



# Transcatheter options for atrial fibrillation treatment: an overview of the ablative techniques currently available and future perspectives

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Atrial fibrillation (AF) is the most common arrhythmia in the adult population and catheter ablation has emerged as an important rhythm-control strategy and is the most common cardiac ablation procedure performed worldwide. The antiarrhythmic drugs have demonstrated moderate efficacy in long-term maintenance of sinus rhythm; moreover, they are often not tolerated and are associated with adverse events. Catheter ablation has proven to be effective in treating AF, although long-term outcomes have been significantly less favorable in persistent AF than in paroxysmal. The current guidelines recommend catheter ablation as class I indication for patients whom antiarrhythmic drugs have failed or are not tolerated, and as first-line rhythm-control therapy in selected patients with symptomatic AF. Advances in technology and innovative ablation protocols resulted in a remarkable improvement of the efficacy outcomes after pulmonary vein isolation. This review seeks to provide an updated report of the current practices and approaches, and to describe the latest advances in technology that aim to improve procedural safety, efficacy and to reduce procedural requirements in terms of duration and fluoroscopy exposure.

**Keywords:** Atrial fibrillation (AF); transcatheter ablation; pulmonary vein isolation (PVI); radiofrequency; cryoablation



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## Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the adult population and catheter ablation (CA) for AF has emerged as an important rhythm-control strategy and is the most common cardiac ablation procedure performed worldwide (1). In the late 90s, the identification by Haïssaguerre *et al.* of pulmonary veins (PVs) electrical activity as the main trigger for AF occurrence (2) led the electrophysiologist community to abandon the attempts to replicate surgical lines developed by Cox and colleagues (3). It has become increasingly evident that the presence of excitable tissues within the PVs and at the left atrium (LA)-PV junction plays a central role in AF occurrence. Following this, the main ablative strategy developed was to

interrupt the electrical connections between PVs and the remaining LA. This technique evolved over time from a segmental approach, targeting the earliest site of activation at PV musculature close to the ostium (4), to an ablation strategy aimed at PVs encircling and guided by an electro-anatomic mapping system (5). Pulmonary vein isolation (PVI) has demonstrated a success rate between 60% to 90% at 12-month follow-up in patients with paroxysmal AF, with a wide variation depending on ECG monitoring during the follow-up, but consistently superior to antiarrhythmic drugs (AAD) in multiple randomized controlled trials (6-8). A durable PVI has a pivotal role in the maintenance of sinus rhythm and in the last few years, many efforts by the scientific community have been made to reduce the PV

reconnections. The left atrial wall is a thin structure with heterogeneous wall thickness, ranging from 1 to 5 mm, with an important inter- and intra-patient variability. Non-transmural ablation is considered a major determinant of post-ablation AF recurrence; El Haddad *et al.* showed that PV reconnection could be due to insufficient lesion depth (9). Nevertheless, PVs are not the only players in the complex phenomenon of AF genesis and maintenance. Although PVI remains the cornerstone of AF ablation, in persistent and long-standing persistent AF, post-ablation long-term outcomes have been significantly less favorable than in paroxysmal AF, reporting a success rate between 40% and 70% (10) and often requiring repeated procedures. Extra-PVs triggers, interstitial fibrous tissue deposition and/or autonomic innervation are probably involved, even if the magnitude of their implication in AF occurrence is still not completely understood and, probably, varies from one patient to another. Ablation strategies combining PVI with additional extra-PV substrate ablation, such as either linear ablation, complex fractionated atrial electrogram ablation, or MRI-guided fibrosis ablation, have been tested to further increase the efficacy of CA but showed mixed results (11,12). Accordingly, a PVI-only approach using radiofrequency (RF) or cryoballoon, with post-ablation confirmation of both entrance and exit block, is the most widespread and used technique. On the other hand, the possibility of injuring some sensitive extracardiac structures represents a major issue up to now, especially near regions where the LA thickness is lower. The introduction of non-thermal energy ablation, such as electroporation, could overcome this limitation, thus representing a game-changer. This review seeks to provide an update report of the current practices and approaches in the field of transcatheter AF ablation, and to describe the latest advances in technology that aim to improve procedural safety, efficacy and to reduce procedural requirements in terms of duration and fluoroscopy exposure.

