Contemporary Ablation Techniques for Atrial Fibrillation: An Evidence-Based Analysis

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May 28, 2022

Abstract

Since the advent of catheter ablation (CA) for atrial fibrillation (AF) in 1998, our understanding of the pathophysiology, as well as our capacity to target triggers and effectively achieve freedom from AF, has come a long way. However, as the average age of the population and the prevalence of chronic diseases increases, the progression of AF from paroxysmal (PAF) into persistent (PersAF) and long-standing persistent AF (LSPAF) is on the rise. Given the complex mechanisms involved and the presence of multiple trigger sites leading to recurrences, managing non-PAF is a challenge for electrophysiologists around the globe. Multiple ablation techniques have been investigated, some of which have shown promising results, but a standardized technique is yet to be elucidated. In this review, we outline the evidence behind contemporary ablation techniques in the treatment of AF.

Introduction

Atrial fibrillation (AF) is the most common prevalent arrhythmia, estimated to affect approximately 33 million individuals worldwide (1). The cumulative incidence of progression from paroxysmal AF (PAF) to persistent AF (PersAF) and long-standing persistent AF (LSPAF) is estimated at 8.1 per 100 patient-years (2). AF is associated with an elevated risk of thromboembolism, stroke, impaired quality of life, and even mortality (3,4), and achieving rhythm control with catheter ablation (CA) has shown to improve outcomes in recent studies (5). Ectopic foci originating in the pulmonary veins (PVs) represent the main arrhythmia mechanism in PAF as established by Haissaguerre et al. in a landmark trial (6), and as such pulmonary vein isolation (PVI) is the mainstay treatment for PA. However, in patients with non-PAF, long-term conditions such as hypertension, heart failure, obesity, and sleep apnea lead to structural and cellular changes induced by chronic inflammation, myocyte death and lymphocyte and fatty infiltration, all leading to fibrosis (7). These structural changes within the atria serve as a conduit for fibrillatory waves as they facilitate re-entrant circuits through the fibrotic tissues (8), and the effectiveness of PVI alone for PersAF and LSPAF is far from acceptable (9).

Given these suboptimal results, different ablation strategies and lesion sets have been proposed to increase CA success in the treatment of non-PAF. We will review current evidence surrounding the different approaches for CA of non-PAF and provide evidence-based guidance on best clinical practice.

Pulmonary Vein Isolation

Ever since PVs were demonstrated to participate in AF initiation, PVI has been offered as a strategy to reduce arrhythmia recurrence. Initial trials which were conducted performing ablation at the PV ostia, demonstrated a significant reduction in AF recurrence; however, this strategy was associated with a high risk of PV stenosis (10-12). This eventually reformed into circumferentially isolating the veins at the level of the antrum, a strategy known as wide antral CA (WACA), which has been shown to minimize complications such as PV stenosis while improving AF free survival (13-15) (Figure 1).

As previously stated, WACA alone may not be sufficient to treat patients with non-PAF (16,17). In a prospective study of 2168 patients with non-PAF (18), AF initiation from non-PV trigger sources was demonstrated in 11% of patients referred for CA. Even for PAF, non-PV triggers are being increasingly recognized, especially in patients with systolic dysfunction and during redo procedures despite isolated PVs(19). These non-PV trigger sources have been identified to arise from the posterior wall (PW) of the left atrium (LA), left atrial appendage (LAA), coronary sinus (CS), superior vena cava (SVC), interatrial septum, crista terminalis (CT), Eustachian ridge, the mitral and tricuspid valve annulus, a persistent left superior vena cava (PLSVC), and its remnant the vein of Marshall (VOM) (19,20).

Several ablation techniques targeting these sources have been tested, notably ablation of complex fractionated atrial electrograms (CFAEs), creation of additional linear lesions, rotor ablation, scar tissue ablation, PW isolation (PWI), LAA electrical isolation (LAAEI), ablation of cardiac veins (including the SVC, CS, VOM), cavo-tricuspid isthmus ablation (CTI), renal denervation (RDN), ganglionated plexi (GP) ablation.

Complex Fractionated Atrial Electrograms (CFAEs)

CFAEs were first described by Nademanee et al. (21) as a pattern of continuous atrial activity originating from areas of functional block and slow conduction, and pivot points of reentrant waves. The STAR AF (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation) trial (22) found PVI + CFAEs ablation had higher freedom from AF when compared to PVI or CFAEs ablation alone after one or two procedures. A similar conclusion was derived from a meta-analysis by Hayward et al. (23). However, additional substrate modification was not found to have any benefit over PVI and ablation of non-PV triggers in a subsequent study (24). Verma et al. conducted the STAR AF II (Approaches to Catheter Ablation for Persistent Atrial Fibrillation) trial (25) with a larger sample size, and no reduction in the recurrence rate of AF was observed when CFAEs ablation was performed in addition to PVI. Although CFAE ablation is associated with an increase in intraprocedural AF termination (26), it does not provide any incremental benefit over PVI alone in the reduction of long-term AF recurrence and is associated with longer procedural and fluoroscopy times (27). (Figure 2)

Linear Lesions

Linear ablation is defined as the creation of lines that serve as electrical barriers with the purpose of achieving a bidirectional conduction block to prevent macro-reentrant circuits. This approach typically targets the mitral and cavo-tricuspid isthmus (CTI), and the roof of the LA (Figure 3). However, achieving durable bidirectional block across the lines is often complicated by the formation of gaps, which in turn have pro-arrhythmic effects (28). The STAR AF II trial showed that empirical roof and mitral isthmus lines had no additive benefit to PVI, and the CLEAR-AF (Catheter Ablation Therapy for Persistent Atrial Fibrillation) trial demonstrated similar results (25,29): although more patients achieved sinus rhythm during ablation with ancillary lines, no long-term benefit was related to this finding. Interestingly, in patients with extensive linear ablations atrial tachycardia (AT) was the most common recurrent arrhythmia, as opposed to patients with circumscribed ablations, who most frequently relapsed with AF. In EARNEST-PVI trial, 85% of patients underwent additional linear ablation and did not have a significantly better outcome than the PVI only group at 12 months(30). When performing mitral isthmus ablation, the use of adjunctive VOM ethanol infusion has been shown to be associated with a higher rate of mitral isthmus block and arrhythmia free survival mainly driven by a lower AT recurrence (31-33).

