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Chapter

# Recent Advances in Catheter Ablation for Atrial Fibrillation and Non-pharmacological Stroke Prevention

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## Abstract

Atrial Fibrillation is a common arrhythmia affecting 6 million people in the United States and 33 million people worldwide, associated with significant morbidity. Whereas restoration and maintenance of sinus rhythm can translate into clinical benefit, early intervention in course of the disease can influence success and efficacy of intervention has been speculative and uncertain over past decade despite several literature and scientific studies. During past three decades catheter and surgical ablation of AF have evolved from an investigational status to a widely offerred definitive treatment now. With recent advances in mapping technology, ablation energy delivery, better understanding of pathogenesis and mechanism of AF there has been a paradigm shift in clinical decision making, patient selection, patient-physician discussion about various rhythm control strategy due to an ever improving safety and efficacy of the procedure. In this chapter we will briefly review the landmark clinical trials that has changed the outlook towards rhythm control strategy beginning from early trials such as AFFIRM, telling us rhythm control was no better than rate control to recent studies and EAST AFNET, which showed benefits of rhythm control. We will discuss differences in ablation strategy, safety and efficacy between paroxysmal AF vs. Persistent/ Longstanding Persistent AF from a trigger and substrate view and pulmonary vein and non pulmonary vein targets for ablation. We will also elaborate on different energy sources for ablation such as Radiofrequency (RF), Cryoablation, newer ablation techniques such as Vein of Marshall alcohol ablation, High Power short duration ablation, Pulsed Field Ablation, Surgical ablation and Hybrid Convergent Ablation etc. Since this chapter is mostly intended towards diagnosis and management of AF in twenty-first century, authors have restricted mainly to recent developments only and purposefully have not expanded on already established preexisting knowledge about topics such as pharmacological rhythm control, rate control, Atrio-Ventricular node ablation with pacemaker implantation, direct current cardio version etc. In conclusion, with recent emerging evidence, importance of rhythm control is being increasingly recognized. Catheter ablation is more commonly performed with improving

safety and efficacy. There are newer technology and ablation strategy available and should be offered to patient while discussing a comprehensive management of AF with careful review of risk benefit analysis.

**Keywords:** catheter ablation, atrial fibrillation, rhythm control, pulmonary vein isolation, pulse field ablation, vein of marshal, cardioneural ablation, ganglionic plexi, high power short duration, cryoablation, radiofrequency ablation, left atrial appendage occlusion, watchman, stroke prevention

## 1. Introduction

Atrial Fibrillation is well known to cause not only substantial morbidity including stroke, congestive heart failure, and late cognitive impairment, dementia [1, 2] but is also associated with reduced survival. In subjects from the original cohort of the Framingham Heart Study, AF was associated with a 1.5- to 1.9-fold mortality risk after adjustment for the preexisting cardiovascular conditions with which AF was related [3]. This common cardiac arrhythmia, that increases in prevalence with advancing age, poses a perplexing treatment situation to clinicians as symptomatology varies in a wide spectrum. Symptoms can be asymptomatic in one extreme to frequent hospitalizations, hemodynamic abnormalities, and even thromboembolic events related to AF [4] which increase morbidity and mortality in the other. Despite numerous trials and scientific data it is inconclusive whereas restoration and maintenance of sinus rhythm is associated with clinically meaningful benefits, preferred strategy of rhythm control e.g. catheter ablation vs. anti arrhythmic drugs etc.

## 2. Brief literature review of landmark trials on benefits of rhythm control

Initial RCTs [5, 6] failed to show superiority of rhythm control on mortality [4], however maintenance of sinus rhythm did show improvement in quality of life and exercise capacity [7, 8]. These particular studies did not include patients with catheter ablation and most patients underwent rhythm control with repeated cardioversions and Antiarrhythmic drugs. Bunch et al. [9] published AF ablation patients have a significantly lower risk of death, stroke, and dementia in comparison to AF patients without ablation. Various experimental studies [10] and scientific position papers [11, 12] have indicated that early intervention with a rhythm-control strategy to prevent progression of AF may be beneficial [4] which eluded to the fact that "AF begets AF" due to electrical and structural myocardial left atrial remodeling. Subsequently, several RCTs have tested the strategy of catheter ablation vs. medical management as discussed below.

MANTRA PAF [13] was one of the initial trials that enrolled 294 patients (June 2005 through 2009) with symptomatic Paroxysmal Atrial Fibrillation (PAF) with no history of antiarrhythmic drug use. These patients were treated with either radiofrequency catheter ablation (146 patients) or therapy with Class IC or Class III antiarrhythmic agents (148 patients) [13]. This trial found no significant difference in cumulative AF burden between both treatment groups over a follow up of 24 months but the burden of symptomatic atrial fibrillation and any atrial fibrillation was significantly lower in the ablation group than in the drug-therapy group. These findings suggested that the efficacy of catheter ablation may be more durable than

that of currently available antiarrhythmic drugs. There was no difference in quality of life between both treatment arms, but a perception of more improvement in physical well-being was seen in the ablation group which authors admitted that this may be attributable in part to a placebo effect. There were 36% of patients who were initially assigned to AAD arm who subsequently required ablation for recurrent atrial fibrillation, a finding signaling that though an initial rhythm control strategy with AAD may be initiated, a minority of such patients may subsequently require catheter ablation for adequate rhythm control. A major limitation of this trial was definition of goal of ablation for atrial fibrillation. At the time of the study, this was defined as elimination of complex high frequency electrograms inside encircled areas around the Pulmonary Veins (PV), but with rapid development of ablation techniques, this end point was no longer valid. A general agreement on end point of ablation is considered complete electrical isolation of pulmonary veins. A change in ablation strategy based on this end point may have potentially changed the outcome of the study.

RAAFT 2 [14]. was another contemporary RCT to MANTRA PAF enrolling 127 patients with symptomatic PAF from Europe and North America between July 2006 to January 2010 and then patients were followed up for 2 years till 2012. Patients were randomized to ablation vs. anti arrhythmic treatment arms. Ablation was performed with circumferential pulmonary vein isolation with demonstration of entrance block into pulmonary vein, with additional ablation such as linear lines in Left Atrium (LA), ganglionic plexi, targeting complex fractionated electrogram, superior vena cava (SVC) isolation, cavotricuspid isthmus (CTI) ablation all at the investigator's discretion [14]. With change in ablation goal when compared to MANTRA PAF, RAAFT 2 trial demonstrated catheter ablation resulted in significantly lower rate of recurrent atrial tachyarrhythmia at 2 years, and reduced the frequency of repeated episodes of AF and thus improvement in quality of life however, recurrence was documented in approximately 50% of patients. Ablation extends the time free of both symptomatic and asymptomatic AF and significantly reduced the recurrence of repeated episodes, potentially having an effect on AF progression [14]. This study was limited by small sample size, and findings restricted to mostly young people with PAF. So authors suggested that when offering ablation as a therapeutic option to patients with paroxysmal AF naive to antiarrhythmic drugs, the risks and benefits need to be discussed and treatment strategy individually recommended.

Rhythm control vs. rate control for AF in patients with heart failure (HF) were studied in multiple studies. In a multi center RCT [15], 1376 patients who had congestive heart failure with EF ≤ 35% were enrolled. Maintenance of sinus rhythm with Antiarrhythmic drugs did not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy. Role of catheter ablation was however not studied in this RCT. Significant proportion of patients do not tolerate anti arrhythmic drugs due to various side effects, is not responsive to AAD, or has difficulty in medication adherence or compliance. Catheter ablation is a suitable alternative for rhythm control. There have been several studies that has shown positive effect of ablation in AF and CHF patients [16–20]. CASTLE AF was a landmark large multi center open labeled randomized control trial [21] where 398 patients were enrolled with symptomatic Paroxysmal or Persistent AF who failed, had unacceptable side effects, or had an unwillingness to take antiarrhythmic drugs. These patients also had New York Heart Association (NYHA) Class II, III, or IV heart failure and a left ventricular ejection fraction (LVEF) of 35% or less. As compared to multiple previous trials showing benefit of catheter ablation [16–20], this was the first trial that tested the effectiveness of catheter ablation in improving rates of hard primary end points such as death

or the progression of heart failure. Primary end point which was a composite of death from any cause and lower rates of hospital admission for heart failure was significantly fewer in the ablation group. In addition there were other secondary outcomes seen such as increase in LVEF and reduction in AF burden.

CABANA trial [1] (published in 2019) was a landmark trial that enrolled 2204 symptomatic AF patients (paroxysmal, persistent and long persistent) from 126 centers over 10 countries and tested catheter ablation vs. medical management with antiarrhythmic and/or rate control medications. Catheter ablation did not significantly reduce the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest, but secondary end point of mortality or CV hospitalization showed a significant 17% relative lower event rate for the catheter ablation group [1]. Post 90 day blanking period, patients were monitored for time to first AF recurrence defined as AF/AFl/AT for ≥30 s. Catheter ablation was associated with a lower AF recurrence rate than drug therapy (50% vs. 69% at 3 years post blanking follow-up). Another significant observation in this study was low rate of procedure related complication seen in catheter ablation group indicating that ablation is feasible. The trial had several limitations [1] such as higher rate of patient withdrawal in drug therapy group, catheter ablation and drug therapy may have changed over the long course of the trial, small percentage of patients may have received only rate control drugs. Comparisons of the intention to treat (ITT) results with the treatment received and per-protocol analyses suggest that the combined effect of crossovers and withdrawals reduced the estimated treatment effect and the precision of the effect size estimates as assessed by ITT. Additionally, potential introduction of bias due to unblinded site adjudication of cause of hospitalization etc. might have affected the results of the study. Authors concluded that the estimated treatment effect of catheter ablation was affected by lower-than-expected event rates and treatment crossovers, which should be considered in interpreting the results of the trial.

