Title: Anatomical targets and expected outcomes of catheter-based ablation of atrial fibrillation in 2020

Short title: Anatomical targets for AF ablation

Authors: Giulio la Rosa, MD[1], Jorge G. Quintanilla, MSEng, PhD[1,2,3], Ricardo Salgado, MD, PhD[2], Juan José González-Ferrer, MD, PhD[2,3,], Victoria Cañadas-Godoy, MD, PhD[2,3], Julián Pérez-Villacastín, MD, PhD[2,3,4], José Jalife, MD[1,3], Nicasio Pérez-Castellano, MD, PhD[2,3,4], David Filgueiras-Rama, MD, PhD[1,2,3].

[1] Centro Nacional de Investigaciones Cardiovasculares (CNIC), Myocardial Pathophysiology Area. Madrid, Spain.

[2] Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Cardiovascular Institute. Madrid, Spain.

[3] Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV). Madrid, Spain.

[4] Fundación Interhospitalaria para la Investigación Cardiovascular (FIC), Madrid, Spain.

Corresponding author: David Filgueiras-Rama.

Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC).

Myocardial Pathophysiology Area. Melchor Fernández Almagro, 3. 28029. Madrid, Spain.

Tel: +34 914531200 (Ext. 1510). Fax: +34 914531265.

Email: david.filgueiras@cnic.es

Disclosures: The authors have no conflicts to disclose.

Abstract

Anatomical-based approaches, targeting either pulmonary vein isolation (PVI) or additional extra PV regions, represent the most commonly used ablation treatments in symptomatic patients with atrial fibrillation (AF) recurrences despite antiarrhythmic drug therapy. PVI remains the main anatomical target during catheter-based AF ablation, with the aid of new technological advances as contact force monitoring to increase safety and effective radiofrequency lesions. Nowadays, cryoballoon ablation has also achieved the same level of scientific evidence in patients with paroxysmal AF undergoing PVI. In parallel, electrical isolation of extra PV targets has progressively increased, which is associated with a steady increase in complex cases undergoing ablation. Several atrial regions as the left atrial posterior wall, the vein of Marshall, the left atrial appendage or the coronary sinus have been described in different series as locations potentially involved in AF initiation and maintenance. Targeting these regions may be challenging using conventional point-by-point radiofrequency delivery, which has opened new opportunities for co-adjuvant alternatives as balloon ablation or selective ethanol injection. Although more extensive ablation may increase intraprocedural AF termination and freedom from arrhythmias during the follow-up, some of the targets to achieve such outcomes are not exempt of potential severe complications. Here, we review and discuss current anatomical approaches and the main ablation technologies to target atrial regions associated with AF initiation and maintenance.

Key words

Atrial fibrillation; ablation; radiofrequency energy; extra pulmonary vein ablation; pulmonary vein isolation; electroanatomical mapping.

INTRODUCTION

Catheter ablation of atrial fibrillation (AF) has evolved from a pioneer procedure in a specific subset of AF patients to the most effective minimally invasive treatment option for symptomatic patients.[1-4] Over the last 20 years, multiple energy sources and a wide variety of ablation strategies have been evaluated to achieve successful pulmonary vein isolation (PVI), while simplifying the procedure and increasing safety outcomes.[5-9] Current technology and ablation approaches achieve high success rates on acute PVI.[10] However, long-term effective PVI remains a technical and clinical challenge. In fact, electrical reconnection of PVs has been identified as one of the main factors associated with AF recurrences during follow-up.[11] Overall, over the last few years long-term success rates of ablation procedures have stood between 60% and 80% for paroxysmal AF and between 50% and 60% for persistent AF, depending on ablation strategies and rhythm monitoring protocols.[11,12] These data are probably related to the intrinsic limitations of anatomical approaches, which pay scant attention to the underlying mechanisms of wave propagation dynamics [13] and to the progression of electrical and structural atrial remodeling that makes other atrial regions sensitive to generate new, more stable high frequency AF sources.[14]

Here, we specifically review state-of-the-art and innovative technologies for anatomically based catheter ablation of AF. We also discuss the main controversies and near-future directions aimed at increasing safety and improving clinical outcomes of catheter ablation of AF.

ANATOMICALLY BASED APPROACHES AIMING AT PULMONARY VEIN ISOLATION

Point-by-point radiofrequency-based pulmonary vein isolation in the 21st century

The most consolidated procedure for AF ablation is point-by-point radiofrequency (RF) delivery via a single-tip catheter usually combined with a 3D mapping system (Figure 1).[4] In 1998, Haissaguerre *et al.* reported that atrial ectopic beats originating from the PVs triggered AF in the majority of patients.[9] Focal ablation of these triggers successfully eliminated AF episodes during the follow-up. Since then, segmental ostial isolation (i.e. selective ablation of PV potentials to electrically isolate muscle sleeve connections between the PV and the left atrium) and empirical ostial isolation of the PVs demonstrated to be more effective than focal ablation to prevent AF recurrences.[15] Wide antral PVI (i.e. circumferential isolation 10-15 mm away from the PV ostium) tried to overcome the risk of PV stenosis reported after ostial ablation during the first stages of technical development for PVI.[16] Patients undergoing antral PVI may show less AF recurrences after 1-year follow-up compared to ostial PV isolation.[17] Wider antral PVI provides additional benefit from the isolation of foci on the atrial aspect of the PV ostia.[18] However, this approach may also require ablation of PVs carina to effectively isolate the veins.[19]

The evolution of catheter technology has also been important in AF ablation, from initial non-irrigated-tip catheters to more effective irrigated-tip technologies.[20] Despite parallel improvements in 3D-electroanatomical mapping, the achievement of contiguous, transmural and permanent lesions using RF delivery remains challenging. Current open-irrigated tip catheters with contact force sensors provide real-time information on the tissue-catheter contact force. This provides significant improvement in lasting electrical isolation of the PVs.[21] Moreover, the combination of contact force with other parameters as power and time has also enabled incorporation of clinical indexes like "ablation index" and "lesion index", which have been proven to be useful in preventing PV reconnection in paroxysmal and persistent AF.[22,23] While insufficient contact force may result in ineffective lesions, excessive contact force may result in complications such as heart wall perforation or esophageal injury.[24,25] The use of contact force monitoring in combination with "ablation index" or "lesion index" has been associated with an improvement in procedural outcomes during follow-up.[21-24] In paroxysmal AF, further implementation of the CLOSE protocol aiming for interlesion distances ≤6 mm and target ablation indexes ≥550 and ≥400 for the anterior and posterior wall/roof, respectively, has shown a single-procedure freedom from atrial tachyarrhythmia of 94% at 12 months follow-up, compared to 80% in the more conventional contact-force-guided ablation group.[26] Current electroanatomical mapping systems have also enabled high-resolution mapping with multi-electrode catheters, which facilities treatment of some recurrences presenting as complex atrial flutter or tachycardia after PVI .[27,28]

A high power-short duration (HPSD) strategy has recently been proposed as a step forward towards improving lesion quality during RF ablation. This strategy has been shown to create wider but shallower lesions in *ex-vivo* and *in-vivo* experimental models[29,30], potentially avoiding damage to sensitive adjacent structures (e.g. esophagus, phrenic nerve) during ablation procedures. The feasibility and safety of the HPSD strategy during AF ablation has already been confirmed in the clinic.[31] It may also decrease procedure and fluoroscopy times, particularly when using novel catheter technologies, such as the QDOT-FAST catheter.[32]

Overall, complication rates using RF delivery to isolate the PVs are low, especially when experienced operators perform the procedure.[4] Table 1 summarizes selected studies on RF-based PVI, with or without additional ablation, mainly focused on current complexity of persistent AF series or significant technical advances.

Cryoballoon-based pulmonary vein isolation

Cryoballoon ablation has emerged as the most common alternative ablation approach for PVI and is now established at the same level of scientific evidence in patients with paroxysmal AF.[11,33] The multicenter FIRE AND ICE trial, which prospectively randomized paroxysmal AF patients to either RF- or cryoballoon-based PVI, demonstrated non-inferiority of cryoballoon ablation versus RF ablation in terms of efficacy and safety (Table 2).[6] The ablation technique requires a balloon catheter, which is cooled using nitrous oxide (Figure 1).[34]

Cryoballoon ablation represents a single-shot ablation modality with a rapid learning curve compared to conventional point-by-point RF-based PVI. It is also a safe tool due to its intrinsic lesions characteristics like well-demarcated margins with preservation of basic underlying tissue architecture and no correlation between lesion size and thrombus formation [35], which reduces thrombogenic risk.[36] Cryoballoon ablation is also associated with a low incidence of major complications, with significant reduction in pericardial effusion and tamponade.[37] Furthermore, the incidence of PV stenosis is a rare finding in patients undergoing cryoballoon ablation.[38]

Recent retrospective observational studies have suggested that cryoballoon ablation may achieve similar rates of freedom from AF than historically reported outcomes after RF-based ablation in persistent and longstanding persistent AF.[33,39,40] Omran *et al.* examined clinical outcomes after ablation with a second-generation cryoballoon in patients with persistent AF (917 patients from 11 studies) and reported an overall rate of AF freedom of 68.9% over a mean follow-up duration of 16.7±3.0 months.[41] However, whether cryoballoon ablation is as effective as RF ablation in patients with persistent forms of AF has not been addressed in randomized control trials. In this context, current evidence of extra PV regions in AF maintenance may limit cryoballoon options to target such complex substrates.

Other single-shot alternatives

Technological innovations and experimental studies have led to the development of new tools aiming to improve long-term outcomes of PVI, reduce procedural times and allow for a faster operator learning curve.

