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Catheter Ablation as First-Line Therapy for Atrial Fibrillation: Ready for Prime-Time?

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Abstract Current guidelines include atrial fibrillation (AF) catheter ablation as part of the management strategy in patients that have failed at least one oral antiarrhythmic drug treatment course. However, growing evidence derived from both randomized and non-randomized studies demonstrate lower rates of AF recurrence and AF burden in patients with paroxysmal AF that are naïve to antiarrhythmic drug treatment. Furthermore, progression from paroxysmal AF to persistent AF appears to be delayed by early catheter ablation of AF. The current review addresses the question of the best timing for ablation in patients with paroxysmal AF and provides the rationale for offering AF ablation as first-line therapy based on the most updated evidence available.

Keywords Atrial fibrillation · Catheter ablation · Paroxysmal · Atrial remodeling

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice with a lifetime risk exceeding 20 % by the age of 80 years [1]. The primary goal of treatment in patients with paroxysmal AF is the relief of symptoms, primarily measured by reducing the frequency, severity, and recurrence of AF. Antiarrhythmic drug (AAD) therapy has been the cornerstone for treatment of paroxysmal AF. However, long-term success and suppression of recurrent AF episodes is suboptimal, and AADs are frequently deemed unsuccessful due to frequent arrhythmia breakthroughs and side effects [2]. Since the introduction of catheter ablation (CA) as a non-pharmacological therapy of AF in 1998 [3], several observational and randomized trials have documented the superiority of CA in maintaining sinus rhythm and preventing recurrences when compared to conventional medical therapy in patients previously failing treatment with at least one AAD. Prolongation of time to recurrence and in some cases, a clinically relevant reduction in the frequency of AF episodes associated with a marked improvement in quality of life have been documented in most studies [4, 5]. None of the former trials or observational studies has been powered to determine whether CA prolongs life or significantly reduces AF-related morbidity particularly stroke.

All current International AF practice guidelines accept that CA should be considered in symptomatic patients with paroxysmal AF who have failed achieving control of AF-related symptoms with AADs (class 1 level of evidence A, 2014 AHA/ACC/HRS Guidelines) [5]. Whether CA provides higher efficacy with comparable safety as AAD is clearly supported by significant evidence. However, the question related with the best timing when CA should be offered in patients presenting primarily with paroxysmal AF remains a matter of debate. Should a trial with AADs be always

required? Does early intervention prevent the progression of paroxysmal AF into persistent or permanent AF, in other words, does AF beget AF in humans? Finally, what is the real efficacy and safety of CA in patients with paroxysmal AF? All of the above questions are critical when offering any therapeutic modality to a patient. The last but not the least, patients' values and preferences also play a role when discussing the need for invasive palliative forms of therapy.

Theoretical Advantages of Early Intervention with Catheter Ablation

Early studies in AF patients have demonstrated clinical progression of AF over time in a significant proportion. Patients with paroxysmal AF have shown an annual risk of progression to chronic AF of 15 [6] and 24.7 % by 5 years [7]. A critical question that remains unanswered is whether early intervention with CA actually changes progression of AF and is paralleled with reduced long-term outcomes. Some available evidence derived from observational cohort studies seems to justify early intervention with CA in patients with AF. Bunch et al. [8] reported the relationship between time of the first diagnosis of AF and time to undergo CA. This observational longitudinal study followed 4535 patients that underwent CA for AF. All the patients had established care provided by a single integrated health care system. Outcomes included AF recurrence at 1 year, stroke, hospital admissions, and death. Using recursive partitioning methodology, the authors determined categories associated with changes in risk from the time of the first AF diagnosis to the first AF ablation and categorized four groups: (1) 30–180 days, (2) 181–545 days, (3) 546–1825 days, and (4) >1825 days. Interestingly, the authors documented significant negative impact on procedural success and AF recurrence with delayed treatment. Similarly, significant trends were observed in all outcomes including death. Albeit the fact that these are observational data, they seem to support early intervention with CA once AF is diagnosed.

