly depolarizing foci [5]. In most cases, it is the combination that results in the development of AF with focal triggers leading to the initiation of reentry that eventually leads to atrial remodeling causing additional focal triggers and perpetuation of reentry.

Table 23.1 CHA2DS2VASC Score

	Condition	Points
C	CHF	1
H	HTN	1
A2	Age ≥75 years	2
D	Diabetes mellitus	1
S2	Prior stroke or TIA or TE	2
V	Vascular disease	1
A	Age 65–74 years	1
SC	Sex (female gender)	1

Until the 1980's, the multiple wavelet hypothesis was widely accepted as the dominant mechanism. The development of the surgical Cox-Maze procedure, first performed in 1987, was predicated on this AF model and the concept that maintenance of AF needs a critical number of circulating wavelets, each of which requires a critical mass of atrial tissue [5]. The multiple thru and thru surgical atrial incisions were designed to interrupt all macro-reentry circuits preventing the ability of the atrium to fibrillate. Procedural success contributed to development of catheter ablation with creation of multiple ablation lines to interrupt reentry.

The focal trigger hypothesis became a major factor for the initiation of AF in the 1990's with identification of rapidly depolarizing ectopic foci in the atrium and pulmonary veins that would trigger AF or act as a rapid driver to maintain AF. These ectopic foci usually originated from myocardial muscle tissue found in the proximal 1–3 cm of the pulmonary (PVs) veins [5] and became the target of catheter ablation.

History and Rationale of AF Catheter Ablation

In 1994, Michel Haissaguerre presented the first successful catheter ablations of AF in three patients [10]. He found rapidly firing foci in the right atrium and successfully treated them with RF catheter ablation. These results supported the concept of a focal mechanism for AF that can be treated by ablation.

The concept of focal triggers was further supported in 1998 in another study by Haissaguerre et al. [11]. They found that the vast majority of the focal triggers of AF were in the proximal portion of the PVs. In the 45 patients studied, a total of 69 triggering foci were found of which 64 (94 %) were found in the proximal few centimeter of the PVs: 31 foci in the left superior, 17 in the right superior, 11 in the left inferior and 6 in the right inferior PV. 4 foci were found in the atrium: 3 in the right atrium and 1 in the posterior left atrium. RF catheter ablation of the triggering foci was undertaken. A single session resulted in successful ablation of the foci in 14 patients, 25 patients required two sessions, and 6 patients required three. At a mean follow-up 8 ± 6 months AF was completely eliminated in 28 patients (62 %) without drug therapy.

As a result, an initial strategy for catheter ablation was to induce AF triggers, map, and ablate the triggers within the PVs. This strategy was limited by the inability to induce AF triggers in up to 1/3 and a high recurrence rate after ablation. Freedom from recurrence of AF at 14 months without drugs was 33 %. An additional 13 % had no AF, but remained on drugs. PV ablation led to PV stenosis in up to 38 %. While treatment of PV stenosis with stenting was possible, a better approach was needed to improve success and decrease complications.

To avoid the need to induce, map and ablate the individual PV triggers, Pappone et al. in 2000, described the technique of PV isolation [12]. This technique was performed using a circular catheter with multiple electrodes on it that was positioned outside each of the PVs which isolated the triggers from the left atrium preventing any triggers inside the PVs from starting AF. Since 2001, the location of the

PV isolation has moved more proximally into the left atrium, resulting in PV antral isolation [13]. PV antral isolation is now the standard for most patients with paroxysmal AF. A search for AF triggers outside the PV may be needed in other patients.

In patients with persistent and especially in long-standing AF, atrial remodeling becomes an important mechanistic factor for maintenance of AF [14] resulting in a high recurrence rate with PV antral isolation alone [14]. To achieve success, these patients often require a more complex ablation strategy which includes lines of linear ablation, ablation of non-PV triggers, ablation of complex fractionated atrial electrograms, extensive ablation of left atrial posterior wall, and/or ablation of the ganglionated plexi [14]. The resultant extensive scar formation can lead to possible adverse consequences in the left atrium [14].