CTI ablation is currently the standard treatment for CTI-dependent atrial flutter (AFL) and has also been proposed as an adjunctive strategy for non-PAF. Pontoppidan et al. (34) conducted a randomized controlled

trial (RCT) on patients with AF undergoing PVI without a history of AFL and failed to show any additional benefit of CTI ablation in terms of freedom from either AF or AFL. Similarly, Mesquita et al. (35) showed in a propensity score analysis that empiric CTI ablation in addition to PVI did not improve AF free survival. Results from a Korean RCT with a longer follow up of 3.4 years were also not in favor of empiric CTI lines (36).Comparable findings were replicated in a sub-group study included in a meta-analysis of 1400 patients, in which CTI ablation did not have any additional benefit in AF with or without AFL (37). These results can be explained by the low frequency of typical AFL after PVI (2.8%), most of which are related to significant right atrial dilation (38). (Figure 4)

Rotors

The idea of rotors as a mechanism for AF has been proposed since 1990 (39,40) and currently is defined as a cyclic activation producing spiral waves which radiate outward into the surrounding tissue around a core of functional block, as opposed to an area of scar tissue, which allow rotors to "move" up to 2-3 cm^2 around the atrium (41). Interestingly, a significant proportion of rotors have been described in the right atrium (an area not normally targeted during AF ablation) (42), making focal impulse and rotor modulation (FIRM) an appealing adjunctive strategy(43). Although the CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) study reported a high degree of freedom from AF with FIRM (42), other studies have demonstrated that, despite the association with a more organized fibrillatory activation within the LA, it does not correlate with an increase in freedom from AF, even after redo procedures (43-46). Furthermore, a head-to-head meta-analysis of six studies including 716 patients (88.5% non-PAF) concluded that FIRM did not add any benefit in improving all-atrial arrhythmia recurrence (47). (Figure 5)

Scar Tissue Ablation

Chronic inflammation and atrial re-modeling lead to areas of fibrosis and scar tissue generation, which serve as substrates for AF. Targeting these areas with either voltage mapping or guided by magnetic resonance images (MRI) has been proposed as an adjunctive strategy. A meta-analysis by Blandino et al. (48) showed that ablation of low voltage areas (LVA) in addition to PVI had a significantly improved freedom from AF at a median follow-up of 17 months.

In contrast, two recent RCTs failed to show any difference in outcomes with MRI-guided fibrosis ablation (49,50)However, in patients with low grade fibrosis (grade I or II) PVI + fibrosis ablation led to a reduction in atrial arrhythmia recurrence (51). Another unique approach called box isolation of fibrotic substrates (BIFA) was successfully tested by Kottkamp et al. (52). Fibrotic areas were identified with voltage mapping and targeted with box isolation and freedom from AF was achieved in 72.2 % of those patients. (Figure 6)

Posterior Wall Isolation (PWI)

The PW of the LA shares its embryologic origin with the PVs (53), which explains its similar electrophysiologic properties and higher arrhythmogenic potential when compared to anterior wall myocytes (54). Furthermore, the PW is exposed to higher stress and tension (which is associated with LVA and electrical scar (55), and is in close proximity to epicardial fat pads and ganglionic plexi (GP), structures known to enhance excitability of the myocardium. The role of GP ablation has been supported in small, randomized studies and a meta-analysis especially for PAF; however, data on long term outcomes is lacking (56-58) (Figure 7). The significant number of AF driver regions located in the PW was further substantiated in a prospective study using non-invasive body surface mapping (59). As such, ablation of the PW has now emerged as an appealing adjunctive strategy to PVI (Figure 8). Several strategies have been developed to achieve PWI, and each approach has theoretical advantages and shortcomings:

- Ablation lines are created either as a single ring encircling the PVs and PW or as a box lesion set, where a roof line connecting the superior PVs and an inferior line between the inferior PVs are done. However, the durability of these lines has remained a challenge due to the formation of conduction gaps.

- Extensive substrate-based ablation, or "debulking of the atrium" where the endpoint is complete electrical silence (60). Nonetheless, although initial results were promising, the small patient population in this study has limited its widespread use.
- A "hybrid" approach, that combines a minimally invasive pericardioscopic epicardial with endocardial ablation, allowing for the formation of durable transmural lesions, while minimizing the risk of injury to adjacent structures(61). Regardless, this strategy is based on a small study, and further trials are required on this novel multi-disciplinary procedure.
- Use of cryoballoon energy to isolate the PW has shown to be promising in two recent RCTs, however complete isolation with cryoablation alone was not achieved in a significant proportion of subjects(62,63). Although no difference in acute complications were reported in these studies, esophageal injury remains a major concern, especially for larger cryoablation balloons. The PIVoTAL study (Comparison of Pulmonary Vein Ablation with or without Left Atrial Posterior Wall Ablation for Persistent AF; NCT03057548) is an ongoing RCT to evaluate the incremental benefit of cryoablation of PWI in addition to PVI.

Despite the evidence behind PW being a vital focus of AF triggers, data regarding its outcomes have been largely conflicting (64-66), perhaps secondary to failure to achieve complete bidirectional block. The RCT PEACEFUL (Electrical Posterior Box Isolation in Persistent Atrial Fibrillation Changed to Paroxysmal Atrial Fibrillation) was unable to find any added benefit of PWI. Reconnection of the PW was observed in all patients who received a second procedure during follow-up (67).