### Current indications for catheter ablation of AF

Evidence regarding the efficacy of CA has been growing in the last decade. AF ablation has been shown to be safe and more effective than AAD for the maintenance of sinus rhythm and for the reduction of symptoms (7,8,13-22). So far, no randomized clinical trial was able to demonstrate mortality reduction in the general AF population. Therefore, indications for CA are mostly based on the presence of symptoms. The current guidelines

recommend CA as class I indication in patients in whom AADs have failed or are not tolerated (1), whereas CA can be proposed as first-line rhythm control therapy (IIa class indication) to improve symptoms in selected patients with symptomatic AF episodes. These current indications are soon to be changed, taking into consideration the results from the EAST trial (23), which showed benefit on hard endpoints even in asymptomatic patients undergoing early rhythm control. Moreover, the EARLY-AF trial (7) showed a higher rate of progression into persistent AF in the AAD arm compared to first-line cryoablation and should push the next guidelines to put first-line ablation as a class I indication at least in patients with high AF-burden. The evidence regarding the benefits of CA in patients with heart failure are rising. Ablation have shown to improve left ventricular ejection fraction (LVEF), quality of life and functional capacity in a recent meta-analysis (24). The CASTLE-AF study (19) showed for the first time a benefit in post-ablation survival in a population of patients with AF, New York Heart Association (NYHA) class II-IV and LVEF <35%. Compared to medical therapy, ablation was associated with a significant reduction of the composite endpoint of death or hospitalization for heart failure decompensation. A recent sub-analysis of the CABANA trial (25) selecting patients with heart failure shows that catheter ablation significantly improved survival, freedom from AF recurrences and quality of life compared with AAD. Despite this growing evidence, further data is still needed for optimizing the selection of ablation candidates as well as for selecting the most appropriate timing for catheter ablation in patients with left ventricular systolic dysfunction.

### Pulmonary veins isolation: techniques, technologies and energy sources

PVI can be achieved through a point-by-point or a one-shot technique (26,27). For the former, the current standard of care is to perform a RF ablation with PVI only approach, and involves the use of three-dimensional (3D) anatomical mapping and a wide-area circumferential ablation line that is deployed with a linear catheter at the PV-antrum junction, aiming to get a continuity between points and with verification of bidirectional conduction block (28). On the other hand, the goal of the one-shot techniques is to deliver few applications (ideally only one) per vein in order to achieve a complete PV isolation. Either way, one of the major determinants in the lesion quality remains the type

of energy used. Briefly, we can divide energy sources into thermal energy (RF, cryoablation, laser) and non-thermal energy (electroporation, ethanol). All the energies available can be delivered with a one-shot technique, whereas only radiofrequency can be used to perform a point-by-point technique.

### Radiofrequency ablation

RF was the first energy adopted for AF ablation and is still the most used worldwide. It is generated at a frequency of 500–1,000 KHz and transmitted between the catheter tip and a skin patch. Even if RF single-shot catheters are currently available (29), RF is mostly delivered with a point-by-point approach. However, this technique is demanding and associated with a long learning curve. Over time, there was significant improvement of RF catheter technologies in order to create a homogeneous ablation lesion set without reducing the safety. The introduction of irrigated-tip catheters was pivotal in this direction (16). Usually, RF ablation with irrigated-tip catheters consists of the delivery of moderate power (20 to 40 W) for 20 to 40 seconds. The amount of energy delivered, the contact and stability are the main determinants of the formation of a transmural and durable lesion. The introduction of ablation catheter with contact force (CF)-sensing capabilities allowed a real-time estimation of both the catheter contact with the atrial tissue and catheter stability. Compared to non-CF sensing catheters, the use of real-time CF-sensing catheters for persistent AF ablation with the aim of a CF of 10–20 g during ablation is associated with shorter procedure time, shorter fluoroscopy time and a reduction in arrhythmia recurrences (30). The introduction of non-fluoroscopic 3D navigation systems allowed improvement of the continuity of the ablation line and localization of the delivered energy (5). The antral approach guided by non-fluoroscopic 3D navigation systems reduced the rates of pulmonary vein stenosis associated with AF ablation. Several studies demonstrated that the introduction of novel markers of ablation lesion quality, such as ablation index (AI) or lesion size index, permitted accurate predictions of the depth and size of the ablation lesions evaluating a composite of power, force, stability and duration (31). Previous analysis also identified that minimum AI values of 540 and 380 were predictive of freedom from acute reconnection in the anterior/roof and the posterior/inferior segments of PVs antrum, respectively. In the CLOSE protocol, it firstly described a new ablation protocol aimed for an interlesion

distance of  $\leq 6$  mm, an AI  $\geq 400$  at the posterior/inferior wall, and  $\geq 550$  at the anterior/superior wall, demonstrating a high-rate of recurrence-free survival at long-term follow-up in a cohort of patients with paroxysmal AF (28). In the CLOSE to CURE study (32), 105 patients underwent RF ablation for paroxysmal AF according to the CLOSE protocol; median atrial arrhythmia burden decreased from 2.68% at baseline to 0% during the first year and remained at 0% during the second year; moreover, single-procedure recurrence-free survival was 87% at one year and 78% at two years, and quality of life improved significantly across all scores. In the recent large non-randomized Surpoint trial (33), Di Biase *et al.* reported the excellent safety and effectiveness outcomes of a standardized AI-guided ablation protocol for paroxysmal AF ablation.

