Vascular complications and recurrences after catheter ablation of atrial fibrillation

PhD thesis

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2. Publications included in the thesis

Riesz TJ, Bencsik G, Sághy L, Pap R. Does organized atrial tachycardia after a pulmonary vein isolation-only procedure portend better outcome of repeat ablation compared to recurrent atrial fibrillation? Journal of Arrhythmia. 2025 Apr;41(2):e70049. SJR indicator: Q2

Kupo P, Riesz TJ, Saghy L, Vamos M, Bencsik G, Makai A, et al. Ultrasound guidance for femoral venous access in patients undergoing pulmonary vein isolation: A quasi-randomized study. Cardiovasc electrophysiol. 2023 May;34(5):1177–82. Scientific paper

Riesz, Róbert Pap The Addition Of Left Atrial Linear Ablation To Pulmonary Vein Isolation Causes Organized Atrial Tachycardia Recurrence: A Meta-Analysis Journal of Atrial Fibrillation & Electrophysiology 18: 2 pp. 67-70. 4 p. 2025 SJR indicator: Q2

3. Introduction

Atrial fibrillation (AF) is a highly prevalent arrhythmia worldwide. In 2016, its global prevalence was 46.3 million individuals. (1) According to the Framingham study, the incidence of AF has tripled over the past 50 years. (2)

3.1.Pathomechanism of atrial fibrillation

Atrial fibrillation can arise from various, often overlapping mechanisms. In otherwise healthy patients, ectopic electrical activity originating from the pulmonary veins (PVs) can trigger unorganized atrial activation. The initially paroxysmal AF may progress to a persistent form causing electrophysiological remodeling, that creates atrial tissue substrates that are conducive to arrhythmogenesis. This remodeling is initially reversible, however, the progressing atrial fibrosis serves as a permanent source of microreentrant circuits – the main mechanism of persistent atrial fibrillation. (3)

On the other hand, different cardiac and extracardiac diseases elevate left atrial pressure and consequently induce left atrial remodeling, strongly associated with atrial fibrillation. The primarily contributing mechanisms – electrical, structural, neurohormonal, metabolic, and anatomic remodeling – often interact synergistically. Inflammation also plays a significant role in altering atrial structure. (4) These changes increase susceptibility to tachyarrhythmias via reentry and ectopic activity. (5)

3.2.Pathomechanism of organized atrial tachycardia (OAT)

OAT encompasses a spectrum of arrhythmias characterized by regular atrial activation. These include focal atrial tachycardia (AT) driven by active foci; and atrial flutter caused by a macroreentrant circuit around the tricuspid annulus (cavotricuspid-isthmus dependent or typical flutter) or other structures such as scars or mitral annulus (atypical flutter). (6) The behavior of OATs remains variable; while catheter ablation often yields favorable outcomes, the presence of atrial fibrosis may indicate advanced atrial remodeling and portend a poorer prognosis.

3.3.Pulmonary vein isolation

Current guidelines recommend catheter ablation with Class I indication as a therapeutic option for AF, offering superior outcomes compared to antiarrhythmic drug therapy. (7–11) Pulmonary vein isolation (PVI) is the suitable ablation technique to electrically separate the arrhythmogenic foci of the PVs from the atria. (7,8,12,13) PVI can be achieved using various modalities, including radiofrequency ablation, cryoablation, (14) and the emerging technique

of pulse field ablation (PFA). (15) Despite technological advancements, conventional point by point ablation remains a valuable approach, due to its comparable effectivity. (16)

Benefits of successful PVI:

AF induces both structural and electrical remodeling of the atria. Persistent restoration of sinus rhythm via PVI promotes reverse remodeling, evidenced by reduction of left atrial (LA) size, and improvement in conduction velocity. (17) In patients with heart failure, AF is associated with increased mortality and stroke compared to those in sinus rhythm. (17,18) Therefore, restoring sinus rhythm through PVI confers significant clinical benefits in this population. (19)

3.4.Intraprocedural adverse events and recurrence after catheter ablation

The development of new techniques aims to enhance procedural efficiency, shorten ablation time, and minimize adverse events.

Although the complication rate of AF ablation procedures is low, they may prolong hospitalization and often interfere with the quality of life of the patients. (20,21) The most frequent complications of these procedures are related to vascular access ranging in frequency from 1% to 13%. (20,22,23)

Traditionally, femoral vein puncture is guided by palpation of the femoral artery below the inguinal ligament and the needle is inserted next to the pulsation to target the femoral vein. However, the position of the femoral vessels in relation to each other is variable. (24) Vascular ultrasound (US) guidance can clarify the anatomy of the femoral vessels, identify variations that may interfere with the puncture, and thereby decrease access-related complications. (Figure 1.)