In a meta-analysis of ten studies including patients with PAF and non-PAF, patients who underwent concomitant PWI experienced less recurrence of all-atrial arrhythmias with significant reduction noted in non-PAF subjects(68).

PWI is associated with certain limitations, including technical difficulties in achieving lesions with durable isolation, thermal esophageal injury, and the concern of atrial mechanical dysfunction. The generation of gaps along the ablation lines or the presence of epicardial and sub-epicardial connections are thought to be the triggers for PW reconnection, even after extensive ablations (69,70). These reconnections have been described in 40-70 % of patients (most frequently in the roof line), despite confirmed bidirectional block and the use of adenosine or isoproterenol during the initial ablation procedure (65,71).

Esophageal injury occurs in 47 % of cases of PWI and can range from erythema or ulceration, to the most life-threatening complication, atrio-esophageal fistula (AEF) formation (72). A large global database recorded the incidence of esophageal perforation and AEF to be 0.016 % and 0.011% respectively (73). Continuous luminal esophageal temperature monitoring could theoretically reduce the risk of esophageal lesions. Termination of ablation is advised when esophageal temperature reaches 38°C, as it can continue to rise above 39°C in at least half of patients, even after stopping ablation (74,75). Other techniques, such as adjusting to low irrigation parameters and mechanical displacement of the esophagus, can be considered. The use of contact-force sensing catheters and restricting contact force to < 20 g has been shown to minimize esophageal injury in a single-center randomized study (76).

The concern for deterioration of LA contractile function has been raised with extensive PW ablation. However, LA contractility is primarily a function of the muscular cells at the anterior, septal, inferior, and lateral walls with negligible contribution from the PW. As such, no decline in LA function has been reported after extensive PW ablation (77,78).

Superior Vena Cava Isolation (SVCI)

The SVC has been recognized as a site responsible for both initiation and perpetuation of AF, and several studies have documented its involvement in PAF and non-PAF (79,80). SVCI is achieved with radiofrequency ablation (RFA), using a segmental approach commencing on the septal aspect of the vascular structure. While ablating the lateral aspect, it is crucial to prevent injury to the phrenic nerve and the sinus node. In up to 10 % of patients, complete isolation of SVC is not feasible, due to the risk of damaging the phrenic nerve. In such patients, ablation of right atrial posterior wall can be employed as an alternative (81). The sinus

node lies laterally and below the SVC; RFA should be promptly discontinued if acceleration of the sinus rate is noted (an imminent sign of sinus node injury). It is also imperative to not perform ablation during isoproterenol infusion to avoid masking injury to the sinus node. Cryoballoon has also been used to achieve SVCI and has improved freedom from AT in PAF subjects.(82)

An empirical approach to SVCI has been investigated in a prospective, randomized study (83), which found no significant differences in maintenance of sinus rhythm without antiarrhythmic drugs . The same conclusion was derived from a meta-analysis by Sharma et al. (84)including a total of 526 subjects, in which no difference in AF recurrence when SVCI was added to PVI across all types of AF. When only PAF was analyzed, empiric SVCI showed a trend towards efficacy but failed to reach statistical significance. Yoshiga et al. (85) investigated the incremental benefit of SVCI in recurrent AF after index procedure of PVI without evidence of PVs reconnections on redo procedures and found that SVCI had a success rate of 74 % vs. 66 % in PVI only group. However, SVCI should be attempted with concomitant ablation of other non-PV triggers to obtain better outcomes (86). (Figure 9)

Coronary Sinus (CS) Isolation

In patients with PersAF and LSPAF, some evidence suggests that the CS is a crucial trigger source for AF (87-90). The muscular sleeves of the CS can potentially serve as either an ectopic trigger or be part of a reentrant circuit for AF (91). Given its variable anatomy and, therefore, alternating trigger sites for AF, CS focal ablation is markedly challenging and time-consuming. Della Rocca et al. (92) found that complete CS isolation was associated with a significantly higher arrhythmia-free survival rate than focal CS ablation with a similar incidence of procedural complications. A recent randomized study revealed better outcomes with elimination of distal CS to LA connections compared to PVI and non-PV trigger ablation (93). Given the close relationship between the esophagus and the CS, continuous monitoring of the esophageal temperature is important to avoid complications (94). While ablating along the septal aspect, close monitoring of PR interval is pertinent. Prompt discontinuation of the ablation is recommended if signs of PR prolongation are detected to avoid injury to the atrioventricular (AV) nodal artery. (Figure 10)

Left Atrial Appendage Electrical Isolation (LAAEI)

The LAA is derived from the primordial LA mainly by the adsorption of the primordial PVs and their branches, explaining its role as a potential site of AF triggers. In a non-randomized population of 987 patients undergoing redo AF ablation, 27 % of patients were noted to have triggers arising from the LAA. Moreover, in 8.7 % of the cases, this was the only source of atrial arrhythmia with no PVs or extra-PV reconnection (95).

