Strategies for Rhythm Control in Atrial Fibrillation

Kumar Narayanan

Abstract
Atrial fibrillation (AF), the most common arrhythmia encountered worldwide, is associated with significant morbidity. The three important considerations with regard to AF management are stroke prevention, rate control, and rhythm control, with the latter two overlapping to some extent. While antiarrhythmic drugs have had limited success as a rhythm control strategy, being limited by side effects and proarrhythmia, catheter ablation has emerged as a potentially better alternative. Current ablation techniques afford good success for paroxysmal AF, especially when done in experienced centers; however, further improvements and innovations are required to improve results for more persistent forms of AF. The current review critically summarizes the present strategies employed for rhythm control in AF and briefly outlines some of the newer developments in this field.

Keywords
Atrial fibrillation, rhythm control, ablation, stroke

Introduction
Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical cardiology practice. It is estimated that approximately 33 million individuals are afflicted with AF worldwide, although robust estimates, especially from the developing world, are lacking. AF can not only cause significant symptoms and reduced quality of life but it has also been shown to result in adverse cardiovascular outcomes including cardiovascular death and heart failure. AF is also a major risk factor for ischemic stroke of the cardioembolic type with resultant major disability. It is generally classified as paroxysmal (lasting or therapeutically terminated < 7 days), persistent (lasting > 7 days; long standing persistent lasting > 1 year), and permanent (AF clinically accepted where attempts to convert to sinus rhythm are no longer pursued). The management of patients with AF involves treating the arrhythmia itself and mitigating the stroke risk associated with AF via anticoagulation in appropriate candidates. The 2 broad approaches adopted for dealing with AF per se are rate control and rhythm control.

Rate Control Versus Rhythm Control in AF
AF results in irregular, fast ventricular rates which is responsible for symptoms as well as potentially adverse effects on cardiac function. To this, one needs to add the loss of atrial contribution to cardiac filling as well as adverse remodeling in the atrium and ventricle over time. Deleterious atrial remodeling spans the spectrum from tachycardia-induced atrial remodeling (due to which “AF begets AF”) to a primary cardiomyopathic process—fibrotic atrial cardiomyopathy—wherein, AF is the result rather than the cause of this cardiomyopathy. The hallmark is atrial fibrosis which produces varied manifestations, including AF, atrial tachycardia, and sinus node dysfunction. The strategy of rate control aims to only reduce ventricular
rates resulting from AF to ameliorate the symptoms, while the rhythm control strategy aims to abolish AF, and restore and maintain sinus rhythm. The landmark Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, comparing these 2 strategies, failed to show a significant benefit for the rhythm control strategy over rate control.\(^8\) However, subsequent subanalyses have suggested that although sinus rhythm is beneficial, this is offset both by adverse effects associated with antiarrhythmic drugs (AADs) used for the purpose as well as by the relatively poor efficacy of drugs in maintaining sinus rhythm in a good proportion of patients.\(^3,10\) In discussing the need for, as well as strategies for rhythm control in AF, it is useful to separately consider acute and chronic rhythm control.

**Acute Rhythm Control**

This refers to the situation where the patient presents with an acute episode of AF, most often symptomatic with rapid ventricular rates. The key elements to consider in deciding on acute rhythm control are the severity of symptoms, hemodynamic stability, and duration of AF. Recent-onset AF with lesser degree of structural heart disease is more likely to convert to sinus rhythm as compared to long-standing AF with greater underlying substrate. However, a recent study suggests that a routine strategy of converting all recent-onset AF may not be necessary, as a good proportion of AF may spontaneously revert within 48 h.\(^11\) Hence, decision-making should take into consideration the overall clinical picture. Potential precipitating factors, such as electrolyte imbalance, infection, cardiac ischemia etc., should always be looked for and corrected. The AF duration is also important for the assessment of acute stroke risk, which is often overlooked. Conversion of AF to sinus rhythm, either by pharmacologic means or direct current (DC) cardioversion, is associated with enhanced stroke risk in the peri-conversion period. This is especially true if the AF has lasted longer than 48 h, but even shorter durations of AF, such as 12 h, carry some risk of stroke.\(^12\) Hence, in AF of > 48 h or unknown duration, adequate anticoagulation should be provided before attempting cardioversion. However, if there is a need to convert the rhythm straightaway, an alternate strategy is to perform a transesophageal echocardiography (TEE) to rule out the presence of a left atrial clot before proceeding with cardioversion.\(^13\) Only in an absolute emergency, where rapid AF is causing hemodynamic compromise, should one proceed with prompt electrical cardioversion even without TEE. The institution of parenteral anticoagulation in the form of unfractionated or low-molecular-weight heparin should always be done early prior to conversion. Furthermore, anticoagulation needs to be continued for a minimum of 4 weeks after cardioversion of AF to account for atrial stunning post restoration of sinus rhythm. Further, long-term continuation of anticoagulation after that is based on individual assessment of stroke risk through well-established risk scores such as the CHADS-VASc score.\(^14,15\)

**Strategies for Acute Rhythm Control**

The 2 methods that can be used to achieve rhythm control in the acute setting are pharmacological conversion via use of AADs and electrical cardioversion.

**Electrical Cardioversion**

Electrical cardioversion by means of DC synchronized shock has a higher efficacy than drugs and is also immediate. Hence, it is the preferred strategy whenever prompt reversion to sinus rhythm is needed such as in cases of hypotension or severe heart failure related to rapid ventricular rates. Synchronization with the QRS is important to avoid triggering ventricular fibrillation. Success of electrical cardioversion depends on the amount of electrical current effectively delivered to the myocardium, an important determinant of which is the transthoracic impedance (TTI). TTI, in turn depends on many factors such as body weight, surface area, chest wall thickness and fat, paddle orientation, prior shocks given, etc. Hence, the energy required for defibrillation can differ from case to case. Biphasic shock waveforms are generally more effective than monophasic waveforms for defibrillation, with a lower energy requirement.\(^16\) Repetitive (stacked) shocks have been said to be useful by lowering TTI, but there is limited evidence for improved efficacy. Either paddles or patches can be used for defibrillation; while patches are more convenient, paddles show some superiority due to lower TTI and more uniform contact. Cardioversion success rate is lower in obese patients as they have greater chest circumference, thickness, more intrathoracic as well as epicardial fat. While there is no uniform standard, cardioversion is initially attempted with energy of 50 to 100 J. If unsuccessful, escalating energies can be used. Most available biphasic defibrillators have a maximum energy of 200 J, but 360 J biphasic shock may succeed when lower energies have failed and can be used if available. Other strategies for failed DC version include different paddle orientation such as anteroposterior (instead of usual anteroapical) or manual pressure augmentation over the patches with a gloved hand which can be performed safely.\(^17,18\) Finally, facilitated cardioversion after loading with AADs, such as amiodarone and vernakalant, may achieve success where simple cardioversion fails.\(^19,20\) Although theoretically DC cardioversion can result in other serious arrhythmias such as ventricular tachycardia (VT) or fibrillation (VF), these are rare and generally occur in the setting of dyselectrolytemia or other drug toxicity, with electrical cardioversion overall displaying good safety.\(^14\) However, DC cardioversion does require sedation/anesthesia with a small attendant risk of related complications.