The role of atrial fibrosis provides another piece of evidence that may be support the need for early intervention with CA in patients with paroxysmal AF. The DECAAF study quantified left atrial fibrosis using delayed enhanced MRI technology at least 30 days prior to undergoing CA for AF [9•]. This multicenter study enrolled 272 patients that underwent CA for different types of AF (65 % paroxysmal), and were followed to determine the role of left atrial fibrosis and recurrence of atrial tachyarrhythmias post CA. The investigators categorized the degree of left atrial fibrosis in four stages: stage 1 (<10 % of atrial wall), stage 2 (10–<20 %), stage 3 (20–<30 %), and stage 4 (≥30 %). Estimated unadjusted cumulative incidence of recurrent arrhythmia by day 325 for stage 1 fibrosis was 15.3 %(95 % CI, 7.6–29.6 %); stage 2, 32.6 % (95 % CI, 24.3–42.9 %); stage 3, 45.9 % (95 % CI, 35.5–57.5 %); and stage 4, 51.1 % (95 % CI, 32.8–72.2 %), and by day 475 was 15.3 % (95 % CI, 7.6–29.6 %), 35.8 % (95 % CI, 26.2–47.6 %), 45.9 % (95 % CI, 35.6–57.5 %), and 69.4 % (95 % CI, 48.6–87.7 %), respectively. The addition of fibrosis to a recurrence prediction model improved predictive accuracy. These findings suggest that disease progression is associated with greater degrees of fibrosis and lower procedure success.

Recently, an observational but well-conducted study evaluating progression of atrial remodeling with medical management or CA of paroxysmal AF was reported [10•]. The authors studied a group of 38 patients with paroxysmal AF who were treated with AADs, a second group of 20 patients with paroxysmal AF who were managed with CA, and a third group of 25 control patients without AF. During a follow-up period of 12 months, the progression of left atrial remodeling was monitored using echocardiography with strain. Recurrence and burden of AF using implantable loop recorders were also monitored. The main finding was that medical management compared with CA was associated with a higher burden of AF 8 % (range, 3–53 %) and with progressive decline in left atrial strain, suggestive of deteriorating left atrial reservoir function. In contrast, the CA group had an overall AF burden of 0 % (range, 0–1 %) and showed reverse remodeling with increased atrial strain suggestive of improved left atrial reservoir function. The central conclusion of this study was that progression of paroxysmal AF is more common with medical management than with CA. The study also suggests that AF itself is a key causative factor in the progression of atrial remodeling in humans, with the remarkable observation that AF progression is linked to arrhythmia burden (AF burden >10 %), validating Allessie et al. concept in humans that "AF begets AF" [11]. In theory, at greater fibrosis proportion or more advanced atrial myopathic stage, the less effective CA becomes. Patients with paroxysmal AF reportedly have lower rates of fibrosis. However, left atrial fibrosis and atrial remodeling progress with every episode of AF. Therefore, theoretically, CA provides the greatest benefit earlier in the disease course, potentially slowing AF progression.

A final hypothetical argument to propose an early intervention using CA for paroxysmal AF may be based on the fact that the risk of stroke increases with the progression of AF. In other words, patients with persistent and permanent AF have a significantly higher risk of stroke compared to patients with paroxysmal AF. In the ARISTOTLE trial, patients with paroxysmal AF had a significantly lower risk of stroke compared to those with persistent or permanent AF (0.98 vs 1.52 % $P = 0.003$, adjusted $P = 0.015$). There was also a trend towards higher mortality in patients with persistent or permanent AF (3.90 vs 2.81 %; $P = 0.0002$, adjusted $P = 0.066$) [12]. Recently, the AVERROES and ACTIVE-A trials reported similar findings in over 6000 patients randomized to apixaban or aspirin. In this study, the CHA_2DS_2-VASc score was

similar in patients with paroxysmal and persistent AF (3.1 ± 1.4), but was higher in patients with permanent AF (3.6 ± 1.5, $P = 0.001$). Yearly ischemic stroke rates were 2.1, 3.0, and 4.2 % for paroxysmal, persistent, and permanent AF, respectively, with adjusted hazard ratio of 1.83 ($P = <0.001$) for permanent vs paroxysmal and 1.44 ($P = 0.02$) for persistent vs paroxysmal AF. Multivariable analysis identified age ≥75 year, female sex, history of stroke or TIA, and AF pattern as independent predictors of stroke, with AF pattern being the second strongest predictor after prior stroke or TIA [13]. These findings provide further evidence that the risk of stroke is not the same in patients with paroxysmal compared to persistent or permanent AF. Similarly, one can speculate that early intervention delays the progression of AF and potentially reduces the risk of stroke. The evidence to support this proposal is still in the making; similarly, CA for AF 15 years ago was felt to be untenable [14].

Does the Current Evidence Support CA as First-Line Therapy of Symptomatic AF?

