

## Should Ablation Be First-Line Therapy and for Whom: The Antagonist Position Benzy J. Padanilam and Eric N. Prystowsky

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# Should atrial fibrillation ablation be considered first-line therapy for some patients?

## *Why Atrial Fibrillation Ablation Should Be Considered First-Line Therapy for Some Patients*

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**A**trial fibrillation (AF) is an increasingly common disease that affects patient morbidity and mortality. To date, treatments of AF have been frustrating, serving at best to palliate this arrhythmia. AF ablation, on the other hand, has emerged as a promising new treatment strategy. In contrast to rate control or antiarrhythmic drugs, ablation offers the possibility of a lasting cure. When ablation was first described, it was prudently reserved as a “last-line” treatment for highly symptomatic patients who were refractory to all other options. However, over the past 5 years, many centers worldwide have been reporting high success rates and few complications with ablation. There is also an increasing consistency in the way in which the procedure is performed, although some of the tools may still differ. AF ablation has reached “prime time,” and it appears appropriate that we expand its indications.

We believe that it is now appropriate to offer AF ablation as first-line therapy for selected patients in experienced centers. Here, we stress the importance of maintaining sinus rhythm, the poor efficacy of nonablative treatments, and the emergence of an effective and safe approach to AF ablation.

### **The Importance of Sinus Rhythm**

Recently, the importance of maintaining sinus rhythm has been called into question. A few large clinical trials have been published comparing treatment strategies for AF. In particular, the AF Follow-up Investigation of Rhythm Management

(AFFIRM),<sup>1</sup> Rate Control Versus Electrical Cardioversion for AF (RACE),<sup>2</sup> and Strategies for Treatment of AF (STAF)<sup>3</sup> trials compared a strategy of rate control and a rhythm control approach using antiarrhythmic drugs. Using an intention-to-treat analysis, these trials concluded that there was no mortality difference between the 2 approaches and that, for the patients enrolled, a rate control approach may be adequate treatment for AF. However, it would be incorrect to extrapolate that sinus rhythm offers no benefit over AF and that effective treatments to maintain sinus rhythm need not be pursued. First, these trials were not comparisons of sinus rhythm and AF. They compared a rate control strategy to a rhythm control strategy that attempted to maintain sinus rhythm but fell very short. The success rates of the rhythm control strategy were very poor (Figure 1). Additionally, many patients in the rate control arm were spontaneously in sinus rhythm by the end of the study periods, from 10% in STAF and RACE to 35% in AFFIRM. When the data from these trials are analyzed according to the patient’s actual rhythm (as opposed to their treatment strategy), the benefit of sinus rhythm over AF becomes apparent. In a recently published “on-treatment” analysis from the AFFIRM investigators,<sup>4</sup> the presence of sinus rhythm was 1 of the most powerful independent predictors of survival, along with use of warfarin, even after adjustment for all other relevant clinical variables. Patients in sinus rhythm were almost half

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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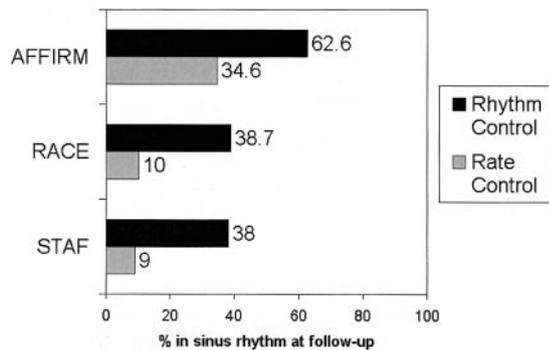
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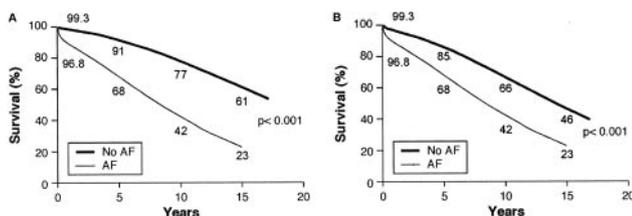
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**Figure 1.** Bar graphs depicting the percentage of patients in sinus rhythm by the end of follow-up in the AFFIRM, RACE, and STAF trials in both the rhythm control and rate control arms. Numbers beside the bars represent the exact percentages of patients in sinus rhythm. Antiarrhythmic medications used in the rhythm control groups did not result in much higher rates of sinus rhythm compared with the rate control groups. References for each of the trials are provided in the text.

as likely to die compared with those with AF (adjusted hazard ratio, 0.53; 99% CI, 0.39 to 0.72;  $P < 0.0001$ ). This benefit, however, was offset by the use of antiarrhythmic drug therapy, which increased the risk of death. The reduction in mortality with sinus rhythm has also been demonstrated in the DIAMOND and CHF-STAT trials.<sup>5,6</sup> These findings are also consistent with large population-based studies that have long shown the negative prognostic impact of AF on survival.<sup>7</sup> Even in an analysis of 46 984 post-coronary bypass patients from 1972 to 2000 at the Cleveland Clinic, we found that survival was significantly reduced in patients with postoperative AF after matching patients for age, comorbidities, left ventricular dysfunction, and left main disease (Figure 2A and 2B).

Finally, it is also important to acknowledge that the patients enrolled in these studies do not represent the full spectrum of AF patients. In particular, patients with “frequent or severe symptoms might have been considered unsuitable...and therefore may not have been enrolled,” according to the AFFIRM investigators themselves.<sup>1</sup> The trial largely excludes the highly symptomatic subgroup that would most benefit



**Figure 2.** Kaplan-Meier curves describing survival in 46 984 post-coronary bypass surgery patients at the Cleveland Clinic from 1972 to 2000. A, Survival is significantly higher in patients without AF when unmatched patients are compared (log rank,  $P < 0.001$ ). B, Survival continues to be significantly higher in patients without AF even after matching them for age, comorbidities, left ventricular dysfunction, and left main disease (log rank,  $P < 0.001$ ).

from sinus rhythm, a subgroup that represents at least one third of all AF patients.<sup>8</sup>

### The Inadequacy of Nonablative Rhythm Control

Unfortunately, apart from AF ablation, the treatments available for maintaining sinus rhythm have poor efficacy and significant drawbacks. Indeed, the failure of AFFIRM, RACE, or STAF in showing any difference between rate and rhythm control is not so much a positive statement for rate control but rather a testimony on the ineffectiveness of the rhythm control methods used. The authors of the STAF trial themselves state that their findings “may suggest that rhythm control failed to demonstrate superiority over rate control because maintenance of sinus rhythm could not be achieved in the long-term [in the rhythm control group].”<sup>3</sup> The main modalities for nonablative rhythm control are antiarrhythmic medication (AAM) and device-based therapy. Device-based therapy has demonstrated poor efficacy in treating AF. Burst atrial pacing may effectively convert atrial tachycardias but fails to terminate or minimize AF.<sup>9</sup> Atrial defibrillators can terminate AF with high acute success rates, but the need for repeated shocks and the resulting patient discomfort often render this option intolerable.<sup>10</sup> Similarly, dual-site atrial pacing has failed to demonstrate any consistent reduction in AF burden or improvement in AF symptoms.<sup>11</sup> Therefore, the mainstay of nonablative rhythm control is AAM.