**Pharmacologic Cardioversion**

Acute pharmacologic cardioversion is accomplished through the use of intravenous antiarrhythmic agents in the emergency room or intensive care unit setting. All antiarrhythmic agents have the potential for proarrhythmia, and therefore,
continuous monitoring of the rhythm and ready availability of defibrillation/resuscitation equipment is a necessity. The agents demonstrated to have efficacy for conversion include class I and class III AADs.

Class I AADs used for acute conversion of AF are flecainide and propafenone, which are typically used in a dosage of 2 mg/kg body weight, given as an infusion for 10 to 20 min. Class I drugs should not be used in the setting of significant structural heart disease such as old myocardial infarction (scar), left ventricular (LV) dysfunction, or LV hypertrophy due to risk of ventricular proarrhythmia. Varying efficacy rates between 50% and 90% have been seen for conversion to sinus rhythm. It has been suggested that flecainide may be more efficacious than propafenone or amiodarone in the acute setting. Intravenous flecainide and propafenone are currently unavailable in India. Another approach would be to load the drugs orally which has been shown to be efficacious, though with a longer time to conversion.

Amiodarone, though conventionally classified as a class III agent, has multiple mechanisms of action and has broad efficacy against several arrhythmias. It is generally given as a slow bolus of 150 mg followed by an infusion protocol over the next 24 h. A meta-analysis of studies showed about 75% efficacy rate for AF conversion in 24 h with amiodarone. Amiodarone has comparable overall efficacy with class Ic drugs; however, it is slower acting and conversion often occurs in a delayed fashion. Unlike class I drugs, amiodarone can be used in the presence of structural heart disease and LV dysfunction. Oral amiodarone is even more slow-acting and has low efficacy for immediate conversion, though small studies have suggested higher conversion rates with very high doses (25-30 mg/kg). Another class III agent recently made available in India is ibutilide, which has a faster onset of action, with most reversions occurring within 30 to 60 min. The usual dose is 1 mg (0.01 mg/kg if weight < 60 kg) given as an infusion over 10 min, with a repeat dose after a

---

**Figure 1. Overview of Approach to Rhythm Control in Atrial Fibrillation**

**Abbreviations:** AAD, antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; LV, left ventricular; LVH, left ventricular hypertrophy; OSA, obstructive sleep apnoea.
10-to-20-min interval if sinus rhythm is not achieved. Ibutilide has a 50% to 60% efficacy rate for conversion of new-onset AF and an even better success rate in case of atrial flutter. Ibutilide can cause prolongation of the QT interval and carries a small risk of triggering polymorphic VT. Hence, rhythm monitoring for at least 6 h post administration is essential. Ibutilide infusion should be stopped even before completion of dose if sinus rhythm is achieved or if nonsustained or sustained VT occurs. Preloading with intravenous magnesium prior to ibutilide is recommended to reduce VT rates. Preloading with intravenous magnesium prior to ibutilide is recommended to reduce VT or sustained VT occurs. Preloading with intravenous magnesium prior to ibutilide is recommended to reduce VT or sustained VT occurs. Preloading with intravenous magnesium prior to ibutilide is recommended to reduce VT or sustained VT occurs. Preloading with intravenous magnesium prior to ibutilide is recommended to reduce VT or sustained VT occurs.

In addition, combination therapy of ibutilide with other agents has been described to improve success rates. Fragakis et al described that pretreatment with esmolol improved ibutilide conversion rates and also reduced QT prolongation and VT risk. In other studies, addition of propafenone or use of ibutilide in patients already on amiodarone therapy has been reported to improve efficacy. Yet another agent vernakalant, demonstrated to have reasonable efficacy for converting recent-onset AF, is currently unavailable in India.

**Chronic Rhythm Control**

**Which Atrial Fibrillation Patients Need Rhythm Control?**

Many patients with AF can have significant symptoms related to the arrhythmia despite rate control and can hence benefit from a rhythm control strategy aimed at chronic maintenance of sinus rhythm (Figure 1). Current guidelines advocate rhythm control only for relief of AF-related symptoms and improvement of quality of life. Although long proposed, there is no concrete evidence to date that chronic rhythm control improves hard cardiovascular outcomes such as cardiovascular death or stroke. Although the AFFIRM trial showed no overall benefit for rhythm control strategy, some points are noteworthy. The patients studied were relatively older (mean age about 70 years), with comorbidities, had left atrial enlargement (65%), many of them had a relatively low AF burden (where rhythm control is less likely to show benefit), and finally anticoagulation was prematurely stopped in many. Rhythm control is especially likely to be beneficial in younger patients with no comorbidities, recent-onset AF, early in the course of disease with normal left atrium (LA) size. Patient preference for a rhythm control strategy is also important to consider in decision-making. It is also the only strategy when rate control has failed. The advent of catheter ablation for AF has especially reignited this debate as maintenance of sinus rhythm by catheter ablation and avoidance of chronic AAD therapy might prevent the offsetting of the benefits of sinus rhythm by AAD adverse effects (as in the AFFIRM trial).

However, evidence to back this premise is still lacking as discussed later below.

**Rhythm Control and Anticoagulation**

Another popular misconception is that rhythm control can be used to avoid anticoagulation. This is lacking in scientific basis and data from AF trials have not demonstrated that successful rhythm control significantly reduces stroke risk making it safe to discontinue anticoagulation. The reasons for this are probably multifactorial. First, confirming that an individual is 100% AF free after institution of a rhythm control strategy is problematic, as short lived, asymptomatic AF episodes are difficult to detect in the absence of continuous monitoring. Such silent episodes can nevertheless pose a risk of stroke. In patients with implanted cardiac devices such as pacemakers and continuous monitoring, even episodes of AF lasting few minutes to hours have been linked to stroke risk. Hence, an apparently successful rhythm control strategy, where a patient experiences major relief from symptomatic AF episodes, may still have a significant residual stroke risk through such silent episodes. This is especially true with regard to drug therapy, where effective maintenance of sinus rhythm may be < 50%. However, even with respect to catheter ablation for AF, pooled data from randomized trials have not shown a significant reduction in stroke risk compared to nonablated subjects. In a 2013 meta-analysis of AF ablation studies, late recurrences were seen in up to 20% of cases even after multiple procedures. Second, the AF–stroke relationship is complex, with the classical view of blood stasis in the left atrium due to AF alone, probably reflecting an oversimplified view. The lack of a clear temporal relationship between AF episodes and stroke reflects this. AF is, to some extent, a marker of adverse cardiovascular substrate with associated atrial cardiomyopathy, atherosclerosis, endothelial dysfunction, etc., all contributing to stroke risk, independent of the arrhythmia as such. Therefore, guidelines recommend continuation of anticoagulation solely based on assessment of individual stroke and bleeding risk using standardized scores established for this purpose, irrespective of a rhythm control strategy. Hence, at present, treating clinicians should not recommend AADs or catheter ablation for AF for the purpose of discontinuing anticoagulation. Ongoing studies such as the OCEAN trial hope to further address the question of whether a long-term truly AF-free period can reduce stroke risk adequately enough to make eventual discontinuation of anticoagulation feasible.