Besides, interest for the high-power short-duration (HPSD) RF ablation is currently growing. This recently explored approach involves the delivery of high-power (ranging from 50 to 90 W) for four to ten seconds, minimizing conductive heating and increasing resistive heating. The idea behind this innovation is that HPSD ablation may minimize the impact of catheter stability as the energy emission is over a shorter period. This approach is feasible and minimizes the RF requirement, whilst maintaining high recurrence-free survival rate (34). Safety seems to improve because of the reduction of lesion depth due to the minimization of conductive heating, but data from randomized trials is still lacking.

Despite these technological improvements some issues regarding RF as an energy source persist. RF is not a cardio-selective energy and as a consequence, the possibility of damage of extracardiac structures remains a major concern. Even if uncommon, atrio-oesophageal fistula remains a dreadful complication due to its dramatic consequences. To modulate RF delivery according to intra-oesophageal temperature monitoring seems not to affect the probability of developing oesophageal lesions (35), but the international consensus on AF ablation still recommends oesophageal temperature probe as Class IIa indication to monitor oesophageal temperature and to titrate RF delivery (1). Finally, steam pop due to overheating of myocardial tissue remains a safety concern for thermal ablation.

### Cryoballoon ablation

Unlike RF ablation, cryoablation is usually performed with a single-shot approach. The contemporary transvenous cryoballoon catheter design consists of a deflectable

catheter with a cryoballoon that is deployed using an “over-the-wire” technique, utilizing a central lumen that permits the positioning of a guidewire into the PV as well as contrast injection. The most used second-generation cryocatheter sprays liquid nitrogen to the distal face of the balloon through equatorial jets. Ablation is realized through the delivery of pressurized cryorefrigerant from an external console to the catheter tip via an ultrafine injection tube. Cryoablation lesion formation is based on convective cooling, whereby the cryorefrigerant absorbs heat from the surrounding myocardium, resulting in cellular damage by ice crystal formation and ischemic cell death (36). Efficacy of cryoballoon ablation for paroxysmal AF ranges from 65% to 80% at 12-month follow-up and recently it has shown to be superior to AAD administration as first-line therapy for the prevention of atrial arrhythmia recurrence in patients with paroxysmal AF in two randomized trials (7,8). Compared with antiarrhythmic drugs, cryoballoon ablation reduces the progression of paroxysmal AF toward persistent forms and reduces the hospitalization rate at three year follow-up (36). Finally, in the multicenter CRYO4PERSISTENT AF trial (37), cryoballoon ablation for the treatment of persistent AF demonstrated a 61% single-procedure success at 12-month post-ablation in addition to a significant reduction in arrhythmia-related symptoms and an improvement to quality of life. Regarding safety concerns, cryoballoon ablation seems to be associated with a lower rate of pericardial effusion and cardiac tamponade, mainly due to the lack of overheating risk. On the other hand, there is a higher incidence of phrenic nerve damage, which occurs in 1.5–2% of procedures, and that is due to cold-induced large axonal loss. However, this complication seems to be very low (<1%) in a recent real-world registry utilizing the third-generation balloon (38).

### Comparison between radiofrequency and cryoballoon ablation

In order to compare the performance of the RF ablation with that of the cryoballoon ablation in a large population of patients with paroxysmal AF, the outcomes of patients undergoing prospective random assignment to RF or cryoballoon ablation were analyzed. The FIRE AND ICE trial (39) randomized 762 patients with drug-refractory paroxysmal AF. After the mean 18-month follow-up, no differences with respect to the efficacy were found; besides, both methods were comparable in terms of safety. Even if repeated ablations, cardioversions and cardiovascular