Indeed, data from several trials have demonstrated that the success of AAM in maintaining sinus is borderline, at best, with increasing failure rates over time. Even amiodarone, considered the most effective AAM, has limited ability to maintain sinus. The largest prospective randomized trial to evaluate the efficacy of amiodarone against other AAMs was the Canadian Trial of Atrial Fibrillation. This trial compared amiodarone and both sotalol and propafenone in maintaining sinus rhythm in patients with at least 1 episode of AF in the past 6 months. After a mean of 16 months’ follow-up, AF recurred in 35% of patients taking amiodarone and 63% of patients taking sotalol or propafenone.<sup>12</sup> However, the true success of amiodarone is definitely  $< 65\%$ . The absence of a placebo arm in CTAF does not allow discernment of the absolute effect of amiodarone, because we cannot know how many patients would have remained in sinus spontaneously. To answer this question, a recent meta-analysis of randomized trials on the efficacy of AAM showed that about one third (32%) of patients were in sinus rhythm in the placebo arms of these trials, whereas 55% of patients in the AAM arms were in sinus.<sup>13</sup> The incremental treatment effects were only 21.5%, 33.1%, and 17.4% for class IA, IC, and III agents, respectively. This somewhat disappointing experience is mirrored in the AFFIRM, RACE, and STAF trials (shown in Figure 1). A substudy of the AFFIRM trial confirmed that the success rate of amiodarone was  $\approx 60\%$  compared with a meager 23% for patients taking class I agents and 38% for patients taking sotalol, whereas 34.6% of patients in the rate



control group were spontaneously in sinus without AAM.<sup>14</sup> Even more disappointing was the RACE trial, which used a very aggressive, stepwise approach to maintaining sinus rhythm: 3 cardioversions and progressive therapy from sotalol to a class Ic agent to amiodarone. Despite this approach, AF had to be accepted in 116 patients (44%), with an additional 18% of patients in AF waiting for their next cardioversion or drug.<sup>2</sup>

AAMs clearly do not cure AF; at best, they are a palliative treatment used to reduce the burden of AF as opposed to eliminating it altogether. It is true that a significant reduction in AF burden may be considered a “success” for some patients in clinical practice. However, it is not well known if a “small” AF burden presents any lesser risk of morbidity and mortality compared with a “large” burden, and the quantitative cutoff point for defining a “low-risk” AF burden has never been defined. Furthermore, in severely symptomatic patients, even 1 brief recurrence a year may be too much. Clearly, there is a need for therapy that can offer a true cure of AF.

For the “lucky” few who are able to maintain sinus rhythm on AAM, these drugs frequently cause debilitating side effects. Discontinuation rates for AAM are consistently high in most trials. In CTAF, 18% of the patients receiving amiodarone and 11% of patients receiving sotalol or propafenone had to discontinue therapy because of adverse effects.<sup>12</sup> In the AFFIRM substudy, 12.3%, 11.1%, and 28.1% of patients taking amiodarone, sotalol, and class I agents, respectively, had to stop taking the drug within 1 year of initiating therapy.<sup>14</sup> Although amiodarone may be the most effective AAM, it is also associated with the most dangerous side effect profile. After 5 years,  $\geq 30\%$  of patients on amiodarone will discontinue therapy because of side effects.<sup>15</sup> Specifically, 4.5% experience intolerable skin discoloration, 3.6% pulmonary fibrosis, 2.7% an intolerable thyroid state, and 1.8% neurological or ophthalmic problems.<sup>15</sup> Certainly, we can do better than offer therapy with such poor efficacy and significant morbidities.

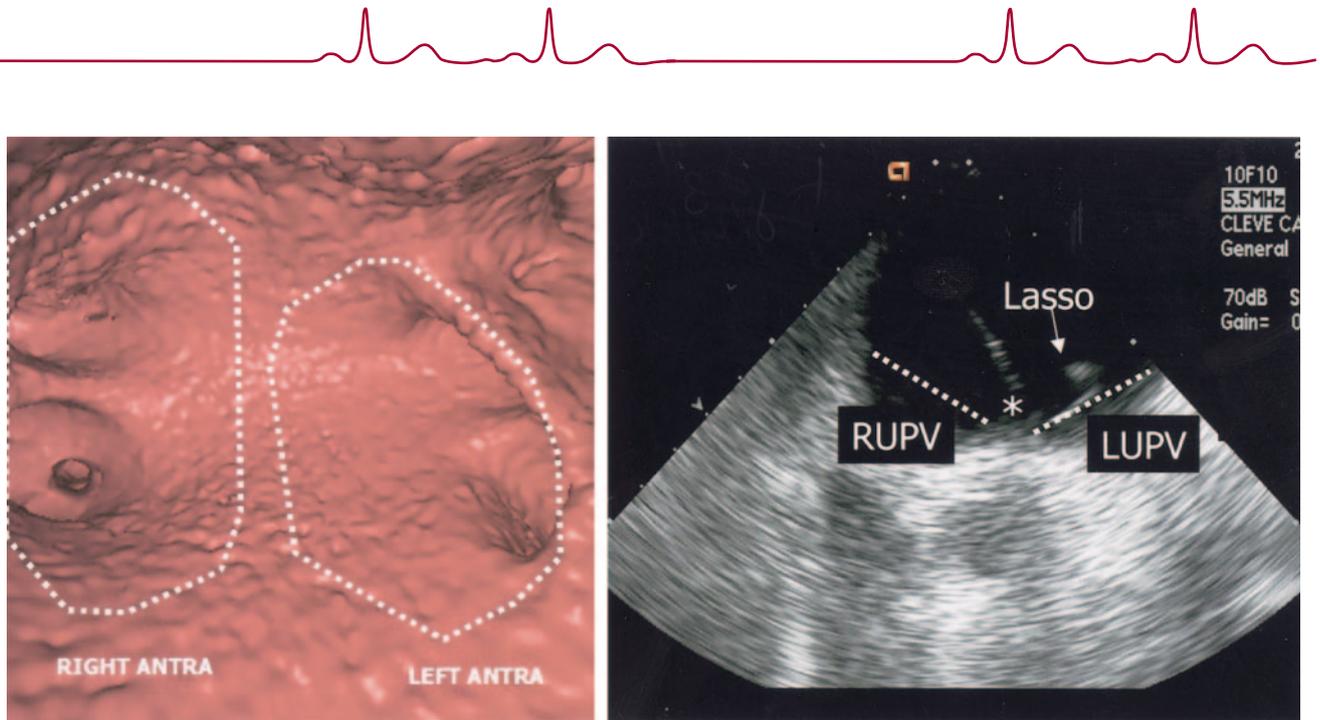
Even more alarming is the observation that AAMs not only produce side effects but also may increase patient mortality. This is a well-established paradigm given the results of the CAST and SWORD trials. In these trials, class I agents and d-sotalol were directly associated with increased mortality when given prophylactically after myocardial infarction.<sup>16,17</sup> The Stroke Prevention in AF Investigators also demonstrated that in patients given AAM for AF, both cardiac mortality and arrhythmic death were significantly increased, particularly in patients with heart failure.<sup>18</sup> Analysis of the AFFIRM population reveals a similar disturbing trend. Use of AAM was associated with an increased risk of mortality after adjustment for other variables, including presence of sinus rhythm (hazard ratio, 1.49;  $P=0.0005$ ).<sup>4</sup> If AAM use and sinus rhythm were not treated as separate variables in the multivariate analysis, AAM use could be made to appear unassociated with any increased mortality. This suggests that what-

ever benefit is obtained by sinus rhythm is offset by the deleterious effects of AAM. Interestingly, it was noncardiac deaths that were increased in the AAM group, which revealed higher rates of pulmonary and cancer-related mortality.<sup>19</sup> Although the direct relationship is not clear, the AFFIRM investigators point out that amiodarone, in particular, has previously been reported to be associated with higher noncardiac mortality in both the EMIAT and AVID trials.<sup>20,21</sup> Because of the inefficacy and dangers with nonablative therapies currently available for maintaining sinus rhythm, alternative treatments are certainly desirable.

### AF Ablation: A Cure Is Available

In contrast to AAM, catheter ablation directly eliminates the inciting factors for AF and offers the possibility of a lasting cure. The goal of present-day AF ablation is to electrically “disconnect” the pulmonary veins (PVs) from the rest of the atrium by ablating around the origin of the veins. When this idea was first proposed several years ago, it was understandably met with some skepticism. However, there is little controversy now that the PVs indeed play a major role in both triggering and maintaining AF, as established by both animal and human models. First, fibrillatory conduction is likely initiated by rapid discharges from 1 or several focal sources within the atria. In their seminal article, Haissaguerre et al<sup>22</sup> nicely demonstrated that in most AF patients (94%), the focus was in  $\geq 1$  of the PVs. Extra-PV sites may trigger AF, but this occurs in the minority, likely no more than 6% to 10% of patients.<sup>23</sup> AF is also perpetuated by microreentrant circuits, or “rotors,” that exhibit high-frequency, periodic activity from which spiral wave fronts of activation radiate into surrounding atrial tissue.<sup>24,25</sup> Conduction becomes slower and less organized with increasing distance from the rotors, likely because of atrial structural remodeling, resulting in fibrillatory conduction. Interestingly, the dominant rotors in AF are localized primarily in the junction between the left atrium (LA) and PVs, as demonstrated by several investigators.<sup>25–27</sup> A recent study has also demonstrated that the PV-LA region has heterogeneous electrophysiological properties capable of sustaining reentry (micro or macro).<sup>28</sup> Finally, vagal inputs may be very important in both triggering and maintaining AF, and many of these inputs are clustered close to the PV-LA junction.<sup>29</sup> Thus, the PVs play a critical role in both triggering and maintaining AF. This was elegantly confirmed with both electrophysiological and histological data in an open-heart, human model involving patients undergoing AF surgery.<sup>30</sup> The mechanism also applies to a wide spectrum of AF patients, including adolescents<sup>31</sup> and adults with structural heart disease.<sup>32,33</sup> Therefore, it does not seem reasonable to continue recommending pharmacological and device-based therapies that, unlike AF ablation, fail to address the “root cause.”