Outcomes and Efficacy of Catheter Ablation

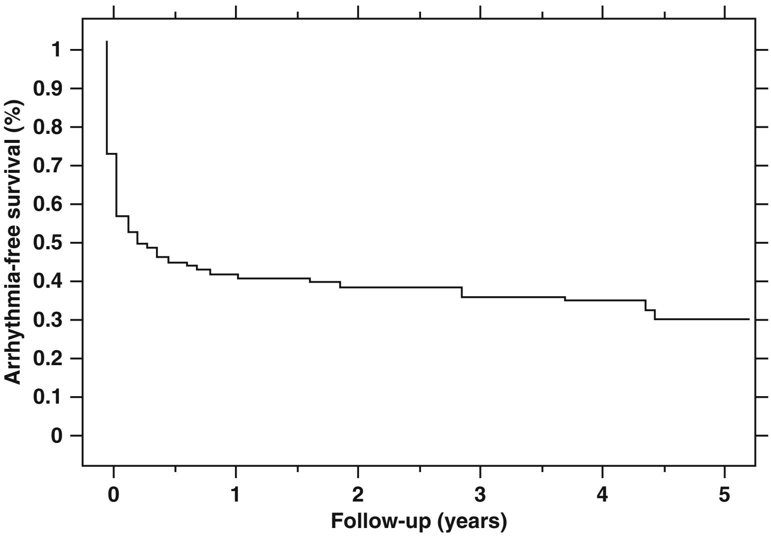
Well-designed large randomized multicenter trails have been the mainstay of cardiovascular research to evaluate outcomes and efficacy for cardiovascular disease for over 30 years. These data are presently lacking for AF ablation. The available data for AF ablation is largely limited to a small number of randomized studies with small sample sizes of <100 in each arm that studied younger patients (<60 years old) with few comorbidities and predominately paroxysmal AF with a short follow-up of a year or two. The end points were usually suppression of AF compared to antiarrhythmic drug therapy rather than the harder clinical end points of morbidity and mortality outcomes. Although the available data are less than ideal, catheter ablation is superior to antiarrhythmic drug therapy in maintaining NSR. Prior studies (AFFIRM [8] and RACE [9]) comparing rate control to rhythm control failed to show the superiority of rhythm control with antiarrhythmic drugs over rate control in most AF cases. Whether a strategy of rhythm control using catheter ablation will be the superior strategy remains unknown.

The most important predictor for success of catheter ablation is the type of AF being treated [12]. Paroxysmal AF has a significantly higher success rate for NSR maintenance than persistent AF which has a higher success rate than long-standing persistent AF. Similarly, variables such as age, concomitant cardiac disease, obesity, sleep apnea, and LA size impact outcome [12].

The 5 year follow up results of catheter ablation for maintaining NSR has been reported by Weerasooriya et al. [15]. The average age at inclusion was 55.7 ± 9.6 years, 64 % had paroxysmal AF, 22 % had persistent AF, and 14 % had long-standing persistent AF. Structural heart disease was present in only 36 %, with 16 % having LVH, and the LVEF was normal at 70 ± 11 %. The CHADS2 score was 0 in 48 %, 1 in 32 % and ≥2 in 20 % of the subjects. For this group of younger, generally healthier patients than the general AF population, freedom from recurrent AF at 5 years was 63 %. However, 51 % required repeat interventions. The 5 year results for freedom from recurrent AF with a single procedure was disappointing at only 29 % (Fig. 23.1). There was an 8.9 % gradual straight line annual recurrence rate of AF after the last ablation attempt over the 5 year follow-up period (Fig. 23.2). The 8.9 % annual recurrence rate after the last ablation attempt is consistent with results from other studies with "long-term" follow-up of 2–3 years. Based on these results, it appears that catheter ablation is not a cure but a treatment for AF that requires continued long term follow-up.