rehospitalizations during the follow-up were not part of the main endpoints of the original trial, an intention-to-treat analysis showed that the cryoballoon ablation group had significantly fewer events during the follow-up, and both patient groups improved in quality-of-life scores after AF ablation (40). On the other hand, cryoballoon ablation was associated with significantly higher radiation exposure. Finally, when patients with re-ablation were analyzed, patients originally treated with cryoablation had also significantly fewer reconnected PVs (41). This issue may raise concern for RF catheter instability in certain left atrial regions; however, in the FIRE AND ICE trial a contact-force catheter was used in less than one third of the patients in the RF group. Moreover, in a recent multicenter, randomized, single-blinded trial, RF ablation and two different regimens of cryoballoon ablation resulted in no difference at one year efficacy endpoint, with greater than 98% burden reduction as assessed by continuous cardiac rhythm monitoring (42). In conclusion, we do not yet have data reporting the superiority of one source of energy, and the source choice depends on center availability and operator experience; however, more robust data are currently available in the literature regarding the outcomes of cryoballoon ablation as first-line rhythm control therapy (7,8,43).

The most representative randomized clinical trials on radiofrequency catheter ablation or cryoablation versus antiarrhythmic drugs in patients with AF are reported in *Tables 1,2*.

### Laser balloon ablation

Recently, the visually-guided laser balloon (VGLB) has been introduced as a new technology for single-shot PVI in patients with AF. It permits a direct visualization of the target atrial tissue during ablation by incorporating an endoscope located at the proximal end of the balloon. Clinical studies have demonstrated that the laser balloon is highly effective in creating transmural and durable lesions (44). The last generation of VGLB catheters has been equipped with a more compliant balloon for favorable PV occlusion and a robotically motor-driven continuous ablation mode. The lack of real-time recording system of intracardiac electrogram compared to cryoballoon techniques is counterbalanced with more possibilities to better engage different sizes and shapes of PVs using tailored inflation of the balloon. Its safety is comparable to cryoballoon and attention should be paid in order to prevent oesophageal

**Table 1** Milestone randomized clinical trials on radiofrequency catheter ablation versus antiarrhythmic drugs in patients with AF

Study [year]	Intervention/ control	ADT in control arm	Included cohort	Ablation catheter	Lesion set	Follow-up months	Main findings	Ref.
Oral <i>et al.</i> [2006]	77/69	Amiodarone	Symptomatic PeAF	8-mm Navistar (Biosense Webster)	PVI + posterior box or roof line + mitral isthmus line	12	↑ recurrence-free survival (74% vs. 58%, P=0.05); 77% crossover from control group to intervention group	(13)
APAF study [2006]	99/99	Flecainide, sotalol or amiodarone	Symptomatic drug resistant PAF	Navistar ThermoCool (Biosense Webster) or 3.5-mm Cool-Path (St. Jude Medical)	PVI + posterior box or roof line + mitral isthmus line	12	↑ recurrence-free survival (86% vs. 22%, P<0.001); ↓ cardiovascular hospitalization (P<0.01)	(14)
A4 study [2008]	53/59	Amiodarone, quinidine, disopyramide, flecainide, propafenone, cibenzoline, dofetilide, and/or sotalol.	Symptomatic PAF	Navistar ThermoCool (Biosense Webster) or 4-mm Navistar (Biosense Webster)	PVI ± additional substrate ablation	12	↑ recurrence-free survival (89% vs. 23%, P<0.001); ↑ QoL; ↑ symptom score; ↑ exercise test	(15)
ThermoCool AF [2010]	106/61	Dofetilide, flecainide, propafenone, sotalol, or quinidine	Symptomatic drug resistant PAF	Navistar ThermoCool (Biosense Webster)	PVI ± additional substrate ablation	9	↑ recurrence-free survival (66% vs. 16%, P<0.001); ↑ QoL; ↓ 30-day major adverse event (4.9% vs. 8.8%)	(16)
MANTRA-PAF [2012]	146/148	Flecainide, propafenone or amiodarone	Symptomatic drug naive PAF	Navistar ThermoCool (Biosense Webster) or 8-mm Navistar (Biosense Webster)	PVI + roof line	24	↑ recurrence-free survival (85% vs. 71%, P=0.004); 36% crossover from control group to intervention group	(6)
RAAF-T-2 [2014]	66/61	Not specified	Symptomatic drug naive PAF	Not specified	PVI + additional substrate ablation (operator discretion)	24	↑ recurrence-free survival (72% vs. 54%, P=0.02); 43% crossover from control group to intervention group	(17)
CAMTAF [2014]	26/24	Not specified	PeAF, NYHA II-IV, LVEF <50%	Not specified	PV antrum isolation + CFAE ± roof or mitral isthmus line	6	↑ mean LVEF (40%±12% vs. 31%±13%, P=0.015); ↑ peak oxygen consumption; better Minnesota questionnaire score	(18)
CASTLE-AF [2018]	179/184	Not specified	AF, NYHA II-IV, LVEF <35%, ICD	Not specified	PVI ± additional substrate ablation	38	↓ composite of death or hospitalization for HF decompensation (28.5% vs. 44.6%, P=0.007)	(19)
CABANA [2019]	1108/1096	Not specified	Symptomatic AF, CHA <sub>2</sub> DS <sub>2</sub> - VASC ≥1	Not specified	PVI ± additional substrate ablation	48	= composite of death, stroke, bleeding, or cardiac arrest (8% vs. 9.2%, P=0.3); ↓ AF recurrence (P<0.01)	(20)