It seems especially unreasonable to avoid AF ablation now that there is much greater consistency in the methodology of the technique. Initially, a multitude of methods for ablating

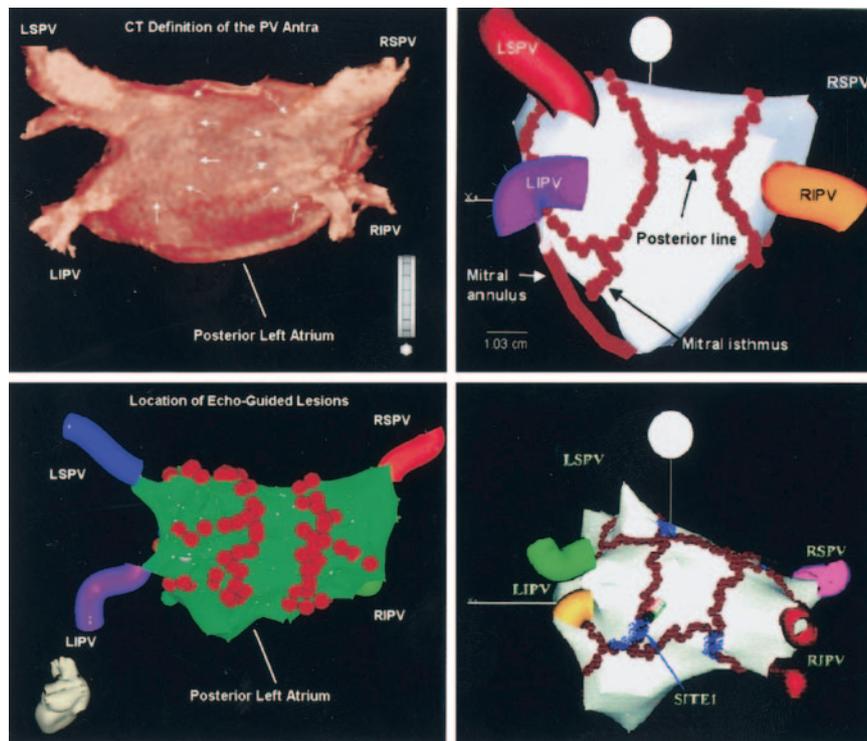


**Figure 3.** CT and intracardiac echocardiographic depiction of the PV antrum. Left, Internal view of the posterior wall of the LA reconstructed from 3D, multislice CT imaging. White dotted lines outline the left upper and lower and the right upper and lower pulmonary venous antra. Note that there is very little space on the posterior atrial wall between the 2 antral outlines. Right, Right upper (RUPV) and left upper (LUPV) pulmonary venous antra as seen by intracardiac echocardiography using a phased-array ultrasound catheter (AcuNav, Siemens Inc) positioned in the right atrium. Dotted lines represent the junctions between the antra and LA. On this echo image, one can appreciate that there is very little space on the posterior wall separating the two antra (\*), as was appreciated on the CT. These images emphasize the necessity of placing ablation lesions well outside the tubular portion of the PVs to include their entire antra.

AF existed.<sup>23</sup> Some were performing “focal” ablative procedures, in which only specific sites exhibiting earliest triggered activity in “culprit” PVs were ablated. Some chose to circumferentially ablate around  $\geq 1$  PV. Others were attempting to mimic the surgical Maze procedure by performing linear lesions in the right atrium and LA. However, after recognizing the limited success and risks associated with some of these approaches, we learned important lessons that have shaped the present-day technique. First, the vast majority of centers performing AF ablation are empirically isolating all 4 PVs. It was quickly recognized that any of the PVs can serve as a trigger and that ablating only a single “culprit” could unmask triggers in another PV.<sup>34</sup> Ablating all 4 PVs was also found to be more effective than ablating only 3.<sup>35</sup> Furthermore, most groups are ablating “outside” the tubular portion of the PV to avoid the risk of PV stenosis and to improve the efficacy of the procedure. This makes sense given that the PV is funnel shaped with a large proximal end, which we call the antrum. The antrum blends into the posterior wall of the LA, and on the posterior wall, there is little space between adjacent antra (Figure 3). Therefore, to encompass as much of the PV structure as possible, ablation needs to be performed around the entire antrum, along the posterior LA wall.<sup>36</sup> Although different groups may refer to ablation in this region by different names such as LA catheter ablation, circumferential PV antrum ablation, or extraostial isolation, the lesion sets produced by the procedures are all very similar (Figure 4).

With time, operator experience, and greater consistency in the technique, AF ablation has proved itself to be a very

effective treatment for AF, with similar success rates being reported by several different groups. In a recent review<sup>23</sup> including 19 studies, the success rates ranged from 6% to 93%. However, some of these studies were published very early on in the ablation experience, and there was a great deal of variation in the technique. Furthermore, the definition of “success” was highly variable, with some groups using off-drug cure as the definition of success and others including patients who could maintain sinus rhythm on AAMs. Looking at the most recent publications from several groups using ablation of all 4 PVs outside the tubular portion, the cure rate off chronic drug therapy is much more consistent, at 80.5% overall (Table 1).<sup>37–42</sup> A further 10% to 20% of patients may become responsive to previously ineffective AAM.<sup>43</sup> Some variation remains, partly because of variations in the precise end point used (see Table 1) and operator experience. However, although the cure rates are not 100%, they are 2- to 3-fold better than anything achievable by AAM. Furthermore, the cures seem to be durable, given the long follow-up (almost three years) reported by some groups<sup>37</sup> and the observation that most recurrences tend to occur early in the follow-up period, and rarely occur very late after ablation.<sup>44</sup> At our own institution, our most recent statistics from multiple operators show a 1-procedure, off-drug success rate approaching 80% and a 2-procedure success rate of  $>90\%$ . As future larger-scale trials evaluating AF ablation are designed, it will be important to ensure a consistent definition of cure (eg, off AAM) and decide on a universal end point (eg, PV isolation) to best interpret the results.



**Figure 4.** Similarity in location of the radiofrequency lesions produced by various groups' approaches to AF ablation. Top left, An outer view of a patient's LA as seen from the posterior aspect using 3D, multislice CT. Seen clearly are the tubular portions of each of the 4 PVs (individually labeled). The borders between the antra of the PVs and the posterior wall of the LA are indicated by small white arrows. Bottom left, A 3D electroanatomic map (CARTO, Biosense Webster Inc) of the LA (same patient as panel above) acquired during AF ablation guided by ICE. With ICE, the borders of the pulmonary vein antra can be accurately defined, and lesions can be placed to completely surround and electrically isolate the antra. Red dots represent the anatomic locations of these lesions produced by ICE-guided ablation. Top left, Location of lesions produced with a CARTO-guided approach described by Morady and colleagues. Reproduced from Oral et al,<sup>40</sup> with permission. Bottom left, Location of lesions produced using another CARTO-guided approach described by Pappone and colleagues. Reproduced from Pappone et al,<sup>29</sup> with permission. In all 3 cases, the location of the lesion sets is similar, encompassing the anterior and posterior borders of all 4 pulmonary vein antra. LSPV indicates left superior PV; LIPV, left inferior PV; RSPV, right superior PV; and RIPV, right inferior PV.