Randomized Clinical Trials

Three randomized clinical trials (RCTs) have explored the question of whether first-line CA therapy is superior to conventional AAD in patients with paroxysmal AF [15–17]. Overall, 491 patients from 30 centers worldwide have been enrolled by these three RCTs (Table 1). The patients included in these trials were mostly younger, predominately male with high burden paroxysmal AF, with minimal structural heart disease, and few comorbidities.

Important differences among these trials are worth highlighting to be able to put the results into perspective. In the RAAFT trials, primary outcome was time to the first recurrence of both symptomatic and asymptomatic atrial tachyarrhythmias. Similarly, monitoring intensity and adherence was higher in the RAAFT-2 trial compared to that in the other RCTs testing the same hypothesis. Finally, given the timeframe in which both trials were designed and published, important differences in technique and radiofrequency ablation technology have occurred. The RAAFT study published in 2005 by Wazni et al. was the first randomized trial to report superiority of CA as first-line therapy [15]. This study enrolled 70 antiarrhythmic drug naïve patients to receive either CA ($N = 33$) or AAD therapy ($N = 37$). Despite the fact that the ablation was not guided by three dimensional electroanatomic mapping and only non-irrigated 8-mm ablation catheters were used, the study reported that CA was superior to AAD therapy with symptomatic AF recurrence rates of 63 % in the AAD vs 13 % in the CA group at 12-month follow-up (80 % relative risk reduction; $P < 0.01$). In addition, hospitalization during follow-up was significantly reduced (9 vs 54 %; $P < 0.001$) in the CA group.

The Primary Outcome of the Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) [16] differed from the RAAFT trials. In this Scandinavian trial, a reduction in cumulative AF burden (symptomatic and asymptomatic) was the chosen primary endpoint. Overall, 294 patients were randomized, and 146 underwent CA compared to 148 AAD. The primary endpoint was not reached; however, at 24 months, AF burden was significantly lower in the CA arm (9 vs 18 %; $P = 0.007$). Similarly, more patients undergoing CA were free from any AF (85 vs 71 %; $P = 0.004$) as well as symptomatic AF (93 vs 84 %; $P = 0.01$).

The relative reduction in the benefit of CA seen in MANTRA-PAF trial compared to RAAFT-1 can be explained by at least two important facts: different ablation strategies and significant crossover.

The RAAFT-2 trial [17] compared CA to AAD therapy as first-line therapy in patients with symptomatic paroxysmal AF. A total of 127 patients were enrolled in 16 centers in North America and Europe. The primary endpoint was time to the first occurrence of symptomatic or asymptomatic atrial tachyarrhythmia (>30 s). After 2 years of follow-up, this endpoint was observed in 72 % of patients randomized to AAD compared to 55 % randomized to ablation (44 % relative risk reduction; $P = 0.02$). Symptomatic atrial tachyarrhythmia was also observed more frequently in patients randomized to AAD compared to patients randomized to ablation (59 vs 47 %, $P = 0.03$). Of note, a 67 % relative risk reduction (HR 95 % CI 0.28–0.4; $P < 0.001$) in recurrence of repeated episodes of atrial tachyarrhythmias was observed. This is an important measure of burden of AF and clinically meaningful for patients in which time to the first recurrence of an AF episode may be meaningless compared to a significant reduction in repeated episodes. Progression from paroxysmal to persistent AF was also significantly reduced by CA 5 % compared to 20 % in patients assigned to AAD (unpublished observation).

Recently, the long-term follow-up of MANTRA-PAF patients has been reported, and after a pre-planned five-year follow-up, CA reduces the burden of AF, the freedom of any AF (86 vs 71 % $P = 0.001$), and the freedom from symptomatic AF (94 vs 85 % $P = 0.015$). Interestingly, the CA group showed a trend towards less progression to persistent AF (3 vs 5 %) [18].

Meta-analysis

The highest level of evidence is usually achieved by meta-analysis of clinical trials. First-line therapy of AF is no exception, and three meta-analysis have been recently published [19, 20••, 21]. Khan et al. reported a 48 % (RR, 0.52; 95 % CI, 0.30–0.91; $P = 0.02$) relative risk reduction in atrial

Table 1 Characteristics and outcomes of randomized and non-randomized studies evaluating catheter ablation as first-line of therapy