In this context, the endoscopic ablation system (EAS; CardioFocus) is a balloon-based ablation system that incorporates a titratable laser energy source and a miniature 2F endoscope that enables endoscopic view of the target PV (Figure 1). A number of studies in small series have demonstrated the feasibility of EAS-guided PVI with convincing acute PVI and a favourable safety profile (Table 2).[8] The recent introduction of the third-generation balloon system HeartlightTM X3 (CardioFocus), which provides real-time balloon sizing and an automated laser source rotation to prevent gaps between applications and reduce application times, warrants new studies to compare ablation outcomes with conventional RF or cryoballoon approaches.

The HELIOSTAR RF Balloon Ablation Catheter (Biosense Webster, Inc.) has recently been introduced as a new single-shot alternative. It conforms to any PV anatomy and has ten irrigated electrodes, which enables the operator to deliver different levels of energy during circumferential or segmental ablation. Its feasibility and safety profiles have been described in the RADIANCE study, in which PVI after a single delivery of RF energy was achieved in 79.6% of patients (39 paroxysmal AF). In the same series, freedom from documented atrial arrhythmia was 86.4% at 12 months of follow-up.[42] Two other balloon ablation systems are also under evaluation, namely the POLARx cryo-ablation catheter (Boston Scientific) and the Luminize RF hot balloon (Boston Scientific).

New energy sources: pulsed field ablation

In recent years, a novel technology called pulsed field ablation (PFA) has demonstrated potential to overcome intrinsic limitations of RF energy and cryoballoon ablation. PFA is a non-thermal ablation technology which uses high amplitude pulsed electrical fields to ablate tissue through the mechanism of irreversible electroporation.[43] Briefly, PFA applies a direct current that generates a high electrical field and produces pores in the phospholipid membranes of the cells, which leads to an irreversible breakdown of the membrane structure and ultimately cell death by apoptosis, with preservation of tissue architecture.[44-46] Overall, animal studies showed an apparent myocardial tissue selectivity.[47] Data also support safety of the system on surrounding intra- and extracardiac structures.[48,49] Unlike thermal-based ablation modalities, high-voltage electric fields can produce irreversible electroporation with negligible heating due to short pulse duration. Moreover, the effects on tissue mainly depend on electric field strength and proximity, but not on direct contact.[50]

Thermal ablation techniques require several seconds or minutes to achieve steady-state temperature gradients and effective lesion formation.[51] Conversely, the effects of PFA are almost instantaneous. A single PFA shot is accomplished within one heartbeat, and typically a lesion is created with 3-to-4 PFA shots.[43] This may potentially shorten ablation times with theoretically less complications risk than single shot approaches. A canine study comparing the effects of PFA with RF delivery directly into the PVs (as an attempt to show a worst-case scenario for PV stenosis) showed progressive stenosis on serial computed tomography scans in the veins subjected to RF-based ablation (45% decrease in luminal diameter compared to baseline), compared with no significant stenosis at 12 weeks in the veins subjected to PFA.[52]

In 2018, the first clinical experience showed that bipolar PFA using a monophasic waveform from the endocardium can achieve 100% acute PVI (Figure 1).[53] However, follow-up data at 3 months were disappointing and only 18% of patients remained with all PVs electrically isolated. As the system went through iterations and investigators gained experience, rates of mid-term PVI isolation rose to 43%, 56% and then 100%.[54] In the latter, patients with symptomatic paroxysmal AF were treated with biphasic pulses at 1800-2000V, with 8 or more pulse deliveries per catheter position, and multiple catheter positions for each vein. This 2-centres study reported a very low complication rate (one pericardial tamponade among 81 patients undergoing PVI) and 87% freedom from atrial arrhythmias at after 1-year follow up (Table 2).[54]

Actually, the optimal strategy using PFA has yet to be determined and relevant considerations about pulse duration, phasicity, pulse shape and frequency need to be established in larger series. Moreover, studies evaluating the durability of PV lesions have not exceeded 3 months of follow-up.[54,55]

Current role of Radiofrequency-based ablation for pulmonary vein isolation: Still the "gold standard"?

Novel technologies for PVI aim at improving the safety profile and clinical outcomes of AF ablation, reducing procedure time and fluoroscopy dosages and shortening the learning curve of the operators. However, from the foregoing discussion and current available data, we can state that in the context of paroxysmal AF patients undergoing PVI, highly experienced operators may get little or no benefit in the main aims claimed by new technologies. Ablation time and procedure time may be very similar between cryoballoon and point-by-point RF delivery when experienced operators perform the procedure,[5] with no significant differences in procedure-related complications and AF freedom after ablation if PVs remain isolated.[5,6] Moreover, catheter-based RF ablation represents a highly versatile tool that is also valid to diagnose and target other arrhythmias in the same procedure.[56] In persistent AF patients, the role of PVs decreases,[57] which also limits the role of those novel technologies specifically designed for PVI. However, the learning curve of single-shot devices is shorter and probably an efficient alternative for paroxysmal AF cases at centres with several operators and limited number of cases per operator and year.[58] This would not allow an operator achieve a sufficient level of proficiency in the use of point-by-point RF energy.[59]

The new perspectives described with PFA appear interesting, which may lead to an efficient alternative in the near future.[54] However, larger series are warranted to support the initial results of PFA in patients. It is worth mentioning, that new technologies should also represent a cost-effective alternative especially if clinical outcomes do not substantially differ compared with catheter-based RF ablation.

The use of high-density mapping is another option to achieve better outcomes using catheter-based RF ablation. Thus, high-density mapping using multipolar catheters with small electrode size (0.4 mm) has shown to be able to detect concealed low-voltage signals that persist after PVI. Moreover, ablation of these targets has been associated with a significant increase in freedom from AF compared to historical controls undergoing traditional PVI alone.[60]

Novel mapping technologies may also abbreviate mapping times and generate highly accurate computed tomography-like resolution images, which may represent useful clinical alternatives in the short-term. As an example, wide-band dielectric-based mapping represents a novel cardiac mapping technology compatible with conventional catheters.[61] More specifically, the KODEX-EPD (KODEX-EPDTM; EPD Solutions, Philips, Eindhoven, The Netherlands) can induce multiple anisotropic fields by 7 external reference patches on the body surface, in combination with any electrodes on diagnostic or ablation catheters inside the patient's body. The system receives and analyzes subtle electrical field transmission and reflection from all catheter electrodes as they are manipulated inside the cardiac chambers.[61] In experimental settings, this technology provides very high-resolution atrial images with ~1-mm error between known and measured distances, and location precision revealing submillimeter approximation between known and measured locations.[62] In the clinic, Maurer *et al.* have also reported the first clinical experience and feasibility to obtain high-resolution left atrial anatomy using this system.[61]

Another advancement in high resolution mapping has been reported using the recently developed AcQMap System (Acutus Medical, Inc, Carlsbad, CA), which uses a combination of ultrasound-based reconstruction of the endocardial surface with simultaneous non-contact acquisition of intracardiac unipolar voltage signals, processed to obtain the distribution of ionic charges and display electrical activation on the generated anatomical shell.[63] The system is able to quickly reconstruct atrial anatomy and create ultra-high-resolution 3D images in real time, with an average 4-fold improvement in spatial and temporal resolution compared with conventional voltage maps. The UNCOVER-AF trial has recently confirmed the feasibility and safety of this novel system during ablation of persistent AF.[64]

ANATOMICALLY BASED APPROACHES BEYOND THE PULMONARY VEINS

Anatomical approaches beyond segmental or ostial PV ablation have been first proposed by Pappone *et al.* with circumferential ablation of the PVs and linear lesions.[16,65] More recent mapping approaches have shown that non-PV atrial regions participate both in AF initiation and maintenance.[56,66] Outside the PVs, atrial ectopic beats triggering AF have been frequently documented in the inferior mitral annulus, the fossa ovalis/limbus region, the Eustachian ridge, the coronary sinus (CS) ostium, the crista terminalis region, and the superior vena cava (SVC).[56] The left atrial posterior wall, the vein of Marshall, the interatrial septum, and the left atrial appendage (LAA) have been also described in different series as locations for AF triggers.[4,67-69] These structures have myocardial cells that retain the ability to automatically depolarize or serve as a substrate for microreentry due to their rapid or heterogeneous conduction, thus acting as independent triggers for AF.[70] The prevalence of non-PV triggers is variable among different studies, although they can be documented in up to 60% of patients with AF.[71] Moreover, extra PV trigger locations may also participate in AF maintenance as areas for driver sources sustaining the overall arrhythmia outside the PVs.[72-74]

Linear atrial ablation

The most common linear atrial lesions performed during AF ablation are the roof line and mitral line. Despite encouraging data coming from the first studies in terms of long-term ablation success in patients with persistent AF,[75,76] one of the main limitations of this approach is probably the challenge of creating complete lines, with the risk of iatrogenic atrial tachycardia or, on the other hand, an increase in complication rates due to higher ablation power, and consequently higher risk of steam pop, perforation and tamponade.[77-79]

Per the 2017 AF Ablation Consensus Statement, the usefulness of empiric linear ablation in the absence of macroreentrant atrial flutter as an initial or repeat ablation strategy for non-paroxysmal AF is not well established (Class IIb).[11]

Isolation of the left atrial posterior wall

The left atrial posterior wall is embryologically related to the PVs and therefore may be a source for AF triggers initiating AF.[80] The posterior wall is also a common location for fibrotic regions identified by either voltage mapping or magnetic resonance imaging (MRI).[81] Interestingly, although posterior wall isolation may result in large areas of the left atrium being rendered electrically silent, the posterior wall contributes relatively little to left atrial function.[67] The latter might support that isolation of the posterior left atrial wall, if effective to improve AF outcomes, would not impact significantly in atrial function.