Although the success of AF ablation appears high, it is especially encouraging that it can be achieved with a very low incidence of complications. Complications from AF ablation include vascular complications secondary to venous access, cardiac perforation/tamponade, valvular injury, embolic

stroke or systemic embolism, esophageal injury, PV stenosis, and proarrhythmia resulting from reentrant tachycardias arising from incomplete ablative lesions. Finta and Haines<sup>23</sup> pooled data from 63 clinical studies on AF ablation encompassing 3339 patients between 1994 and 2003. Cerebrovas-

**TABLE 1. Success Rates of Most Recent Studies Using Ablation of All PVs Outside the Tubular Segment**

Study	Year	Patients	Age, y	Parox, %	SHD, %	Tool(s)	End Point	AF Free (Off Drugs), %	Follow-Up, d
Ouyang et al <sup>37</sup>	2004	41	63±9	100	NA	CARTO	PV Isolat'n	76*	178
Haissaguerre et al <sup>38</sup>	2004	70	53±8	NA	43	Fluoro	PV Isolat'n	79	210
Mansour et al <sup>40</sup>	2004	40	55±10	80	13	CARTO	PV Isolat'n	75	330
Marrouche et al <sup>41</sup>	2003	259	54±11	51	21	ICE	PV Isolat'n	87†	347
Oral et al <sup>39</sup>	2003	40	54±11	100	3	CARTO	EGM Red'n	88	365
Pappone et al <sup>36</sup>	2003	589	65±9	69	6	CARTO	EGM Red'n	79	861
Total		1039						81.0	

Parox indicates paroxysmal; SHE, structural heart disease; Fluoro, fluoroscopy only; Isolat'n, isolation; and EGM Red'n, reduction of local electrogram amplitude (usually >70%). CARTO is an electroanatomical mapping system (Biosense Webster).

\*Success was 95% off drugs after a second procedure.

†Success was 90% off drugs in patients with microbubble monitoring by ICE.

**TABLE 2. Complication Rates Compiled From 1033 Patients in the Studies in Table 1**

Complication	Events, n	Rate, %	Range in Studies, %
Transient ischemic attack	4	0.4	0–3
Permanent stroke	1	0.1	0–1
Severe PV stenosis (>70%, symptomatic)	3	0.3	0–3
Moderate PV stenosis (40–70%, asymptomatic)	13	1.3	0–5
Tamponade/perforation	5	0.5	0–3
Severe vascular access complication	3	0.3	0–4

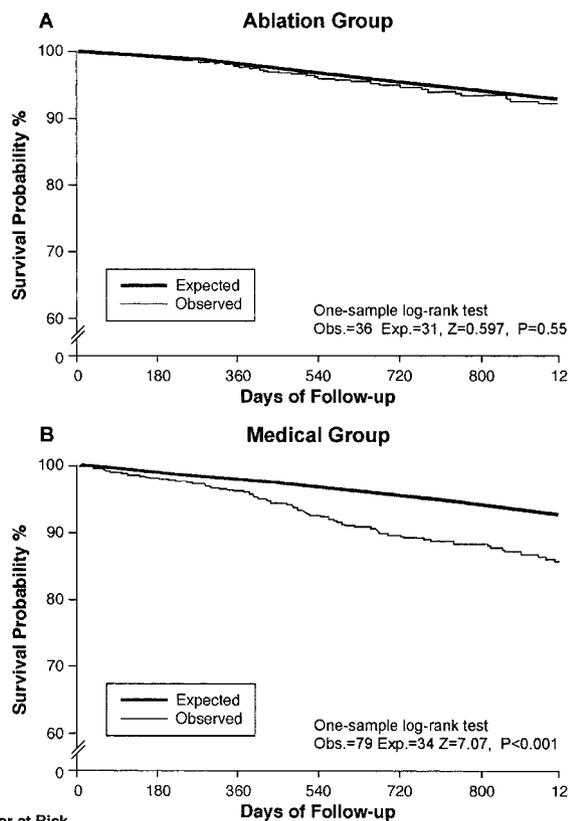
cular events occurred in an average of 1.0% of patients, manifest PV stenosis in 0.9%, and atrial macroreentry tachycardia in 29%. When only the more recent reports using a more consistent technique are reviewed, the complication rates are similar if not lower (Table 2). The complication rates are continuing to fall with more recent modifications to the technique and presently available technologies. For example, aiming for higher activated clotting times of 300 to 400 seconds can reduce the chance of thromboembolism without increasing bleeding risk,<sup>45</sup> and ablation outside the tubular portion of the veins greatly minimizes the risk of PV stenosis. Char formation, tissue disruption, and esophageal injury can also be avoided with strict limitations on radiofrequency energy output<sup>46</sup> and avoidance of ablating directly on top of the esophagus. Intracardiac echocardiography (ICE) has been demonstrated to be a particularly effective (and readily available) tool to minimize procedural complications. By providing real-time imaging, ICE allows one to perform safe transseptal access and avoid ablating within the PVs to prevent stenosis.<sup>42</sup> Furthermore, by titrating radiofrequency energy output to prevent microbubble formation on ICE, tissue disruption and coagulum formation causing stenosis and embolic events can be minimized.<sup>42</sup> Procedure-related atrial flutters can also be avoided if care is taken to document total electrical isolation of the PVs at the level of the antra, thereby eliminating the triggers for flutter. With an ICE-guided PV antrum isolation technique, our rate of flutter recurrence after ablation is very low at <3%.<sup>47</sup> We have also shown that in patients with both typical atrial flutter and AF, both arrhythmias can be treated with PV antrum isolation alone by eliminating the common trigger<sup>48</sup> in most cases. Other groups have successfully used additional linear ablation lesions to avoid postablation flutters such as a line across the mitral valve isthmus.<sup>39</sup> Newer technologies to reduce complications and improve the ease of performing ablation are also imminent, including real-time 3D CT and electro-anatomic mapping integration, robotic/magnetic-controlled catheter systems, and balloon-guided systems.

With such a high success rate and a low attendant complication rate, it is not surprising that current evidence shows that AF ablation not only is more effective than nonablative therapy but also may reduce both the morbidity and mortality associated with medical therapy. In a controlled, long-term

study (median follow-up, 900 days), Pappone et al<sup>37</sup> reported that 589 patients who underwent AF ablation had significantly improved survival compared with 582 matched patients who received antiarrhythmic medications. Survival among the ablated patients did not differ significantly from the expected survival of healthy, age- and gender-matched persons of the Italian population (Figure 5). The total number of adverse events, including stroke, were much less in the ablated group, and freedom from AF was significantly higher (78% versus 37% in the ablated and medical groups, respectively;  $P<0.001$ ). The Cleveland Clinic is leading a prospective, randomized, multicenter trial comparing AF ablation as first-line therapy to AAM known as the Radiofrequency Ablation for Atrial Fibrillation Trial (RAAFT). A randomized pilot study has already been completed in Europe involving a total of 70 patients, 33 randomized to ablation and 37 to AAM. Results are shown in Figure 6, with symptomatic AF recurring in 63% of AAM patients compared with only 13% of ablation patients ( $P<0.05$ ). Ablated patients also experienced greater improvements in quality of life and had fewer adverse events. Others have also reported similar results in head-to-head comparison,<sup>49</sup> and other trials are underway. Ablation may even be more cost-effective than medical therapy. Weerasooriya et al<sup>50</sup> demonstrated that assuming a conservative ablation cure rate of 72% after 1.5 procedures, the initially high cost of ablation would offset the ongoing costs of AAM by 3 years; after 4 years, ablation becomes more cost-effective, and the benefit continues to increase thereafter. AF ablation is clearly superior than our current standard of care, and with data showing greater efficacy, less morbidity and mortality, and even less cost, it seems reasonable that ablation be moved up to first-line therapy for some patients.

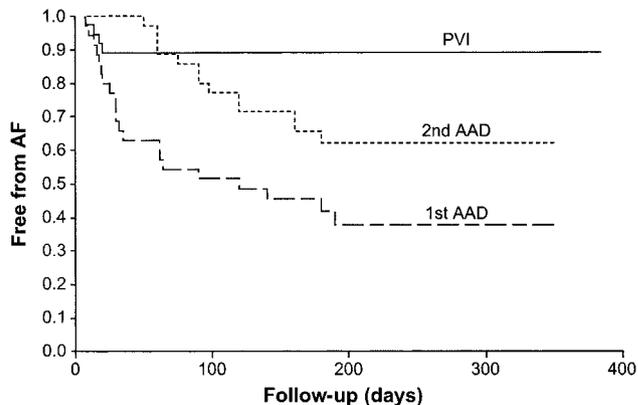
### Ablation: For Whom and By Whom?