With initial belief that rhythm control strategy is not superior over rate control, based on AFFIRM study published in early first decade of twenty-first century, we have witnessed through several trials discussed above, the evolution of scientific evidence demonstrating efficacy of ablation strategy in improving quality of life, improvement of heart failure symptoms, improvement of exercise tolerance, survival benefits, reduce hospitalization etc. A monumental trial that brought a paradigm shift is EAST AFNET 4 [22]. This study was published in 2020 and sought to compare early rhythm control vs. usual care. This was a multi center randomized trial that enrolled over 2700 patients from 135 sites in 11 countries. Early rhythm control required antiarrhythmic drugs or atrial fibrillation ablation, as well as cardioversion of persistent atrial fibrillation, to be initiated early after randomization. Usual care arm patients were initially treated with only rate control therapy and rhythm-control therapy was used only to mitigate uncontrolled atrial fibrillation–related symptoms during adequate rate-control therapy. The trial was stopped for efficacy at the third interim analysis after a median of 5.1 years of follow-up per patient. The first primary outcome was a composite of death from cardiovascular causes, stroke (either ischemic or hemorrhagic), or hospitalization with worsening of heart failure or acute coronary syndrome [22]. First primary outcome event was found to have occurred less often in patients assigned to early rhythm control than in patients assigned to usual care achieving a conclusion that early rhythm control was beneficial that was associated with lower risk of adverse cardiovascular outcomes [22]. The results of this study

was different from previously published studies comparing rhythm vs. rate control because of incorporation of catheter ablation which is a powerful tool for restoring sinus rhythm.

Another recent study, STOP-AF First [23] was published in 2021 which compared the efficacy of cryoballoon ablation over AAD in patients with symptomatic paroxysmal AF. Cryoballoon ablation as initial therapy was superior to drug therapy for the prevention of atrial arrhythmia recurrence in patients with paroxysmal atrial fibrillation with low procedure related adverse events.

There are three modes for rhythm control: Electrical (direct current cardioversion), Pharmacological (Antiarrhythmic mediation) and catheter ablation. With the scope of this chapter we will focus more on evolution and rapid advent of catheter ablation strategy over past few years (**Figure 1**).

Current AHA/ACC/HRS Atrial Fibrillation guidelines [4] and 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation recommend catheter ablation in patients with symptomatic PAF (COR Class I) who are intolerant or refractory to Class I or Class III AAD, or ablation as initial strategy before trial of AAD (COR Class IIa). In recent 2019 focused update new recommendation have been added as AF catheter ablation may be reasonable in selected patients with symptomatic AF and HF with reduced left ventricular (LV) ejection fraction (HFrEF) to potentially lower mortality rate and reduce hospitalization for HF based on evidence from CASTLE AF data (COR Class IIb, LOE B-R) (**Table 1**) [24].
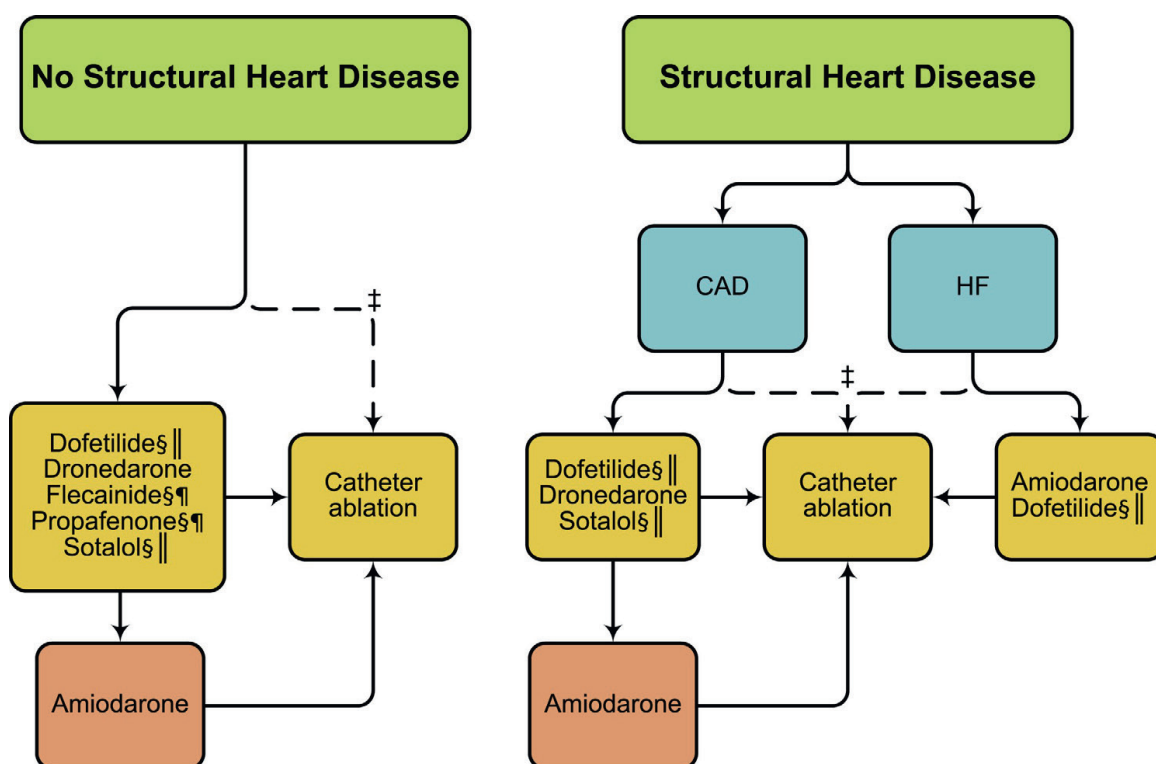


**Figure 1.**
*Strategies for rhythm control in patients with paroxysmal\* and persistent AF†. \*Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (Class IIa recommendation). †Drugs are listed alphabetically. ‡Depending on patient preference when performed in experienced centers. §Not recommended with severe LVH (wall thickness > 1.5 cm). ‖Should be used with caution in patients at risk for torsades de pointes ventricular tachycardia. ¶Should be combined with AV nodal blocking agents. AF indicates atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy. Adopted from [4].*

| COR | LOE | Recommendation |
| --- | --- | --- |
| Class I | A | Ablation useful in Symptomatic PAF who are refractory/intolerant to at least one Class I/III AAD |
| Class IIa | B | Ablation reasonable in recurrent symptomatic PAF before trial of Class I/III AAD |
| Class IIa | A | Ablation reasonable in Persistent symptomatic AF who are refractory/intolerant to at least one Class I/III AAD |
| Class IIa | B-NR | It is reasonable to offer AF ablation as an alternative to pacemaker implantation in patients with tachy-brady syndrome. |
| Class IIb | B-R | Ablation reasonable in selected patients with symptomatic AF and HFrEF) to potentially lower mortality rate and reduce hospitalization for HF [24] |
| Class IIb | B | Ablation reasonable in long standing symptomaticPersistent AF (>12 months) who are refractory/intolerant to at least one Class I/III AAD |
| Class IIb | B | Ablation reasonable in Persistent symptomatic AF before trial of Class I/III AAD |

**Table 1.**
*Professional society guideline recommendations for atrial fibrillation catheter ablation.*

## 3. Catheter ablation of atrial fibrillation

Pathogenesis of AF is incompletely understood. Broadly generalized, there is a trigger that initiate AF and there is a perpetuating factor that sustain the arrhythmia. Usually a PAC or a focal atrial tachycardia triggers atrial fibrillation that further creates a rapid irregular multiple wavelets of depolarization.

Dr. Cox in 1987 first described surgical ablation of atrial fibrillation [25] by creating multiple scars by "cut and sew" technique to create lines of conduction block to prevent atrial reentry and allow sinus impulses to activate the entire atrial myocardium, thereby preserving atrial transport function postoperatively. However, application of the maze III operation has been limited by the morbidity and risk associated with sternotomy-thoracotomy and cardiopulmonary bypass, as well as by limited adoption by cardiothoracic surgeons [26]. Seminal publication by Dr. Michel Haïssaguerre [27] in 1998 that pulmonary vein ectopics are frequent triggers for AF and ablation of these foci can treat AF laid the initial foundation for catheter ablation of AF. With the success of surgical lines, catheter ablation was tried with different curve sheaths but procedure was fraught with high complication rates and exceedingly high fluoroscopic times. Initial catheter ablations tried to target Right Atrium (RA) by creating Intercaval lines along the interatrial septum and Cavotricuspid isthmus line and target Left Atrium (LA) by creating three or four lines. Pappone and Co workers published Circumferential Radiofrequency Ablation of Pulmonary Vein Ostia with electroanatomic guidance is safe and effective in either paroxysmal or permanent AF [28].