The standard lesion set for posterior wall isolation involves creation of a box with a superior line connecting the right and left superior PVs and an inferior line connecting the right and left inferior lines. The right and left borders of the box-like lesion set are created from the RF lesion sets encircling the PVs (Figure 2). Natale and colleagues were early proponents of posterior wall isolation in patients with persistent AF suggesting that significantly improves freedom from AF.[82] In particular, this group of investigators compared PVI alone in 20 consecutive patients undergoing persistent AF ablation versus PVI and empiric posterior wall isolation (plus or minus SVC isolation) in 32 consecutive patients. The results showed that freedom from recurrent arrhythmias during the follow-up off antiarrhythmic drugs (AADs) was superior in patients undergoing PVI plus posterior wall isolation compared with patients undergoing PVI alone (65 vs. 20% at 1 year).[83] However, results from other centres have shown that posterior wall isolation did not provide additional benefit to PVI or other extensive ablation strategies (Table 3).[84,85] Cutler and colleagues have indicated that an individualized strategy of posterior wall isolation, only when low-voltage (< 0.5 mV) areas are present within the target region, may result in improved AF freedom during the follow-up.[86] A recent meta-analysis of these studies has suggested an overall relative reduction in AF recurrence of 45% when PVI is complemented with posterior wall isolation.[87] It is worth mentioning that the lack of specificity of this strategy and the potential risk of damaging the oesophagus when delivering extensive lesion sets in the posterior wall (~2-4 mm thick), makes of this a risky complementary approach when attempting to improve AF ablation outcomes. Monitoring intraluminal oesophagus temperature represents a clinical option to prevent oesophagus injury.[88]

The AF Ablation Consensus Statement endorses that the posterior wall isolation may be considered during initial or repeat AF ablation for no paroxysmal AF.[11]

Isolation of the superior vena cava

The SVC is one of the most important non-PV foci for AF initiation. Approximately, 5-20% of patients may have an arrhythmogenic SVC related to AF episodes.[89] Histologically, myocardial atrial sleeves extend into the SVC for up to 2-5 cm and these sleeves harbour ectopic pacing cells that can spontaneously depolarize and trigger AF.[90,91]

Only a limited number of randomized trials have been conducted to assess the role of empiric SVC isolation (Figure 2) in addition to PVI and the results have been inconclusive (Table 3).[92] A recent metanalysis by Sharma *et al.* evaluated AF recurrence rates, procedure times, fluoroscopy times and adverse events in all available randomized controlled trials comparing PVI alone versus empiric SVC isolation in addition to PVI.[93] The authors analysed 3 randomized clinical trials with a total population of 526 patients. The analysis showed no differences in AF recurrences between a PVI strategy versus SVC isolation plus PVI. This was consistent for all types of AF. Similarly, the authors did not find statistically significant differences between the two groups in procedural and fluoroscopy time and in terms of periprocedural adverse events.[93] This, together with safety concerns like the potential risk of phrenic nerve and sinus node damage, which lie laterally and below the SVC, respectively, significantly reduces enthusiasm for the procedure.[94]

In brief, currently available data do not provide enough scientific evidence in support of systematic SVC isolation in AF ablation procedures. Accordingly, the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) consensus statement on catheter ablation of AF do not recommend SVC isolation as a routine approach.[11]

Isolation of the coronary sinus

The CS is widely recognized as a focal source of AF triggers.[56] Moreover, the CS may also host AF drivers sustaining fibrillation dynamics.[72] This role as a critical driver for AF maintenance may be explained by the fact that the CS is surrounded by a myocardial sleeve whose fibre direction abruptly changes with respect to the contiguous left atrial wall.[95] The latter may facilitate the generation and maintenance of rotational drivers within a heterogeneous substrate. Interestingly, electrical disconnection of the interface between the CS and the left atrium has been shown to terminate AF episodes that persist after PVI in 30-46% of cases.[96] Complete CS isolation can be achieved by targeting first the vessel from the endocardium, with the ablation catheter positioned at the level of the infero-lateral mitral valve annulus parallel to a decapolar catheter positioned inside the CS, and then epicardially, with the ablation catheter positioned inside the CS starting distally and continuously dragged back to the CS ostium.

A recent study by Mohanty and colleagues has shown that targeting the CS (Figure 2) and the LAA in patients with AF recurrences after PVI may result in high rates of arrhythmia free off AADs during the follow-up. The authors analysed 305 consecutive patients referred for AF ablation after ≥2 PVI procedures and atrial arrhythmia recurrences during the follow-up. At the index procedure, a total of 79 patients underwent empirical isolation of the LAA and CS, of whom 62 (78.5%) were arrhythmia-free during the follow-up. During repeat ablation, 38 patients received empirical LAA and CS isolation and 31 (82%) of them were in sinus rhythm at the end of 1-year follow-up (Table 3).[97] The study does not specifically address the independent role of the LAA and CS on decreasing AF recurrences. Of note, an important precaution should be taken when ablating proximally in the CS, given its vicinity to the AV node. The PR interval must be carefully monitored with immediate RF energy discontinuation in case of PR prolongation. The CS is also in close relationship with the oesophagus. Therefore, real-time oesophageal temperature monitoring should be performed to decrease the risk of cardio-oesophageal fistula.[98]

Altogether, the data indicate that in patients with AF recurrences and confirmation of PVI, empirical isolation of the CS may represent an ablation target in the absence of other documented triggers. However, this approach is not exempt of potential severe complications and the decision to empirically isolate the CS should be carefully considered by the physician in charge.

Ablation at the ligament of Marshall

The ligament of Marshall is an epicardial vestigial fold that marks the location of the embryological left SVC and contains the vein of Marshall, muscular fibres and the left dorsal pathway of vagal innervation to the cardiac autonomic ganglia.[99] It runs from the mid-distal CS through the posterolateral left atrium, up to the epicardial aspect of the ridge between the left superior PV and LAA. The ligament of Marshall has been implicated in the genesis of AF as a source of ectopic beats with a connection pathway with the neighbouring myocardium and left PVs, and via its autonomic innervation.[68]

It is possible to target endocardially the ligament of Marshall area (Figure 2) by delivering RF at the mid-lateral left atrium (between the CS and left inferior PV) and up to the ridge.[68] Alternatively, direct ethanol injection in the vein of Marshall (Figure 2) has shown to be an effective way to achieve rapid ablation of the entire region associated with the ligament of Marshall without significant complications.[100] Initial attempts were performed to modulate AF induction by parasympathetic responses elicited through high-frequency stimulation in the ligament of Marshall, which were successfully abolished by ethanol injection (Table 3).[101] The first randomized controlled clinical trial in patients with persistent AF undergoing their first catheter ablation has recently reported that the addition of vein of Marshall ethanol infusion to catheter ablation, compared with catheter ablation alone, increased the likelihood of remaining free of AF or atrial tachycardia at 6 and 12 months (49.2% vs 38% after a single procedure).[102] The MARS-AF trial (vein of Marshall ethAnol for Recurrent perSistent AF) is another randomized controlled study currently on-going in patients with persistent AF, including also patients with prior ablation.

Ablation of cardiac ganglia

The autonomic nervous system plays a major role in the initiation and maintenance of AF. In particular, cardiac ganglia form the intrinsic cardiac autonomic nervous system and innervate the myocardial PV sleeves with sympathetic and parasympathetic nervous fibres.[103] The cardiac ganglia tend to cluster around regions with frequent CFAEs and exhibit parasympathetic responses with high-frequency stimulation reflected as transient AV block or >50% increase in mean R-R interval during AF. Cardiac ganglia stimulation promotes AF by action potential duration shortening and increased sarcoplasmic reticulum calcium release in the PV myocardium, allowing early after-depolarizations, and affecting conduction time.[104]

One randomized study in patients with paroxysmal AF showed that the addition of cardiac ganglia ablation (Figure 2) to standard PVI resulted in higher success rates than PVI or ganglia ablation alone (74 vs. 56 vs. 48%, respectively) during a 2-year follow-up period.[105] Another study by Pokushalov and colleagues randomized 264 patients with non-paroxysmal AF to PVI plus cardiac ganglia ablation versus PVI plus empirical linear ablation. The results showed no statistically significant differences in single procedure freedom from recurrent AF off AADs at 1-year follow-up. However, extending the follow-up to 3 years showed higher long-term ablation success with cardiac ganglia ablation (Table 3).[106]

Other studies have questioned the benefit of targeting cardiac ganglia in patients undergoing AF ablation. Driessen and colleagues studied a series of patients undergoing thoracoscopic AF ablation (59% with persistent AF), in which patients were randomized to thoracoscopic AF ablation alone or additional epicardial ganglionated plexi ablation targeting the four major cardiac ganglia and the ligament of Marshall (Table 3).[107] After 1-year follow-up, there were no statistically significant differences in AF recurrence rates between groups. However, complications as major bleeding and sinus node dysfunction requiring pacemaker implantation were more frequent in the arm undergoing cardiac ganglia ablation.[107] Moreover, experimental data in sheep undergoing epicardial cardiac ganglia ablation have shown degeneration of remote atrial and ventricular epicardial nerves, which was more evident at 2-3 months after ablation.[108] The potential clinical consequences of this observation in a translational animal model have not been addressed. Therefore, clinical approaches aiming to target cardiac ganglia should be considered with caution. In fact, the HRS and the EHRA state that the usefulness of autonomic ganglia ablation as an ablation strategy for patients with AF is not well established.[11]

Electrical isolation of the left atrial appendage

The LAA has also been identified as a source of atrial arrhythmias as it can potentially trigger and sustain AF. Recently, the multicentre BELIEF trial showed that empirical electrical isolation of the LAA in addition to PVI could improve long-term freedom from atrial arrhythmias without increasing complications.[69] Similar results were reported by other investigators using cryoballoon ablation to isolate the LAA (Table 3).[109] Heeger *et al.* have reported that LAA isolation can also be achieved targeting wide areas with linear ablation in the left atrium or during extensive ablation of CFAEs at the anterior wall and the left atrial isthmus.[110] These initial series consistently reported that complex persistent AF cases undergoing PVI and additional LAA isolation show a slight incremental benefit in AF freedom during the follow-up. However, it is important to highlight that patients will be at much higher risk of thrombus formation inside the LAA and thromboembolic events despite achieving current criteria for oral anticoagulation. It is not well established whether LAA closure is a viable option to reduce the risk of thromboembolism after isolation of the LAA, without the requirement of permanently intensified oral anticoagulation.[110,111] Perhaps a minimally invasive surgical approach to perform LAA isolation and closure in the same procedure would be more efficient in well-trained centres.