Although we advocate for AF ablation as a first-line therapy, we do not yet believe that it should be offered first to all patients with AF. We acknowledge that large-scale, comparative clinical trials have yet to be performed and that these data are required before recommending ablation as first-line therapy for a very broad AF population. The studies to date have included only highly symptomatic, paroxysmal or persistent AF patients who have already failed medical therapy,



**Figure 5.** Kaplan-Meier curves depicting mortality benefit of AF ablation over time. A, Observed mortality of patients who have undergone AF ablation (observed) is no different from age- and gender-matched healthy patients from the general (expected) Italian population (log rank,  $P=0.55$ ). B, In contrast, patients undergoing medical treatment for AF who are matched in baseline characteristics to the ablation group (observed) have significantly increased mortality compared with the same age- and gender-matched healthy (expected) Italian population (log rank,  $P<0.001$ ). Reproduced from Pappone et al<sup>37</sup> with permission.

with minimal or moderate structural heart disease. This group experiences considerable morbidity and mortality from AF, with exacerbation of heart failure, poor exercise tolerance, and a major reduction in quality of life. These patients were also, for the most part, excluded from the large rate and rhythm control trials. In our experience and in many others', rhythm control with AAM is not only ineffective and poorly tolerated but only delays an inevitable ablation. Therefore, if first-line ablation is offered, it should at least be considered for those patients with symptomatic AF, mild to moderate structural heart disease, and paroxysmal or persistent AF. AF should be recurrent and should not be secondary to a transient, treatable cause. Ablation may particularly benefit younger patients with lone AF who are frequently symptomatic and for whom very-long-term antiarrhythmic and anticoagulation poses higher risks and lifestyle costs. Asymptomatic or minimally symptomatic AF patients may also benefit



**Figure 6.** Kaplan-Meier curves depicting freedom from AF in patients undergoing AF ablation by PV antrum isolation (PVI) compared with being treated with an antiarrhythmic drug (AAD) from the pilot study of the RAAFT. Seventy patients with symptomatic, mostly paroxysmal AF were randomized to PVI ( $n=33$ ) or AAD ( $n=37$ ). Overall recurrence of symptomatic AF was 13% in the PVI group compared with 63% in the AAD group treated with their first drug ( $P<0.05$ ; mean follow-up time,  $8.5\pm 3.2$  months). Even after patients were switched from a first AAD to a second AAD, recurrence still remained significantly higher compared with the PVI arm ( $P<0.05$ ).

from ablation and sinus rhythm in the long term, but until further clinical data are available, it is difficult to justify an invasive procedure to a patient who may not be aware that they have a problem.

There will be a time in the near future when AF ablation can be offered as first-line therapy to a broader AF population. Data already exist showing that good ablative success can be achieved in patients with impaired left ventricular function,<sup>32</sup> previous cardiac surgery or valvular heart disease,<sup>33</sup> and advanced age.<sup>51</sup> We have also found that the cure rate after 2 ablations is similar in both paroxysmal and nonparoxysmal AF patients.<sup>52</sup> The only group that seems destined to fail ablation is that with extensive, preexistent LA scarring.<sup>53</sup> Although at the present time this can be identified only invasively, noninvasive methods may soon become available to detect advanced atrial myopathy. In the future, novel therapies to slow or even reverse the scarring process may help make AF more amenable to ablation.

Another important limitation of AF ablation is that it is being performed only at a few select centers in most countries and is not yet widely available. Therefore, it is prudent that only centers with considerable experience in performing AF ablation should consider offering ablation as first-line therapy. As with any new invasive or surgical procedure, the benefit is highly operator dependent. The present reality will gradually evolve, and advances such as robotically controlled catheters and real-time MRI or CT imaging will eliminate operator experience as a component affecting the outcome of ablative procedures.

### Conclusions

AF is an arrhythmia associated with increased morbidity and mortality, and it is in the patient's best interest to pursue

effective and safe treatments to eliminate this disease. Current therapies, especially AAM, not only are ineffective but also pose a threat to patient quality of life and even longevity. In the hands of experienced operators, AF ablation is an effective, safe, and established treatment for AF that offers an excellent chance for a lasting cure. Unlike other therapies, ablation tackles AF at its electrophysiological origin. Therefore, it is about time that AF ablation be used as a first-line option for selected patients with this disease. There is no reason to be afraid of marching toward a future when growing experience plus evolving technology will allow us to apply ablation to most AF patients, and the question of using ablation as first-line therapy will no longer be such a “burning issue.” To paraphrase the Wright brothers, “If you don’t go further than your front yard fence, you will discover nothing.”

### Acknowledgments

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## *Should Ablation Be First-Line Therapy and for Whom: The Antagonist Position*

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**A**trial fibrillation (AF), the commonest cardiac arrhythmia with an adverse prognosis, has an estimated prevalence of 0.4% in general population.<sup>1</sup> The disease is associated with significant morbidity related to symptoms, heart failure, and thromboembolism.<sup>2</sup> Although AF is generally considered a non-life-threatening arrhythmia, it was associated with a 1.5- to 1.9-fold excess mortality after adjustment for preexisting cardiovascular conditions in the Framingham Heart Study.<sup>3</sup> In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, a strategy of heart rate control was equivalent to heart rhythm control in terms of quality of life and all-cause mortality but superior in reducing hospitalizations.<sup>4</sup> Anticoagulation with warfarin is maintained in either strategy if the patient has risk factors for thromboembolism. The major reason to pursue sinus rhythm in patients with AF is to improve their symptoms and quality of life. No studies have shown a reduction in stroke or heart failure when rhythm control is attempted in patients with AF.

Once the decision to achieve rhythm control in a given patient has been made, physicians have to determine the best means of achieving this objective. Multiple randomized trials have demonstrated a modest but highly significant efficacy for antiarrhythmic medications.<sup>5</sup> The limited long-term efficacy and high incidence of side effects of antiarrhythmic medications have prompted physicians to consider nonpharmacological therapies for AF.<sup>6</sup> It has also been postulated, in a retrospective subanalysis of the AFFIRM study, that a strategy to maintain sinus rhythm without the adverse effects of antiarrhythmic medications may confer a survival advantage.<sup>7</sup> In a nonrandomized study, Pappone et al<sup>8</sup> compared the outcomes in a selected group of 589 patients who underwent circumferential pulmonary vein ablation with 582 age- and gender-matched cohort patients who received antiarrhythmic medications to maintain sinus rhythm. After a median follow-up of 900 days, the observed survival was longer and quality of life was better for patients who underwent ablation. Although these findings are intriguing, they require confirmation in a prospective randomized controlled trial.

### **Determinants of First-Line Therapy**

The issue under discussion here is not whether a catheter ablation cure of AF is either possible or useful in many patients but whether it should be used as “first-line” therapy. Thus, it is important to establish reasonable criteria to define first-line therapy. In our view, 3 requisites should be met for any new treatment to attain this status: (1) knowledge of the short-term and long-term risks, (2) knowledge of the short-term and long-term benefits, and (3) an equivalent or superior risk-to-benefit ratio of the proposed treatment compared with established therapies. The following discussion reviews the data on catheter ablation of AF as they pertain to these 3 important issues. As we will show for most patients, the evidence does not support catheter ablation as first-line therapy for AF.