**Strategies for Chronic Rhythm Control**

The 2 major strategies for chronic rhythm control are AADs and catheter ablation. Before going into these, it is
important to address underlying risk factors which initiate and perpetuate AF.

**Management of Risk Factors: Underlying Substrate**

Unlike many other supraventricular arrhythmias, AF is often a systemic disease, precipitated and maintained by risk processes which are common to other cardiovascular pathologies as well. Most important among these are systemic hypertension, obesity, and obstructive sleep apnea (OSA). These factors result in adverse effects such as LV hypertrophy, diastolic dysfunction, left atrial enlargement and fibrosis, which in turn serve as substrate for AF. Fixation on AADs/catheter ablation often leads to lack of attention to adequate control of underlying risk factors, which can significantly impede a successful rhythm control strategy.

Targeting the underlying processes which result in AF has been referred to as “upstream therapy” which helps both prevent AF as well as improve success of rhythm control strategies in established AF.

Recent work has especially focused on obesity and OSA in relation to AF. OSA is associated with adverse atrial remodeling and increases AF recurrences. Continuous positive airway pressure therapy can effectively ameliorate OSA symptoms and also reduce AF recurrences. Similarly, lifestyle interventions aimed at weight reduction and optimal control of other cardiovascular risk factors are very important and have been shown to reduce AF burden and improve maintenance of sinus rhythm. In the latest American College of Cardiology/American Heart Association guidelines, risk factor modification has been accorded a class I recommendation; however, most of the data supporting this recommendation comes from a single center. While good control of hypertension is in itself beneficial in reducing AF, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been proposed to have specific benefits in this regard and it is reasonable to prefer these drugs for hypertension management in the setting of concomitant AF.

**Anti-arrhythmic Drugs**

Similar to acute rhythm control, AADs, mainly belonging to Class I and Class III, can be used to reduce AF recurrences and maintain sinus rhythm on a long-term basis. The choice and dosing of AADs depends on the extent of structural heart disease, and frequency and severity of AF.

The class I agents propafenone and flecainide are available in India in oral formulation and can be used for chronic rhythm control. They have reasonable efficacy in maintaining sinus rhythm and can be preferred as first-line agents, given the lack of significant long-term toxicity, such as in case of amiodarone. However, class I agents are contraindicated for use in the presence of significant structural heart disease, including significant coronary artery disease, LV hypertrophy, and LV systolic dysfunction, due to risk of ventricular proarrhythmia. The other potential concern with class III agents is that they may slow the arrhythmia cycle length, thereby converting AF to slower atrial flutter, with possibility of 1:1 rapid conduction to the ventricle. This can result in paradoxically faster heart rates, worsening of symptoms, and hemodynamic compromise. Hence, it is prudent to co-prescribe atrioventricular nodal blocking agents such as beta blockers with class I AADs.

Class III AADs for treating AF include amiodarone, sotalol, and dofetilide; the last one being unavailable in India. Another agent, dronedarone was shown to be effective, but was withdrawn due to potential for hepatic toxicity, although later analyses suggest that this risk may not be excessive. Amiodarone has better efficacy in maintaining sinus rhythm compared to the class I agents, but has several potential toxicities in the long run, including thyroid, pulmonary, and ocular toxicity. Sotalol can cause QT prolongation, with a small risk for torsades-de-pointes; hence, initiation of therapy should be preferably done in inpatient setting with monitoring of the QT interval.

**Pill-in-the-Pocket Approach**

A strategy for patients with infrequent, but symptomatic AF episodes is the so-called pill-in-the-pocket approach, where the patient self-doses with a loading dose of flecainide (typically 200-300 mg) or propafenone (typically 450-600 mg) at the onset of a perceived AF episode. This has been shown to be a safe and effective approach with >90% success rates and further avoids unnecessary daily AAD therapy in the long run.

Overall, AADs may work well for chronic rhythm control in a subset of patients, but are hampered by limited efficacy and side effects. Pharmacogenetically directed therapy of specific agents may help select patients better and achieve better efficacy with AADs in the future.

**Catheter Ablation for Atrial Fibrillation**

The seminal discovery by Haissaguerre et al on the role of ectopic foci in pulmonary veins (PV) triggering AF opened the doors for catheter ablation targeting such foci. The field of AF ablation has expanded since then to incorporate not only ablation of AF triggers, but also various methods of ablating the atrial substrate which maintains AF.

**Who Is the Right Candidate for AF Ablation?**

Ablation has been shown to be superior to AADs for maintenance of sinus rhythm in several studies. Success rates for achievement of sinus rhythm at 1 year have ranged from 70% to 80%, especially for paroxysmal AF. Persistent and long-standing persistent AF have lower success rates. The longer the duration of AF, the more structural changes are likely to happen to the atrium, making both achievement and maintenance of sinus rhythm more difficult. A meta-analysis...
of trials combining all forms of AF showed success rates of 50% to 60% for catheter ablation. Therefore, recurrences after ablation are common, requiring second or sometimes multiple procedures.60

Since ablation is theoretically a better method of eliminating AF without adverse effects related to AADs, it has been hoped that it could potentially improve hard cardiovascular outcomes, such as mortality and stroke, beyond relieving AF-related symptoms. Observational, nonrandomized studies have suggested such a potential benefit; however, these are subject to unmeasured confounders and bias.57,61 The randomized, controlled, CABANA trial, comparing catheter AF ablation with drug therapy did not show an improvement in a composite outcome of cardiovascular death, stroke, cardiac arrest, or major bleeding with ablation. AF recurrence and attendant hospitalization was less frequent, as expected, with the ablation group.62 Similarly, quality of life measures related to superior relief of AF-related symptoms are reported to be better with ablation.63,64 Overall, currently there is no concrete evidence that AF ablation improves hard cardiovascular outcomes, although there is low recurrence compared to drugs and quality of life is improved. Further ongoing trials such as the EAST-AFNET-4 trial may bring greater clarity in this regard.65

**Special Situation: AF Ablation in Heart Failure With LV Systolic Dysfunction**

AF and heart failure often coexist and together it is a challenging combination to manage. AF can worsen LV systolic function and heart failure, and restoration of sinus rhythm may be particularly beneficial in this setting. Several small studies have reported an improvement of LV function as well as reduction in heart failure symptoms with AF ablation in the setting of reduced ejection fraction.66,67 Two large randomized trials, namely the AATAC trial and the CASTLE-HF trial, demonstrated improvements in LV function and a reduction in mortality with AF ablation in patients with heart failure.68,69 Similarly, the CAMERA-MRI study showed greater improvement in LV ejection fraction with catheter ablation compared to rate control alone, particularly in the absence of LV scar.70 Current guidelines, however, accord only a class IIb recommendation for AF ablation as a means to reduce mortality in heart failure patients, in part, due to concerns regarding the comparator arm and dropouts in the CASTLE-HF trial.15,71 No such data is available for AF ablation in heart failure with preserved ejection fraction.