AF, atrial fibrillation; ADT, antiarrhythmic drug therapy; PeAF, persistent atrial fibrillation; PVI, pulmonary vein isolation; QoL, quality of life; PAF, paroxysmal atrial fibrillation; NYHA, New York Heart Association; CFAE, complex fractionated atrial electrogram; LVEF, left ventricle ejection fraction; ICD, implantable Cardioverter-Defibrillator; HF, heart failure.

**Table 2** Milestone randomized clinical trials on cryoablation versus antiarrhythmic drugs in patients with AF

Study [year]	Intervention/ control	ADT in control arm	Included cohort	Ablation catheter	Lesion set	Follow-up months	Main findings	Ref.
STOP AF pivotal [2013]	163/ 82	Flecainide, propafenone, or sotalol	78% PAF and 22% PeAF	Arctic front (Medtronic)	PVI	12	↑ recurrence-free survival (69.9% vs. 7.3%, $P<0.001$ ); ↑ QoL; 3.1% PV stenosis, 1.5% 12-month phrenic nerve palsy	(21)
Cryo-FIRST [2021]	107/111	Class I or III	Symptomatic drug naïve PAF	Arctic front advance (Medtronic)	PVI	12	↑ recurrence-free survival (82.2% vs. 67.6%, $P=0.01$ ); ↓ incidence rate of symptomatic palpitation	(22)
STOP AF First [2021]	104/99	Class I or III	Symptomatic drug naïve PAF	Arctic front advance (Medtronic)	PVI	12	↑ recurrence-free survival (75% vs. 45%, $P<0.001$ ); ↑ QoL; = adverse event rate (14% vs. 14%)	(7)
EARLY-AF [2021]	154/149	Not specified	Symptomatic drug naïve PAF	Arctic front advance (Medtronic)	PVI	12	↑ recurrence-free survival (57.1% vs. 32.2%, $P<0.001$ ); = adverse event rate (3.2% vs. 4.0%)	(8)

AF, atrial fibrillation; ADT, antiarrhythmic drug therapy; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PVI, pulmonary vein isolation; QoL, quality of life; Cryo, cryoablation.

lesions (using temperature probe) and phrenic nerve lesions.

### Pulsed field electroporation

Pulsed field electroporation is a new approach that uses a non-thermal energy. The pulsed field ablation (PFA) uses sub-second electric fields to create microscopic pores in cell membranes, a process called electroporation, which produces cell necrosis selectively in the myocardium. One of the most interesting aspects of this new ablation source is that different tissues have different target thresholds, and cardiomyocytes having the lowest one. This characteristic allows for modulation of PFA to preferentially deliver myocardial damage, sparing extracardiac structures such as the esophagus or peripheral nerves that have higher thresholds. The 12-month outcomes in three multicenter study including 121 patients with paroxysmal AF have been recently published (45). PV remapping was performed to seek lesion durability. Reconnection rate was 15% but decreased to 4% in patients treated with optimized biphasic energy PFA waveform. In these patients, arrhythmia-free survival was 85% at 1 year.

These promising results have raised the expectations for PFA. However, some aspects of PFA should still be clarified. First, catheter design should be improved to minimize the amount of ablation lesion. So far, the good results in terms of lesion durability are counterbalanced by a significant

amount of atrial tissue being irreversibly injured. As a consequence, macro-reentrant atrial tachycardias that have its critical isthmus linked to the PFA lesion are not infrequent. Second, new complications specifically related with this energy source are being described with the spreading of this approach, for example, coronary arterial spasm (46). Finally, it is unknown if the lack of autonomic modulation by using a myocardium selective source could influence the long-term efficacy of the ablation. In conclusion, further studies are needed to corroborate preliminary data as well as to confirm the safety of this ablation source, however, PFA could be a game-changer in catheter ablation of AF.