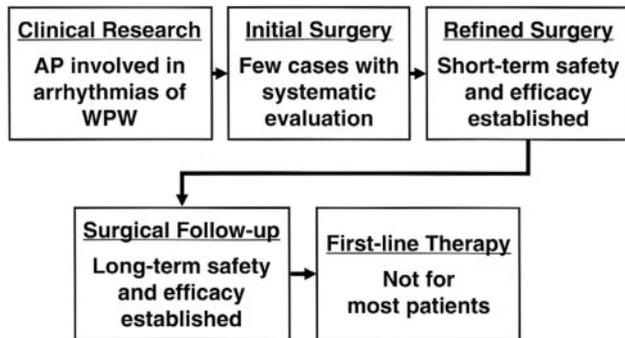
### **Nonpharmacological Therapy for Wolff-Parkinson-White Syndrome**

Nonpharmacological treatment for Wolff-Parkinson-White (WPW) syndrome is a paradigm against which nonpharmacological therapy for other cardiac arrhythmias should be compared. Figure 1 reviews the evolution of the surgical approach to cure WPW syndrome. In 1930, Wolff, Parkinson, and White combined the observations of a bundle-branch block with an abnormally short PR interval in individuals with paroxysms of tachycardia into what we now recognize as the WPW syndrome. Still, it took decades of observations of outstanding electrocardiographers and finally invasive clinical electrophysiologists to unravel the pathophysiology of AV reentry.<sup>9</sup>

The path taken to understand this very important arrhythmia solidified 1 certain thing: its clinical relevance in humans. As more knowledge on mapping the location of an accessory pathway became available, the next logical step was for a visionary team of researchers to attempt a surgical cure for this arrhythmia, as was done by Dr Will Sealy and colleagues at Duke University.<sup>10</sup> Initially, surgery was used very infrequently, and each case was systematically evaluated. Over many years, the surgical approach was refined until it became an established method of treatment.<sup>9</sup> Long-term safety and efficacy were established, and the quality of



**Non-pharmacologic Therapy for WPW Syndrome: A Paradigm**



**Figure 1.** Development of surgical therapy for WPW syndrome. See text for details.

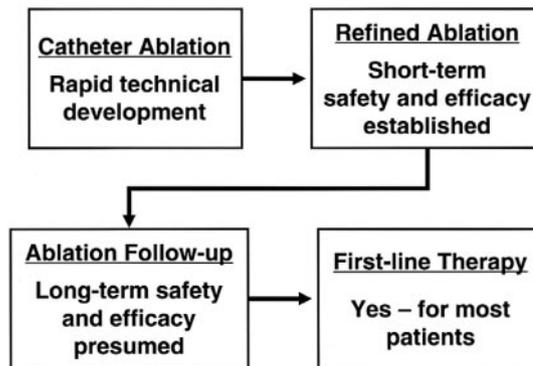
life for up to 18 years after surgery was excellent.<sup>11</sup> Even with the short-term and long-term risks and benefits known, many, if most, electrophysiologists still did not recommend it as first-line therapy for most patients with WPW syndrome, although it clearly was a first-line treatment for high-risk groups and younger patients.

In Figure 2, the nonpharmacological treatment paradigm for WPW syndrome shifts to the development of catheter ablation to cure patients with these arrhythmias. The surgical experience provided the electrophysiologist with an in-depth understanding of an anatomic approach to ablate accessory pathways, and the major hurdles were to develop deflectable tipped catheters with appropriate electrode surfaces and energy sources that would enable a catheter-based approach for ablation. The technical challenges were resolved rather quickly, and short-term safety and efficacy were established.<sup>12</sup> Because the long-term safety and efficacy of the surgical approach had been established, it was presumed that a similar outcome could be expected from the catheter-based approach. Thus, the marked reduction in morbidity and mortality of catheter ablation compared with surgery advanced catheter ablation as first-line therapy of patients with the WPW syndrome even in the absence of prospective randomized clinical trials.

**Nonpharmacological Therapy for AF**

The journey to a surgical approach to cure patients with AF took a strikingly different course than that for patients with WPW syndrome (Figure 3). There were nearly no reasonable experimental models to study WPW syndrome, but a plethora of models, including computer simulations, were used to investigate the pathophysiological basis for AF.<sup>2</sup> Sherf and coworkers<sup>13,14</sup> proposed that AF was caused by an ectopic focus, but most investigators sided with Moe et al,<sup>15,16</sup> who advanced the concept of the multiple wavelet hypothesis. In this concept, AF is maintained by multiple independent wavelets moving around functionally refractory tissue. The

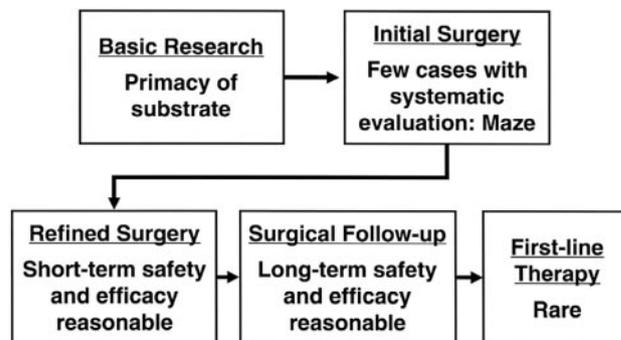
**Non-pharmacologic Therapy for WPW Syndrome: A Paradigm**



**Figure 2.** Development of catheter ablation therapy for WPW syndrome. See text for details.

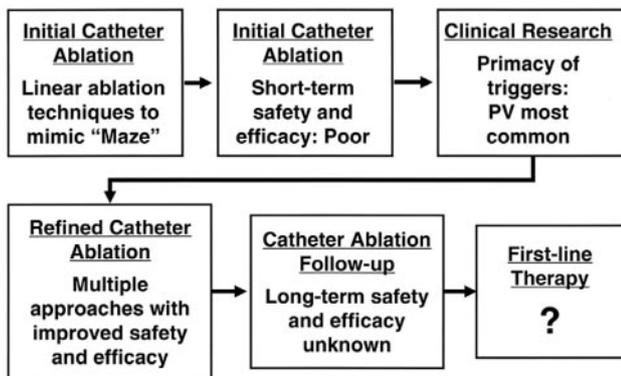
maintenance of AF depends on the probability that electrical activity can be sustained by a sufficient number of active wavelets at any point in time. The pioneering surgical approach to cure AF developed by Dr Cox<sup>17</sup> was based on the pathophysiological mechanism of the multiple wavelet hypothesis. The surgical approach was designed to make critical incisions in the right and left atria that would develop barriers to conduction and thereby prevent maintenance of AF. The atrial incisions direct sinus impulses to a path or a “maze” to reach the AV node, and the surgical approach has been called the maze procedure. This procedure was refined over time, and short-term safety and efficacy are reasonably well established. For example, among the 178 patients undergoing several iterations of the maze procedure from 1987 to 1996, 93% were arrhythmia free in the absence of antiarrhythmic medications with a 3-month to 8.5-year follow-up.<sup>17</sup> Thus, both short-term and long-term safety and efficacy appear reasonable with this technique. Despite a high success rate of the surgical maze procedure to cure AF, the requirement of open heart surgery with its attendant risks have clearly

**Non-pharmacologic Therapy for Atrial Fibrillation**



**Figure 3.** Development of surgical therapy to cure AF. See text for details.

### Non-pharmacologic Therapy for Atrial Fibrillation



**Figure 4.** Development of catheter ablation therapy to cure AF. See text for details.

limited the acceptance of this procedure as a first-line therapy, and it is rarely used for this purpose. Surgical approaches using the maze and the more current pulmonary vein isolation procedures are very reasonable “add-on” techniques in patients undergoing other forms of cardiac surgery.

### Catheter Ablation to Cure AF

Figure 4 summarizes the odyssey of the development of a catheter ablation approach to cure AF. Based on the success of the surgical maze procedure, the initial catheter ablation approach attempted to create a series of linear ablation lines in the right and left atrium to mimic the surgical maze approach.<sup>18,19</sup> The use of linear ablation lines within the left atrium yielded a success rate often in the 40% to 50% range, but the relatively high complication rates dampened enthusiasm for this ablation approach.<sup>18,19</sup> Linear ablations in the right atrium have demonstrated limited success on follow-up.<sup>20–22</sup>

The long buried and forgotten observations on an ectopic focus theory for AF suddenly reemerged with the seminal observation of Haissaguerre and colleagues<sup>23</sup> on the existence of pulmonary vein ectopy that caused AF. The majority of focal sources of AF occur within  $\geq 1$  of the pulmonary veins, and elimination of these ectopic areas can prevent AF.<sup>21</sup> The importance of this observation by Haissaguerre et al that the clinical occurrence of AF was often related to an ectopic focus cannot be overstated. Although this observation does not negate the contribution of reentry in maintaining AF in patients, it swiftly caused a sea change in the clinical ablation approach to cure patients with AF. Furthermore, it has led to a resurgence in basic research directed at understanding the pathophysiological mechanisms of AF.

Most focal sources of AF have been found within the pulmonary veins. However, foci have been described in the left atrial posterior wall, superior vena cava, crista terminalis, vein of Marshall, coronary sinus, and interatrial septum in as many as 28% of patients.<sup>24</sup> Focal ablation within the pulmo-

nary vein was guided by activation mapping. In the first series of 45 patients with paroxysmal AF undergoing focal ablation, 62% were free of symptomatic AF after a mean follow-up of 8 months, and  $\approx 70\%$  of these patients required  $>1$  procedure.<sup>23</sup> In another series of 79 patients, Chen et al<sup>25</sup> reported an 86% success rate at a mean follow-up of 6 months. The long procedure times, absence of good end points, frequent recurrences, and relatively high incidence of complications such as pulmonary vein stenosis prompted further research into ablation approaches.