In summary, AF ablation is at present mainly advocated for symptomatic patients with AF who are refractory or intolerant to at least one AAD.15 It is reasonable as a first-line alternative for selected patients, namely, younger patients with highly symptomatic, paroxysmal AF without structural heart disease and normal LA size, who may not wish to take long-term AADs and in whom success of AF ablation is also likely to be high (Table 1).72 In patients with the so-called tachy-brady syndrome where atrial arrhythmias (including AF) can alternate with episodes of bradycardia, ablation may be considered upfront, as giving AADs risks worsening bradycardia and syncope. Also in highly active subjects such as athletes, use of AADs leads to heart rate reduction that may lessen exercise capacity and hence ablation can be considered as first option in such cases. Finally, ablation may improve cardiovascular outcomes in select patients with heart failure with reduced LV systolic function, especially if the LV dysfunction is believed to be due to AF-induced tachycardiomyopathy. Although formal guidelines do not recommend AF ablation in asymptomatic individuals, a 2017 Heart Rhythm Society expert consensus statement suggested that ablation may be considered in select asymptomatic patients with paroxysmal or persistent AF when performed by an experienced operator following a detailed discussion of the risks and benefits. This recommendation was made before the publication of the CABANA trial, based on the possibility of a potential benefit toward stroke or mortality reduction.73

**Table 1. The Ideal Candidate for AF Ablation**

| 1. | Paroxysmal atrial fibrillation |
| 2. | Highly symptomatic |
| 3. | No structural heart disease with normal left atrial size |
| 4. | No comorbidity such as hypertension, obesity, and sleep apnea |
| 5. | Relatively young and physically active (sound reason to avoid long-term antiarrhythmic drugs) |
| 6. | Tachycardiomyopathy solely due to AF |

**Special Situation: Rheumatic Heart Disease**

In the Indian context, AF in patients with rheumatic heart disease is an important issue to consider, which has not been well studied overall, as rheumatic heart disease is not prevalent in the West. Rheumatic mitral stenosis is associated with LA dilatation and fibrosis. As such rheumatic heart disease-associated AF is more difficult to treat in view of the significant substrate. In a small study, Vora et al reported about 70% success in maintaining SR with AADs with improvement in exercise capacity and quality of life; however, > 70% of patients had undergone valvular intervention.74 Indeed performing early balloon mitral valvotomy may be important as rheumatic mitral stenosis-induced atrial stretch leads to significant adverse electrophysiologic remodeling in the LA which can be reversed by balloon mitral valvotomy.75 Limited studies have suggested improved success when either AAD or catheter ablation is combined with a strategy of balloon mitral valvotomy.76,77
Techniques in AF Ablation

AF ablation is mostly performed within the LA and techniques can be broadly divided into ablation of triggers which initiate AF (PV and non-PV foci) and ablation of atrial substrate which maintains AF. While the former is always done, substrate ablation is generally reserved for more persistent forms of AF and its added utility remains unclear.

Imaging in AF Ablation

Pre- and periprocedure imaging has an important role in AF ablation. Computed tomographic scan of the LA with high resolution is commonly performed prior, both to look for LA clot and have foreknowledge of the PV anatomy. Usually, during ablation, a 3-dimensional shell of the LA is created, aided by electroanatomic mapping systems and merged with the preprocedural computed tomographic scan to have optimal anatomic guidance for LA ablation. Intraprocedural echocardiography, either using TEE or intracardiac echocardiography, is often used which is again useful to rule out LA thrombus just before the procedure, to guide atrial septal puncture for LA access and for early detection of any intraprocedural pericardial effusion due to chamber perforation. Intraprocedural echocardiography is almost universally used in the USA to avoid the need for full general anesthesia and endotracheal intubation needed for the use of TEE; however, it is considerably more expensive than TEE. Performance of AF ablation with near zero fluoroscopy using exclusive intracardiac echocardiography guidance has also been described to avoid radiation. Another described role of imaging is to quantify LA fibrosis (which portends a poorer prognosis) using contrast-enhanced magnetic resonance imaging. The Delayed Enhanced MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation (DECAAF) study revealed that extent of atrial fibrosis detected by magnetic resonance imaging was independently linked to recurrence of AF.

Ablation of Trigger: Pulmonary Vein Isolation and Non-PV Sources

Pulmonary vein isolation (PVI) remains the cornerstone of AF ablation (Figure 2). With the discovery of ectopic PV foci triggering AF, initial strategies involved limited radiofrequency (RF) ablation within the PVs to eliminate such foci. However, since ablation within the veins could result in PV stenosis, isolation of the entire PV from the LA using wide antral circumferential ablation became the method of choice, encompassing all 4 PVs to take care of potential new sources developing in the future.

PVI is commonly done using point-by-point ablation around the PV ostia using RF energy; although, some newer techniques, especially the cryoballoon (see later), have emerged. It is important to achieve reliable and durable PVI, as the most common reason for AF recurrence post ablation is PV electrical reconnection.

Durable PVI depends in turn on making effective transmural (spanning entire myocardial thickness) lesions. Studies have shown that lack of adequate tissue contact can be an important reason for not achieving a good lesion. Hence, catheters incorporating contact force information using pressure sensors at the tip are widely used now and these have been reported to improve success.

Figure 2. AF Ablation: Pulmonary Vein Isolation Using Radiofrequency Catheter Ablation or Cryoballoon
Source. Reproduced with permission from Piccini P, Fauchier L. Rhythm control in atrial fibrillation. Lancet. 2016;388:829-840.
rates. A systematic protocol (CLOSE protocol) aiming for close, contiguous lesions (< 6 mm interlesion distance) with adequate power, duration, and contact force (ablation index) has been described to further improve ablation success. The acute procedural end point of PVI is complete isolation of all 4 PVs. A circular multi-electrode catheter is commonly used at the PV ostium (Figure 2) to record the PV signals. Disappearance of these signals (“silent” PV) or their dissociation from the LA signals is the end point for PVI. For the latter end point, it is usual to test for bidirectional block between the PV and LA by pacing maneuvers. Intravenous adenosine testing to bring out any dormant residual connections between PV and LA, with further ablation to abolish such residual connections, has been shown to improve success.

In a small proportion of patients, AF is triggered by ectopic activity from non-PV sources. Such sources include the superior vena cava (SVC), coronary sinus, ligament of Marshall, Crista terminalis, and the posterior left atrial wall. When AF does not terminate or recur despite properly confirmed PVI, extra-PV triggers should be sought and ablated. Isoproterenol infusion helps bring out ectopic activity from extra-PV triggers. The SVC is a common source of extra-PV triggers and systematic isolation of the SVC has been shown to be beneficial, especially in paroxysmal AF; however, SVC isolation may not be possible to achieve in all patients due to the proximity of the right phrenic nerve and sinoatrial node.