Since then, different approachs for catheter ablation for atrial fibrillation have evolved such as segmental ostial PV Isolation, circumferential antral Pulmonary vein isolation (PVI), wide area circumferential LA ablation, catheter Maze (lines to connect the ipsilateral pairs of the PVs and a line to link the left PV encircling lesion to the mitral annulus), complex fractionated electrogram ablation (CFAE), Box lesion sets with linear lines ("floor line" and "roof line") to isolate posterior wall, Left atrial Appendage (LAA) isolation, Superior Vena Cava (SVC) isolation, autonomic ganglionated plexi ablation or Cardioneural ablation, alcohol ablation of vein of Marshal etc. There is no clear consensus about efficacy of one approach over another,
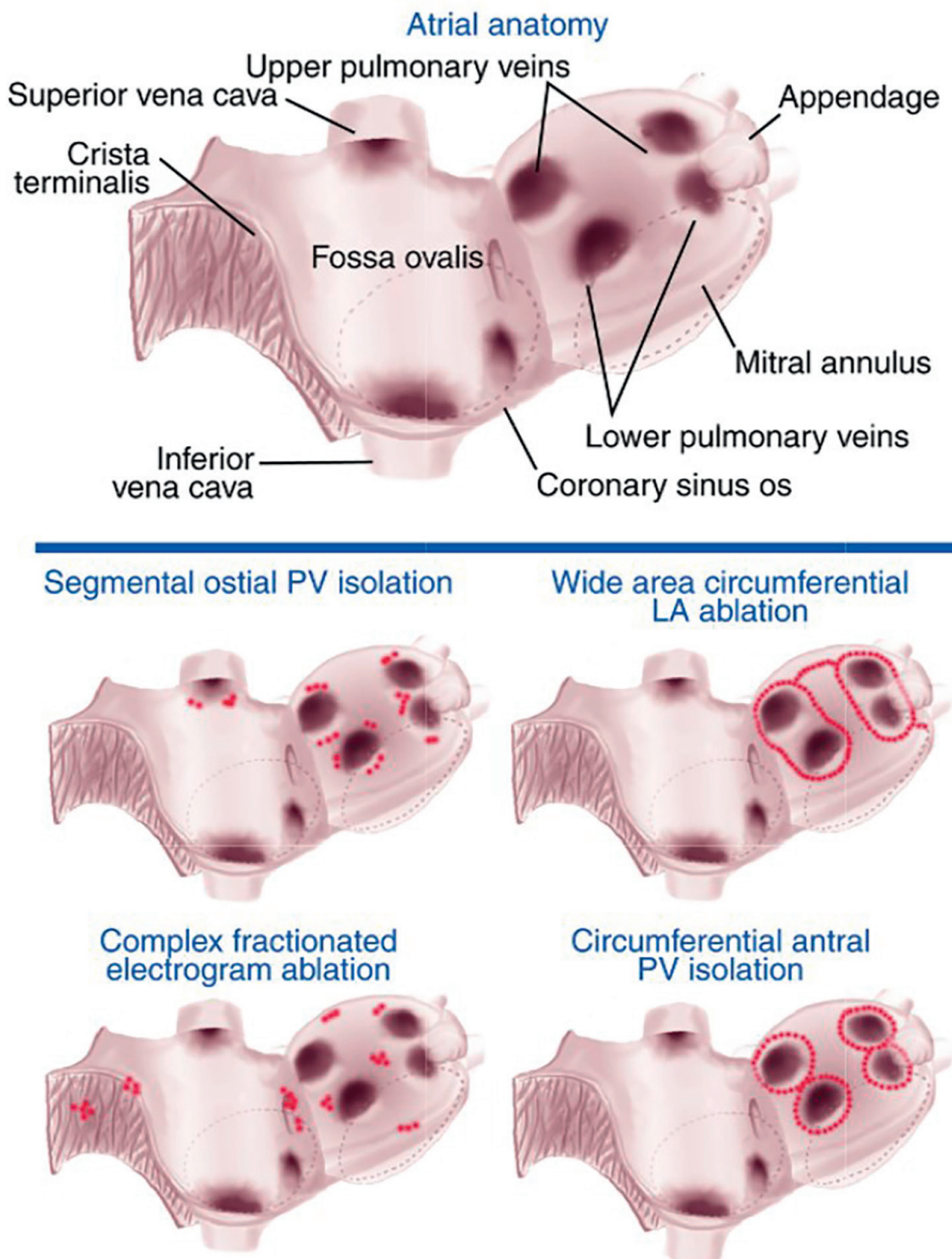
**Figure 2.**
*Schematic diagram of various approaches of catheter ablation shown. Red circles are ablation lesions. Picture adopted from [26].*

but approaches often vary between paroxysmal Atrial Fibrillation and persistent Atrial Fibrillation. In PAF targeting the trigger for Atrial Fibrillation with wide antral circumferential ablation of bilateral PVs may prove sufficient in freedom from recurrent AF/AFl/AT. In contrast, patients with persistent Atrial Fibrillation, both trigger and substrate needs to be ablated and ablation may be necessary beyond routine PVI which may include posterior wall isolation or additional linear lines in left atrium depending on operator's discretion (**Figure 2**).

## 3.1 Substrate based ablation for persistent/long persistent atrial fibrillation: targeting pulmonary and non pulmonary vein triggers

Though PV are most frequent triggers for AF, investigators have shown several non PV triggers, incidence ranging between 3.2% and 47%, especially in Persistent/ Long standing Persistent AF. Triggers have been demonstrated in SVC (common in female patients), LA posterior wall, (common in patients with enlarged LA), Crista terminals, Left atrial appendage, Coronary sinus, Ligament of Marshall, Interatrial septum. Additionally, SVTs such as AVN reentrant tachycardia (AVNRT) and AV reentrant tachycardia (AVRT) can be identified in up to 4% in unselected patients referred for AF ablation and can serve as a triggering mechanism for AF [26]. Previous studies have suggested a benefit to intervention with ablation before drug failure, because a shorter "diagnosis-to-ablation" time is associated with lower rates of arrhythmia recurrence or repeat procedures and fewer hospitalizations [29–31].

STAR AF II [32] was a randomized trial that compared efficacy of three different approaches to catheter ablation of AF in patients with Persistent AF. They randomized patients into three arms: (1) PVI alone (2) PVI with CFAE (3) PVI and Linear ablation lines along the LA roof and Mitral Isthmus. Primary outcome of the study was to see any documented episode of atrial fibrillation lasting longer than 30 s and occurring after the performance of a single ablation procedure, with or without the use of antiarrhythmic medications. Clinical assessments, 12-lead electrocardiograms, and 24-h Holter-monitor recordings were obtained at baseline and at 3, 6, 9, 12, and 18 months after the initial ablation. Study showed no reduction in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary-vein isolation. Recurrence of atrial arrhythmia despite extensive ablation on a substrate based approach with targets beyond PV such as CFAE, linear lines probably created iatrogenic areas of arrhythmogenesis potentially from incomplete ablation of areas with complex electrograms or conduction gaps in linear lines.

A meta-analysis of 113 studies including 18,657 patients examined the impact of ablation approach on outcomes associated with Persistent or Long standing persistent AF [33]. Findings of this meta-analysis supports the findings of the STAR AF II trial, with collated results indicating that a simpler PVI approach (57% success) yields at least equivalent single-procedure results (or potentially better) compared with more complex substrate ablation techniques including PVI + Linear ablation lines (46%), PVI + CFAE (46%), and PVI + Linear ablation lines + CFAE (33%) as currently performed and reported. This study also concluded that the efficacy of a single-AF ablation procedure for Persistent or Long standing persistent AF is 43%; however, can be increased to 69% with the use of multiple procedures and/or anti-arrhythmic drug.

## 3.2 Left atrial appendage electrical isolation/vein of marshall alcohol ablation

BELIEF trial [34] is an RCT that included 173 patients with long standing persistent atrial fibrillation that were randomized into two arms: (1) Standard ablation arm that comprised of an extended PV antrum ablation plus non-PV trigger ablation (2) standard ablation plus empirical electrical left atrial appendage isolation. Primary end point of the study was freedom from atrial arrhythmia (AF, A Fl, AT) defined as >30 s after initial 12 weeks blanking period while off anti arrhythmic drugs, secondary end points were 12-month post-procedure incidence of stroke, death, and rehospitalization. Trial results showed that in patients with Long standing Persistent

AF, empirical isolation of LAA improved long-term freedom from atria arrhythmia without increasing complications. An important finding to consider however is life long need for uninterrupted anticoagulation in patients who underwent LAA isolation as post procedure lack of proper mechanical function in the LAA may contribute to stroke.

Recently, Alcohol ablation of Vein of Marshall (VoM) has gained significant attention. This method of ethanol infusion into VoM in addition to catheter ablation was investigated in VENUS [35] RCT. 343 patients with Persistent AF were randomized into catheter ablation alone vs. catheter ablation with VoM ethanol infusion. Primary end point was freedom from AF/AT > 30 s without AAD at 6 and 12 months, several secondary endpoints including AF burden, freedom from AF after multiple procedures, perimitral block, and others were studied. VoM is the embryological remnant of left superior vena cava is implicated as AF trigger, parasympathetic and sympathetic innervation contributing to AF, located in the mitral isthmus contributing to perimitral atrial tachycardia. Results of this study concluded that addition of VoM ethanol infusion to catheter ablation increased the likelihood of remaining free of AF or atrial tachycardia at 6 and 12 months. Adverse events were not significantly different between both group: intraprocedural pericardial effusion occurred in two patients in VoM ethanol infusion group (one in ablation only group), subacute pericardial effusion requiring drainage occurred in four patients (two in each group), symptomatic inflammatory pericarditis not requiring drainage occurred in 11 patients in the VoM ethanol infusion group and in 6 in the catheter ablation group. The benefits of VoM ethanol infusion in addition to
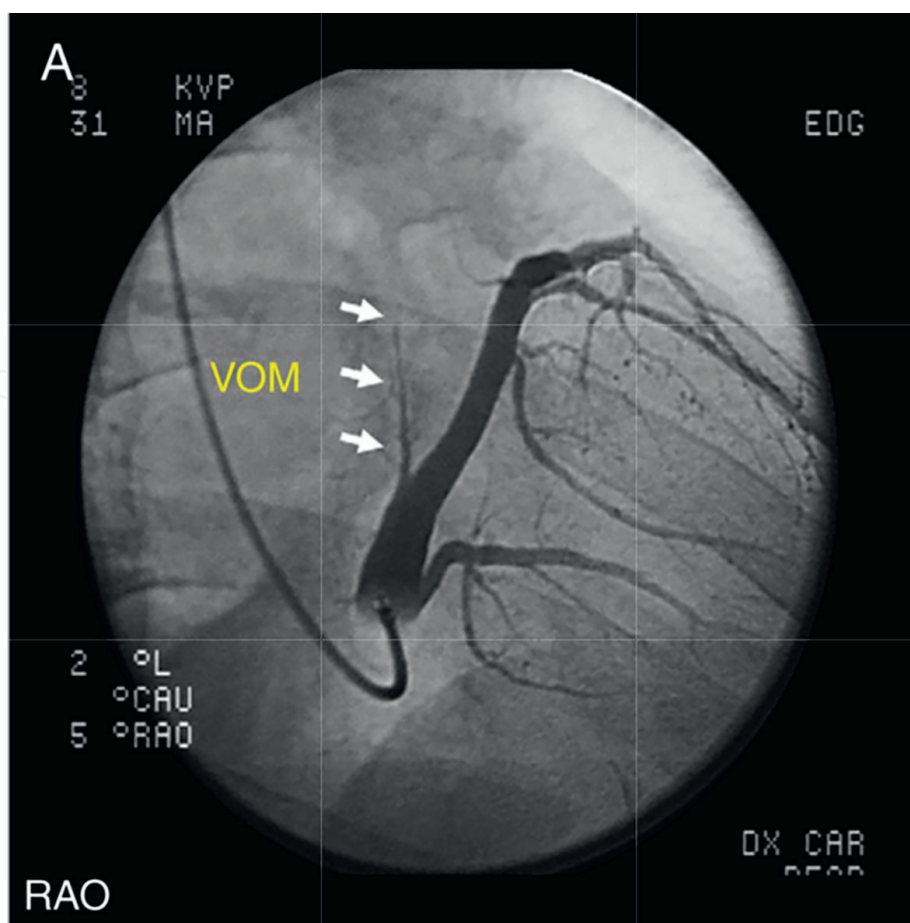