The most recent techniques target electrical isolation of the entire pulmonary vein musculature from the left atrium as the end point, and several approaches have been proposed. Electrophysiological breakthroughs from the pulmonary veins to the left atrium are often multiple and were identified by circumferential mapping at the venous ostia. Radiofrequency ablation at sites of earliest activation eliminated all pulmonary vein potentials.<sup>26,27</sup> In a study of 70 patients and a mean follow up of  $4 \pm 5$  months, 73% were free of AF without antiarrhythmic medications, although 29 patients had a second ablation procedure to obtain these results.<sup>26</sup> There were no instances of pulmonary vein stenosis, and elimination of pulmonary vein potentials was suggested as an ablation end point.<sup>26</sup>

An anatomic approach, guided by a nonfluoroscopic navigation system (CARTO), was described by Pappone et al.<sup>28</sup> Radiofrequency ablations are delivered circumferentially outside the pulmonary vein ostium. Of the 26 patients who underwent this procedure at a mean follow up of  $9 \pm 3$  months, 85% were free of AF, including 62% without antiarrhythmic medications.<sup>28</sup> In a subsequent study of 251 patients from the same group, the overall success was 80%, and only 13 of these patients were taking antiarrhythmic medications.<sup>29</sup> The success rate was higher for paroxysmal AF (85%) compared with persistent AF (68%). Modification of these techniques with electrogram-based pulmonary vein antrum isolation has also reported high success rates.<sup>30</sup> Another approach recently described has involved targeting complex fractionated electrograms for ablation.<sup>31</sup> At a 1-year follow-up, 110 of 121 patients (91%) were free of AF, including 10 patients still taking antiarrhythmic medications.

### Long-Term Efficacy

The concept of “cure” for a chronic disease like AF should be approached with caution. Epidemiological studies indicate an increased incidence of AF with increasing age and diseases such as hypertension. Aging can lead to electrophysiological and electroanatomic changes in the atria that may provide a substrate for maintenance of AF. Thus, AF may be a disease in which multiple mechanisms are operative, and eliminating triggers and possible modification of substrates with pulmonary vein isolation procedures may not result in long-term cure after initial clinical success.

An area of concern is the lack of long-term efficacy of pulmonary vein ablation techniques. Relatively high cure



rates using only right atrial linear ablations at initial follow-ups did not hold up over time.<sup>20–22</sup> Similarly, high success rates of 86% were reported with focal pulmonary vein ablation in an initial report of a 6-month follow-up, and subsequent follow-up reported lower success.<sup>25,32</sup> Several reports have claimed >80% cure rates with circumferential pulmonary vein ablation techniques during relatively short mean follow-up periods ranging from 6 to 14 months.<sup>29,30,33</sup> Whether these results will stand the test of time is unknown.

Another troubling problem is the significant variance of success among laboratories using similar techniques of ablation.<sup>34,35</sup> The procedures are technically challenging and highly operator dependent, which may explain the differences in outcomes. Because initial data are usually reported from very experienced centers, the risk-to-benefit ratio for the same procedure may be quite different at other institutions.<sup>36</sup>

Making efficacy of AF ablation even harder to define is the well-known occurrence of asymptomatic AF.<sup>37</sup> Studies reporting only symptomatic AF episodes after ablation could overestimate success, especially during short-term follow-up. In a study of 60 patients who became asymptomatic after pulmonary vein ablation, 12% reported symptoms and documented AF when given an event recorder almost 2 years after the ablation.<sup>38</sup> Some patients may have an apparent threshold burden of AF below which it remains asymptomatic, and AF during sleep often goes undetected. It is possible that radiofrequency ablation may change symptomatic AF to asymptomatic AF in some patients. This is important not only to quantify the true success of the procedure but also to make decisions regarding anticoagulation in patients at high risk for stroke. In the AFFIRM trial, the risk of thromboembolism persisted in patients who were clinically maintaining sinus rhythm with antiarrhythmic medications, perhaps because of clinically undetected episodes of AF in these patients.<sup>4</sup> Patients cured of symptomatic AF after a radiofrequency ablation procedure could be in an analogous situation.

In summary, short-term efficacy of the various pulmonary vein ablation techniques appears to be reasonably good but often requires >1 procedure and temporary or prolonged antiarrhythmic medication use. Long-term efficacy defined in years is still lacking.

### Comparison of Techniques

At present, most investigators are using techniques to isolate electrically the pulmonary veins from the left atrium or to modify the left atrial substrate around the pulmonary veins. Different methods have been proposed,<sup>39–41</sup> but few comparative data have been published. There is debate whether isolation of pulmonary veins is essential to cure AF.<sup>42</sup> Oral et al<sup>33</sup> compared segmental ostial ablation and circumferential pulmonary vein ablation. Success rates were reported to be 88% with circumferential pulmonary vein ablation compared with 67% for segmental isolation of pulmonary veins. However, the follow-up period was short ( $164 \pm 100$  days), and the number of patients small (40 in each group). Variable use of

antiarrhythmic medications after ablation in different studies further complicates meaningful comparisons of procedural success.

In addition to the pulmonary vein ablation techniques, some investigators propose isolation of the superior vena cava, cavotricuspid isthmus ablation, or addition of linear ablation lesions in the left atrium. Whether these adjunctive ablations improve outcome and which patients should be targeted for them need more investigation. No prospective studies have been performed comparing any of these ablation techniques with medical therapy.

### Complications of Ablation

Few therapies, pharmacological or otherwise, can be administered without safety concerns. Potassium channel blocking antiarrhythmic medications (class III) can cause torsade de pointes, amiodarone is associated with a variety of organ toxicities, and sodium channel blocking agents (class I) can increase mortality when used in patients with structurally abnormal hearts and coronary artery disease.<sup>2</sup> However, the use of antiarrhythmic medications other than amiodarone is rarely associated with organ toxicity or life-threatening proarrhythmia in patients with structurally normal hearts. Unfortunately, complications of ablation can occur in any patient, including those with normal hearts, and previously unknown complications may emerge with changes in techniques, wider ablation experience, or longer follow-up.

#### *Pulmonary Vein Stenosis*

Pulmonary vein stenosis of variable degrees was commonly seen after focal ablation inside the pulmonary veins.<sup>25,27</sup> The incidence of this complication has been dramatically reduced by changes in technique. In one study, a reduction in power delivery and limiting ablations to the pulmonary vein ostia eliminated acute pulmonary vein stenosis (defined as >50% diameter reduction) detected by venography immediately after ablation.<sup>26</sup> In another study, no patients had pulmonary vein stenosis on follow-up transesophageal echocardiograms when ablations were delivered outside the pulmonary vein ostium under CARTO guidance.<sup>29</sup> However, a relatively high incidence of pulmonary vein stenosis was reported by another group (36% overall and 17% severe) using the CARTO-based circumferential pulmonary vein ablation approach.<sup>35</sup> Titration of radiofrequency energy delivery by visualizing microbubble formation with intracardiac echocardiography is also reported to reduce the incidence of pulmonary vein stenosis.<sup>30,43</sup> The true incidence is likely underreported unless postprocedure imaging techniques are used because pulmonary vein stenosis can be asymptomatic.<sup>43</sup> The long-term effects of even mild to moderate pulmonary vein stenosis are unclear.

#### *Thromboembolism*

Embolic stroke is a well-recognized complication of pulmonary vein ablation. The incidence has varied from 0% to 5%<sup>23,44</sup>; one group recently reported a 2.5% incidence of

stroke.<sup>45</sup> Intracardiac echocardiography has documented left atrial thrombus attached to the mapping catheter or sheath in 24 of 232 patients (10.3%) even when activated clotting time was maintained >250 seconds.<sup>46</sup> Newer, more aggressive anticoagulation strategies and use of intracardiac echocardiography<sup>30</sup> may reduce the frequency of this dire complication.