Atrial scar isolation to eliminate the atrial substrate

Theoretically, an abnormal, heterogeneous atrial substrate facilitates atrial arrhythmias and AF.[112] However, the actual interplay between scar regions and the underlying mechanisms associated with AF initiation and maintenance are not fully understood in patient-specific substrates. Three-dimensional computational models integrating optical mapping-derived functional properties and high-resolution MRI-derived structural data have provided insights into structural fingerprints associated with AF drivers that consisted of intermediate wall thickness, intermediate fibrosis and twisted myofibre orientation.[113] Such encouraging data notwithstanding, atrial substrate modification (Figure 2) guided by electro-anatomical mapping or MRI-derived imaging still represents an anatomical approach to potentially increase AF freedom after ablation.[114] Voltage-based scar areas have been conservatively defined as those with a bipolar voltage of <0.5 mV using a conventional ablation catheter with 3.5-mm tip electrodes. However, point-by-point mapping such low voltage areas is highly dependent on the underlying rhythm (sinus rhythm vs. extrasystole or AF), the electrode contact with tissue, the atrial myocardium thickness, among other variables that will affect the target areas for substrate elimination.[115] Mapping with multielectrode catheters with close inter-electrode spacing will yield smaller surface areas of scar versus mapping with larger tip ablation catheters.[116] Mapping during AF, for example, typically yields lower voltages than during sinus rhythm. This indicates that voltage cut-off criteria will depend on the rhythm at the time of mapping.[117] Recent evidence indicates that the spatial distribution of mean voltage values during AF better correlates with late gadolinium enhancement-derived atrial fibrosis than voltage-derived values during sinus rhythm. A mean voltage threshold of 0.35 mV during AF yielded a sensitivity of 75% and specificity of 79% in detecting late gadolinium enhancement atrial fibrosis compared with 63% and 67%, respectively, using voltage-mapping criteria during sinus rhythm.[118] However, significant limitations prevent proper identification of atrial scar tissue *in vivo*. Thus, there is a lack of a *gold standard* reference to properly adjust scar criteria depending on the mapping electrodes and the underlying rhythm. While many investigators have agreed on cut-offs for low voltages and dense scar <0.5 mV and <0.2 mV, respectively [116,119], it is also possible to register electrograms with cut-off values <0.2 mV.[114] The latter might indicate few surviving atrial myocardial fibers, although the relevance of such heterogeneous tissue on AF initiation or maintenance has not been established.

Initial series in redo paroxysmal and non-paroxysmal AF cases with low voltage areas reported that box isolation of atrial scar areas achieved a 1-year freedom from AF/atrial tachycardia in 72.2% of patients after a single procedure.[120] Targeting low voltage areas in patients with persistent AF undergoing RF has been also associated with AF termination during the procedure in 73% of cases after 11±9 minutes of radiofrequency delivery. AF-termination sites colocalized within low voltages areas in 80% and at border zones in 20%.[119]

However, results on atrial substrate elimination are still limited to small and mostly single-centre experiences. In one multicentre trial (STABLE SR), the addition of scar ablation to circumferential PVI and cavotricuspid isthmus ablation showed similar results on freedom from documented atrial tachyarrhythmias at 18 months of follow-up than more extensive ablation with additional linear lesions and defragmentation.[121]

Recent studies using late gadolinium enhancement cardiac MRI have also shown potential to identify fibrous tissue in the atria. Moreover, MRI-derived extensive tissue fibrosis identification in the left atrium has been associated with poor outcomes after catheter ablation of AF.[122] Nevertheless, it must be noted that heart motion during imaging acquisition and partial volume effects using current standard imaging resolution may significantly affect atrial wall delineation and fibrous tissue identification, especially in the thin atrial wall.[118,123] Moreover, scar classification is highly dependent on centre experience, the specified image contrast criteria and continuity thresholds. To date, there is no consensus on uniform standard criteria for atrial scar identification using MRI. This hinders the inter-series reproducibility of MRI-derived atrial scar measurements. Nevertheless, imaging atrial fibrosis using cardiac MRI is rapidly evolving to a tool that can be potentially used to improve clinical outcomes after AF ablation. In the on-going DECAAF II trial (NCT02529319) patients are being randomized to undergo conventional PVI or PVI + fibrosis-guided ablation. This study will give further insights into the impact of targeting fibrotic areas on AF ablation outcomes.

In summary, the optimal catheter-based ablation strategy to eliminate scar areas potentially related to AF maintenance in persistent AF remains unknown and its usefulness is not well established.[10]

Isolation of large scar areas may lead to long RF delivery time and potentially increase complications. New studies are warranted to understand the role of the atrial substrate on wave propagation dynamics and determine which specific scar areas should be targeted, if necessary.

IMPLICATIONS FOR CLINICAL PRACTICE AND CONCLUSIONS

Effective PVI remains the cornerstone of catheter-based AF ablation. AF ablation has progressively evolved over the last 20 years with the introduction of new technologies, such as contact-force sensing, single-shot devices, multi-electrodes mapping systems and the study of new targets in addition to PVs, in parallel to a steady increase in complex cases undergoing ablation. Electrical isolation of some of these regions, mainly using RF delivery, has increased acute AF termination and AF freedom during the follow-up. However, many of these atrial regions are empirically isolated without robust underlying supportive mechanistic insights. Moreover, some regions may require ablating extensive areas because of lack of specificity on such targets. This is highly relevant since the larger the ablated area outside the PVs the higher the risk of severe complications or stiff left atrial syndrome, which further complicate clinical management.[124]

In the last few years, a debate has arisen about the use of AF catheter ablation strategies in the context of structural heart disease (e.g. hypertrophic cardiomyopathy, congenital heart disease). The idea is supported by operators with vast experience in other clinical scenarios and technological advances that enable physicians a more detailed characterization of the underlying substrate and a time-efficient approach.[125,126] However, available data indicate that ablation of anatomical targets (PVI, linear lesions and posterior wall ablation, among others) and CFAE regions still warrants more studies to reduce recurrences by optimizing patient selection, and address the prognostic impact during the follow-up.

In line with current guidelines and the technological advances discussed in this manuscript, we propose a differentiated flow-chart for ablation of anatomical targets in paroxysmal and non-paroxysmal AF (Figure 3). In particular, when ablating patients with paroxysmal AF, PVI represents the gold standard approach, either using point-by-point radiofrequency or cryoballoon.[6] The use of other techniques and energy sources for PVI still require further investigation and should be considered with caution (Figure 3A).[8,42,54] In case of AF recurrences after a 3-month blanking period, a redo procedure should evaluate PVs reconnections and lesion gaps and, in case of electrical reconnection of one or several PVs, repeat PVI and consider additional targets as in non-paroxysmal AF (Figure 3B). Further recurrences in paroxysmal AF may move the treatment into more complex scenarios like persistent AF.

In persistent AF, PVI still represents the first line of invasive treatment using catheter-based RF delivery or cryoballoon.[33] In case of AF recurrences, overt extraPV triggers during the first procedure (e.g. spontaneous or under isoproterenol challenge) or long-standing AF episodes, patients could benefit from targeting sites with the highest concentration of non-PV triggers, as left atrial posterior wall, coronary sinus and superior vena cava (Figure 3B).[127] In these cases, point-by-point RF delivery represents the strategy of choice,[56,85,92,97] although the use of cryoballoon ablation on the left atrial posterior wall has been also recently reported (Figure 3B).[128]

In case of symptomatic persistent AF recurrences, it would be reasonable to move forward to a third step and target other anatomical regions that have been potentially associated with AF maintenance as mitral isthmus, cardiac ganglia, ligament of Marshall, atrial scar regions and LAA (Figure 3B). In this context, point-by-point RF delivery still represents the most accredited strategy,[69,78,106,107,119,120] with the exception of the ligament of Marshall and the LAA, for which direct ethanol injection in the vein and cryoballoon ablation,[102,109] respectively, have shown to be an effective way to achieve rapid ablation of such regions.

Novel approaches should definitely refine our understanding of AF dynamics and identify patient-specific ablation strategies and anatomical targets aiming to minimize the extent of atrial ablation and increase freedom from atrial arrhythmias during follow-up.

FUNDING

This work was supported by the European Regional Development Fund, the Spanish Ministry of Science and Innovation (SAF2016-80324-R) and the Fundación Interhospitalaria para la Investigación Cardiovascular (FIC). The Centro Nacional de Investigaciones Cardiovasculares (CNIC) is supported by the Spanish Ministry of Science and Innovation and the Pro-CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-0505). GLR has received a fellowship grant from the joint program between the Heart Rhythm Association of the Spanish Society of Cardiology (ARC) and CNIC.

AUTHORS´ CONTRIBUTION: Concept/design: DFR and GLR. Drafting article: GLR, DFR, JGQ, JJ, NPC. Critical revision of article: All authors. Approval of article: All authors. Funding secured by DFR.