Study	No. of patients	Randomized	Groups	Age (Yr.)	Male (%)	HTN (%)	DM (%)	EF (%)	Paroxysmal AF (%)	Freedom from AF recurrence (%)
RAAFT-1 [15]	70	Yes	CA	53 ± 8	NR	25	NR	53 ± 5	97	87*
			AAD	54 ± 8		28		54 ± 6	95	37*
MANTRA-PAF [16]	294	Yes	CA	56 ± 9	68	29	4	NR	100	85*
			AAD	54 ± 10	72	36	7		100	71*
RAAFT-2 [17]	127	Yes	CA	56 ± 9	77	42	1.5	61 ± 5	98.5	45*
			AAD	54 ± 12	74	41	6.6	61 ± 7	96.7	28*
Tanner et al. [29]	72	No	First-line CA	58 ± 11	78	78	5	62 ± 7	74	78*
			Second-line CA	59 ± 9	77	77	4.5	59 ± 10	67	64*
Namdar et al. [32]	18	No	CA+	44 ± 9	83	NR	6	58 ± 3	100	89
FREEZEplus registry [34]	373	No	Cryoablation	60 (52–69)	59	58	6.2	60 (55–60)	100	71
			Radiofrequency	65 (54–72)	59	74	8.3	60 (58–60)		61

+ PVI with cryoablation

Abbreviations: *HTN* hypertension, *DM* diabetes mellitus, *EF* ejection fraction, *NR* not reported

* $P < 0.05$

tachyarrhythmia recurrence in patients undergoing CA [19]. More recently, Hakalahti et al. have also reported similar results with a 43 % relative risk reduction in recurrent AF favoring CA [20••]. As the RAAFT-1 trial was possibly biased by lack of blinding of outcome assessment, an analysis excluding this trial showed that CA was still associated with significantly higher freedom from recurrent atrial tachyarrhythmias (RR, 0.70, 95 % CI 0.51–0.96; $P = 0.03$). Finally, Santangeli et al. included both RCTs and observational studies and reported a success rate of CA of 67 % compared to 48 % in the AAD group (OR, 0.36; 95 % CI, 0.24–0.54; $P < 0.001$) [21].

Quality of Life

Quality of life (QOL) changes have been reported in all the three RCTs. Different QOL scales have been used, and overall at baseline impairment was moderate probably related with younger healthier patients. In the RAAFT-1 trial, the improvement in the QOL in the CA group was significantly higher than that in the AAD group at 6-month follow-up [15]. In the RAAFT-2 trial, QOL improved in both strategies. The improvement from baseline to 1 year was higher in the ablation group; however, there was no significant difference among the treatment groups [17].

In the MANTRA-PAF trial, QOL was also significantly improved from baseline to 24-month follow-up with both strategies. However, the improvement was more pronounced in the CA group, as observed in the physical scales of SF-36, in EQ-visual analogue scale, and in the number of reported arrhythmia-related symptoms [16, 22]. In summary, both strategies improve QOL in patients with paroxysmal AF that are naïve to therapy; however, CA seems to provide a consistently superior improved QOL.

Safety Profile

Catheter ablation is an interventional procedure and inherently carries a higher risk profile than drug therapy. Nonetheless, most of the adverse events associated with CA are procedure-related and promptly addressed and solved at the time of ablation. In contrast, the risk of adverse events with AAD is ongoing and is maintained throughout the exposure to therapy.

The most recent meta-analysis reports in detail the complications related with CA and AAD [20••]. The most serious acute complication related with CA is tamponade and was reported in seven cases with a 3 % rate that is within the expected rates for an interventional procedure of this type. Significant pulmonary vein stenosis was reported in one case (0.4 %) out of the 238 patients undergoing CA. Symptomatic bradycardia that led to either change in AAD or pacemaker insertion was reported in eight cases (3.3 %). Stroke was rare

(0.2 %) and not different among therapeutic strategies. Similarly, there was no difference in hospital admissions within patients randomized to CA or AAD. Mortality was tracked in all the trials but death occurred only in the MANTRA-PAF trial reporting three deaths in the CA group (one stroke, one prostate cancer, and one sudden death) and four in the AAD group (two lung cancer, one myocardial infarction, and one sudden death).

Taken together, current data indicate that complication rates are comparable between the two treatment strategies with CA causing more acute usually procedure-related severe adverse events compared to AAD therapy.

These findings are in the context of RCTs, which tend to have a strict methodology for reporting adverse events. The "real-world" estimates of complication of CA have been reported previously, and an international survey reported a 6 % incidence of major complications (tamponade, stroke, pulmonary vein stenosis, or death) [23]. A recent update of this survey highlights that CA is being offered to sicker patients (older patients, non-paroxysmal AF, larger atria, and other cardiac comorbidities), and reports a lower complication rate (4.5 %) probably related with center and operator experience [24].

The safety of CA has also been supported by larger surveys reporting only 32 deaths (0.1 %) occurring during or after AF ablation in 32,569 patients [25], and several other studies documenting improved procedure safety [26, 27].