The RCT BELIEF (Left Atrial Appendage Isolation in Patients with Longstanding Persistent AF Undergoing Catheter Ablation) (96), showed promising results with empiric LAAEI after both index and redo procedures. Among patients who had recurrences and underwent redo ablations, LAAEI was performed in all cases and re-isolated in cases of reconnections. Late LAA reconnections were observed in 37 % of the redo cases. RF and fluoroscopic times were comparable, with no increase in complications. The incremental benefit of LAAEI in addition to PVI was also demonstrated in two meta-analyses including approximately 2000 patients with non-PAF (97,98). This benefit persisted during a 5-year follow-up of 1092 individuals in a propensity score-matched multicenter cohort study. No differences in acute complications or thromboembolic events were evidenced in patients on continued oral anticoagulation (OAC) treatment (99). (Figure 11)

In a propensity score-matched study by Yorgun et al. (100), cryoballoon-based isolation of the PVs and LAA delivered promising results without a significant increase in complications. However, 4 % of the study population had left circumflex artery vasospasm, which resolved with intracoronary nitrate, and 1 % had left phrenic nerve (LPN) injury. It is crucial to prevent mapping and ablation deep into the LAA, as it is a thin structure, and ablation within the lumen is associated with a higher risk of perforation and LPN injury. Imaging integration with cardiac computed tomography and electroanatomic mapping prior to ablation, can help mitigate the potential risk of coronary injury (101). Periprocedural imaging and paced mapping can also delineate the anatomical relationship of the LPN with the LAA, and in case of close proximity a segmental

isolation approach should be considered (102).

The thromboembolic risks associated with LAAEI have been a major concern and have shown mixed results. Rillig et al. (103) showed that at a median follow-up of 6 months after LAAEI, 6 % of patients developed stroke or transient ischemic attack, and 21 % were found to have LAA thrombus on transesophageal echocardiogram (TEE). However, all 3 patients had AF recurrence at the time of stroke, and one was off OAC at the time of event. In contrast, no significantly increased risk for thromboembolic events was reported in the LAAEI groups from two meta-analyses, even after a mean follow-up of 40.5 months (97,98). In a large observational study of 1854 consecutive patients with AF receiving LAAEI along with PVI, thromboembolic events were mainly seen in those who had abnormal LAA function. Moreover, patients who were off OAC, receiving subtherapeutic doses, or were non-compliant had thromboembolic complications at higher rates (104). Interestingly, in patients who had normal LAA function on TEE at 6 months, OAC was discontinued irrespective of the CHA_2DS_2-VASc score, and no thromboembolic events were seen during 2.3 years of follow-up.

For patients in whom long-term OAC is not suitable after LAAEI, LAA occlusion could be considered (105). Another alternative for electrical and mechanical isolation of the LAA is the ligation of the appendage with Lariat, a suture delivery device (SentreHEART, Redwood, CA, USA). This approach has been under investigation, and initially, concerns regarding procedural complications, such as pericardial effusion and the need for urgent cardiac surgery, were reported (106,107). Lakireddy et al. demonstrated improvement in procedural success rate and mortality, while also showing greater freedom from AF recurrence at 1 year follow-up (108). In contrast, the aMAZE (LAA Ligation Adjunctive to PVI for Persistent or Long-standing Persistent Atrial Fibrillation, NCT) trial failed to demonstrate significant differences in arrhythmia recurrence in patients undergoing left atrial ligation + PVI vs. PVI alone (109).

Persistent Left Superior Vena Cava (PLSVC) and the Vein of Marshall (VOM)

PLSVC occurs when the left superior cardinal vein fails to regress to the VOM, as should normally occur (110). A recent study described the possible arrhythmogenic role of PLSVC (111). Data on the use of cryotherapy for isolation of SVC (112) and PLSVC (113,114) has been limited to a few cases but appears to be an attainable alternative.

The VOM is a vestigial fold, which marks the site of the embryological left SVC. This structure has been particularly important in the setting of atrial tachycardias and AFL post-AF ablation (115). In most cases, the VOM triggers can be detected by direct cannulation of the CS with a multipolar catheter. Direct ethanol injection into the VOM has been described, as it allows for specific ablation of the vascular structure, its intrinsic electrical activity, the mitral isthmus, the neighboring myocardium, associated PV connections, and parasympathetic innervation (116). Chugh et al. (117) reported 56 cases in which the VOM was a therapeutic target based on pacing data. The mapping was suggestive of VOM-mediated LA–PVs connections, or VOM-mediated macro-reentrant circuits, or focal tachycardias. The RCT VOM Ethanol Infusion for Persistent Atrial Fibrillation (VENUS)has shown improved freedom from AT/AF with additional VOM ethanol infusion in patients undergoing their first CA (118). However, in patients undergoing redo ablation, addition of VOM EI did not improve outcomes(119). Interestingly as described before, adjunctive VOM EI with linear ablation had favorable outcomes in PersAF(33). (Figure 12)

Renal Denervation (RDN)

RDN has been hypothesized to decrease AF recurrence rate by ablating the renal sympathetic efferent and afferent nerves that interact with the central autonomic nervous system. The ERADICATE-AF trial (Effect of Renal Denervation and Catheter Ablation vs Catheter Ablation Alone on Atrial Fibrillation Recurrence Among Patients with Paroxysmal Atrial Fibrillation and Hypertension) analyzed 302 patients with PAF and showed improved AF freedom with the addition of RDN to PVI (120). Two recent meta-analyses also supported the idea of additional RDN (121,122). However, these studies have been primarily performed on patients with PAF. The SYMPLICITY AF trial (Renal Nerve Denervation in Patients with Hypertension and Paroxysmal and Persistent Atrial Fibrillation; NCT02064764) is a multicenter trial which explores the

efficacy and safety of additional RDN over PVI.

Final Remarks

Despite the available evidence on the techniques, a standard ablative approach in patients has not yet been elucidated. The figures summarize the most up-to-date evidence on ablation strategies, with each study being scored according to its design and methodology. The final score for each method represents the overall strength of the evidence, either in favor or otherwise. However, we also recommend for the selection of any additional strategy to be guided by the operators' experience, the availability of technological resources (e.g., specialized mapping software, contact force catheters), and patient characteristics.

Decreasing the number of unnecessary ablation lesions within the LA is of paramount importance, as recurrent AT is generally associated with previous lesions (123). As such, strategies that have consistently demonstrated a lack of clinical benefit (i.e., CFAE ablation, CTI ablation) should not be performed, except as a part of a study protocol. Importantly, when managing patients with non-PAF the probability of repeat procedures should be clearly explained to patients, as these might increase the long-term success rate (124).