**Figure 3.**
*Coronary sinus venogram showing vein of Marshall. Picture adopted from [26].*

| | Recommendation | Class | LOE |
|---|---|---|---|
| PVI by catheter ablation | Electrical Isolation of PV during all AF ablation procedure | Class I | A |
| | Achievment of Isolation requires at a minimum, assessment and demonstration of entrance block into the PV. | Class I | B-R |
| | Monitoring for 20 min following initial isolation | Class IIa | B-R |
| | Administration of Adenosine to see if reconnection occurred, demonstration of exit block, pace capture ablation strategy may be considered | Class IIb | B-R B-NR |
| CTI ablation | If there is history of typical A Fl or inducible during ablation, CTI ablation is recommended | Class I | B-R |
| Ablation strategies to be considered for use in conjunction with PV isolation | If linear ablation is performed, mapping and pacing maneuvers should be performed to check for line completeness If reproducible focal trigger outside PV ostium that initiates AF are seen, ablation should be considered | Class I Class IIa | C-LD C-LD |
| | Posterior wall isolation might be considered for initial or repeat ablation of persistent or long- standing persistent AF | Class IIb | C-LD |

**Table 2.**
*Professional society recommendations for catheter and surgical ablation strategies and endpoints.*

catheter ablation was attributed to elimination of AF trigger, achieving more reliable perimitral block, enhanced atrial denervation (**Figure 3**).

2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation recommends following Atrial fibrillation ablation strategies, techniques, and endpoints (**Table 2**).

### 3.3 High power short duration (HPSD) ablation

High power short duration (HPSD) ablation strategy is a newer approach in effective lesion formation. Conventionally AF ablation has been performed with low power long duration (LPLD) at 25–35 W power delivery for 30–60 s per lesion. Success of AF ablation is dependent on durability of lesions that in turn is influenced by several variables like catheter stability, orientation of ablation catheter (perpendicular vs. parallel), time duration, effective power and current delivered at catheter tip, transmurality of lesion etc. HPSD (50–80 W power for 5 s) was initially described by Bhaskaran et al. [36] in 2016 as safe and effective as the conventional ablation. Current definition of HPSD varies between power of 50–90 s and time duration of 2–20 s. Based on principles of biophysics of Radiofrequency (RF) ablation, HPSD is believed to cause majority of tissue death via resistive heating and, as a result, theoretical advantages have been proposed, including optimized lesion geometry, reduced collateral tissue damage and increased durability of electrical isolation, in addition to obvious benefits in reduction in procedural duration [37]. Winkle et al. [38] reported very low complication rates with HPSD (45–50 W for 2–10 s) compared to LPLD (35 W for 20 s) in total of 13,974 ablations performed in 10,284 patients, of these, 11,436 ablations performed in the posterior wall. They also found HPSD ablations shorten procedural and total RF times and create more localized and durable lesions. Recently, Very High Power Short

Duration (vHPSD) with 90 W for 4 s with a novel catheter design (THERMOCOOL SMARTTOUCH SF-5D System) was studied in Q DOT FAST trial [39] where 52 patients with PAF underwent ablation with no deaths, stroke, atrioesophageal fistula, pulmonary vein stenosis, or unanticipated adverse device effects. This study showed safety, feasibility and short term efficacy of vHPSD ablation along with substantial reduction in procedural and fluoroscopic time. Currently there is an ongoing prospective clinical trial (HIPAF) comparing two strategies: HPSD-PVI (70 W over 5 s posterior and 7 s anterior) ablation vs. Cryo PVI [40].

### 3.4 Pulsed Field Ablation (PFA)

So far, RF or Cryo ablation has been the only two available technologies for endocardial ablation of Atrial Fibrillation. In recent years, clinical research on an emerging modality for cardiac ablation has demonstrated significant advantages over existing thermal ablation modalities. Irreversible Electroporation is a non thermal modality with emerging application in the field of cardiology with more selective and effective ablation with minimal surrounding tissue damage. Dr. Steven Mickelsen at University of Iowa developed Pulsed Field Ablation (PFA) system and adapted catheters to deliver pulsed field electricity to the tissue for treating AF with his start up called "IOWA APPROACH" in 2012 later known as FARAPULSE Inc., which was later acquired by Boston Scientific in 2020.

Pulsed Field Ablation (PFA) is based on the premise of irreversible electroporation, where trains of high voltage, short duration energy are pulsed to create an electric field of substantial strength to injure tissue. The principle of electroporation has been used in a wide variety of practices ranging from gene therapy to tumor ablation but has only recently been applied to cardiac ablation. It is the unique properties of the cell membrane that are manipulated during electroporation. Cell membrane is composed of a phospholipid bilayer that is stabilized by Van der Waals forces that allow for aqueous pores to form in the membrane due to molecular water interactions across the cell membrane. The application of an electric field amplifies the molecular interaction of the water molecules across the cell membrane disrupting the Van der Walls forces of the phospholipid bilayer to create aqueous pores. If an electric field of substantial strength and duration is applied to the cell, these aqueous pores can become stabilized resulting in permanent disruption to the permeability of the cell membrane resulting in an apoptotic like cell death, which is termed irreversible electroporation or PFA (**Figure 4**).

RF ablation is associated with very low rate of complications but include pulmonary vein stenosis, atrio-esophageal fistula. Similarly Cryoablation is associated with low rate of complications as well but include phrenic nerve palsy. In contrast during PFA ultra rapid (microseconds to nanoseconds) electrical energy is delivered to destabilize cell membrane by forming irreversible nanoscale pores resulting in ell death, however threshold field strength for tissue necrosis is different for different tissues such as myocardium, blood vessels, nerve fibers thus rendering a great advantage of tissue selectivity. This differential tissue sensitivity to pulsed electrical fields is believed to decrease collateral damage. This single shot ablation technology in addition to being associated with clinical safety, success and durability has significantly reduced procedural time [41].

So far there have been three Multicenter studies three multicenter studies with PFA system: (IMPULSE [A Safety and Feasibility Study of the IOWA Approach Endocardial Ablation System to Treat Atrial Fibrillation], PEFCAT [A Safety
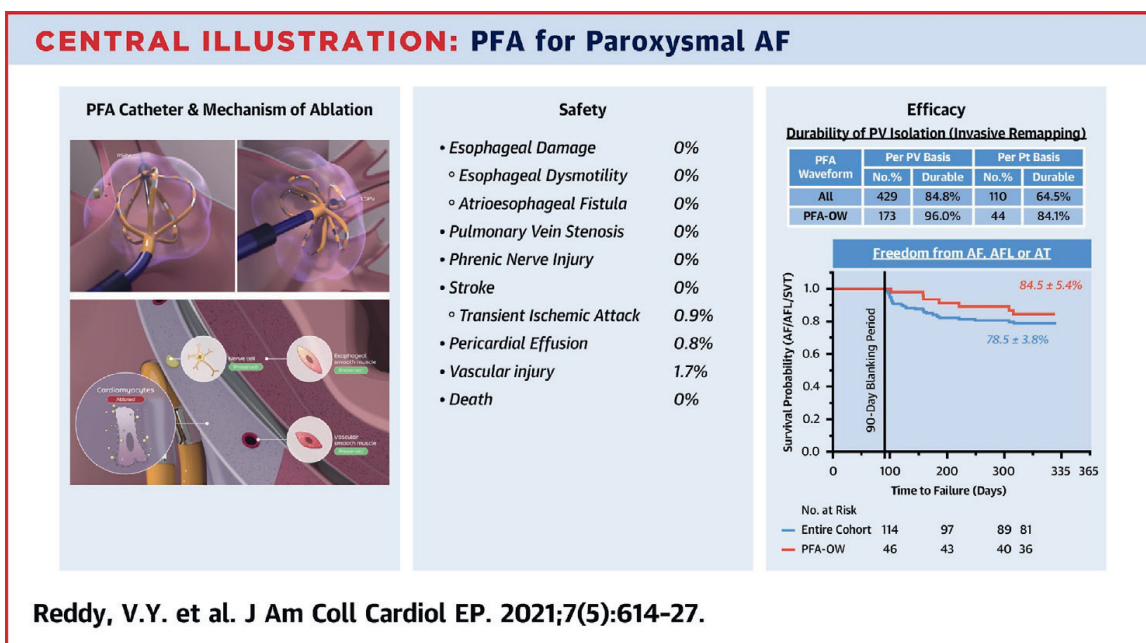
**Figure 4.**
*Figure adopted from Reddy [41].*

and Feasibility Study of the FARAPULSE Endocardial Ablation System to Treat Paroxysmal Atrial Fibrillation], and PEFCAT II [Expanded Safety and Feasibility Study of the FARAPULSE Endocardial Multi Ablation System to Treat Paroxysmal Atrial Fibrillation]). Reddy et al. [41] reported 1 year outcome of PFA in patients with PAF from these three trials. In a patient cohort of 121 patients, acute PVI with PFA was achieved in 100% of patients, primary adverse event occurred in 2.5% of patients (2 pericardial effusion, 1 transient ischemic attack, 1 hematoma), Freedom from recurrence of any atrial arrhythmia at 1 year was around 78%. In >100 patients and with 5 operators, the mean procedure times were only 96.2 ± 30.3 min, inclusive of ~20 min of voltage mapping time after PVI which is faster than procedure times with other technologies. With increased operator experience and elimination of voltage mapping, procedure times should improve further. PVI with a "single-shot" PFA catheter results in excellent PVI durability and acceptable safety with a low 1-year rate of atrial arrhythmia recurrence ushering in a new era in the front of modern day advanced Atrial Fibrillation management.