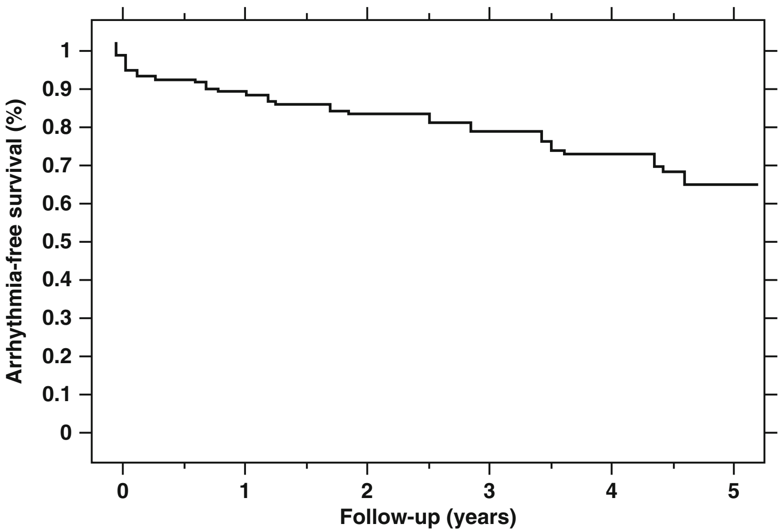
In a recently reported randomized trail comparing radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal AF (RAFFT-2), 61 patients in the antiarrhythmic drug group and 66 patients in the radiofrequency ablation group were followed for 2 years for recurrence and quality of life measures [16]. The patients had an average age of 55 years old, little comorbidity, an average LVEF of 61 %, a normal or mildly increased LA size, and a median CHADS2 score of 0. These patients do not represent the typical AF population. Recurrence of AF occurred in 72.1 % with antiarrhythmics and 54.5 % with ablation at 2 years follow-up. There was no difference in the quality of life measures between the groups at baseline and during the study at the 1 year follow-up. There was a 9 % rate of serious adverse events with ablation, with pericardial effusion and tamponade occurring in 6 % [16] (Table 23.2).

In the above study, ablation was superior to antiarrhythmics; however, 54.5 % with ablation experienced recurrent AF at 2 year follow-up and quality of life measures were similar [16]. If the follow-up would be extended to 5 years and the 8.9 % annual recurrence rate of AF observed in other long term studies occurred in this population, 81.2 % of the ablation patients would be predicted to have experienced recurrence.



Number at risk	100	36	33	31	29	10

Fig. 23.1 Single Procedure Success. Kaplan-Meier event-free survival curve after a single catheter ablation attempt (Reproduced from Weerasooriya et al. [15], with permission of Elsevier)



Number at risk	100	78	71	67	54	18

Fig. 23.2 Multiple Procedure Success. Kaplan-Meier event-free survival curve after the last catheter ablation attempt (Reproduced from Weerasooriya et al. [15], with permission of Elsevier)

Table 23.2 Randomized trials of catheter ablation

RAAFT-2 (paroxysmal AF)

RX	#	Age (mean)	LA Size (cm)	LVEF %	HTN %	DM %	CHADS2 (mean)	Recurrent AF >30 s @ 2 years	QOL score baseline	QOL score @ 1 year
AAD	61	54.3 years	4.3	60.8	41.0	6.6	0.7	72.1 %	0.84	1
CA	66	56.3 years	4.0	61.4	42.4	1.5	0.5	54.5 %	0.86	1
P value		.30	.09	.65	.87	.14	.48	.02	>.99	.25

SARA study (persistent AF)

RX	#	Age (mean)	LA Size (cm)	LVEF %	Free from AF>24 h @ 1 year	Free from any recurrent AF>30 s @ 1 year	QOL score baseline	QOL score @ 1 year
AAD	48	55 years	4.27	60.8	43.7 %	29.2 %	49.3	53.0
CA	98	55 years	4.13	61.1	70.4 %	60.2 %	42.0	56.8
P value					.002	<0.001		.41

AAD antiarrhythmic drug treatment, *CA* catheter ablation, *QOL* score quality of life score: EQ5D Tariff score in RAAFT-2 and AF-QoL score in SARA Study