### Extra-pulmonary veins ablation

#### Linear, rotor, complex fractionated electrograms and extra-pulmonary vein trigger ablation

Despite the technological innovations of the recent years, the efficacy of AF ablation in cases of persistent and long-standing persistent AF remains lower compared to those reported for paroxysmal AF. In a recent meta-analysis (10), PVI for persistent AF ablation achieved an arrhythmia-free survival rate of 66.7% at 12-month. With the objective to improve AF ablation efficacy, especially in patient with persistent AF, more extensive ablation beyond the PVI has been proposed. Unfortunately, no strategy has yet generated

enough evidence to replace PVI as the standard of care during the first ablation procedure and the studies report mixed results. Ablation strategies combining PVI with additional substrate ablation, such as either linear ablation, complex fractionated atrial electrograms (CFAEs) ablation, or MRI-guided fibrosis ablation, failed to demonstrate better outcomes than PVI-only approach (11,12).

Mapping and ablating extra-PV focal triggers has been proposed in addition to the PVI. Numerous anatomical structures have been suggested as possible non-PV triggers for AF induction: the left atrial appendage (LAA), the LA posterior wall, the superior vena cava, amongst others. However, this approach has practical limitations because the induction of atrial ectopy in the electrophysiology lab can be challenging, especially if ablation is performed under sedation or general anesthesia. Besides, even if atrial ectopy is provoked, the relationship between the ectopic atrial focus and AF occurrences usually remains unproven. In a large observational series of 7,129 patients undergoing CA for AF, the presence of a LAA trigger was documented in only twenty-one patients (0.3%) (47). In the BELIEF trial (48), LAA isolation has shown to improve the efficacy of the ablation in patients with long-standing persistent AF. However, this strategy was associated with an unreasonable risk of stroke, especially in those patients in whom anticoagulation was discontinued during the follow-up. Remarkable practical issues of this approach that should be mentioned include that LAA electrical isolation is technically challenging, requiring a high amount of RF delivery, is associated with a high reconnection rate even for an experienced operator, and generally also requires LAA occlusion. The results of the recently published VENUS trial suggest that the addition of vein of Marshall ethanol infusion to PVI improves the efficacy of CA in patients with persistent AF (49). Further research is needed to confirm these results and, specially, to assess the safety of this approach.

CFAEs are defined as complex fractionated potentials or low-voltage electrograms with a short cycle length of <120 ms over a ten second period; however, the endpoints of CFAEs ablation are not clearly defined, and in the Alster-Lost-AF randomized trial, PVI plus additional CFAEs ablation demonstrated no clinical benefit over the classic PVI-only approach (50).

The roof line, the mitral isthmus line and the posterior wall isolation (PWI) are frequent linear ablation approaches for substrate modification in patients with persistent AF. However, it is difficult to achieve a durable and complete

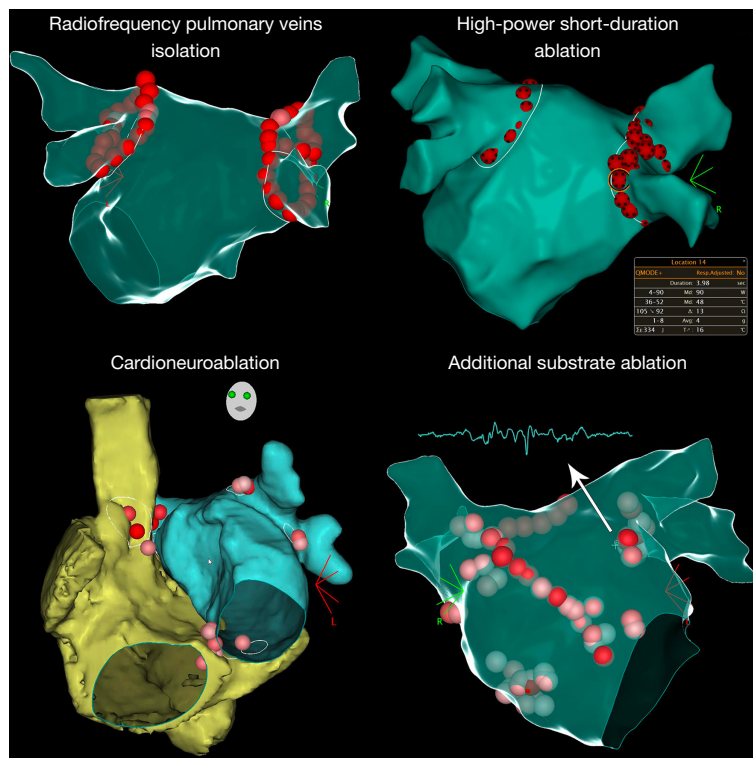
bidirectional conduction block across these lines. Besides, these strategies can result in a higher occurrence of atrial tachycardia and atypical atrial flutter due to reentry around the ablation lesions or through re-conduction across the previous line. In the same way, achieving a complete PWI can be challenging, owing to associated oesophageal heating. Studies regarding PWI efficacy showed mixed results, not confirming an incremental benefit of PWI (51).