REFERENCES

1. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA.* 2019;321(13):1261-1274.
2. 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;133(17):1637-1644.
3. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med.* 2018;378(5):417-427.
4. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2020.
5. Perez-Castellano N, Fernandez-Cavazos R, Moreno J, et al. The COR trial: a randomized study with continuous rhythm monitoring to compare the efficacy of cryoenergy and radiofrequency for pulmonary vein isolation. *Heart Rhythm.* 2014;11(1):8-14.
6. Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med.* 2016;374(23):2235-2245.
7. Dewire J, Calkins H. Update on atrial fibrillation catheter ablation technologies and techniques. *Nat Rev Cardiol.* 2013;10(10):599-612.
8. Reissmann B, Budelmann T, Wissner E, et al. Five-year clinical outcomes of visually guided laser balloon pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation. *Clin Res Cardiol.* 2018;107(5):405-412.
9. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339(10):659-666.
10. Filgueiras-Rama D, Merino JL. The Future of Pulmonary Vein Isolation – Single-shot Devices, Remote Navigation or Improving Conventional Radiofrequency Delivery by Contact Monitoring and Lesion Characterisation? *Arrhythmia & Electrophysiology Review.* 2013;2(1):59–64.
11. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. *Europace.* 2018;20(1):157-208.

12. Ziegler PD, Koehler JL, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. *Heart Rhythm.* 2006;3(12):1445-1452.
13. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med.* 2015;372(19):1812-1822.
14. Lillo-Castellano JM, Gonzalez-Ferrer JJ, Marina-Breysse M, et al. Personalized monitoring of electrical remodelling during atrial fibrillation progression via remote transmissions from implantable devices. *Europace.* 2019.
15. Marchlinski FE, Callans D, Dixit S, et al. Efficacy and safety of targeted focal ablation versus PV isolation assisted by magnetic electroanatomic mapping. *J Cardiovasc Electrophysiol.* 2003;14(4):358-365.
16. Pappone C, Rosanio S, Oreto G, et al. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. *Circulation.* 2000;102(21):2619-2628.
17. Proietti R, Santangeli P, Di Biase L, et al. Comparative effectiveness of wide antral versus ostial pulmonary vein isolation: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol.* 2014;7(1):39-45.
18. Pappone C, Santinelli V. Segmental pulmonary vein isolation versus the circumferential approach: is the tide turning? *Heart Rhythm.* 2004;1(3):326-328.
19. Lin YJ, Tsao HM, Chang SL, et al. The distance between the vein and lesions predicts the requirement of carina ablation in circumferential pulmonary vein isolation. *Europace.* 2011;13(3):376-382.
20. Perez-Castellano N, Villacastin J, Salinas J, et al. Cooled ablation reduces pulmonary vein isolation time: results of a prospective randomised trial. *Heart.* 2009;95(3):203-209.
21. Kautzner J, Neuzil P, Lambert H, et al. EFFICAS II: optimization of catheter contact force improves outcome of pulmonary vein isolation for paroxysmal atrial fibrillation. *Europace.* 2015;17(8):1229-1235.
22. Hussein A, Das M, Riva S, et al. Use of Ablation Index-Guided Ablation Results in High Rates of Durable Pulmonary Vein Isolation and Freedom From Arrhythmia in Persistent Atrial Fibrillation Patients: The PRAISE Study Results. *Circ Arrhythm Electrophysiol.* 2018;11(9):e006576.
23. Leo M, Pedersen M, Rajappan K, et al. Power, Lesion Size Index and Oesophageal Temperature Alerts During Atrial Fibrillation Ablation: A Randomized Study. *Circ Arrhythm Electrophysiol.* 2020;13(10):e008316.
24. Kuck KH, Reddy VY, Schmidt B, et al. A novel radiofrequency ablation catheter using contact force sensing: Toccata study. *Heart rhythm.* 2012;9(1):18-23.
25. Thiagalingam A, D'Avila A, Foley L, et al. Importance of catheter contact force during irrigated radiofrequency ablation: evaluation in a porcine ex vivo model using a force-sensing catheter. *J Cardiovasc Electrophysiol.* 2010;21(7):806-811.
26. Phlips T, Taghji P, El Haddad M, et al. Improving procedural and one-year outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol. *Europace.* 2018;20(FI_3):f419-f427.
27. Ptaszek LM, Chalhoub F, Perna F, et al. Rapid acquisition of high-resolution electroanatomical maps using a novel multielectrode mapping system. *J Interv Card Electrophysiol.* 2013;36(3):233-242.
28. Rottner L, Metzner A, Ouyang F, et al. Direct Comparison of Point-by-Point and Rapid Ultra-High-Resolution Electroanatomical Mapping in Patients Scheduled for Ablation of Atrial Fibrillation. *J Cardiovasc Electrophysiol.* 2017;28(3):289-297.
29. Bhaskaran A, Chik W, Pouliopoulos J, et al. Five seconds of 50-60 W radio frequency atrial ablations were transmural and safe: an in vitro mechanistic assessment and force-controlled in vivo validation. *Europace.* 2017;19(5):874-880.
30. Leshem E, Zilberman I, Tschabrunn CM, et al. High-Power and Short-Duration Ablation for Pulmonary Vein Isolation: Biophysical Characterization. *JACC Clin Electrophysiol.* 2018;4(4):467-479.
31. Winkle RA, Moskovitz R, Hardwin Mead R, et al. Atrial fibrillation ablation using very short duration 50 W ablations and contact force sensing catheters. *J Interv Card Electrophysiol.* 2018;52(1):1-8.
32. Reddy VY, Grimaldi M, De Potter T, et al. Pulmonary Vein Isolation With Very High Power, Short Duration, Temperature-Controlled Lesions: The QDOT-FAST Trial. *JACC Clin Electrophysiol.* 2019;5(7):778-786.

33. Aryana A, Singh SM, Kowalski M, et al. Acute and Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation Using the Second-Generation Cryoballoon versus Open-Irrigated Radiofrequency: A Multicenter Experience. *J Cardiovasc Electrophysiol.* 2015;26(8):832-839.
34. Ozcan C, Ruskin J, Mansour M. Cryoballoon catheter ablation in atrial fibrillation. *Cardiol Res Pract.* 2011;2011:256347.
35. Lustgarten DL, Keane D, Ruskin J. Cryothermal ablation: mechanism of tissue injury and current experience in the treatment of tachyarrhythmias. *Prog Cardiovasc Dis.* 1999;41(6):481-498.
36. Khairy P, Chauvet P, Lehmann J, et al. Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. *Circulation.* 2003;107(15):2045-2050.
37. Rottner L, Fink T, Heeger CH, et al. Is less more? Impact of different ablation protocols on periprocedural complications in second-generation cryoballoon based pulmonary vein isolation. *Europace.* 2018;20(9):1459-1467.
38. Thomas D, Katus HA, Voss F. Asymptomatic pulmonary vein stenosis after cryoballoon catheter ablation of paroxysmal atrial fibrillation. *J Electrocardiol.* 2011;44(4):473-476.
39. Koektuerk B, Yorgun H, Hengeoez O, et al. Cryoballoon Ablation for Pulmonary Vein Isolation in Patients With Persistent Atrial Fibrillation: One-Year Outcome Using Second Generation Cryoballoon. *Circ Arrhythm Electrophysiol.* 2015;8(5):1073-1079.
40. Akkaya E, Berkowitsch A, Zaltsberg S, et al. Second-generation cryoballoon ablation for treatment of persistent atrial fibrillation: Three-year outcome and predictors of recurrence after a single procedure. *J Cardiovasc Electrophysiol.* 2018;29(1):38-45.
41. Omran H, Gutleben KJ, Molatta S, et al. Second generation cryoballoon ablation for persistent atrial fibrillation: an updated meta-analysis. *Clin Res Cardiol.* 2018;107(2):182-192.
42. Dhillon GS, Honarbakhsh S, Di Monaco A, et al. Use of a multi-electrode radiofrequency balloon catheter to achieve pulmonary vein isolation in patients with paroxysmal atrial fibrillation: 12-Month outcomes of the RADIANCE study. *J Cardiovasc Electrophysiol.* 2020;31(6):1259-1269.
43. Bradley CJ, Haines DE. Pulsed Field Ablation for Pulmonary Vein Isolation in the Treatment of Atrial Fibrillation. *J Cardiovasc Electrophysiol.* 2020.
44. Lavee J, Onik G, Mikus P, Rubinsky B. A novel nonthermal energy source for surgical epicardial atrial ablation: irreversible electroporation. *Heart Surg Forum.* 2007;10(2):E162-167.
45. Golberg A, Yarmush ML. Nonthermal irreversible electroporation: fundamentals, applications, and challenges. *IEEE Trans Biomed Eng.* 2013;60(3):707-714.
46. Matsuki N, Ishikawa T, Imai Y, Yamaguchi T. Low voltage pulses can induce apoptosis. *Cancer letters.* 2008;269(1):93-100.
47. Al-Khadra A, Nikolski V, Efimov IR. The role of electroporation in defibrillation. *Circ Res.* 2000;87(9):797-804.
48. Wittkampf FHM, van Es R, Neven K. Electroporation and its Relevance for Cardiac Catheter Ablation. *JACC Clin Electrophysiol.* 2018;4(8):977-986.
49. Neven K, van Es R, van Driel V, et al. Acute and Long-Term Effects of Full-Power Electroporation Ablation Directly on the Porcine Esophagus. *Circ Arrhythm Electrophysiol.* 2017;10(5).
50. Livia C, Sugrue A, Witt T, et al. Elimination of Purkinje Fibers by Electroporation Reduces Ventricular Fibrillation Vulnerability. *J Am Heart Assoc.* 2018;7(15):e009070.
51. Haines DE. Determinants of Lesion Size During Radiofrequency Catheter Ablation: The Role of Electrode-Tissue Contact Pressure and Duration of Energy Delivery. *J Cardiovasc Electrophysiol.* 1991;2(6):509-515.
52. Howard BT, Haines D, Verma A, et al. Pulsed Field Ablation Reduces Pulmonary Vein Stenosis Risk: An Advanced Model for Assessment of PV Stenosis. American Heart Association; 5 Nov 2018, 2018; Chicago.
53. Reddy VY, Koruth J, Jais P, et al. Ablation of Atrial Fibrillation With Pulsed Electric Fields: An Ultra-Rapid, Tissue-Selective Modality for Cardiac Ablation. *JACC Clin Electrophysiol.* 2018;4(8):987-995.
54. Reddy VY, Neuzil P, Koruth JS, et al. Pulsed Field Ablation for Pulmonary Vein Isolation in Atrial Fibrillation. *J Am Coll Cardiol.* 2019;74(3):315-326.
55. Stewart MT, Haines DE, Verma A, et al. Intracardiac pulsed field ablation: Proof of feasibility in a chronic porcine model. *Heart Rhythm.* 2019;16(5):754-764.