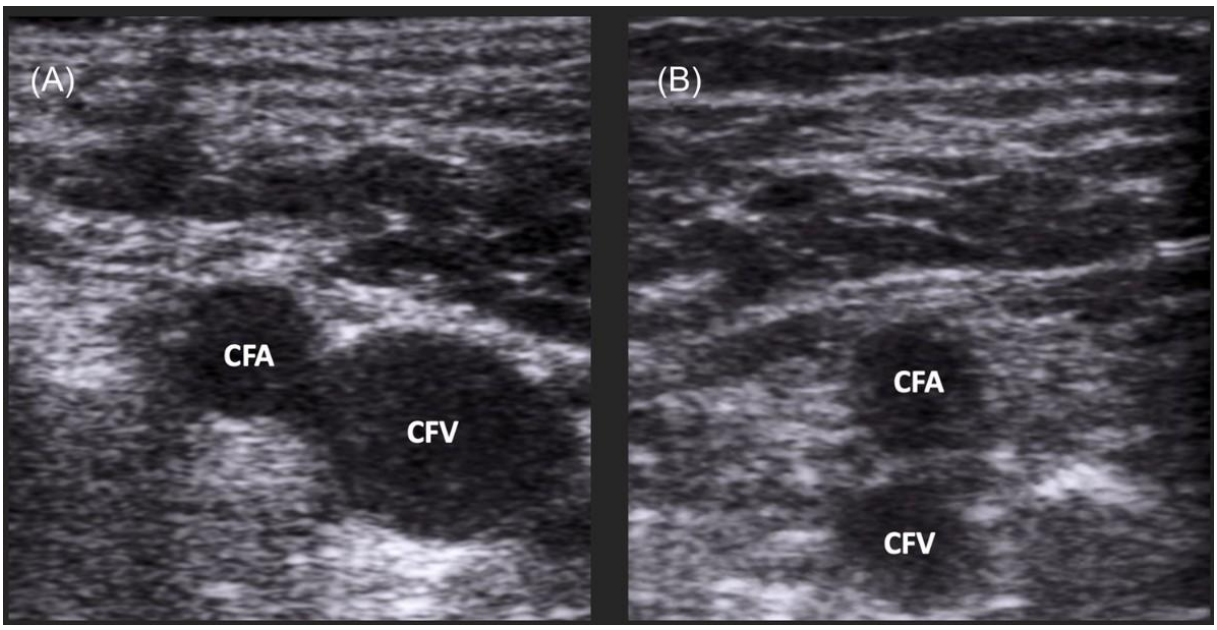


Figure 1 Illustrative examples of two-dimensional vascular ultrasound images of the femoral vessels with usual (A) and unusual (B)localization. CFA, common femoral artery; CFV, common femoral vein.1

Routine use of US to guide femoral access during electrophysiology (EP) procedures has been advocated, however, its universal adoption has been hampered by the lack of randomized-trial data unequivocally showing its benefit. Prior meta-analyses demonstrated that US guidance for femoral vein punctures in EP procedures reduces the rate of both major and minor vascular complications. (25,26) To date, only one randomized controlled trial (RCT) investigated the potential benefits associated with the use of US for femoral venous access in patients undergoing AF ablation procedures. (27) Although US guidance improved intraprocedural outcomes, there was no difference in the major complication rates presumably due to the lower-than-expected complication rate in the conventional arm.

Therefore, we performed a quasi-randomized comparison of patients undergoing AF ablation with or without US guidance for femoral vein punctures, taking advantage of the fact that during a certain period only one of two procedure rooms was equipped with a suitable US device.

Despite advances in technology, arrhythmia recurrence after catheter ablation of AF remains common, often necessitating (sometimes multiple) repeat procedures. Recurrence may result from incomplete isolation or ongoing electric and structural remodeling. While gap-related arrhythmias respond well to redo ablation, advanced remodeling may lead to further recurrences despite multiple redo ablations. Thus, optimal patient selection is crucial to maximalize success rates and minimize unnecessary procedures and associated risks.

Recurrent arrhythmias can be classified based on ECG morphology into AF or OATs. OATs are frequently driven by micro- and macroreentrant circuits, often involving anatomical structures such as AV valves or regions of atrial scarring. These scars may result from prior damage of left atrial tissue (28) or can be iatrogenic, following catheter ablation procedures.

Although no sound evidence to support it, modification of the extra-PV atrial substrate is frequently attempted during ablation for AF in addition to PVI. A commonly adopted technique is left atrial linear ablation (LALA) including creation of a roof line connecting superior PVs and/or a mitral line either posterior or anterior to the left atrial appendage. (29) Incomplete or reconnected linear lesions may create the conditions for reentry and lead to OAT involving the gaps. (30,31) Several studies have compared the results of AF ablation using PVI-only versus PVI + LALA and some have reported the rate of OAT recurrence as a secondary outcome. To investigate the relationship between LALA and recurrent OAT we performed a meta-analysis of studies where PVI-only and PVI + LALA strategies were compared, and the outcome was reported separately for recurrent AF and OAT.