A recent randomized study including 324 patients with persistent AF showed better outcomes by adding LA low-voltage areas ablation to PVI isolation (52). In the same vein, after the initial promising results of additional magnetic resonance-guided LA fibrosis ablation, the results of the DECAAF-II trial concluded that this approach is not superior to PVI alone in patients with persistent AF (12).

It was reported in literature that high-frequency rotors and focal impulses could be important for sustaining AF (53). This is of particular interest in patients with long-standing persistent AF. A range of technologies, such as high-density basket mapping catheters, have been used to identify and to map this high-frequency rotational activity. However, preliminary findings of the prospective randomized REAFFIRM trial reported no reduction in the rate of recurrent AF when rotor ablation was performed in addition to PVI in a cohort of patients with persistent AF. In the electrophysiological practice, an extensive ablation approach aimed to eliminate CFAEs and/or rotors is demanding and could also have pro-arrhythmic effects. Though, the benefit of these approaches should still be proven. There is an ongoing trial with the purpose of re-evaluating the additional benefit of rotational/focal activity ablation in addition to PVI compared with PVI-alone and PVI plus posterior wall isolation (STAR-AF 3 trial, NCT04442113).

### Cardioneuroablation

The autonomic nervous system is an important factor in AF occurrence. It is well known that parasympathetic activation contributes to the onset and the perpetuation of AF, especially but not only, in patients with predominantly “vagal” AF. Autonomic imbalance causes the shortening of the atrial effective refractory periods and increases ectopy, especially arising from the pulmonary vein myocytes that have a shorter action potential duration and a greater sensitivity to both cholinergic and adrenergic stimulation. As a consequence, ganglionated plexuses on the epicardial surface of the atrium has become a target for ablation. Pappone *et al.* initially described that patients who



**Figure 1** Point-by-point approaches for AF catheter ablation. AF, atrial fibrillation.

underwent PVI and in whom vagal reflexes were completely abolished after ablation had less AF recurrences during follow-up (54). Ganglionated plexus ablation in addition to PVI seems to significantly improve freedom from atrial tachycardia/AF recurrences with respect to a PVI-only approach (55). However, which is the best method to localize these plexuses and how many plexuses should be ablated are still matter of debate.

Finally, renal denervation has recently emerged as a complement to PVI in AF therapy. In the ERADICATE-AF randomized clinical trial (56), 302 patients with AF and hypertension were randomized to PVI or renal denervation plus PVI; freedom from AF, flutter or tachycardia at 12-month was 57% and 72%, respectively ( $P=0.006$ ).

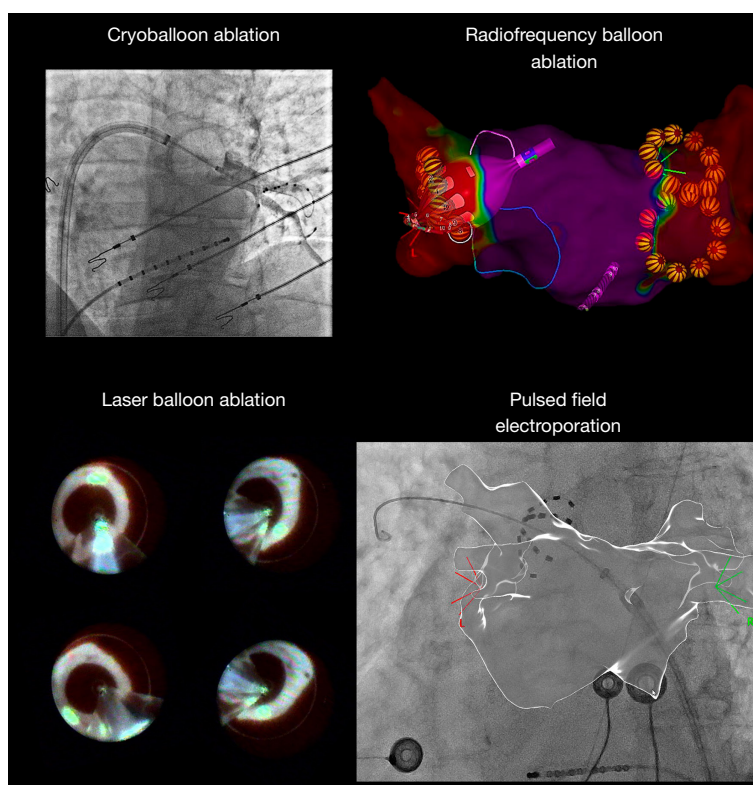
Illustrations of point-by-point and one-shot approaches for AF ablation are shown in *Figures 1,2*.