Ablation of Atrial Substrate

While PVI is almost universally performed, several other adjunct ablation techniques have been described that aim at disrupting the atrial substrate which is responsible for maintaining and perpetuating AF. These techniques, in a sense, are similar in basis to the Cox-Maze surgery for AF, which, through multiple incisions (or more recently RF or cryo) in the atria, aims to produce lines of electrical interruption that would make it difficult for reentrant circuits to sustain. Most strategies for persistent AF are empiric addition of lesions to PVI. The most commonly performed adjunct ablations are creation of ablation lines in the LA, cavitricuspid isthmus, and ablation of complex fractionated atrial electrograms within the LA. Examples of linear ablation lines in LA include roof line (connecting superior PVs), mitral isthmus line, and “box” isolation of LA posterior wall using RF lines connecting the PVI circles superiorly and inferiorly along the posterior wall. Some others have described ablating low voltage areas within the LA. The LA appendage is a complex structure with important physiologic and electrical properties that has been implicated in the genesis/maintenance of AF. Electrical isolation of the LA appendage through catheter ablation, surgical excision, or percutaneous ligation has been reported to reduce AF recurrence. One concern with pure electrical isolation (by ablation) is risk of stroke due to stasis of blood and this approach needs further study. While several groups claim improved success rates with their specific techniques of adjunct ablation, systematic evidence for an added benefit over and above PVI is lacking. The STAR AF II trial, which randomized patients with persistent AF to PVI alone versus PVI plus additional substrate ablation, failed to show a significant difference in outcomes with added ablation. Moreover, extensive ablation could also be potentially proarrhythmic, resulting in complex LA flutters due to gaps in ablation lines. Thus, ablation of persistent forms of AF with extensive substrate ablation strategies is plagued by both higher rates of AF recurrence and occurrence of new flutters which may require multiple follow-up procedures.

Another described approach has been ablation of so-called rotors driving AF, which suggests that AF may be maintained by localized rotors and focal impulses rather than completely

### Table 2. Complications of AF Ablation

| Complication                        | Reason                        | Avoidance/Management                                      |
|-------------------------------------|-------------------------------|-----------------------------------------------------------|
| Air/thromboembolism                 | Air in circuit/clot formation in LA | Attention to circuits, high flow oxygen, adequate periprocedural anticoagulation; see text |
| Cardiac perforation/tamponade       | Catheter injury               | Continuous hemodynamic monitoring, pericardiocentesis     |
| PV stenosis                         | Ablation within the PV        | Mark PV ostium carefully; PV angioplasty if symptomatic   |
| Vascular complications: hematoma, pseudoaneurysm | Access site complications | Local pressure, surgical repair if needed                 |
| Diaphragmatic paralysis             | Inadvertent phrenic nerve injury | Pacing for phrenic capture; usually self-resolving with time |
| Atrioesophageal fistula             | Collateral damage to esophagus during ablation | See text                                                  |
| Iatrogenic atrial flutters          | Gaps in ablation lines        | Minimize ablation gaps; antiarrhythmics/repeat ablation   |

**Abbreviations:** LA, left atrium; PV, pulmonary vein.
random, chaotic reentrant fronts. A specialized mapping system developed to identify such rotors was reported to have good success initially\textsuperscript{96} but could not be replicated in subsequent studies.\textsuperscript{96}

**Complications of AF Ablation**

It is important to bear in mind that AF ablation has a small, but nonnegligible risk (5% to 7%) of serious adverse events. Possible complications of AF ablation are listed in Table 2. Periprocedural embolic stroke is a major issue, which should be avoided by ensuring no LA-appendage clot by imaging, meticulous attention to intraprocedural anticoagulation (activated clotting time > 300 s), and using irrigated ablation, minimizing chances of charring at catheter tip. It is now recommended to perform AF ablation without interruption of oral anticoagulation, both vitamin K antagonists and novel oral anticoagulants.\textsuperscript{73} Phrenic nerve injury can occur as the right phrenic nerve is anatomically close to SVC and right superior pulmonary vein, while left phrenic nerve is related to LA appendage. Prior to ablation in these areas, high-output pacing should be performed to look for diaphragmatic capture and if present, RF delivery should be avoided or energy reduced. Phrenic nerve injury tends to recover spontaneously in most cases.\textsuperscript{97} Atrioesophageal fistula (due to the close relationship between the LA and esophagus) is a dreaded and largely lethal complication. Monitoring of esophageal luminal temperature with a probe, especially while ablating on the posterior LA wall, with discontinuation of ablation if there is $\geq 1^\circ C$ temperature rise, is followed by many centers. Strategies to reduce esophageal thermal injury include esophageal deviation using preshaped deviators and luminal cooling methods.\textsuperscript{64,98-100} The risk of complications could be potentially even higher with less experienced operators and centers.\textsuperscript{101} Hence, a practical framework for decision-making regarding AF ablation has to take into account the issues of recurrence, procedural risk, cost, and balance it against the expected benefit from the procedure, which depends upon the extent of morbidity caused by AF in a given case.

**Newer Technologies and Approaches in AF Ablation**

Alternate energy sources, other than RF, have been explored for AF ablation. The most widely implemented so far in clinical practice has been cryoenergy, in the form of the cryoballoon (Figure 2). In this approach, a balloon is inflated flush against the PV ostia and freezing temperature delivered through the use of liquid nitrogen in the balloon. This freezes and ablates a circumferential zone of tissue around the PV, thus achieving a “one-shot” PV isolation compared to the more cumbersome point-by-point RF ablation. The cryoballoon can potentially simplify the procedure and reduce ablation time. Comparative studies show equivalent efficacy of the cryoballoon compared to traditional RF, with reduced procedural time and similar complication rates, except for right phrenic nerve palsy, which is reported to be higher with the cryoballoon, though mostly transient in nature.\textsuperscript{102,103}

Similarly, thermal balloons and laser balloons\textsuperscript{104} have been used, as well as a circumferential RF catheter which can deliver RF at multiple points at once. Advanced imaging and remote navigation/robotic technologies are also being utilized; all the aforementioned techniques attempt to both improve efficacy as well as simplify the procedure and make it less labor-intensive.\textsuperscript{105} The balloon-based and remote navigation ablation technologies are currently unavailable in India. Another area of active research, not only for AF, but also for other arrhythmias as well, is the role of neuromodulation. It is well known that the autonomic nervous system has an important facilitatory role in the pathogenesis of various arrhythmias, and the use of sympathectomy to treat VTs is one example of a therapeutic application.\textsuperscript{106} The LA is richly innervated with autonomic ganglia and considerable interest has focused on the role of modifying or ablating epicardial ganglionic plexi to treat AF. Interestingly, inadvertent achievement of axonal interruption of connections from ganglionic plexi to PVs, during PVI has been proposed to be at least partly contributory to the success of PVI as a means of AF ablation.\textsuperscript{107} Stimulation of the vagus, using low-level tragus stimulation has been shown to suppress AF and reduce levels of inflammatory cytokines.\textsuperscript{108}

A newer and innovative approach is irreversible electroporation. This is the application of an electrical field, using DC energy, to create irreversible pores in cell membranes, thereby leading to cell death. Hence, electroporation relies on nonthermal damage unlike RF. In addition, the electrical threshold for electroporation has been seen to differ by cell type, thus opening up the promise of delivering tissue-specific ablation and avoiding collateral damage to close, crucial structures such as PVs, esophagus, and coronary arteries. Ongoing research in this field could open up new horizons in catheter ablation.\textsuperscript{109}