## 3.5 Cryoablation for atrial fibrillation

An alternative mode of PAF ablation is Cryoablation. STOP AF [42] trial compared Cryoablation and AAD and demonstrated the safety and effectiveness of Cryoablation therapy as an alternative to antiarrhythmic medication for the treatment of patients with symptomatic PAF, for whom at least one AAD has failed. RF ablation requires operator skill and training and longer time for catheter navigation to complete point by point ablation around the pulmonary veins. In contrast, cryoballoon is a balloon catheter which is positioned inside pulmonary vein and with good occlusion, with a single Cryo application pulmonary vein isolation can be achieved rather simply with short procedure time. FIRE and ICE trial [43] compared both technologies (RF vs. Cryo ablation) and found Cryoablation was non inferior to radiofrequency ablation with respect to efficacy, no significant difference in overall safety between two methods. The mean total procedure time was shorter in the cryoballoon group than in

the radiofrequency group (124 vs. 141 min, $P < 0.001$), as was the left atrial dwell time (the length of time the catheter was present in the left atrium during the procedure). The mean total fluoroscopy time was shorter in the radiofrequency group than in the cryoballoon group (17 vs. 22 min, $P < 0.001$) due to navigational capabilities utilizing 3D electroanatomic mapping system with RF ablation. Though both methods (RF vs. Cryo) had similar outcomes in terms of safety, Incidence of Phrenic nerve Injury was slightly
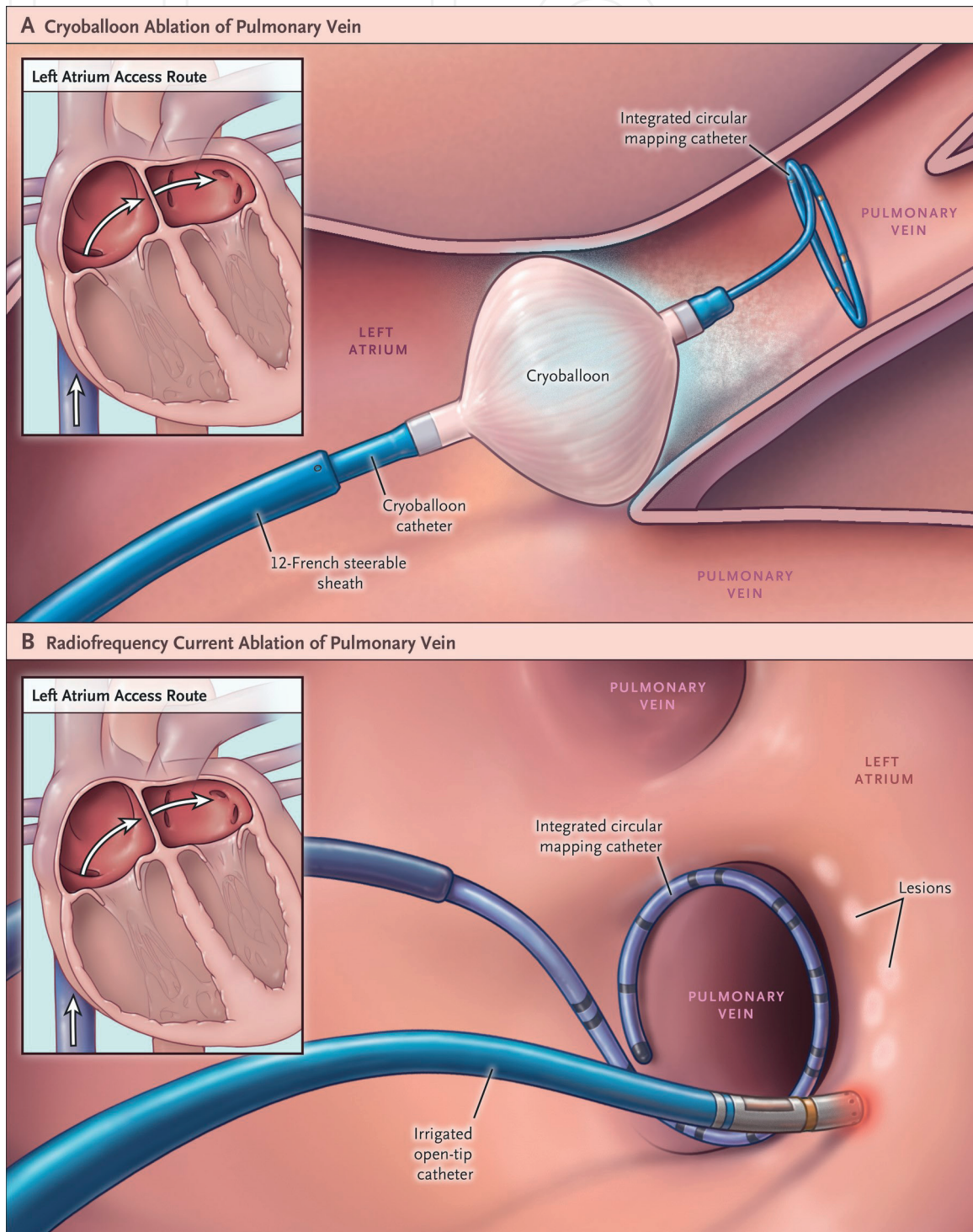


**Figure 5.**
*Cryoballoon ablation system. There is an integrated circular mapping catheter. Balloon is inflated in the pulmonary vein and single shot application of subzero temperature is delivered to the pulmonary vein antrum. Bottom figure shows an RF ablation catheter which delivers heat energy with a point by point application around the pulmonary vein antrum. Picture courtesy FIRE AND ICE trial investigators [43].*

higher in Cryoablation group, but this was substantially lower compared to reported incidence of Phrenic nerve injury in STOP AF trial group (**Figure 5**).

### 3.6 Cardio-neural alablation

Role of Autonomic nervous system in initiation and maintenance of AF has been a great area of interest to understand the pathophysiology of AF. Intrinsic autonomic nervous system [44] is believed to comprise of primarily 5 major ganglionated plexi (GP) located in the epicardial fat pads- superior left GP, Inferior Left GP, Anterior Right GP, Inferior right GP and Ligament of Marshal). GPs predominantly contain parasympathetic neurons but also sympathetic neurons (**Figure 6**).

It is challenging to localize GP with endocardial mapping and hence ablation effectiveness has remained controversial. One technique described to localize major GP is to elicit AV block with High frequency stimulation (HFS) [46, 47]. GPs are consistently located in areas of Left atrial fractionated atrial potential (LA FAP) [44, 46–52] commonly seen around coumadin ridge LAA-Left PV region, ligament of marshall, superior left FAP area, inferoposterior FAP, anterior right FAP. HFS at Cycle length 50 ms, 12–15 V, 10 ms
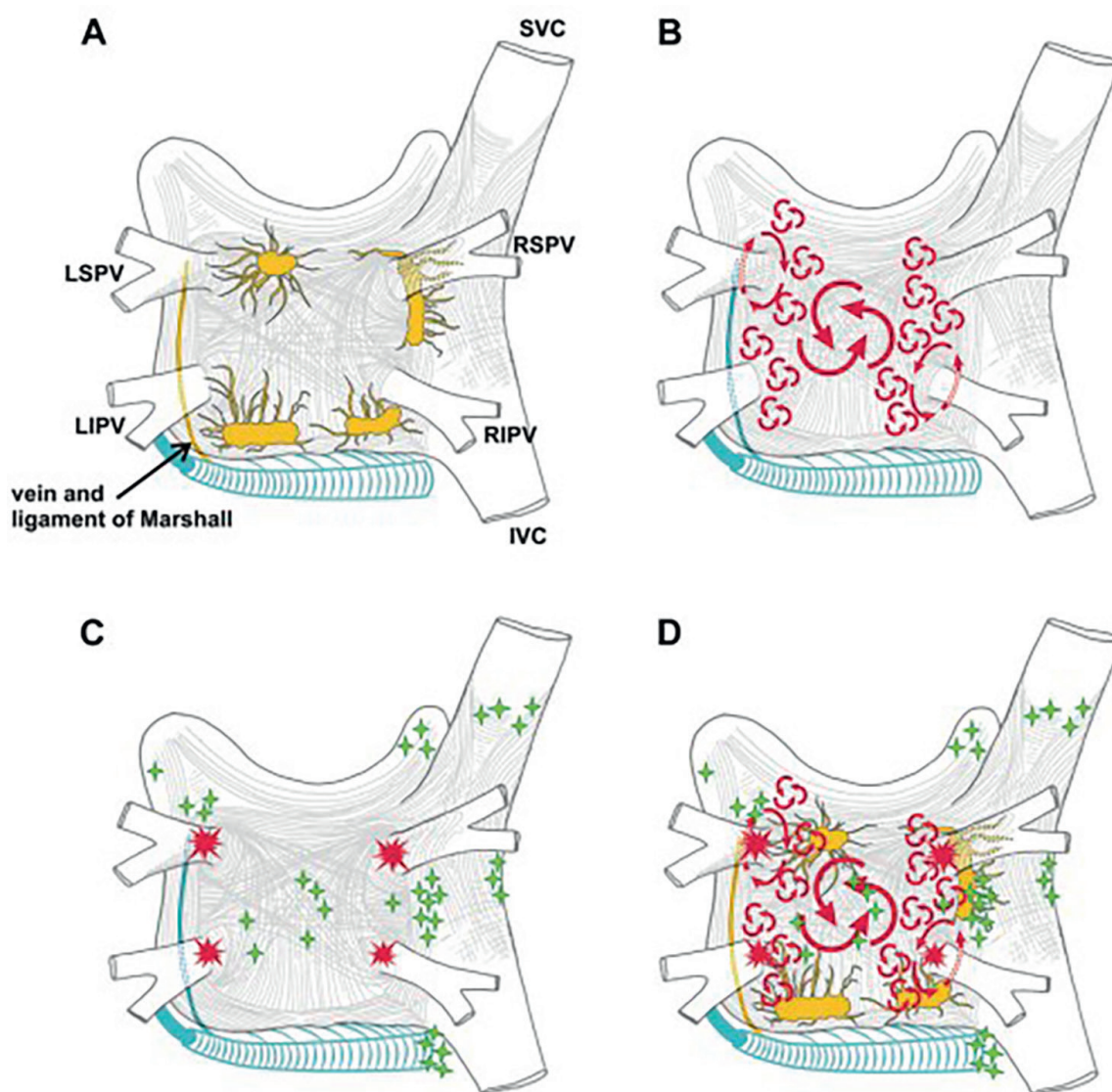


**Figure 6.**
*Schematic diagram of major ganglionate Plexi (shown in yellow) and axons. Picture adopted from [45].*

pulse width is delivered to [47, 52] and if AV block is seen (increase in R-R interval >50% during AF) and RF ablation is performed at each site exhibiting a positive HFS response. Ablation of each of the five GP areas usually requires 2–12 (median 6) RF applications. 124,582. HFS is not very sensitive to identify GP. There are other markers such as onset of PV fire from PV other than adjacent GP. There is also significant interplay between GP. AV block is mediated by inferior right GP, hence HFS of other GPs activate Inferior Right GP which innervates the AV node. If a GP is ablated along the course to Inferior Right GP, HFS may not elicited AV block. So it is usually advisable to ablate GP in the order starting with Marshal tract, superior Left, anterior right, inferior left and finally inferior right.