### Hybrid ablation

Endocardial CA can be combined with minimally invasive thoracoscopic epicardial ablation. Hybrid ablation (HA) for AF consists of a Cox-Maze lesion set applied via minimally invasive thoracoscopic approach followed

by CA, which treats gaps in the lesion set and targets any additional atrial re-entrant circuits. Recent studies reported variations regarding the energy sources used, the surgical approach, the timing of the surgical and catheter components of the procedure, the ablation lesion set applied, the management of the LAA, and the medical management of these patients. A recent meta-analysis (57) showed that in a cohort of patients with persistent AF, HA was superior to conventional ablation in maintaining sinus rhythm (71% *vs.* 50%,  $P<0.001$ ), but on the other hand, HA had a significantly higher complication rate. The recently published CONVERGE trial (Convergence of Epicardial and Endocardial Ablation for the Treatment of Symptomatic Persistent AF) is a prospective, multicenter, randomized controlled trial (58). One hundred and fifty-three patients with persistent and long-standing persistent AF and indication for an ablation procedure were randomized to CA *vs.* convergent HA. This trial was hailed as a potential breakthrough, demonstrating superiority of HA over CA. The downside was that major adverse events occurred in 8% of the HA arm and 0% of the CA arm. The real need of an invasive approach in patients with persistent AF, which is often only mildly symptomatic, should be





**Figure 2** One-shot approaches for AF catheter ablation. Courtesy of Carlo de Asmundis (UZ Brussel-Vrije University, Brussels, Belgium), Cheryl Teres (Lausanne University Hospital, Lausanne, Switzerland), and Gennaro Miracapillo (Ospedale della Misericordia, Grosseto, Italy). AF, atrial fibrillation.

carefully evaluated, and appropriate patient selection is fundamental.

### Zero- or nearly zero-fluoroscopy approaches

Historically, all AF ablations were performed under fluoroscopy guidance. Recently, the awareness of risk associated with radiation exposure to patients and professional staff has significantly increased. Several studies demonstrated the direct relationship between the radiation dose and the lifelong risk of both deterministic and stochastic side effects. An important effort was therefore made to minimize radiation exposure, as recommended by the American College of Cardiology in the ALARA statement: keep the radiation “as low as reasonably achievable”. Technological advances such as 3D navigation systems have enabled the reduction of radiation use, even allowing a nearly zero-fluoroscopy approach (5). Concerns regarding trans-septal access have limited the fluoroscopy approach for LA ablations. In this setting, there is

growing evidence that the use of the electro-anatomical maps and the navigation system combined with intracardiac echocardiography to guide trans-septal puncture allows reduction or even elimination of fluoroscopy (59), with the downside of the need for an additional venous puncture, a trained cardiologist and an increase in procedural cost. Moreover, a recent study reported a series of 111 patients demonstrating the procedural feasibility of a transesophageal echocardiography-guided CA for AF with a complete or near-complete avoidance of radiological exposure (60).

A representative case of zero-fluoroscopy approach for AF radiofrequency ablation was reported and explained via audio recording in the presentation (*Video 1*).

### Conclusions

CA is a widespread and fundamental therapeutic strategy for rhythm-control in AF patients. Advances in technologies and strategies have increasingly led to an improvement in

efficacy, safety and a reduction in procedural requirements. The innovations and new evidence are continuing to expand the indications of CA as first-line therapy in symptomatic patients and now also as an early rhythm-control strategy in asymptomatic patients. Despite the progress in CA techniques, long-term outcomes after a single procedure remain suboptimal in patients with persistent and long-standing persistent AF. PVI remains the therapeutic cornerstone of CA for all AF types; further investigations are required to determine new appropriate strategies when PVI-alone is insufficient. Ongoing research may offer new therapeutic targets and options for AF patients with difficult-to-treat arrhythmia.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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