Lastly, mobile and wearable heart monitors including smartwatches, bands etc. are increasingly being studied. Mobile sensors capable of generating medical grade electrocardiograms have been developed. Use of such devices can greatly improve diagnostic capabilities and early detection of recurrent AF after ablation.\textsuperscript{110}

**Surgical AF Ablation and Hybrid Strategies**

As mentioned before, the traditional cut-and-sew Maze procedure uses multiple incisions within the atria, isolating the PVs, appendages, as well as creating additional block lines to the mitral annulus, coronary sinus etc., all of which make it difficult for reentrant circuits to sustain. While long-term success rates have been reported to be good, the traditional Maze procedure is complex with a significant risk of complications. Recently, RF energy, cryo probe,
and even diathermy have been used as alternatives to surgical incisions, potentially simplifying the procedure. Surgical Maze is difficult to recommend as a standalone procedure, but should be strongly considered in patients with AF undergoing other cardiac surgery.¹¹¹ Newer minimally invasive approaches have been developed, using thorascopy and specially designed clamps which can provide single-shot PVI. In addition, hybrid approaches are also being tried that combine traditional endocardial catheter ablation with thorascoscopic minimally invasive surgical ablation.¹¹² The long-term efficacy and safety of such techniques need to be determined.

Finally, another “hybrid” strategy is to combine AF ablation with AADs. While traditionally, ablation for arrhythmias is performed with an expectation of stopping all antiarrhythmic medications post procedure, this may not always be optimal for a complex arrhythmia such as AF. Studies have suggested that continuing antiarrhythmics post ablation can lead to longer AF-free periods, reducing recurrence and need for repeat ablation. Moreover, drugs previously ineffective at maintaining sinus rhythm may be effective after modification of triggers and substrate by AF ablation.¹¹³ Hence, such a hybrid strategy warrants consideration in some patients.

Conclusions and Future Directions

AF is a multifactorial arrhythmia encountered not only by cardiologists but by almost all physicians at some point. A rhythm control strategy aims to achieve and maintain sinus rhythm and is especially warranted in patients with significant symptoms or LV dysfunction. AF ablation, targeted at both triggers of AF as well as substrate modification, has emerged as a promising modality to achieve sinus rhythm, sans the adverse effects of AADs. However, concrete evidence for an improvement in hard outcomes via ablation, such as cardiovascular mortality and stroke, is lacking; and at present, ablation is mainly recommended for symptomatic patients who are refractory or intolerant to AADs. Significant rates of recurrence and periprocedural complications constitute important limitations of current AF ablation strategies. Newer modalities such as electroporation, neuromodulation, and hybrid surgical approaches may improve AF rhythm control strategies in the near future. Finally, the importance of adequate anticoagulation for stroke prevention, in at-risk patients, has to be always borne in mind, irrespective of the rhythm or rate control strategy used in AF.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

References

1. Chugh SS, Havmoeller R, Narayanan K., et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation. 2014 February 25;129(8):837-847.
2. Benjamin EJ, Wolf PA, D’Agostino RB, Silberschatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart study. Circulation. 1998 September 8;98(10):946-952.
3. Conen D, Chae CU, Glynn RJ, et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA. 2011 May 25;305(20):2080-2087.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke. 1991 August;22(8):983-988.
5. Yin GSC, Howard DPJ, Paul NLM, et al. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study. Circulation. 2014 October 7;130(15):1236-1244.
6. Schotten U, Verheule S, Kirchhoff P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev. 2011 January;91(1):265-325.
7. Kottkamp H. Fibrotic atrial cardiomyopathy: a specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications. J Cardiovasc Electrophysiol. 2012 July;23(7):797-799.
8. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002 December 5;347(23):1825-1833.
9. Maan A, Zhang Z, Qin Z, et al. Impact of treatment crossovers on clinical outcomes in the rate and rhythm control strategies for atrial fibrillation: Insights from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial. Pacing Clin Electrophysiol. 2017 July;40(7):770-778.
10. Guglin M, Chen R, Curtis AB. Sinus rhythm is associated with fewer heart failure symptoms: insights from the AFFIRM trial. Heart Rhythm. 2010 May;7(5):596-601.
11. Pluymakers NAHA, Dudink EAMP, Luermans JGLM, et al. Early or delayed cardioversion in recent-onset atrial fibrillation. N Engl J Med. 2019 March 18;380(16):1499-1508.
12. Nuotio I, Hartikainen JKE, Grönberg T, Biancari F, Airaksinen KEJ. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. JAMA. 2014 August 13;312(6):647-649.
13. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med. 2001 May 10;344(19):1411-1420.
14. Bonfanti L, Annovi A, Sanchis-Gomar F, et al. Effectiveness and safety of electrical cardioversion for acute-onset atrial fibrillation in the emergency department: a real-world 10-year single center experience. Clin Exp Emerg Med. 2019 March;6(1):64-69.
15. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019 July 9;74(1):104-132.

16. Inácio JFS, da Rosa M dos SG, Shah J, et al. Monophasic and biphasic shock for transthoracic conversion of atrial fibrillation: systematic review and network meta-analysis. *Resuscitation*. 2016 March;100:66-75.

17. Voskoboinik A, Moskovich J, Plunkett G, et al. Cardioversion of atrial fibrillation in obese patients: results from the cardioversion—BMI randomized controlled trial. *J Cardiovasc Electrophysiol*. 2019;30(2):155-161.

18. Kirchhof P, Eckardt L, Loh P, et al. Anterior-posterior versus anterior-lateral electrode positions for external cardioversion of atrial fibrillation: a randomised trial. *Lancet Lond Engl*. 2002 October 26;360(9342):1275-1279.

19. Manios EG, Mavrakis HE, Kanoupakis EM, et al. Effects of amiodarone and diltiazem on persistent atrial fibrillation conversion and recurrence rates: a randomized controlled study. *Cardiovasc Drugs Ther*. 2003 January;17(1):31-39.

20. Müssigbrodt A, John S, Kosiuik J, Richter S, Hindricks G, Bollmann A. Vernakalant-facilitated electrical cardioversion: comparison of intravenous vernakalant and amiodarone for drug-enhanced electrical cardioversion of atrial fibrillation after failed electrical cardioversion. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2016 January;18(1):51-56.

21. Markey GC, Salter N, Ryan J. Intravenous flecainide for emergency department management of acute atrial fibrillation. *J Emerg Med*. 2018;54(3):320-327.

22. Boriani G, Capucci A, Lenzi T, Sanguinetti M, Magnani B. Propafenone for conversion of recent-onset atrial fibrillation. A controlled comparison between oral loading dose and intravenous administration. *Chest*. 1995 August;108(2):355-358.

23. Hilleman DE, Spinler SA. Conversion of recent-onset atrial fibrillation with intravenous amiodarone: a meta-analysis of randomized controlled trials. *Pharmacotherapy*. 2002 January;22(1):66-74.

24. Chevalier P, Durand-Dubieff A, Burri H, Cucherat M, Kirkorian G, Touboul P. Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *J Am Coll Cardiol*. 2003 January 15;41(2):255-262.