56. Dixit S, Marchlinski FE, Lin D, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. *Circ Arrhythm Electrophysiol.* 2012;5(2):287-294.
57. Sanders P, Berenfeld O, Hocini M, et al. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. *Circulation.* 2005;112(6):789-797.
58. Sairaku A, Yoshida Y, Nakano Y, et al. Who is the operator, that is the question: a multicentre study of catheter ablation of atrial fibrillation. *Europace.* 2016;18(9):1352-1356.
59. Eckardt L, Frommeyer G, Sommer P, et al. Updated Survey on Interventional Electrophysiology: 5-Year Follow-Up of Infrastructure, Procedures, and Training Positions in Germany. *JACC Clin Electrophysiol.* 2018;4(6):820-827.
60. Segerson NM, Lynch B, Mozes J, et al. High-density mapping and ablation of concealed low-voltage activity within pulmonary vein antra results in improved freedom from atrial fibrillation compared to pulmonary vein isolation alone. *Heart Rhythm.* 2018;15(8):1158-1164.
61. Maurer T, Mathew S, Schluter M, et al. High-Resolution Imaging of LA Anatomy Using a Novel Wide-Band Dielectric Mapping System: First Clinical Experience. *JACC Clin Electrophysiol.* 2019;5(11):1344-1354.
62. Romanov A, Dichterman E, Schwartz Y, et al. High-resolution, real-time, and nonfluoroscopic 3-dimensional cardiac imaging and catheter navigation in humans using a novel dielectric-based system. *Heart Rhythm.* 2019;16(12):1883-1889.
63. Grace A, Willems S, Meyer C, et al. High-resolution noncontact charge-density mapping of endocardial activation. *JCI Insight.* 2019;4(6).
64. Willems S, Verma A, Betts TR, et al. Targeting Nonpulmonary Vein Sources in Persistent Atrial Fibrillation Identified by Noncontact Charge Density Mapping: UNCOVER AF Trial. *Circ Arrhythm Electrophysiol.* 2019;12(7):e007233.
65. Pappone C, Oreto G, Lamberti F, et al. Catheter ablation of paroxysmal atrial fibrillation using a 3D mapping system. *Circulation.* 1999;100(11):1203-1208.
66. Quintanilla JG, Perez-Villacastin J, Perez-Castellano N, et al. Mechanistic Approaches to Detect, Target, and Ablate the Drivers of Atrial Fibrillation. *Circ Arrhythm Electrophysiol.* 2016;9(1):e002481.
67. Verma A, Marrouche NF, Yamada H, et al. Usefulness of intracardiac Doppler assessment of left atrial function immediately post-pulmonary vein antrum isolation to predict short-term recurrence of atrial fibrillation. *Am J Cardiol.* 2004;94(7):951-954.
68. Kurotobi T, Ito H, Inoue K, et al. Marshall vein as arrhythmogenic source in patients with atrial fibrillation: correlation between its anatomy and electrophysiological findings. *J Cardiovasc Electrophysiol.* 2006;17(10):1062-1067.
69. Di Biase L, Burkhardt JD, Mohanty P, et al. Left Atrial Appendage Isolation in Patients With Longstanding Persistent AF Undergoing Catheter Ablation: BELIEF Trial. *J Am Coll Cardiol.* 2016;68(18):1929-1940.
70. DeSimone CV, Noheria A, Lachman N, et al. Myocardium of the superior vena cava, coronary sinus, vein of Marshall, and the pulmonary vein ostia: gross anatomic studies in 620 hearts. *J Cardiovasc Electrophysiol.* 2012;23(12):1304-1309.
71. Santangeli P, Marchlinski FE. Techniques for the provocation, localization, and ablation of non-pulmonary vein triggers for atrial fibrillation. *Heart Rhythm.* 2017;14(7):1087-1096.
72. Quintanilla JG, Alfonso-Almazan JM, Perez-Castellano N, et al. Instantaneous Amplitude and Frequency Modulations Detect the Footprint of Rotational Activity and Reveal Stable Driver Regions as Targets for Persistent Atrial Fibrillation Ablation. *Circ Res.* 2019;125(6):609-627.
73. Miller JM, Kalra V, Das MK, et al. Clinical Benefit of Ablating Localized Sources for Human Atrial Fibrillation: The Indiana University FIRM Registry. *J Am Coll Cardiol.* 2017;69(10):1247-1256.
74. Narayan SM, Baykaner T, Clopton P, et al. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). *J Am Coll Cardiol.* 2014;63(17):1761-1768.
75. Willems S, Klemm H, Rostock T, et al. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. *Eur Heart J.* 2006;27(23):2871-2878.

76. Pappone C, Manguso F, Vicedomini G, et al. Prevention of iatrogenic atrial tachycardia after ablation of atrial fibrillation: a prospective randomized study comparing circumferential pulmonary vein ablation with a modified approach. *Circulation.* 2004;110(19):3036-3042.
77. Knecht S, Hocini M, Wright M, et al. Left atrial linear lesions are required for successful treatment of persistent atrial fibrillation. *Eur Heart J.* 2008;29(19):2359-2366.
78. Matsuo S, Yamane T, Date T, et al. Completion of mitral isthmus ablation using a steerable sheath: prospective randomized comparison with a nonsteerable sheath. *J Cardiovasc Electrophysiol.* 2011;22(12):1331-1338.
79. Wolf M, El Haddad M, Fedida J, et al. Evaluation of left atrial linear ablation using contiguous and optimized radiofrequency lesions: the ALINE study. *Europace.* 2018;20(FI_3):f401-f409.
80. Douglas YL, Jongbloed MR, Gittenberger-de Groot AC, et al. Histology of vascular myocardial wall of left atrial body after pulmonary venous incorporation. *Am J Cardiol.* 2006;97(5):662-670.
81. Oakes RS, Badger TJ, Kholmovski EG, et al. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. *Circulation.* 2009;119(13):1758-1767.
82. Di Biase L, Santangeli P, Natale A. How to ablate long-standing persistent atrial fibrillation? *Current opinion in cardiology.* 2013;28(1):26-35.
83. Bai R, Di Biase L, Mohanty P, et al. Proven isolation of the pulmonary vein antrum with or without left atrial posterior wall isolation in patients with persistent atrial fibrillation. *Heart Rhythm.* 2016;13(1):132-140.
84. Tamborero D, Mont L, Berruezo A, et al. Left atrial posterior wall isolation does not improve the outcome of circumferential pulmonary vein ablation for atrial fibrillation: a prospective randomized study. *Circ Arrhythm Electrophysiol.* 2009;2(1):35-40.
85. Lim TW, Koay CH, See VA, et al. Single-ring posterior left atrial (box) isolation results in a different mode of recurrence compared with wide antral pulmonary vein isolation on long-term follow-up: longer atrial fibrillation-free survival time but similar survival time free of any atrial arrhythmia. *Circ Arrhythm Electrophysiol.* 2012;5(5):968-977.
86. Cutler MJ, Johnson J, Abozguia K, et al. Impact of Voltage Mapping to Guide Whether to Perform Ablation of the Posterior Wall in Patients With Persistent Atrial Fibrillation. *J Cardiovasc Electrophysiol.* 2016;27(1):13-21.
87. He X, Zhou Y, Chen Y, Wu L, Huang Y, He J. Left atrial posterior wall isolation reduces the recurrence of atrial fibrillation: a meta-analysis. *J Interv Card Electrophysiol.* 2016;46(3):267-274.
88. Koranne K, Basu-Ray I, Parikh V, et al. Esophageal Temperature Monitoring During Radiofrequency Ablation of Atrial Fibrillation: A Meta-Analysis. *Journal of atrial fibrillation.* 2016;9(4):1452.
89. Higuchi K, Yamauchi Y, Hirao K, et al. Superior vena cava as initiator of atrial fibrillation: factors related to its arrhythmogenicity. *Heart Rhythm.* 2010;7(9):1186-1191.
90. Hashizume H, Ushiki T, Abe K. A histological study of the cardiac muscle of the human superior and inferior venae cavae. *Arch Histol Cytol.* 1995;58(4):457-464.
91. Chen SA, Chiang CE, Yang CJ, et al. Sustained atrial tachycardia in adult patients. Electrophysiological characteristics, pharmacological response, possible mechanisms, and effects of radiofrequency ablation. *Circulation.* 1994;90(3):1262-1278.
92. 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;21(1):1-5.
93. Sharma SP, Sangha RS, Dahal K, Krishnamoorthy P. The role of empiric superior vena cava isolation in atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. *J Interv Card Electrophysiol.* 2017;48(1):61-67.
94. Ejima K, Kato K, Iwanami Y, et al. Impact of an Empiric Isolation of the Superior Vena Cava in Addition to Circumferential Pulmonary Vein Isolation on the Outcome of Paroxysmal Atrial Fibrillation Ablation. *Am J Cardiol.* 2015;116(11):1711-1716.