When it comes to persistent AF, the available data on outcome and efficacy are very limited. The only randomized, multicenter, controlled trail that has been published to date is the SARA study [17]. This compared catheter ablation to antiarrhythmic drug in persistent AF – 146 were randomized 2:1 to ablation (98 patients) or antiarrhythmic drug therapy with a Class III or IC drug (48 patients). The patients were again young with an average age of 55 years and had few comorbidities and concomitant cardiac disorders. Their LA sizes were only mildly enlarged and an average LVEF was 61 %. The follow-up was only for 1 year. The primary outcome was defined as freedom from an episode of AF or flutter lasting >24 h or requiring cardioversion after a 3 months blanking period. Secondary outcomes included freedom from any recurrence of AF or flutter lasting ≥30 s after the 3 month blanking period, hospitalization related to arrhythmia, cardioversion, therapeutic crossover, AV node ablation, quality of life questionnaire at baseline and 6 and 12 months, and complications. In the ablation arm, 36 % received antiarrhythmic drug therapy thruout the follow-up period and 8.2 % underwent a second ablation procedure. No patients in the antiarrhythmic drug group underwent an ablation prior to completing the study or having a primary outcome event.

The results of the SARA study [17] for the primary outcome were that 70.4 % in the ablation group and 43.7 % in the antiarrhythmic drug group had freedom from sustained episodes of AF at 12 months ($p = 0.002$). The secondary end point of freedom from any AF or atrial flutter lasting >30 s were 60.2 % in the ablation group and 29.2 % in the antiarrhythmic drug group during the 12 month follow-up ($p < 0.001$). The need for cardioversion was higher with antiarrhythmics (50 % vs 34.7 %, respectively). Hospitalizations due to arrhythmia recurrence were similar. There were no significant differences in AF quality of life scores between groups. There was a 6.1 % periprocedural complication rate during the ablation procedure and one patient developed symptomatic PV requiring stenting (Table 23.2).

The results of the SARA study [17] provide evidence that radiofrequency ablation is superior to antiarrhythmic drug therapy for maintaining NSR in a select group followed only 12 months. The subjects were relatively young (average age 55 years) without significant comorbidities or concomitant cardiac disease. Despite the improvement in maintaining NSR with ablation, there was no benefit in decreasing hospitalization or improving quality of life scores and there was a 7 % complication rate related to ablation.

There are no randomized trials comparing catheter ablation to antiarrhythmic drug therapy in long-standing AF [18]. As mentioned above, the changes in the left atrium that occur with long-standing AF usually require a more extensive and complex ablation strategy. These more extensive ablation strategies result in more extensive scar formation in the left atrium [14].

The 5 year results of a study using a sequential catheter ablation strategy for long-standing persistent AF has been reported [18]. These subjects had an average age of 61 years, only 16 % had structural heart disease, LA size was moderately enlarged, and LVEF was 60 ± 7 %. After the first ablation procedure, NSR was maintained at 5 years in 20.3 %. After multiple procedures (up to 5 procedures), sinus rhythm was maintained at 5 years in 45 %, including 26 % who were receiving antiarrhythmic drugs. Patients with a duration of long-standing persistent of >2 years were 2.81 times more likely to relapse to AF. In those who underwent >1 redo, the incidence of atrial tachycardia as a clinical arrhythmia increased. The arrhythmia was felt to be related to scar formation in the LA [19].

Catheter ablation for long-standing persistent AF is a challenging procedure for the electrophysiologist. The more extensive ablation approach requires a careful evaluation of the risk/benefit ratio. Longer procedure and fluoroscopy times along with an increased risk of complications including atrial tachycardia need to be considered [5, 19]. Randomized trials are needed to evaluate to outcomes of various ablation strategies.