Pokushalov et al. showed regional ablation at the anatomic sites of the left atrial GP can be safely performed and enables maintenance of sinus rhythm in 71% of patients with paroxysmal AF for a 12-month period [53]. Katritsis et al. [54] randomized 242 patients with Paroxysmal AF into PVI alone with circumferential antral lesions, GP ablation alone, and combination of PVI with GP ablation. Freedom from AF or AT was achieved in 44 (56%), 39 (48%), and 61 (74%) patients in the PVI, GP, and PVI + GP groups, respectively ($P$ = 0.004 by log-rank test). Study concluded that addition of GP ablation to PVI confers a significantly higher success rate compared with either PVI or GP alone in patients with PAF. Pokushalov et al. [55] conducted an RCT in persistent/long standing persistent AF patients including 264 patients randomized into two ars: PVI + Linear Line (LL) ($n$ = 132) and PVI + GP ($n$ = 132) to see whether GP or LL ablation can be a better adjunct to PVI. Sinus rhythm at 12 months (47% vs. 54%) and 3 years (34% vs. 49%) were found to be higher in the PVI + GP group. On the other hand, PVI + LL ablation group had higher incidence of Left Atrial Flutter.

Driessen et al. in AFACT [56] study compared surgical epicardial GP ablation in addition to PVI and found no improvement in outcome.

Current HRS/EHRA expert consensus states that usefulness of ablation of autonomic ganglia as an initial or repeat ablation strategy for paroxysmal, persistent, and long-standing persistent AF is not well established (Class IIb, LOE B-NR).

## 4. Changing landscape of safety and efficacy of catheter ablation at current era

AF ablation is a relatively complex procedure with approximately 4.5% risk of a major complication and is only available in specialized centers. But currently, this procedure is being increasingly offered to patients, and even sicker patients. With early recognition and prevention of complications, advances in technology, increased operator experience, AF ablation has become a more widely and frequently performed safe and effective procedure with low complication rates.

An updated worldwide survey on safety and efficacy of catheter ablation of AF in humans was conducted by Cappato et al. [57] between 2003 and 2006 on 20,825 procedures amongst 16,309 patients.

Complications associated with catheter ablation of Atrial Fibrillation (**Table 3**):

Vascular access complications such as hematoma, arteriovenous fistula, pseudoaneurysm etc. are low nowadays due to almost universal use of ultrasound guided vascular access. Various esophageal temperature monitoring probes (e.g. CIRCA) or Esophageal cooling devices are available that has reduced the rate of catastrophic complications like atrio-esophageal fistula.

3-D Electroanatomic mapping (EAM) and high definition (HD) mapping in the modern era has significantly improved efficacy and safety of ablation and has reduced

| Type of complication | No. of patients | Rate, % |
|---|---|---|
| Death | 25 | 0.15 |
| Tamponade | 213 | 1.31 |
| Pneumothorax | 15 | 0.09 |
| Hemothorax | 4 | 0.02 |
| Sepsis, abscesses, or endocarditis | 2 | 0.01 |
| Permanent diaphragmatic paralysis | 28 | 0.17 |
| Total femoral pseudoaneurysm | 152 | 0.93 |
| Total artero-venous fistulae | 88 | 0.54 |
| Valve damage/requiring surgery | 11/7 | 0.07 |
| Atrium-esophageal fistulae | 6 | 0.04 |
| Stroke | 37 | 0.23 |
| Transient ischemic attack | 115 | 0.71 |
| PV stenoses requiring intervention | 48 | 0.29 |
| Total | 741 | 4.54 |

**Table 3.**
*Procedural risks and complication rates with catheter ablation of atrial fibrillation.*

procedural time and fluoroscopy time. There are 3 mapping systems widely available CARTO (Biocense Webster Inc., Diamond Bar, California), EnSite NavX (St Jude Medical, St Paul, Minnesota), Rhythmia (Boston Scientific Inc., Marlborough, MA, USA). Pre procedural imaging, cardiac CT or MRI, integration with 3-D mapping systems further allows for increased procedural accuracy and safety. Phased array Intracardiac Echocardiogram is routinely used to aid in the visualization of cardiac anatomy, esophageal proximity to the posterior LA, pulmonary vein anatomy, catheter navigation, transeptal puncture and even tissue changes during ablation lesion delivery. The CARTO3 mapping system has the advantage of Integrated ICE (CARTOSOUND) allowing for direct integration of ICE images into the EAM system, however ICE is used in conjunction with all three mapping systems. Bidirectional steerable Navigational sheaths such as VIZIGO (Biocense Webster Inc., Diamond Bar, California) which can be visualized with EAM systems have facilitated in safe catheter navigation and reduced fluoroscopy time.

In recent years, mapping catheter technology for AF ablation has improved significantly. HD mapping catheters with unique form factors with small electrode size, spacing and orientation allows for optimized electrogram collection allowing for better assessment of electrical properties of tissue, fractionated potentials, acquire accurate anatomy/geometry, wavefront propagation etc. Deflectable mapping catheters such as PentaRay or OctaRay (CARTO, Biocense Webster), IntellaMap Orion (Boston Scientific, Marlborough, MA, USA), HD Grid (Abbott, St Pail, MN) have their unique advantages each contributing to efficacy and safety of ablation procedure. INTELLAMAP ORION High Resolution mapping catheter is a basket catheter with 64 electrodes that is capable of high definition electro-anatomical mapping providing more accurate and greater resolution. OCTARAY is a novel multielectrode catheter for high-resolution atrial mapping that has proven its utility for mapping ablation gaps and provide high resolution mapping. With improvement in software technology mapping systems are also able acquiring more points in ultrashort time, tissue proximity indicator, wavefront

annotation algorithm incorporating unipolar and bipolar electrograms increasing accuracy of map and identify ablation gaps or critical targets for ablation.

With improvement in software technology, new algorithms in the mapping systems enable acquisition of data in automated, efficient, and accurate process that reduces the dependence on the system operator. Future endeavors into HD mapping of AF include the use of novel algorithms, Artifical Intelligence (AI) neural networks and non contact mapping methodologies for the identification of AF triggers and drivers.

Probably, the greatest improvement in catheter ablation has been the rapid improvement in ablation catheter and energy delivery technology. The first RF ablation catheters were non irrigated and hence were associated with risk of coagulation and char formation at the catheter tissue interface resulting in risk of embolism. With development of open irrigated ablation catheter energy delivery has become more efficient and safer. Further development in catheter technologies include the introduction of feedback mechanisms to determine catheter contact including contact force catheters and local impedance technologies. These technologies allow for assessment of catheter tissue contact, tissue proximity, electrical and mechanical coupling and quality of lesion formation.

Equipped with modern imaging, mapping or navigational ability, irrigated ablation catheters, AF catheter ablation is now emerging as a standard of care for rhythm control in modern era with shorter procedural time, reduced fluoroscopic time, low procedural complication rates probably even lesser compared to initially reported complications in the earlier publications. Current literature suggests 60–90% improvement in selected patient with medically refractory AF and 2–3 fold better than achievable with AAD [26].

## 5. Surgical ablation of atrial fibrillation

As mentioned above Maze III procedure has proven very effective in preventing recurrence of Atrial Fibrillation however has been limited by surgical morbidities and hence a stand alone maze procedure in the absence of any other cardiac surgery indications was difficult to justify. Since then, several other iteration of Maze III procedure has evolved most using linear lines to isolate pulmonary veins and posterior wall, though less efficacious than COX Maze procedure [58, 59]. Results from PRAGUE 12 study showed more patients stayed in sinus rhythm when surgical ablation was added to cardiac/valve surgery in patients with AF. 117 patients were randomized to receive the modified Maze surgical ablation procedure (RF or Cryo based on surgeon's preference) and 107 patients underwent surgery only. 60.2% of patients with surgical ablation were in sinus rhythm at 1 year compared to 35.5% ($P$ = 0.002) and interestingly this benefit was entirely driven by improvement in long persistent and permanent AF patient group [26].

Current guideline (2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation) [45] recommendations regarding surgical ablation for AF is as follows (**Table 4**).