The ongoing PLEA trial (Systematic Evaluation of Ablation Techniques for Non-Paroxysmal Atrial Fibrillation; NCT04216667) is a multicenter, RCT that will offer further insight into the efficacy and safety of different empirical ablation strategies in non-PAF.

Conclusion

Contributions from non-PV triggers have a significant influence on the progression of PersAF and LSPAF, making it imperative to execute other strategies beyond PVI. With the development of novel approaches, more RCTs are needed to compare each strategy in a head-to-head fashion and to evaluate their efficacy and safety. Importantly, current evidence seems to demonstrate that the use of scar, CFAE and FIRM ablation have no role in the current management of non-PAF, as there is no evidence demonstrating improved outcomes but they are associated with significantly higher risk of procedure related complications. Other strategies, including PWI and LAAEI, are currently being studied and may play a significant role in reducing AF recurrence. Further randomized controlled trials are needed to guide the most appropriate therapy in this group of patients.

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Evidence Scoring system

Only observational studies (OS), propensity scored (PS) studies, randomized controlled trials (RCT), and meta-analysis (MA) of ablation strategies for PAF and non-PAF were included. OS, PS and MA were excluded if there was no PVI only control group for comparison. For the meta-analyses, only the largest and/or latest published were included.

A positive score favors technique implementation, while a negative score indicates that there are no additional benefits with the approach. AF evidence-based scores were calculated by considering the different weights of the studies, as described below.

- OS (yellow)were scored as +1/-1
- PS studies(gold) were scored as +2/-2. Additional points were given depending on the interventional arm population (+1/-1 if $<$ 500 patients, +2/-2 if between 500-1000 patients, or +3/-3 if $>$ 1000 patients).
- RCT (orange) were scored as +3/-3. Additional points were given depending on the interventional arm population (+1/-1 if $<$ 100 patients, +2/-2 if between 100-200 patients, or +3/-3 if $>$ 200 patients).
- MA (red) was scored as +2/-2 if only included OS; +3/-3 if included RCTs and OS; +4/-4 if included RCT, PS and OS; +5/-5 if only included RCT. If it included only RCTs, additional points were given depending on the interventional arm population (+1/-1 if $<$ 500 patients, +2/-2 if between 500-1000 patients, or +3/-3 if $>$ 1000 patients).

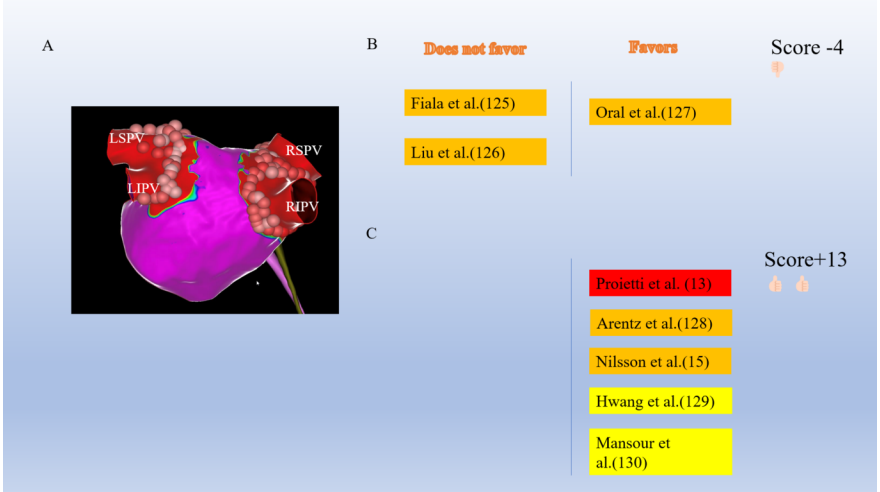

Fig. 1 A: Electroanatomical map of left atrium showing PVI. Studies comparing WACA versus ostial PVI in B: PAF (125-127)C: PAF and non-PAF(13,15,128-130)

LSPV; left superior pulmonary vein, LIPV; left inferior pulmonary vein, RSPV; right superior pulmonary vein, RIPV; right inferior pulmonary vein, WACA; wide antral catheter ablation, PVI; pulmonary vein isolation

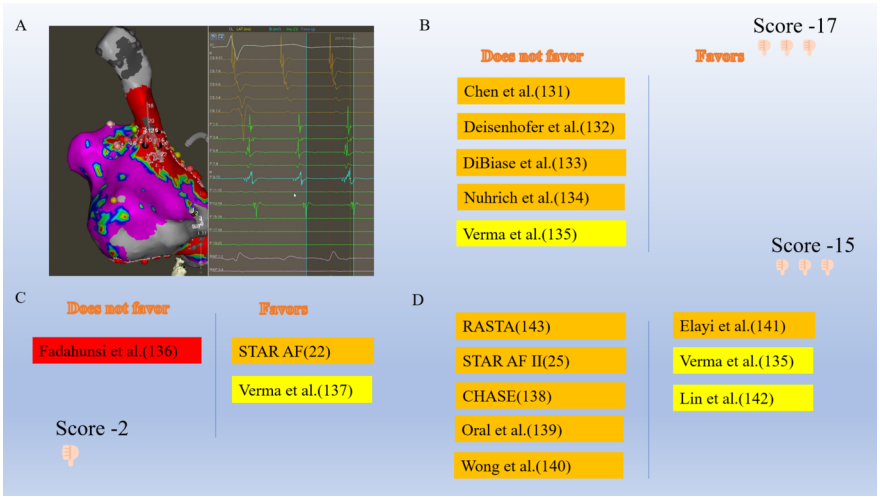

Fig. 2 A: Complex fractionated atrial electrogram (CFAE) ablation. Studies comparing CFAE with PVI in B: PAF(131-135), C: PAF and non-PAF(22,136,137), D: non-PAF only (25,135,138-143)