Patient Selection for Ablation

The role of catheter ablation for AF in the overall patient population is unclear. The available studies related to its efficacy, as mentioned earlier, have largely been limited to a small group with predominately paroxysmal AF and are significantly younger with fewer comorbidities than the general population with AF. In this select group, ablation is superior to antiarrhythmic drug therapy in maintaining NSR. Catheter ablation still has a significant recurrence rate of AF over time and frequently requires repeat ablation procedures to maintain NSR. In patients who are not significantly symptomatic in AF while on medical therapy, studies have failed to show an improvement in quality of life measures with ablation [16, 17]. At the present time there is insufficient evidence to support the use of catheter ablation to reduce all-cause mortality, stroke, or heart failure. Serious complications related to an AF ablation procedure are not uncommon, reported in ~6 % of procedures [5]. The present guidelines for the management of AF recommend the chronic continuation of anticoagulation therapy based on the CHA2DS2-VASc score irrespective of the results of ablation [7, 20].

The patient selection for ablation needs to be individualized depending on numerous factors including age, sex, type and duration of AF, presence of structural heart disease, LA size, presence of comorbidities, response to rate control therapy, failure or intolerance of antiarrhythmic drug therapy, and provision of patient-informed consent. The primary indication for AF ablation is for significantly symptomatic paroxysmal AF that is refractory or intolerant to at least one Class I or III antiarrhythmic medication when a rhythm control strategy is desired (Class I, EOL:A) [5, 6]. Prior to consideration for ablation, assessment of the procedural risk and outcomes is recommended (Class I, EOL:C) [5, 6]. These two are the only Class I recommendations according to the 2014 ACA/AHA guidelines [6].

The 2014 guidelines consider catheter ablation as a reasonable initial strategy for the management of recurrent symptomatic paroxysmal AF when a rhythm control strategy is warranted prior to therapeutic trials of antiarrhythmic drug therapy, after weighing risks and outcomes of drug and ablation therapy (Class IIa, EOL:B) [6]. They also consider ablation as a reasonable option for selected patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication (Class IIa, EOL: A) [6].

A weaker recommendation is considered for symptomatic persistent AF prior to a trial of antiarrhythmic drug therapy (Class IIb, EOL:C) or for symptomatic long-standing AF refractory or intolerant to antiarrhythmics, when a rhythm control strategy is warranted (Class IIb, EOL:B) [6]. AF ablation is not warranted and is considered harmful for the restoration of NSR with the sole intent of avoiding anticoagulation (Class III, EOL:C) [6].

There are ongoing clinical trials that are assessing the role of ablation for reducing mortality, stroke, or heart failure compared to standard care with rate and/or rhythm control drugs. Their results will not be available for a few years. These are the CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) and the EAST (Early Therapy of Atrial Fibrillation for Stroke Prevention Trial) studies. We should proceed cautiously in widening the indications for AF catheter ablation until the results of these and other future studies are available.

Conclusions

1. The general population with AF is usually elderly with multiple comorbidities and concomitant cardiac disorders, and high CHA2DS2-VASc scores.
2. Anticoagulation is recommended for AF patients with a CHA2DS2-VASc score ≥ 2.
3. A rate control strategy is not inferior to rhythm control with medication and rate control may be advantageous to rhythm control.
4. Focal triggers predominantly in the proximal PVs and altered atrial myocardial substrate resulting in multiple reentry wavelets that are the underlying mechanisms for AF are potentially amenable to catheter ablation.
5. Catheter ablation of AF is superior to antiarrhythmic drug therapy for maintaining NSR.
6. There is a high recurrence rate of AF after ablation over the long term that frequently requires repeat ablation.
7. There is a significant complication rate related to each ablation procedure.
8. The role of ablation compared to a rate or rhythm control strategy with medication in managing the general population with AF is unsettled.
9. Chronic anticoagulation therapy based on the CHA2DS2-VASc score is still required despite the apparent success of ablation.
10. The published trials of ablation almost exclusively involve significantly younger patients with fewer comorbidities or concomitant cardiac disease than the general population with AF and the trials have a short follow up. Therefore, these cannot be necessarily applied to the general AF population.
11. At the present time catheter ablation should be limited to younger patients with paroxysmal or persistent AF who are significantly symptomatic despite standard medical therapy.
12. Broader application of ablation should await results of on-going long term trials.

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