### 5.1 Hybrid convergent procedure

Although PVI has shown great efficacy in PAF, endocardial catheter ablation in patients with persistent and long standing persistent AF has reduced success rate. Posterior wall of LA is a complex anatomical structure in terms of atrial myofiber orientation which was demonstrated by Pashakhanloo et al. [60]. There is also

endo-epicardial dissociation with complex 3D wavefront propagation, and endocardial mapping alone may not identify epicardial substrate, similarly endocardial ablation may not be enough to modify epicardial substrate. To overcome this limitation, a newer

| COR | LOE | Recommendation |
|---|---|---|
| Class I | B-NR | Concomitant Open surgical ablation at the time of concomitant surgery such as Mitral Valve surgery is recommended in Symptomatic patients with Paroxysmal, Persistent or Long standing Persistent AF: |
| | | 1. who are refractory or intolerant to at least one Class I or III antiarrhythmic medication |
| | | 2. Prior to initiation of antiarrhythmic therapy with a Class I or III antiarrhythmic medication |
| Class I<br>Class IIa | B-NR<br>B-NR | Concomitant closed (such as CABG and AVR) surgical ablation of atrial fibrillation is recommended for symptomatic Paroxysmal, Persistent or Long standing Persistent AF |
| | | 1. who are refractory or intolerant to at least one Class I or III antiarrhythmic medication |
| | | 2. Prior to initiation of antiarrhythmic therapy with a Class I or III antiarrhythmic medication |
| Class IIa | B-NR | Stand alone and Hybrid ablation of AF is recommended for Symptomatic AF patients refractory or intolerant to at least one Class I or III antiarrhythmic medication |
| | | 1. Paroxysmal: who have failed one or more attempts at catheter ablation, intolerant/refractory to AAD and prefer a surgical approach, after review of the relative safety and efficacy of catheter ablation vs. a stand-alone surgical approach. |
| | | 2. Persistent and long standing persistent: who have failed one or more attempts at catheter ablation, and prefer a surgical approach, after review of the relative safety and efficacy of catheter ablation vs. a stand-alone surgical approach. |

**Table 4.**
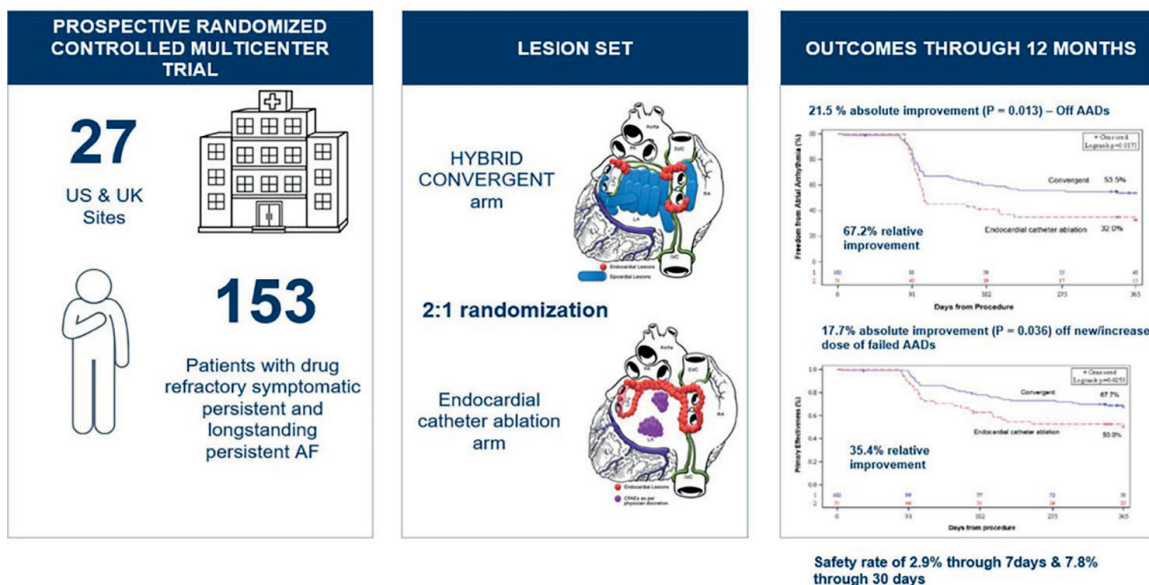*2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus on surgical ablation for AF.*



**Figure 7.**
*Figure adopted from DeLurgio et al. [61].*

hybrid convergent approach with endo-epicardial ablation was compared to endocardial ablation alone in the CONVERGENT [61] trial by DeLurgio et al. (**Figure** 7).

One-hundred fifty-three patients were randomized 2:1 to Hybrid Convergent vs. catheter ablation. Epicardial ablation was performed with unipolar radiofrequency device (EPi-Sense, AtriCure, OH). Pericardial access was gained through a transdiaphragmatic or subxiphoid approach, and the radiofrequency device was positioned inside a pericardioscopic cannula with an endoscope. Primary outcome was freedom from AF/AFl/AT without AAD or previously failed AAD without increase in dosage. Study concluded that Hybrid Convergent procedure has superior effectiveness compared to the catheter ablation for the treatment of persistent and long-standing persistent atrial fibrillation.

Both findings from PRAGUE 12 study and CONVERGENT trial provides unique insight into understanding the mechanism of Persistent and long standing persistent AF and offers new treatment options for this variety of AF which is more difficult to tackle with endocardial ablation alone.

## 6. Device detected atrial fibrillation

Device detected or subclinical atrial fibrillation (SCAF) is a term that broadly encompasses AT detected by cardiac implantable electronic devices (CIEDs), which include implantable cardiac monitors, dual-chamber pacemakers, dual-chamber implantable cardioverter-defibrillators, and cardiac resynchronization therapy devices. There is no consensus about role of anticoagulation in this unique group of patients, though it is believed to affect as many as one-third of the U.S. population. Current guidelines recommend OAC for stroke and systemic embolism prophylaxis in patients with non valvular atrial fibrillation based on CHADSVasc2 score irrespective of Paroxysmal, persistent/long standing persistent or permanent category. False detection may occur due to oversensing of far field R wave, noise, or runs of Premature atrial complexes (PAC) or undersensing may misdiagnose true AT and hence all device detected Atrial high response events (AHRE) require further verification by physician.

The temporal relationship between atrial fibrillation and stroke is not as well understood, and in some patients, episodes of AF are not detected until months after a stroke. Though studies like CRYSTAL AF [62] and EMBRACE [63] has shown increased trend of anticoagulation prescription by physicians amongst patients with cryptogenic stroke who has AF detected with an implantable loop monitor or an event monitor for 30 days, there was reduced trend towards starting anticoagulation amongst patients with CIED detected AF without cryptogenic stroke [64]. Multiple studies, including MOST, TRENDS, and ASSERT trials have added insight into this unique clinical situation of SCAF. Subgroup analysis of 316 patients from MOST (MOde Selection) trial in patients with sinus node dysfunction showed AHRE (atrial rate > 220 beats/min for 10 consecutive beats) was an independent predictor of mortality or nonfatal stroke and AF, indicating that pacemaker patients with sinus node dysfunction and AHRE were more than 2.5 times as likely to die or have a stroke, and were 6 times as likely to develop AF than those without AHRE [65]. TRENDS [66] study prospectively looked at 2486 patients with pacemakers or defibrillators that monitor AT/AF burden (defined as the longest total AT/AF duration on any given day during the prior 30-day period) and concluded that AT>5.5 h was significantly associated with increased risk of thromboembolic event in patients with ≥1 stroke

risk factor (heart failure, hypertension, age ≥65 years, diabetes, or prior thromboembolic event) and emphasized the notion that Thromboembolism risk is a quantitative function of AT/AF burden. In the ASSERT study, subclinical episodes of AT, defined as atrial rates ≥190 beats/min lasting >6 min, were associated with an increased risk of ischemic stroke [67]. Stroke risk was incremental with longer duration of AT but similar risk between AT of 6–24 h duration, or >24 h duration, stroke risk increased with the number of subclinical AT episodes [68]. IMPACT [69] trial had a predefined anticoagulation plan. Anticoagulation protocol was initiated if AT (defined as ≥200 beats/min for 36 of 48 beats) was detected≥48 h in patients with $CHADS_2$ score ≤2 with discontinuation of anticoagulation if there were no AT recurrences detected for 30 days, CHADS2 scores of ≥3 to 4 would initiate anticoagulation for device-detected AT ≥24 h in 2 days, with discontinuation if there were no AT recurrences detected for 90 days, patients with CHADS2 scores ≥5 to 6, or with a history of prior thromboembolism were prescribed anticoagulant therapy for any AT, without discontinuation, regardless of AT recurrence [68]. Data Monitoring Committee recommended trial termination on the basis of failure to demonstrate a meaningful difference in outcome with the interventional strategy. There was no significant difference between groups in the primary outcome, which was the composite of ischemic stroke, systemic embolic, and major hemorrhagic events, or in all-cause mortality.

Guidelines are unclear about role of anticoagulation in device detected SCAF. One school hypothesizes there is lack of scientific evidence to prove benefit of anticoagulation in SCAF and there is no clear consensus regarding "how much is too much device detected AF" based on varying duration of AF seen in various trials. Other school argues that there is lack of temporal relationship between AF and stroke/thromboembolism reflecting AF is marker for increased risk of stroke or systemic thromboembolism and hence anticoagulation if initiated with detection of AF may prevent stroke. It is accepted that risk of stroke is independent of duration (Paroxysmal or persistent) of AF or symptoms of AF in patients with clinical AF and mostly governed by risk factors for stroke (e.g. CHADSVasc2 risk calculator tool). There is no answer to whether AF-related stroke risk varies on the method of AF detection e.g., 12 lead ECG, Holter monitor, Implantable loop monitor or pacemaker-defibrillator. It is established that SCAF is a common clinical situation and eventually on longitudinal follow up many of these patients eventually develop clinical AF. Thus device detected AF offers an opportunity for closer monitoring of this patient population, and initiation of anticoagulation should be based on risk of stroke guided by tools as $CHADSVsac_2$ score profile after patient-physician discussion based on patient preference and values.

## 7. Non pharmacological stroke prevention/left atrial appendage occlusion

AF increases the risk of stroke [70] 5 times, irrespective of Paroxysmal, Persistent or permanent nature, symptomatic or asymptomatic status, and thromboembolism occurring with AF is associated with a greater risk of recurrent stroke, more severe disability, and mortality. Role of anticoagulation in prevention of stroke and systemic embolism have been already established (**Figure 8**).