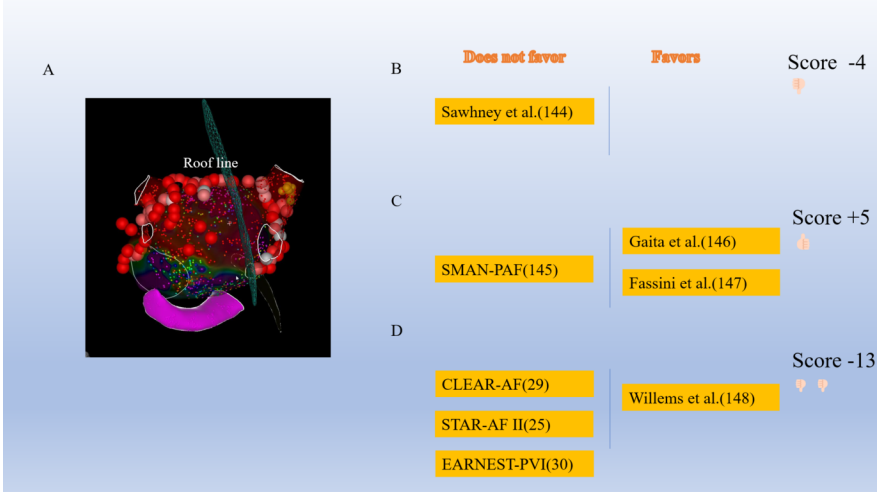

Fig. 3 A: Electroanatomical map showing roof line ablation. Studies comparing additional linear lesions with PVI in B: PAF(144), C: PAF and non-PAF(145-147), D: non-PAF only(25,29,30,148)

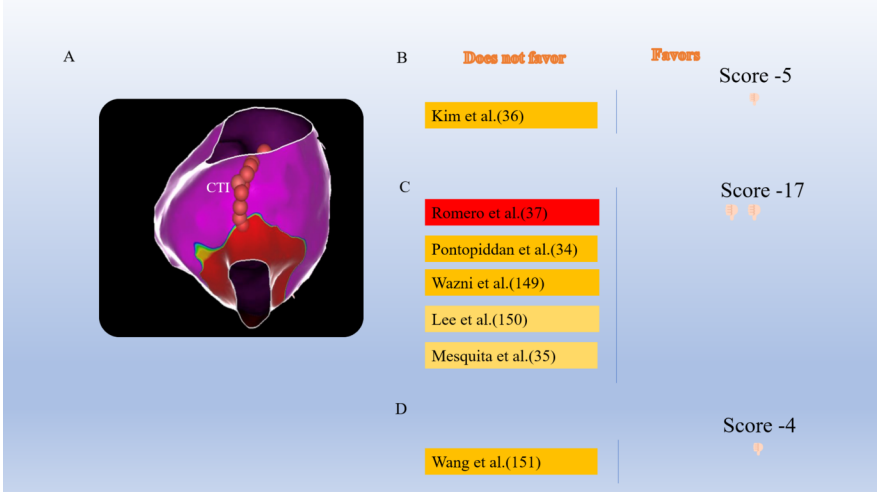

Fig. 4 A: Electroanatomical map showing cavo-tricuspid isthmus (CTI) line ablation. Studies comparing CTI ablation with PVI in B: PAF(36), C: PAF and non-PAF(34,35,37,149,150), D: non-PAF only(151)

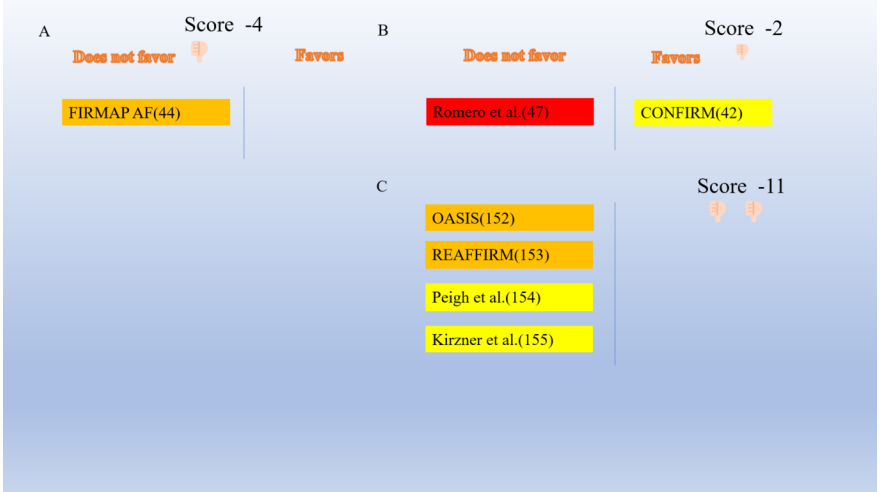

Fig. 5 Studies comparing rotor ablation with PVI in A: PAF(44), B:PAF and non-PAF(42,47), C: non-PAF only(152-155)