### **Atrioesophageal Fistula**

Left atrium to esophagus fistulas have occurred after intraoperative radiofrequency ablation of AF<sup>47</sup> and recently have been reported after catheter ablation.<sup>48,49</sup> Patients usually present with sudden neurological symptoms or endocarditis after an initial unremarkable postoperative course. Atrioesophageal fistula, thus far reported only after circumferential pulmonary vein ablations,<sup>48,49</sup> may be related to the more extensive ablation lesions applied to the posterior left atrium. In the surgical series, 4 of 387 patients undergoing intraoperative radiofrequency ablation developed atrioesophageal fistula.<sup>47</sup> Three patients survived after extensive esophageal resection, and 1 died of massive air embolism. Among the 3 reported cases after catheter ablation, 2 patients died, and 1 survived after emergency cardiac and esophageal surgery. Risk factors for this potentially fatal complication have not been established.<sup>47</sup> The true incidence and strategies to prevent this complication with catheter ablation require further study.

### **Left Atrial Flutter**

Reentrant rhythms may originate in the left atrium related to scars of catheter ablation of AF. In a series of 44 patients who underwent linear left atrial ablations, left atrial flutter appeared in 31 patients on follow-up.<sup>19,50</sup> Interestingly, left atrial flutter was not inducible at the end of the initial ablation procedure. Left atrial flutter has also been reported after circumferential pulmonary vein ablation procedures in 2.5% to 20% of patients<sup>33,35</sup> and may appear months after the initial ablation. Late appearance of atrial flutter may indicate remodeling or extension of ablation scars setting up macroentry.

### **Other Complications**

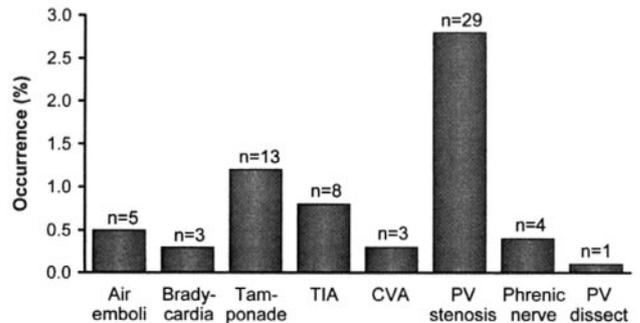
Figure 5 shows the major complications with pulmonary vein ablation in >1000 patients studied.<sup>18</sup> Complications additional to those listed above include air embolism, cardiac tamponade, phrenic nerve damage, and mitral valve damage. It should be noted that a variety of ablation techniques were used over time and that the incidence of various complications is likely to be less with refinement of techniques and more experience.

In summary, the short-term safety of the newer ablation techniques has improved, but serious and life-threatening complications persist. The long-term safety is unknown.

### **Publication Bias**

Publication bias is a widely recognized phenomenon that occurs because of the influence of study results on the chances of publication. Studies with positive results are more

### **Major Complications With Pulmonary Vein Ablation in 1,049 Patients (7 Series)**



**Figure 5.** Major complications associated with pulmonary vein (PV) ablation procedure to cure AF. TIA indicates transient ischemic attack; CVA, cerebrovascular accident. Reproduced with permission from Reference 18.

likely to be published than studies with negative results, leading to a preponderance of positive results in the literature.<sup>51</sup> Journals with a high citation impact factor are more likely to publish studies with positive results, and tendency toward publication bias is greater with observational studies than with randomized clinical trials.<sup>52</sup> Thus, conclusions based only on a review of published data should be interpreted cautiously, especially for observational studies like AF ablation. Underreporting of complications and low procedural success is certainly a possibility.

### **Conclusions**

Our requisites for a first-line therapy are known short-term and long-term risks and benefits and a demonstrated risk-to-benefit ratio equivalent or superior to that of alternative treatments. Ultimately, the cost-effectiveness of the treatment should also be taken into account. As shown in Figure 4, we think that long-term safety and efficacy of catheter ablation to cure AF are unknown, and we do not feel that it should be recommended as first-line therapy for most patients with AF. Unlike catheter ablation of WPW syndrome, where excellent short-term and long-term efficacy and minimal procedural complications enabled it to become first-line therapy even in the absence of prospective randomized controlled trials, catheter ablation of AF is associated with variable short-term efficacy, unknown long-term efficacy, and significant procedure-related complications. Our position should not be taken as an indictment against catheter ablation of AF, which we do routinely at our institution. Rather, it reflects the current state of the art of this procedure. We fully expect future advances in techniques and technology and demonstration of the outcomes of ablation in prospective randomized trials to move ablation to a first-line therapy for AF.

Are there circumstances in which catheter ablation might be considered as an initial therapy? We think there are, and exceptions to the general rule might include patients with

very symptomatic AF who refuse antiarrhythmic medications, patients in whom the only antiarrhythmic choice is long-term amiodarone, and possibly patients at high risk for stroke who refuse or cannot take long-term warfarin therapy. Regarding the last group, one has to recognize that there is no long-term follow-up showing a reduction in stroke risk in patients apparently cured of AF with catheter ablation. Such patients may require constant long-term rhythm monitoring, eg, with an implanted loop recorder.

Other less common situations might be young patients with paroxysmal AF and sinus node dysfunction who may not tolerate antiarrhythmic medications without a permanent pacemaker. Significant improvement in sinus node function was reported, eliminating the need for pacing, after curative ablation of AF in such patients.<sup>53</sup> The long-term morbidity associated with a pacemaker, in addition to the risks related to antiarrhythmic drug therapy, might tilt the balance in favor of ablation as a first-line treatment in these selected patients. Although clinical judgment is important in deciding the best course of therapy in these individual circumstances, catheter ablation should not be the first-line therapy for most AF patients at the present time.

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## Response to Padanilam and Prystowsky

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**D**rs Padanilam and Prystowsky argue that unlike the WPW paradigm, insufficient long-term outcome data and an unclear risk-to-benefit ratio of ablation compared with alternative therapies should prevent us from using ablation as a first-line therapy for AF. However, unlike the majority of WPW cases, AF is associated with both increased morbidity and mortality,<sup>1</sup> necessitating more aggressive treatment. Furthermore, the lack of efficacy and known harm of alternative pharmacological therapy for AF cannot be underestimated.<sup>1</sup> Of course, significant complications can and do occur with ablation, but with a new-found sensitivity to power titration, proper catheter handling, and direct visualization with technologies such as intracardiac echocardiography, much of this risk can be minimized.<sup>2</sup> We fully agree that more long-term outcome data are warranted, but data already exist showing excellent results beyond 2.5 years,<sup>3</sup> and in our own center, we have found cure rates persisting beyond 3 years. Occurrence of asymptomatic AF after ablation also has been found to be very uncommon in patients with previously symptomatic AF.<sup>4,5</sup> Although we presented some very promising prospective data on ablation compared with drug therapy for AF from the RAAFT trial, we agree that larger studies are required. Technology and techniques of ablation also will continue to evolve, further improving success and minimizing risk. However, we still feel strongly that, with the available data and technology, there is justification for experienced centers to offer first-line ablation to patients with symptom-

atic AF, mild to moderate structural heart disease, and paroxysmal/persistent AF. As further data and research become available, we may expand ablation to a broader population in the future.

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## *Response to Verma and Natale*

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**V**erma and Natale forward the position that ablation to cure AF should be first-line therapy. It is important to stress some similarities between us, the most important of which is that large numbers of patients require sinus rhythm to feel better. We also agree that ablation to cure AF is an exciting and useful new treatment option. That said, we disagree that an ablation cure for AF is ready for “prime time” universal application as first-line therapy. Actually, even Verma and Natale cannot support this position, stating “. . . it is prudent that only centers with considerable experience in performing AF ablation should consider offering ablation as first-line therapy.”

When a potential curative treatment becomes available for a chronic disease, it is easy to get ahead of the data and offer it as first-line therapy. However, before venturing into widespread use of ablation in broad AF populations, one should do

due diligence and systematically compare it with established therapies. Despite the claim by Verma and Natale, no studies have, to the best of our knowledge, demonstrated increased mortality associated with antiarrhythmic drug use in patients with AF and structurally normal hearts. Dofetilide and amiodarone may not worsen survival when used in patients with heart failure. Antiarrhythmic therapy “delaying the inevitable ablation” may actually benefit the patient as further technical refinements become available in the future. Although we generally feel that antiarrhythmic drugs should be tried first, we realize, and state, that there are situations in which ablation may be preferable as first-line therapy. Far from being nihilistic regarding ablation to cure AF, we look forward to the time when we can offer it as first-line therapy to our patients on the basis of scientific data.