Procedural complication rates are linked with operator experience and volume of the centers performing CA. A recent analysis using data from the U.S. national inpatient sample registry reported in-hospital complications among 93,801 AF ablations performed between 2000 and 2010 [28]. This registry captured events at low- and large-volume centers and showed that complication rates were significantly affected by annual operator experience and annual hospital volume. This finding highlights the importance of operator experience needed to safely perform CA as first-line therapy of AF.

Is Catheter Ablation as First-Line of Therapy Being Adopted in Real World?

The registries provide insights of our daily practice. The best registries are population-based as they avoid center and patient selection biases. The 4th annual survey of the Japanese Catheter Ablation Registry of Atrial Fibrillation (J-CARAF) has been recently published [30]. Compared with the third survey, it showed that CA ablation was performed as first-line of therapy more frequently than before. This trend was consistent throughout the four surveys suggesting that this approach is being elected more often.

The European Snapshot Survey on Procedural Routines in Atrial Fibrillation (ESS-PRAFA), designed by the European Heart Rhythm Association, collected consecutive patients data regarding the routine practice of AF ablation in Europe. This survey, conducted over a 6-week period from September to October 2014, showed that ablation had been offered as first-line of therapy to a small portion of patients (11.5 %) [31]. Although authors highlight that 14.7 % of patients with persistent AF underwent ablation also as first-line therapy which was not recommended by the guidelines.

As expected, a different source of energy has been also tested as first-line therapy during catheter ablation procedures [32]. The FREEZE-cohort study is a prospective, observational, and worldwide study that evaluates safety and effectiveness of cryoablation for PVI in patients with paroxysmal and persistent AF [33]. Overall, 373 of 4184 (8.9 %) patients were identified as first-line PAF patients undergoing AF ablation. After 1.4 years of follow-up, freedom from AF/atrial tachycardia was similar between RF 61 % and cryoablation 71 %, $P = 0.11$ [34]. Major events occurred similarly (cryoablation 1.6 % vs RF 3.7 % $P = 0.22$).

Clinical Perspective and Conclusions

The principle that "AF begets AF" has also been recently documented in humans [10•], and attempting to reverse both structural and electrical remodeling seems an attractive concept. Further evidence that offering CA as first-line treatment in paroxysmal AF will in fact subsequently reverse remodeling is needed. The appropriate time to refer our patients for AF ablation remains unknown although the evidence derived from recent studies favors an early intervention potentially affecting the disease course.

Should CA for AF be offered as first-line therapy to all "naïve" AAD patients presenting with AF? Clearly, we are not there yet particularly in older patients (>65 years.); LA > 5.0 mm; multiple risk factors including sleep apnea and obesity; and centers with low experience. Of note, a complete electrophysiological study is warranted particularly in patients under the age of 50 years, at the time of CA for AF, as not infrequently younger patients may have a supraventricular tachycardia that triggers AF; similarly, in the case of pulmonary vein isolation, younger patients in some instances have a "trigger vein" that can be targeted potentially sparing the need for further extensive ablation.

The CCS-AF guidelines recently updated their recommendations and provide the following advice that may be useful: "We suggest catheter ablation to maintain sinus rhythm as first-line therapy for relief of symptoms in highly selected patients with symptomatic, paroxysmal AF (Conditional Recommendation, Moderate-Quality Evidence) [35]. The 2014 ACC/AHA/HRS state the following: "In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm-control strategy before therapeutic

trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy" (class IIa, level of evidence: B) [5]. Many of the questions posed in this review may be answered by the ongoing Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA, NCT00911508). This large-scale randomized trial is assessing the role of rate vs. rhythm control strategies and hypothesizes that CA will be superior to AAD therapy in reducing the incidence of the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest in patients with AF [36]. The trial has recruited over 2200 patients and will likely provide a definitive answer to the long-standing question of rate vs rhythm control strategies in AF.

First and foremost, the nonnegotiable adherence to our Hippocratic oath of "*Primum non nocere*" should always take precedence over our quest for glory. An honest discussion with the patient, with a proper knowledge of his/her values and preferences and clear understanding of the expectations of the procedure outcomes, risks, and complications, will ensure the success in any particular case.

Compliance with Ethical Standards

Conflict of Interest Aldo G. Carrizo declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent In the RAAFT-2 study (reference 17), Dr. Morillo conducted this trial, and informed consent was obtained from all individual participants included in the study.

This article does not contain any studies with animal subjects performed by any of the authors.

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