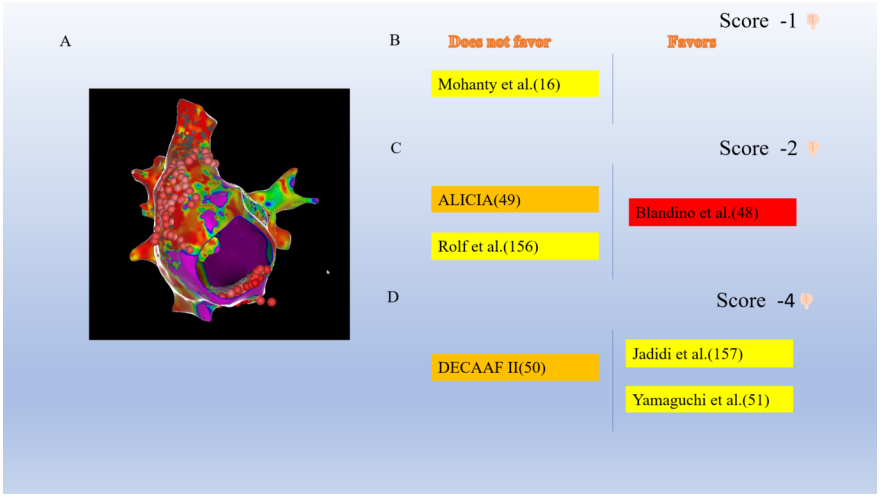

Fig. 6 A: Scar tissue ablation. Studies comparing ablation of scar tissue with PVI in B: PAF(16), C: PAF and non-PAF(48,49,156), D: non-PAF only(50,51,157)

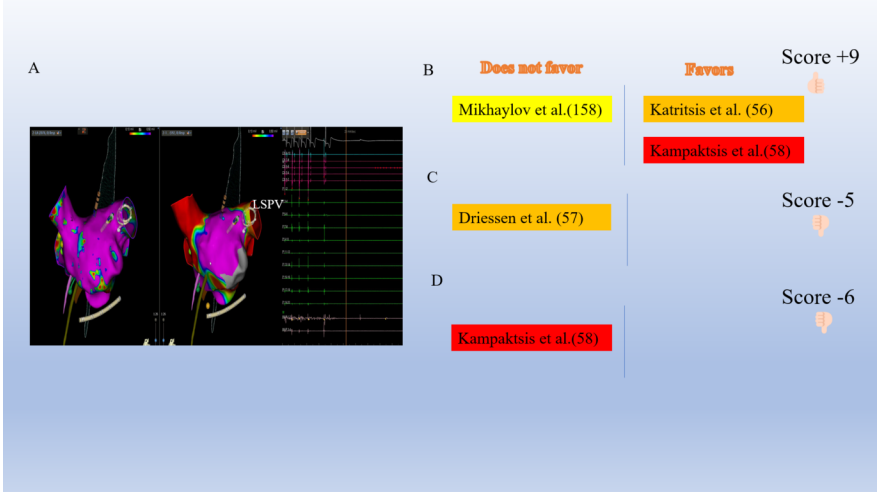

Fig. 7 A: Ganglionated plexi ablation. Studies comparing GP ablation with PVI in B: PAF(56,58,158), C: PAF and non-PAF(57), D: non-PAF only(58)

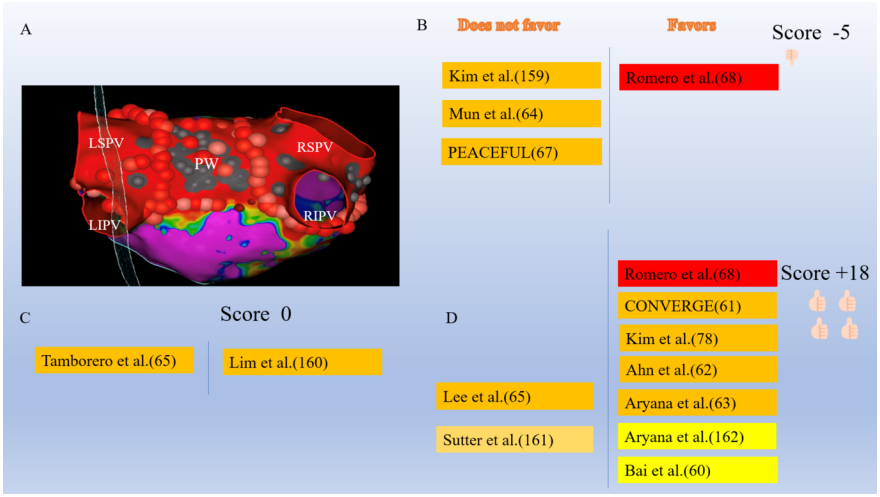

Fig. 8 A: Electroanatomical map showing posterior wall and pulmonary vein isolation. Studies comparing PWI with PVI in B: PAF(64,67,68,159) C: PAF and non-PAF(65,160), D: non-PAF only(60-63,66,68,78,161,162)

LSPV; left superior pulmonary vein, LIPV; left inferior pulmonary vein, RSPV; right superior pulmonary vein, RIPV; right inferior pulmonary vein; PW, posterior wall

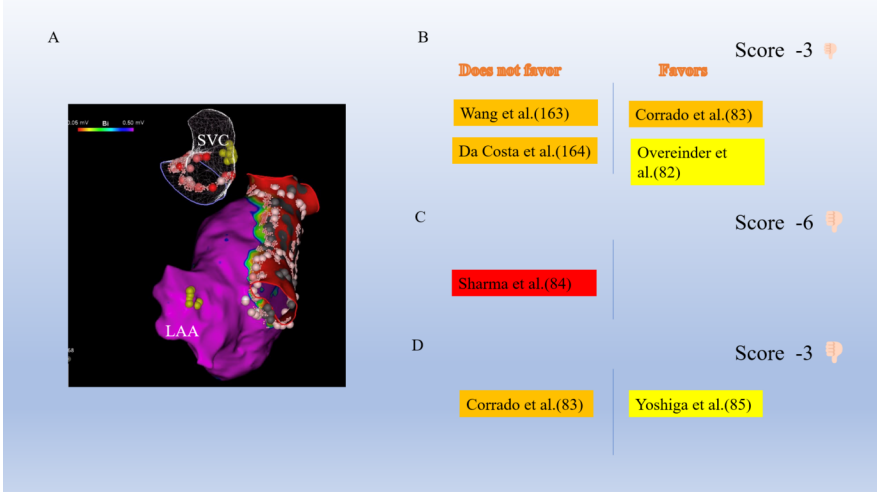

Fig. 9 A: Electroanatomical map superior vena cava isolation. Studies comparing SVCI with PVI in B: PAF(82,83,163,164), C: PAF and non-PAF(84), D: non-PAF only(83,85)