95. Sanchez-Quintana D, Lopez-Minguez JR, Pizarro G, Murillo M, Cabrera JA. Triggers and anatomical substrates in the genesis and perpetuation of atrial fibrillation. *Current cardiology reviews.* 2012;8(4):310-326.
96. Haissaguerre M, Hocini M, Takahashi Y, et al. Impact of catheter ablation of the coronary sinus on paroxysmal or persistent atrial fibrillation. *J Cardiovasc Electrophysiol.* 2007;18(4):378-386.
97. Mohanty S, Trivedi C, Gianni C, et al. Procedural findings and ablation outcome in patients with atrial fibrillation referred after two or more failed catheter ablations. *J Cardiovasc Electrophysiol.* 2017;28(12):1379-1386.
98. Gunes MF, Gokoglan Y, L DIB, et al. Ablating the Posterior Heart: Cardioesophageal Fistula Complicating Radiofrequency Ablation in the Coronary Sinus. *J Cardiovasc Electrophysiol.* 2015;26(12):1376-1378.
99. Kim DT, Lai AC, Hwang C, et al. The ligament of Marshall: a structural analysis in human hearts with implications for atrial arrhythmias. *J Am Coll Cardiol.* 2000;36(4):1324-1327.
100. Dave AS, Baez-Escudero JL, Sasaridis C, Hong TE, Rami T, Valderrabano M. Role of the vein of Marshall in atrial fibrillation recurrences after catheter ablation: therapeutic effect of ethanol infusion. *J Cardiovasc Electrophysiol.* 2012;23(6):583-591.
101. Baez-Escudero JL, Keida T, Dave AS, Okishige K, Valderrabano M. Ethanol infusion in the vein of Marshall leads to parasympathetic denervation of the human left atrium: implications for atrial fibrillation. *J Am Coll Cardiol.* 2014;63(18):1892-1901.
102. Valderrabano M, Peterson LE, Swarup V, et al. Effect of Catheter Ablation With Vein of Marshall Ethanol Infusion vs Catheter Ablation Alone on Persistent Atrial Fibrillation: The VENUS Randomized Clinical Trial. *JAMA.* 2020;324(16):1620-1628.
103. Pauza DH, Skripka V, Pauziene N, Stropus R. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. *Anat Rec.* 2000;259(4):353-382.
104. Krul SP, Meijborg VM, Berger WR, et al. Disparate response of high-frequency ganglionic plexus stimulation on sinus node function and atrial propagation in patients with atrial fibrillation. *Heart Rhythm.* 2014;11(10):1743-1751.
105. Katritsis DG, Pokushalov E, Romanov A, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. *J Am Coll Cardiol.* 2013;62(24):2318-2325.
106. Pokushalov E, Romanov A, Katritsis DG, et al. Ganglionated plexus ablation vs linear ablation in patients undergoing pulmonary vein isolation for persistent/long-standing persistent atrial fibrillation: a randomized comparison. *Heart Rhythm.* 2013;10(9):1280-1286.
107. Driessen AHG, Berger WR, Krul SPJ, et al. Ganglion Plexus Ablation in Advanced Atrial Fibrillation: The AFACT Study. *J Am Coll Cardiol.* 2016;68(11):1155-1165.
108. Puodziukynas A, Kazakevicius T, Vaitkevicius R, et al. Radiofrequency catheter ablation of pulmonary vein roots results in axonal degeneration of distal epicardial nerves. *Auton Neurosci.* 2012;167(1-2):61-65.
109. Yorgun H, Canpolat U, Kocyigit D, Coteli C, Evranos B, Aytemir K. Left atrial appendage isolation in addition to pulmonary vein isolation in persistent atrial fibrillation: one-year clinical outcome after cryoballoon-based ablation. *Europace.* 2017;19(5):758-768.
110. Heeger CH, Rillig A, Geisler D, et al. Left Atrial Appendage Isolation in Patients Not Responding to Pulmonary Vein Isolation. *Circulation.* 2019;139(5):712-715.
111. Rillig A, Tilz RR, Lin T, et al. Unexpectedly High Incidence of Stroke and Left Atrial Appendage Thrombus Formation After Electrical Isolation of the Left Atrial Appendage for the Treatment of Atrial Tachyarrhythmias. *Circ Arrhythm Electrophysiol.* 2016;9(5):e003461.
112. Jalife J. Deja vu in the theories of atrial fibrillation dynamics. *Cardiovasc Res.* 2011;89(4):766-775.
113. Zhao J, Hansen BJ, Wang Y, et al. Three-dimensional Integrated Functional, Structural, and Computational Mapping to Define the Structural "Fingerprints" of Heart-Specific Atrial Fibrillation Drivers in Human Heart Ex Vivo. *J Am Heart Assoc.* 2017;6(8).
114. Kottkamp H, Bender R, Berg J. Catheter ablation of atrial fibrillation: how to modify the substrate? *J Am Coll Cardiol.* 2015;65(2):196-206.
115. Josephson ME, Anter E. Substrate Mapping for Ventricular Tachycardia Assumptions and Misconceptions. *JACC: Clinical Electrophysiology.* 2015;1(5):341-352.

116. Anter E, Tschabrunn CM, Josephson ME. High-resolution mapping of scar-related atrial arrhythmias using smaller electrodes with closer interelectrode spacing. *Circ Arrhythm Electrophysiol.* 2015;8(3):537-545.
117. Yagishita A, S DEO, Cakulev I, et al. Correlation of Left Atrial Voltage Distribution Between Sinus Rhythm and Atrial Fibrillation: Identifying Structural Remodeling by 3-D Electroanatomic Mapping Irrespective of the Rhythm. *J Cardiovasc Electrophysiol.* 2016;27(8):905-912.
118. Qureshi NA, Kim SJ, Cantwell CD, et al. Voltage during atrial fibrillation is superior to voltage during sinus rhythm in localizing areas of delayed enhancement on magnetic resonance imaging: An assessment of the posterior left atrium in patients with persistent atrial fibrillation. *Heart Rhythm.* 2019;16(9):1357-1367.
119. Jadidi AS, Lehrmann H, Keyl C, et al. Ablation of Persistent Atrial Fibrillation Targeting Low-Voltage Areas With Selective Activation Characteristics. *Circ Arrhythm Electrophysiol.* 2016;9(3).
120. Kottkamp H, Berg J, Bender R, Rieger A, Schreiber D. Box Isolation of Fibrotic Areas (BIFA): A Patient-Tailored Substrate Modification Approach for Ablation of Atrial Fibrillation. *J Cardiovasc Electrophysiol.* 2016;27(1):22-30.
121. Yang B, Jiang C, Lin Y, et al. STABLE-SR (Electrophysiological Substrate Ablation in the Left Atrium During Sinus Rhythm) for the Treatment of Nonparoxysmal Atrial Fibrillation: A Prospective, Multicenter Randomized Clinical Trial. *Circ Arrhythm Electrophysiol.* 2017;10(11).
122. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA.* 2014;311(5):498-506.
123. Siebermair J, Kholmovski EG, Marrouche N. Assessment of Left Atrial Fibrosis by Late Gadolinium Enhancement Magnetic Resonance Imaging: Methodology and Clinical Implications. *JACC Clin Electrophysiol.* 2017;3(8):791-802.
124. Gibson DN, Di Biase L, Mohanty P, et al. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors. *Heart Rhythm.* 2011;8(9):1364-1371.
125. Providencia R, Elliott P, Patel K, et al. Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Heart.* 2016;102(19):1533-1543.
126. Guarguagli S, Kempny A, Cazzoli I, et al. Efficacy of catheter ablation for atrial fibrillation in patients with congenital heart disease. *Europace.* 2019;21(9):1334-1344.
127. Santangeli P, Zado ES, Hutchinson MD, et al. Prevalence and distribution of focal triggers in persistent and long-standing persistent atrial fibrillation. *Heart Rhythm.* 2016;13(2):374-382.
128. Iacopino S, Paparella G, Capulzini L, et al. Posterior box isolation as an adjunctive ablation strategy during repeat ablation with the second-generation cryoballoon for recurrence of persistent atrial fibrillation: 1-year follow-up. *J Interv Card Electrophysiol.* 2019;56(1):1-7.