There is a debate in the literature whether recurrence after catheter ablation of AF in the form of OAT portends a better prognosis, compared to recurrent AF. Several authors reported a more favorable outcome of redo procedures when the recurring arrhythmia was OAT, as compared to recurrent AF. (32–35) However, these and other studies also report the conflicting finding of more advanced left atrial (LA) remodeling (more dilated LA, more persistent AF, older age etc.) in patients with recurrent OAT, (34–36) a factor consistently associated with more recurrences. (37,38) The explanation for this discrepancy may lie in the fact that substrate modification (linear and/or electrogram-guided ablation) was attempted in addition to PVI during the index procedure in the above studies. These extra-pulmonary vein (PV) ablations are well known for their potential to cause iatrogenic OAT (39) and their utility in AF-suppression is limited, if any. (40) Therefore, some of the patients who recurred with OAT might have had their AF controlled by PVI but experienced a man-made arrhythmia. If the latter is eliminated during a redo procedure their prognosis can be more favorable than those who failed PVI in the first place. It follows that arrhythmia recurrence in the form of OAT may not be a favorable prognostic sign in case of a PVI-only initial strategy. We tested this hypothesis in a retrospective investigation.

4. Aims and objectives

Our studies address two key aspects of optimizing the risk-benefit ratio of AF ablation: minimizing the risk of local complications during femoral puncture and improving patient selection for redo ablations based of ECG morphology – specifically distinguishing between recurrent OAT and AF.

Regarding the mitigation of procedure-related adverse events, we conducted a quasi-randomized comparison of palpation-guided versus US-guided femoral puncture techniques, evaluating their respective complication rates.

To elucidate the mechanism of post-PVI OAT, we performed a meta-analysis assessing whether additional LALA beyond PVI increases OAT recurrence.

Furthermore, through a retrospective study, we investigated whether the ECG morphology of recurrent arrhythmia following a PVI-only ablation serves as a prognostic indicator for the success of repeat ablation.

5. Materials and methods

5.1. Quasi-randomized comparison of US- and palpation-guided puncture

Patient population of the study comprised consecutive patients older than 18 years undergoing pulmonary vein isolation (PVI) for AF with standard indications, on uninterrupted anticoagulant treatment, who were prospectively included. Patients on novel oral anticoagulants did not skip any dose even in the morning of the procedure. The target international normalized ratio for those who were taking vitamin K antagonist was 2.0–3.0. We excluded patients referred for a redo procedure. Patients were grouped based on whether US guidance was used for femoral venous access. Allocation to each of the two groups was quasi-randomized according to which of the two procedure rooms the patient was scheduled in, without preference. Only one of the rooms had vascular US capability and all venous punctures during procedures in this room were performed US guided. The conventional, palpation-based method was applied in the other room in all cases. Both procedure rooms were equally equipped except for the US machine. The same four novice operators in rotation, with no relevant previous experience in US-guided vascular access performed venous punctures in both rooms. For vascular US an 8 MHz linear transducer connected to a portable echocardiograph (Vivid I; GE Health Medical) was used. The transducer was covered with a sterile sleeve and placed at a 90°angle to the course of the vein at the groin to obtain a transverse view for vascular US-guided femoral vein puncture. After local anesthesia, an 18-G needle was used for femoral vein puncture and guidewire insertion. Two punctures were performed on both left and right femoral veins. An 11- and a 6-Fr sheath was inserted in the left, while an 8- and an 8.5-Fr long sheath was placed in the right femoral vein. PVI was performed using point-by-point radiofrequency ablation supported by CARTO electroanatomical mapping system (Biosense Webster Inc.). Intracardiac echo-cardiography (ICE) was applied to guide the procedure including transseptal puncture. Heparin was administrated intravenously just before transseptal puncture, when tenting of the fossa ovalis was visualized by ICE. Activated clotting time (ACT) was targeted between 300 and 350 s during the procedure. The endpoint for the procedures was PVI after 20 min waiting period. When the procedural endpoint was achieved, catheters were removed and transseptal sheaths were pulled back to the right side of the heart. Reversal of heparinization with intravenous protamine was applied followed by sheath removal at ACT < 200 s and manual compression until hemostasis was achieved. A compressive bandage was applied over both groins and was left in place for 6 h. Patients were discharged on the 1st postoperative day. The occurrence of vascular complications was systematically evaluated during the hospitalization.