SVC; superior vena cava, LAA; left atrial appendage

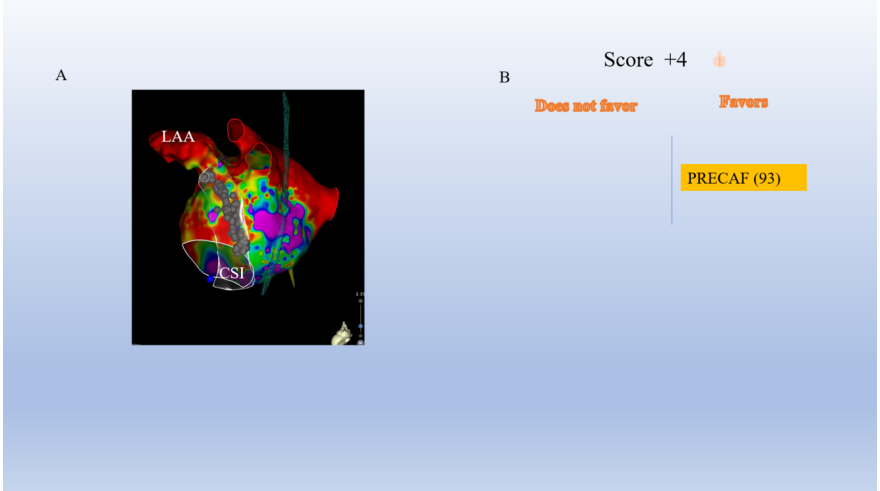

Fig. 10 A: Post ablation electroanatomical map showing coronary sinus isolation (CSI) B: Study comparing CSI with PVI and non-PV trigger ablation(93) LAA; left atrial appendage, CS; coronary sinus

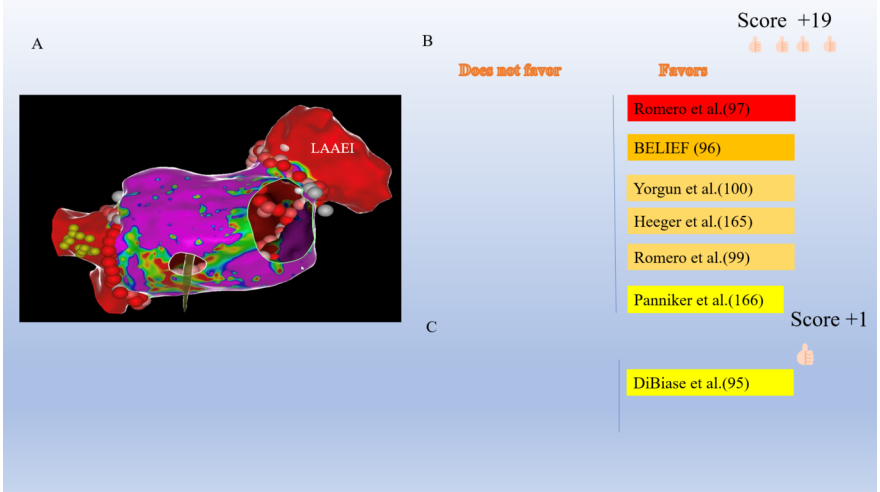

Fig.11 A: Electroanatomical map showing left atrial appendage electrical isolation. Studies comparing LAAEI with PVI in B: non-PAF(96,97,99,100,165,166), C: PAF and non -PAF(95) LAAEI; left atrial appendage electrical isolation

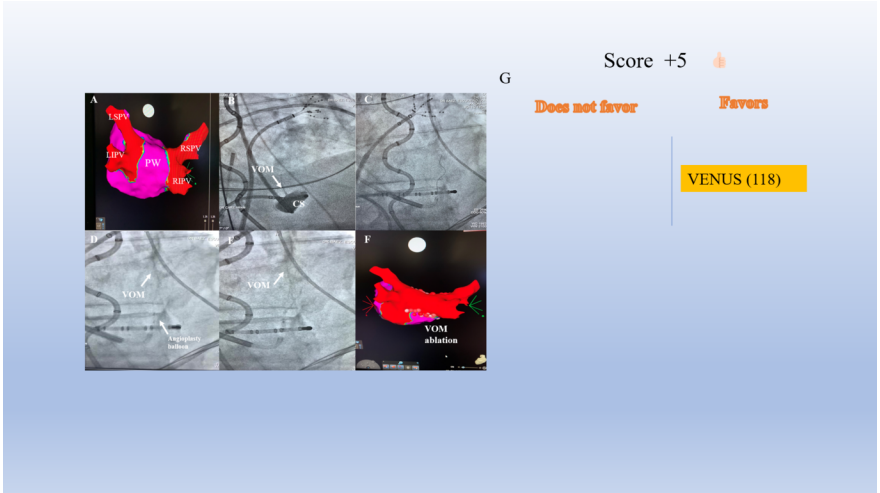

Fig.12 A: Electroanatomical map before ethanol infusion of vein of Marshall (VOM) showing isolated pulmonary veins. B: VOM originating from coronary sinus (CS) on right anterior oblique fluoroscopic view C: Wire placement D: VOM visualization E: Ethanol injection into VOM F: Electroanatomical map of left atrium post VOM ethanol infusion G: VENUS trial in favor of VOM ethanol infusion(118).