25. Deneer VHM, Borgh MBI, Kingma JH, Lie-A-Huen L, Brouwers JRBJ. Oral antiarrhythmic drugs in converting recent onset atrial fibrillation. *Pharm World Sci*. 2004 April;26(2):66-78.

26. Vinson DR, Lugovskyka N, Waron EM, et al. Ibutilide effectiveness and safety in the cardioversion of atrial fibrillation and flutter in the community emergency department. *Ann Emerg Med*. 2018 January;71(1):96-108.e2.

27. Patsilinakos S, Christou A, Kafkas N, Nikolaou N, Antonatos D, Katsanos S, et al. Effect of high doses of magnesium on converting ibutilide to a safe and more effective agent. *Am J Cardiol*. 2010 September 1;106(5):673-676.

28. Fragakis N, Bikias A, Delithanasis I, et al. Acute beta-adrenoceptor blockade improves efficacy of ibutilide in conversion of atrial fibrillation with a rapid ventricular rate. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2009 January;11(1):70-74.

29. Korantzopoulos P, Kolettis TM, Papathanasiou A, et al. Propafenone added to ibutilide increases conversion rates of persistent atrial fibrillation. *Heart Br Card Soc*. 2006 May;92(5):631-634.

30. Glatter K, Yang Y, Chatterjee K, et al. Chemical cardioversion of atrial fibrillation or flutter with ibutilide in patients receiving amiodarone therapy. *Circulation*. 2001 January 16;103(2):253-257.

31. McIntyre WF, Healey JS, Bhattacharjee AK, et al. Vernakalant for cardioversion of recent-onset atrial fibrillation: a systematic review and meta-analysis. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol*. 2019 August 1;21(8):1159-1566.

32. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008 June 19;358(25):2667-2677.

33. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002 December 5;347(23):1834-1840.

34. Dalen JE, Alpert JS. Silent atrial fibrillation and cryptogenic strokes. *Am J Med*. 2017 March;130(3):264-267.

35. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014 June 26;370(26):2467-2477.

36. Hagens VE, Crijns HJGM, Van Veldhuisen DJ, et al. Rate control versus rhythm control for patients with persistent atrial fibrillation with mild to moderate heart failure: results from the RAte Control versus Electrical cardioversion (RACE) study. *Am Heart J*. 2005 June;149(6):1106-1111.

37. Barra S, Baran J, Narayanan K, et al. Association of catheter ablation for atrial fibrillation with mortality and stroke: a systematic review and meta-analysis. *Int J Cardiol*. 2018 September 1;266:136-142.

38. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc*. 2013 March 18;2(2):e004549.

39. Barra S, Narayanan K, Boveda S, et al. Atrial fibrillation ablation and reduction of stroke events: understanding the paradoxical lack of evidence. *Stroke*. 2019 October;50(10):2970-2976.
40. Verma A, Ha ACT, Kirchhof P, et al. The optimal anti-coagulation for enhanced-risk patients post-catheter ablation for atrial fibrillation (OCEAN) trial. *Am Heart J.* 2018;197:124-132.

41. Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on atrial fibrillation. *Eur Heart J.* 2005 November;26(22):2422-2434.

42. Hess PL, Kim S, Piccini JP, et al. Use of evidence-based cardiac prevention therapy among outpatients with atrial fibrillation. *Am J Med.* 2013 July;126(7):625-632.e1.

43. Dimitri H, Ng M, Brooks AG, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. *Heart Rhythm.* 2012 March;9(3):321-327.

44. Naruse Y, Tada H, Satoh M, et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. *Heart Rhythm.* 2013 March;10(3):331-337.

45. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol.* 2014 December 2;64(21):2222-2231.

46. Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol.* 2015 May 26;65(20):2159-2169.

47. Bhunya R, Singh M, Sethi A, et al. Prevention of recurrent atrial fibrillation with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers: a systematic review and meta-analysis of randomized trials. *J Cardiovasc Pharmacol Ther.* 2011 June;16(2):178-184.

48. Pritchett ELC, Page RL, Carlson M, Undesser K, Fava G. Rythmol Atrial Fibrillation Trial (RAFT) investigators. Efficacy and safety of sustained-release propafenone (propafenone SR) for patients with atrial fibrillation. *Am J Cardiol.* 2003 October 15;92(8):941946.

49. Kirchhof P, Andresen D, Boseh R, et al. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. *Lancet Lond Engl.* 2012 July 21;380(9838):238-246.

50. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med.* 1989 10;321(6):406-412.

51. Tamargo J, Capucci A, Mabo P. Safety of flecainide. *Drug Saf.* 2012 April;35(4):273-289.

52. Comelli I, Pigna F, Cervellin G. 1:1 atrial flutter induced by flecainide, whilst the patient was at rest. *Am J Emerg Med.* 2018;36(11):2131.e3-2131.e5.

53. Boriani G, Blomström-Lundqvist C, Hohnloser SH, et al. Safety and efficacy of dronedarone from clinical trials to real-world evidence: implications for its use in atrial fibrillation. *Eur J Cardiovasc Pharmacol Ther.* 2019 10;36(11):2131.e3-2131.e5.

54. Freeman R, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Eur J Cardiovasc Pharmacol Ther.* 2019 10;36(11):2131.e3-2131.e5.
66. Khan MN, Jaïs P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med. 2008 October;23;359(17):1778-1785.

67. Hunter RJ, Berriman TJ, Diab I, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol. 2014 February;7(1):31-38.

68. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation. 2016 April 26;133(17):1637-1644.

69. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med. 2018 February 1;378(5):417-427.

70. Prabhu S, Taylor AJ, Costello BT, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. J Am Coll Cardiol. 2017 October 17;70(16):1949-1961.

71. Packer M, Kowey PR. Building castles in the sky: catheter ablation in patients with atrial fibrillation and chronic heart failure. Circulation. 2018 August 21;138(8):751-753.

72. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA. 2014 February 19;311(7):692-700.

73. HRS/EHRA/ECAS/APHRS/SOLAECE. Expert consensus statement on catheter and surgical ablation of atrial fibrillation (PubMed) 2017. https://pubmed.ncbi.nlm.nih.gov/29016840/?from_term=hrs+consensus+atrial+fibrillation&from_pos=1. Accessed May 17, 2020.

74. Vora A, Karnad D, Goyal V, et al. Control of rate versus rhythm in rheumatic atrial fibrillation: a randomized study. Indian Heart J. 2004 April;56(2):110-116.

75. John B, Stiles MK, Kuklik P, et al. Reverse remodeling of the atria after treatment of chronic stretch in humans: implications for the atrial fibrillation substrate. J Am Coll Cardiol. 2010 March 23;55(12):1217-1226.

76. Machino T, Tada H, Sekiguchi Y, et al. Hybrid therapy of radiofrequency catheter ablation and percutaneous transvenous mitral commissurotomy in patients with atrial fibrillation and mitral stenosis. J Cardiovasc Electrophysiol. 2010 March;21(3):284-289.

77. Jayaram AA, Shukla AN, Shah S, Nayak V, Prabhu S, Pai U. Sinus rhythm in rheumatic mitral stenosis after balloon mitral valvotomy: is it feasible? J Clin Diagn Res. 2017 February;11(2):OC01-05.