Figure legends

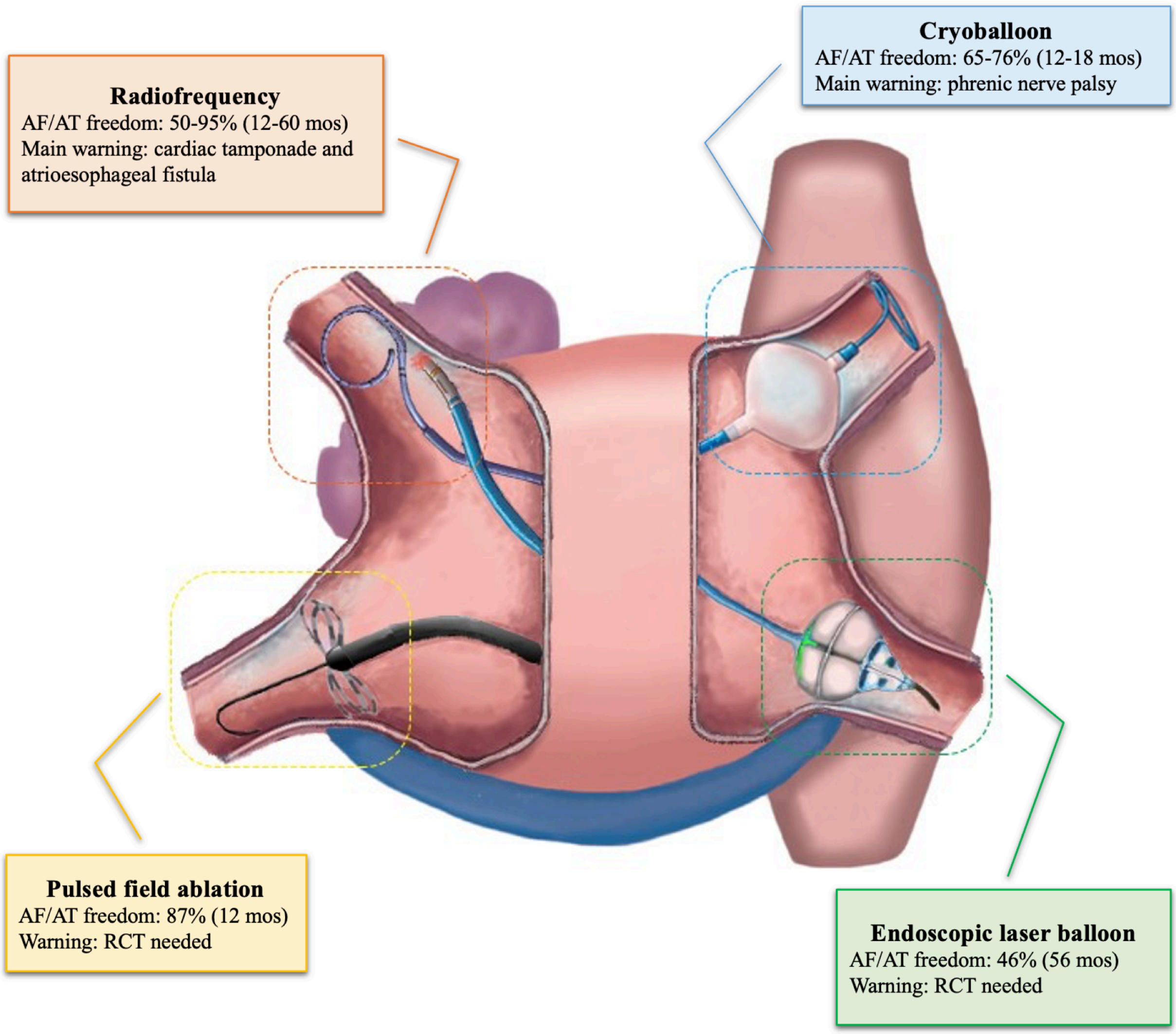

Figure 1. Schematic representation of current energy sources and ablation outcomes after pulmonary vein isolation. AF, atrial fibrillation; AT, AT, atrial tachycardia; mos, months; RCT, randomized controlled trial.

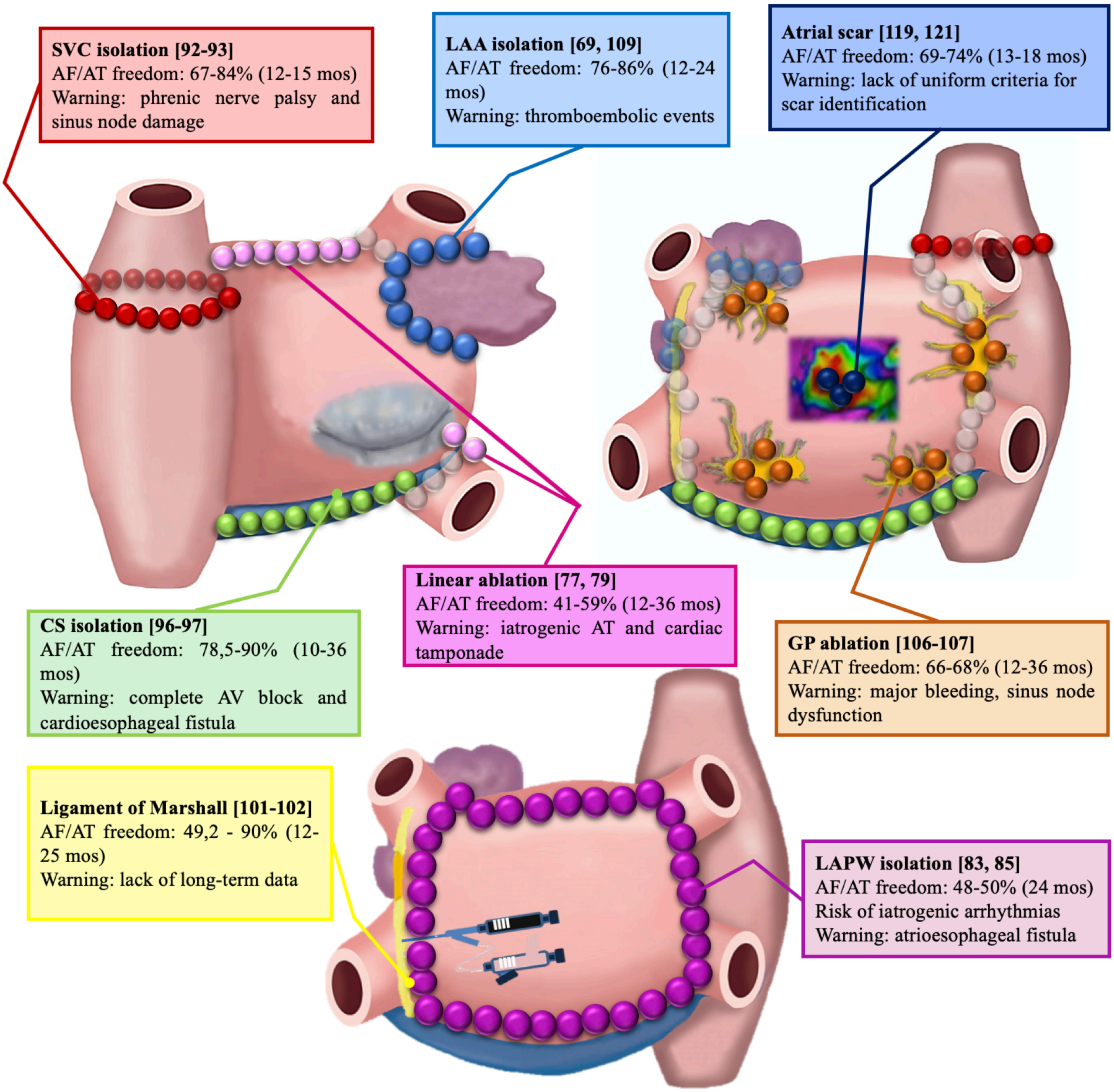

Figure 2. Current non-pulmonary vein strategies in atrial fibrillation ablation. Non-PV targets are shown along with PVI (transparent ablation sites) in the antero-posterior view (upper left) and postero-anterior view (upper right and bottom panel). AF, atrial fibrillation; AT, atrial tachycardia; AV, atrioventricular; CS, coronary sinus; LAA, left atrial appendage; LAPW, left atrial posterior wall; PVI, pulmonary vein isolation; SVC, superior vena cava.

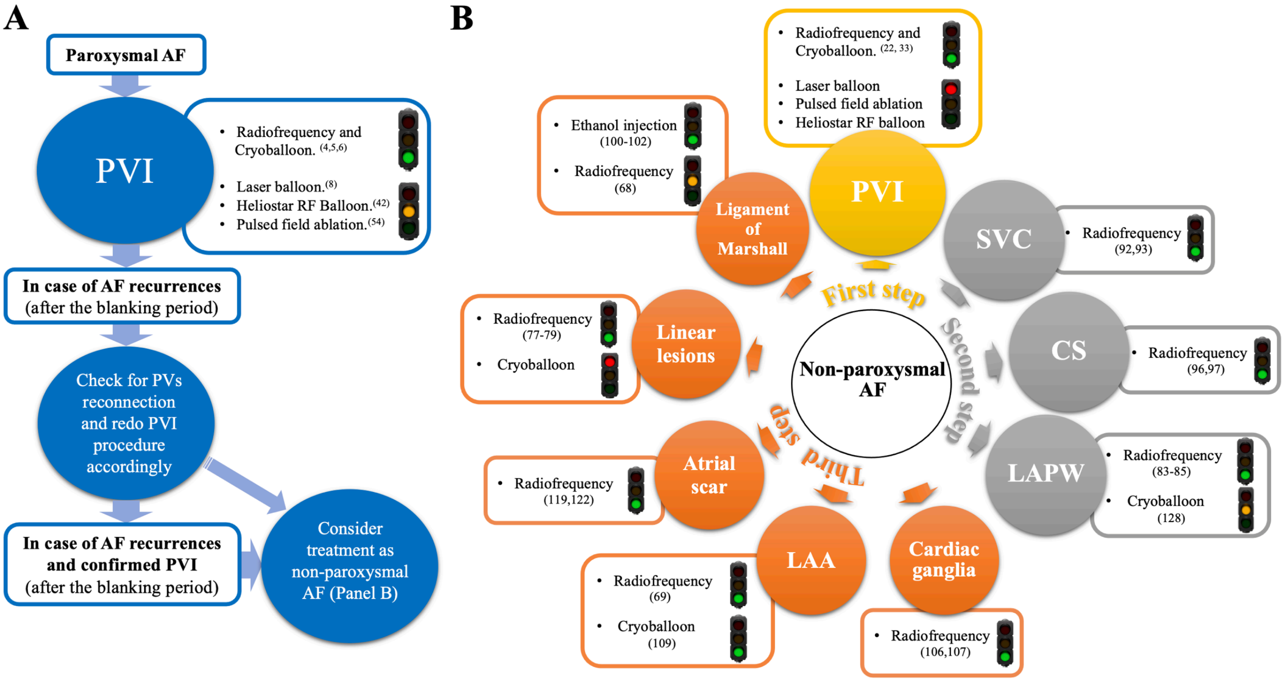

Figure 3. Flow-chart for ablation of anatomical targets in paroxysmal and non-paroxysmal AF. Suggested approaches for patients with paroxysmal (A) and non-paroxysmal (B) AF undergoing catheter ablation. Although PVI is undoubtedly the cornerstone of AF ablation, the specific combination of other anatomical targets may vary among centers. See text for details. Green, orange and red lights indicate levels of scientific evidence, from higher (green light) to intermediate (orange light) and lower levels (red light). AF: atrial fibrillation; CS: coronary sinus; PVI: pulmonary vein isolation; LAA: left atrial appendage; LAPW: left atrial posterior wall; RF: radiofrequency; SVC: superior vena cava.