New target specific oral anticoagulation agents such as Dabigatran, Rivaroxaban, Apixaban, Edoxaban and Betrixaban are available. Some have shown superior efficacy over Coumadin while others proved non inferior to coumadin. Reversal agents
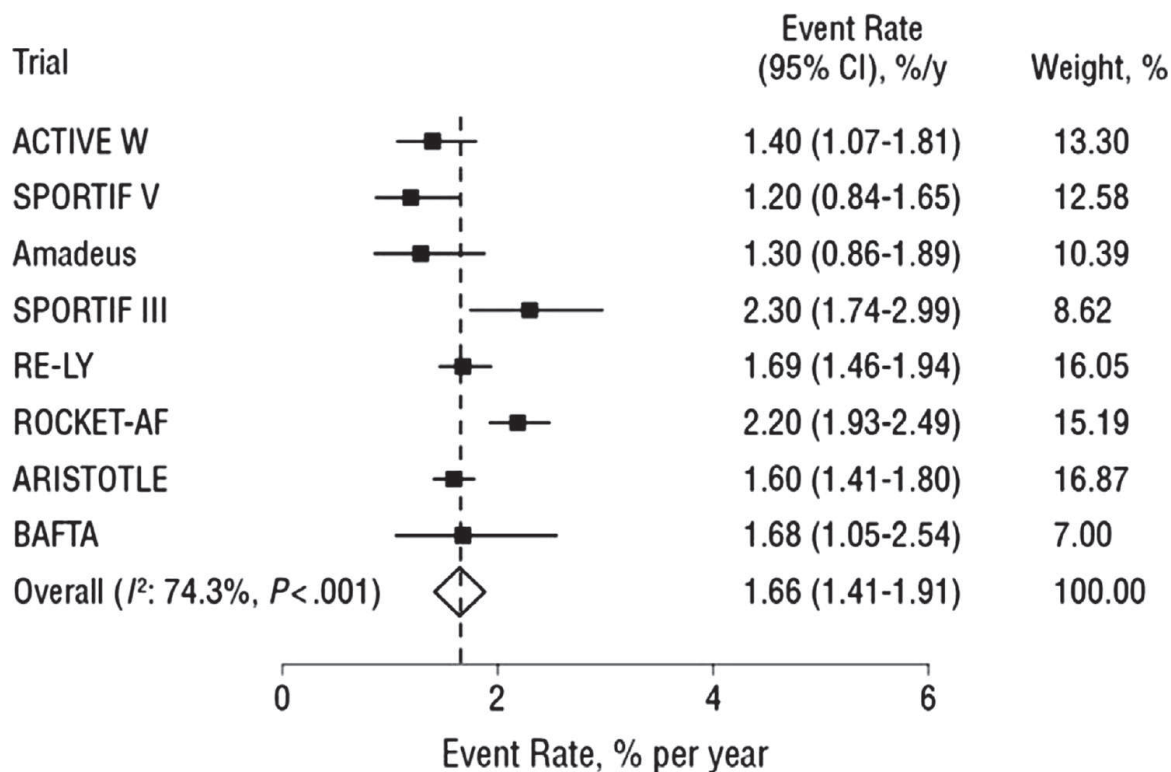
**Figure 8.**
*Meta-analysis of landmark trials showing role of anticoagulation in patients with non valvular atrial fibrillation.*

are available. However, bleeding risk is a major concern with use of anticoagulation. Coumadin has narrow time in therapeutic range, multiple drug and food interaction and need for lifelong anticoagulation. People who cannot tolerate oral anticoagulation but are at increased risk of stroke requires non pharmacological stroke prevention. LAA is the primary source of thromboembolism in AF [71] and obliteration of LAA is associated with reduction of stroke. There are two different approaches available for LAA occlusion percutaneously. One is plugging the appendage with a device like WATCHMAN (Boston Scientific, Natick, MA) or Amplatzer cardiac plug (St. Jude Medical, Plymouth, MN). Other approach is to ligate the LAA with an epicardial approach using LARIAT device, (SentreHEART, Redwood City, CA) which requires transeptal and subxiphoid approach. With LARIAT device, Acute closure rate is high with low rate of leak however procedure success is limited due to bleeding.

Holmes et al. [72, 73] published the initial safety and feasibility data in 66 patients who underwent LAA occlusion with WATCHMAN. No strokes occurred during follow up despite discontinuation of anticoagulation, there were two patients with device embolization, two cardiac tamponade, one air embolism, two deaths not related to device. But in subsequent larger RCT and LAAO registries complication rates were much lower with increasing operator experience. PROTECT AF [72, 73] was a large multi center RCT that compared LAAO with WATCHMAN device to anti-coagulation with coumadin. After 3.8 years of follow up, LAAO showed non inferior-ity and also superiority compared to coumadin in preventing combined outcome of stroke and embolism, cardiovascular death, all cause death. Similarly, PREVAIL [74] trial assessed the safety and efficacy of LAAO in patients with Non valvular Atrial Fibrillation (NVAF) compared to long term warfarin therapy and showed LAAO was noninferior to warfarin for ischemic stroke prevention or SE >7 days' post-procedure, and procedural safety has significantly improved. There are two large registries now

CAP (Continued access to PROTECT-AF) and CAP 2 (continued access to PREVAIL) that provides long term safety and efficacy of LAAO with WATCHMAN for stroke prevention. Data from these two longest and largest registries showed LAAO with WATCHMAN device is safe and effective therapy for stroke prevention in NVAF. Though PROTECT-AF data showed non inferiority and superiority of LAAO over Warfarin, complication rates were higher. This was addressed in the subsequent PREVAIL trial. There was however, unexpectedly low rate of ischemic stroke in Warfarin cohort. This was believed to be due to relatively small patient population followed for relatively short duration. A subsequent metanalysis of these two trials by Reddy et al. [75] showed ischemic stroke/Systemic embolism rate was numerically higher with LAA Closure, but this difference did not reach statistical significance (HR: 1.71; $P$ = 0.080). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAA closure. Procedure safety has significantly improved after next generation of WATCHMAN device called WATCHMAN FLX was designed. PINNACLE FLX [76] study enrolled around 400 patients who underwent WATCHMAN FLX implantation. Primary efficacy endpoint was effective LAA closure defined by ≤5 mm peridevice flow, secondary efficacy endpoint was ischemic stroke or systemic embolism at 24 months, primary safety end point was all cause death, ischemic stroke/systemic embolism, device or procedure related adverse event requiring surgery or major end-vascular intervention within 7 days following the procedure or hospital discharge whichever is later. Ischemic stroke occurred in 0.5%, no death, pericardial effusion or device embolization were reported, implant success rate was 99%. 96.2% of patients were able to discontinue NOAC at 45 day follow up. The next generation device WATCHMAN FLX has shown further safety and efficacy of the procedure overcoming the initial limitations of LAAO seen during PROTECT-AF trial. Currently there is another ongoing large RCT which has completed enrolling patients (OPTIONS clinical trial) that will compare safety and effectiveness of LAA closure to OAC therapy after AF ablation. CHAMPION-AF trial is ongoing and comparing WATCHMAN FLX as a first line stroke risk reduction therapy vs. NOAC for NVAF patients.

Surgical ligation of LAA is usually performed with internal sewing or stapling. Procedure is limited by bleeding, and residual stump which acts a source of thrombus. AtriClip is an external clip that is a newer technique for surgical LAA occlusion under direct visualization in patients undergoing open Cardiothoracic surgical procedure. 3.5 year follow up showed stable clips, no LAA thrombi, or neurological event, and no neck >1 cm.

Current AHA/ACC/HRS guidelines recommend as follows for non pharmacological stroke prevention (**Table 5**):

| COR | LOE | Rcommendation |
| --- | --- | --- |
| Class IIb | B-NR | Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation |
| Class IIb | B-NR | Surgical occlusion of the LAA may be considered in patients with AF undergoing cardiac surgery, as a component of an overall heart team approach to the management of AF. |

**Table 5.**
*AHA/ACC/HRS recommendation for non pharmacological stroke prevention.*

## 8. Conclusion

Atrial Fibrillation is a commonly prevalent arrhythmia with increasing prevalence and incidence. There have been significant development in the field of AF treatment in recent years which has changed physician's outlook towards this growing arrhythmia epidemic. With several recent RCTs and other wealth of scientific evidence, benefits of early rhythm control is being increasingly recognized. Catheter ablation is safe and effective, feasible in controlling AF burden, improving quality of life, reduce hospitalization, improve heart failure symptoms and exercise capacity, reduce hospitalization and offers mortality benefit in patients with reduced LV systolic function. Mapping and ablation technology has significantly improved in recent years and is still growing and evolving. Various modalities for ablation such as RF along with its different strategic ramifications such as VoM alcohol ablation, substrate modification, Cryo-Ablation, PFA or Hybrid Convergent procedures have opened up more treatment choices available to both Paroxysmal and Persistent/Long standing persistent Atrial Fibrillation patients. Stroke prevention with LAA occlusion has proven effective and successful in patients who cannot tolerate or have a contraindication for long term anticoagulation.

## Abbreviations/acronyms

| | |
|---|---|
| ACC | American College of Cardiology |
| AF | Atrial Fibrillation |
| AFl | Atrial Flutter |
| AHA | American Heart Association |
| AHRE | Atrial High response event |
| AT | Atrial tachycardia |
| AAD | Antiarrhythmic drug |
| CFAE | Complex Fractionated Atrial Electrogram |
| CIED | Cardiac Implantable Electronic Device |
| CTI | Cavo tricuspid Isthmus |
| CHF | Congestive Heart Failure |
| COR | Category of Recommendation |
| EAM | Electroanatomic mapping |
| EF | Ejection Fraction |
| HD | High Definition |
| HF | Heart Failure |
| HFS | High Frequency Stimulation |
| HFrEF | Heart Failure with Reduced Ejection Fraction |
| HFpEF | Heart Failure with Preserved Ejection Fraction |
| HPSD | High Power Short Duration |
| HRS | Heart Rhythm Society |
| ITT | Intention to Treat |
| LA | Left Atrium |
| LAA | Left Atrial Appendage |
| LAAO | Left Atrial Appendage Occlusion |
| LA FAP | Left Atrial Fractionated atrial potential |
| LL | Linear Line |
| LOE | Level of Evidence |

| | |
|---|---|
| LPLD | Low Power Long Duration |
| LVEF | Left Ventricular Ejection Fraction |
| NOAC | Novel oral anticoagulant |
| NVAF | Non valvular Atrial Fibrillation |
| PAC | Premature Atrial Complex |
| PAF | Paroxysmal Atrial Fibrillation |
| PFA | Pulsed Field Ablation |
| PV | Pulmonary vein |
| PVI | Pulmonary Vein Isolation |
| RA | Right Atrium |
| RCT | Randomized Clinical Trial |
| RF | Radiofrequency |
| SCAF | Subclinical Atrial Fibrillation |
| SVC | Superior Vena Cava |
| vHPSD | Very High Power Short Duration |
| VoM | Vein of Marshall |
| W | Watts |

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