78. Lyon E, Tsyanov A, Abdrakhmanov A, et al. Nonfluoroscopic catheter ablation of paroxysmal atrial fibrillation. Pacing Clin Electrophysiol. 2018;41(6):611-619.

79. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAF study. JAMA. 2014 February 5;311(5):498-506.

80. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. 2012;9(4):632-696.e21.

81. Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. Circ Arrhythm Electrophysiol. 2009 December;2(6):626-633.

82. Ouyang F, Tilz R, Chun J, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation. 2010 December;7;122(23):2368-2377.

83. Marijon E, Fazaa S, Narayan K, et al. Real-time contact force sensing for pulmonary vein isolation in the setting of paroxysmal atrial fibrillation: a pilot study. J Cardiovasc Electrophysiol. 2018;4(1):99-108.

84. Taghji P, El Haddad M, Philips T, et al. Evaluation of a strategy aiming to enclose the pulmonary veins with contiguous and optimized radiofrequency lesions in paroxysmal atrial fibrillation: a pilot study. JACC Clin Electrophysiol. 2018;4(1):99-108.

85. Macle L, Ka鲱ry P, Weerasooriya R, et al. Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicentre, randomised superiority trial. Lancet Lond Engl. 2015 August 15;386(9994):672-679.

86. Lin W-S, Tai C-T, Hsieh M-H, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. Circulation. 2003 July 1;107(25):3176-3183.

87. Elayi CS, Di Biase L, Bai R, et al. Administration of isoproterenol and adenosine to guide supplemental ablation after pulmonary vein antrum isolation. J Cardiovasc Electrophysiol. 2013 November;24(11):1199-1206.

88. Corrado A, Bonso A, Madalosso M, et al. Impact of systematic isolation of superior vena cava in addition to pulmonary vein antrum isolation on the outcome of paroxysmal, persistent, and
permanent atrial fibrillation ablation: results from a randomized study. J Cardiovasc Electrophysiol. 2010 January;21(1):1-5.

89. Ruaengsri C, Schill MR, Khiabani AJ, Schuessler RB, Melby SJ, Damiano RJ. The Cox-maze IV procedure in its second decade: still the gold standard? Eur J Cardiothorac Surg Off J Eur Assoc Cardiothorac Surg. 2018 April 01;53(suppl_1):i19-25.

90. Nery PB, Thornhill R, Nair GM, Pena E, Redpath CJ. Scar-based catheter ablation for persistent atrial fibrillation. Curr Opin Cardiol. 2017;32(1):1-9.

91. Nishimura M, Lupercio-Lopez F, Hsu JC. Left atrial appendage electrical isolation as a target in atrial fibrillation. JACC Clin Electrophysiol. 2019;5(4):407-416.

92. Scott PA, Silberbauer J, Murgatroyd FD. The impact of adjunctive complex fractionated atrial electrogram ablation and linear lesions on outcomes in persistent atrial fibrillation: a meta-analysis. Eur J Cardiovasc Electrophysiol J Work Groups Card Card Card Electrophysiol Eur Soc Cardiol. 2016 March;18(3):359-367.

93. Verma A, Jiang C, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015 May 7;372(19):1812-1822.

94. Haisissaguere M, Hocini M, Sanders P, et al. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. J Cardiovasc Electrophysiol. 2005 November;16(11):1138-1147.

95. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel W-J, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol. 2012 August 14;60(7):628-636.

96. Buch E, Share M, Tung R, et al. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: a multicenter experience. Heart Rhythm. 2016 March;13(3):636-641.

97. Sacher F, Jais P, Stephenson K, et al. Phrenic nerve injury after catheter ablation of atrial fibrillation. Indian Pacing Electrophysiol J. 2007 January 1;7(1):1-6.

98. Parikh V, Varadaraj V, Hanita J, et al. Feasibility, safety, and efficacy of a novel preshaped nitinol esophageal deviator to successfully deflect the esophagus and ablate left atrium without esophageal temperature rise during atrial fibrillation ablation: the DEFLECT GUT study. Heart Rhythm. 2018;15(9):1321-1327.

99. John J, Garg L, Orosey M, Desai T, Haines DE, Wong WS. The effect of esophageal cooling on esophageal injury during radiofrequency catheter ablation of atrial fibrillation. J Interv Card Electrophysiol Int J Arrhythm Pacing. 2020 June;58(1):43-50.

100. Arbelo E, Brugada J, Blomström-Lundqvist C, et al. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. Eur Heart J. 2017 May 1;38(17):1303-1316.

101. Deshmukh A, Patel NJ, Pant S, et al. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. Circulation. 2013 November 5;128(19):21042112.

102. Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol. 2013 April 23;61(16):1713-1723.

103. Kuck K-H, Brugada J, Fünkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med. 2016 June 9;374(23):2235-2245.

104. Bhattacharya R, Reddy YY. Visually-guided laser balloon ablation of atrial fibrillation: a “real world” experience. Rev Esp Cardiol (Engl Ed). 2016 May;69(5):474-476.

105. Mahida S, Berte B, Yamashita S, et al. New ablation technologies and techniques. Arrhythmia Electrophysiol Rev. 2014 August;3(2):107-112.

106. Narayanan K, Chugh SS. Sympathectomy for patients with catecholaminergic polymorphic ventricular tachycardia. Circulation. 2015 June 1;131(25):2169-2171.

107. Stavrakis S, Nakagawa H, Po SS, Scherlag BJ, Lazzara R, Jackman WM. The role of the autonomic ganglia in atrial fibrillation. JACC Clin Electrophysiol. 2015;1(1-2):1-13.

108. Stavrakis S, Humphrey MB, Scherlag BJ, et al. Low-level transcutaneous electrical vagus nerve stimulation suppresses atrial fibrillation. J Am Coll Cardiol. 2015 March 10;65(9):867-875.

109. DeSimone CV, Kapa S, Asirvatham SJ. Electrophoration: the past and future of catheter ablation. Circ Arrhythm Electrophysiol. 2014 August;7(4):573-575.

110. Goldberg RL, Sciacca RR, Riga T, et al. Recurrent atrial fibrillation/flutter detection after ablation or cardioversion using the AliveCor KardiaMobile device: iHEART results. J Cardiovasc Electrophysiol. 2019 November;30(11):2220-2228.

111. Robertson JO, Lawrance CP, Maniar HS, Damiano RJ. Surgical techniques used for the treatment of atrial fibrillation. Circ J Off J Jpn Circ Soc. 2013;77(8):1941-1951.

112. Krul SPJ, Driessen AHG, van Boven WJ, et al. Thoracoscopic video-assisted pulmonary vein antrum isolation, ganglionated plexus ablation, and periprocedural confirmation of ablation lesions: first results of a hybrid surgical-electrophysiological approach for atrial fibrillation. Circ Arrhythm Electrophysiol. 2011 June;4(3):262-270.

113. Duyschaever M, Demolder A, Philips T, et al. Pulmonary vein isolation with vs. without continued antiarrhythmic drug treatment in subjects with recurrent atrial fibrillation (POWDER AF): results from a multicentre randomized trial. Eur Heart J. 2018 April 21;39(16):1429-1437.