The primary endpoint was the composite rate of major and minor vascular complications. The frequency of prolonged hospitalization was also compared between the two groups. Major vascular complications included groin hematoma, arteriovenous fistula, or pseudoaneurysm. Hematoma was considered as a major vascular complication if it met type 2 or higher Bleeding Academic Research Consortium (BARC) criteria (requiring nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care, or prompting evacuation). The type 1 BARC criteria define bleeding as nonactionable and not causing the patient to seek unscheduled medical attention, and hematomas that met these criteria were considered minor vascular complications. 13 The definition of prolonged hospitalization in this study referred to a patient's stay in the hospital more than one night following the completion of the ablation procedure. The protocol of the study is in accordance with the Declaration of Helsinki and the study protocol was approved by the regional ethics committee. All patients provided written informed consent.

5.2.Meta-analysis (PVI-only vs. PVI+LALA)

In our meta-analysis, full-text articles were selected from PubMed based on the following search string: "atrial fibrillation" and "pulmonary vein" and ablation and (linear or line) and (flutter or macroreentry or reentry) identifying 176 entries, between 1993 and June 2024. The references of selected papers were also inspected for relevant articles. Studies or subgroups of studies were included if they compared PVI-only and PVI + LALA (roof and/or mitral lines) approaches. Subgroups or studies were excluded if left atrial posterior wall (box-) isolation, electrogram-based ablation or low-voltage zone ablation was performed in more than 10% of the patients and when the number of patients with recurrence of OAT was not specified.

Mantel–Haenszel odds ratios (MH-OR) with 95% confidence intervals (CI) were calculated for pooled OAT and AF recurrence rates in a standard random-effect meta-analysis. From studies where mapping of recurrent OAT was performed, the pooled rate of iatrogenic arrhythmia (i.e. OAT involving previous LALA) was calculated. The I^2 test was used to determine the degree of heterogeneity across the studies. Subgroup analyses were conducted to explore the source of heterogeneity. Analyses were performed using Comprehensive Meta-Analysis v3.3.070 (Biostat, Inc., USA).

5.3.Retrospective study (OAT vs. AF recurrence)

In our retrospective study, 185 consecutive patients were included, who had redo ablation between January 2009 and December 2019 to treat recurrence of atrial arrhythmia following an index PVI. We excluded patients with linear ablation other than at the cavotricuspid isthmus (CTI) and those with electrograms-based ablation at the index procedure. To examine the effect of a history of typical atrial flutter, subgroups were created comprising those with or without a history of CTI ablation before or during the index procedure. Baseline characteristics of the study population are shown in Table 4. The study was approved by the institutional review board (222/2019-SZTE).

All patients gave written informed consent before the ablations. During the index procedure, all patients underwent antral PVI, without empirical left atrial linear ablation. Ablation of the CTI was carried out at the index procedure in patients with documented or induced typical atrial flutter. Non-CTI dependent atrial macroreentry occurring during the index procedure was typically not targeted. Spontaneously occurring non-PV triggers were targeted at the discretion of the treating physician. Isoproterenol provocation was not routinely performed at the index procedure. Radiofrequency (RF) energy was applied with a deflectable, open-irrigated catheter, using a point-by-point technique, around ipsilateral PVs. Ablation at the interPV carina was not part of the lesion set. Adenosine testing after PVI was typically not performed. The procedures were guided by intracardiac echocardiography and a real-time, 3D non-fluoroscopic navigation system (NavX or CARTO). The mapping system was used to create a left atrial shell, in the placement and titration of ablation lesions. However, mapping of left atrial voltage was not routinely performed. A circular mapping catheter was used for the recording of PV potentials and the verification of the isolation. Complete isolation of all the PVs after a 30-min waiting period was the endpoint of the procedure.

Patients had follow-up visits 3 months, 6 months, and 1 year after the index procedure, and yearly thereafter. Symptom status, 12-lead ECG, 24-h or 1-week Holter ECG, and transtelephonic ECG were used for assessing AF recurrence. Asymptomatic recurrences were sought by 1-week Holter monitoring at least six months after the procedure. Recurrences were defined as any atrial arrhythmia lasting more than 30 s. Recurrent AF was defined by irregularly irregular R-R intervals, absence of distinct P waves and irregular atrial activations on surface and/or intracardiac ECG. OAT was defined by regular atrial activation and fixed or regularly irregular RR intervals. Patients who experienced both recurrent OAT and AF during follow-up after the index procedure were enrolled in the AF recurrence group. The same categorization

was used when analyzing the type of recurrence after redo procedures. The mechanism of OAT was determined during the redo procedure, except for patients with ECG documented typical flutter undergoing empirical CTI ablation in sinus rhythm. Paroxysmal arrhythmia was defined by termination spontaneously or by cardioversion within 7 days. Patients with persistent AF had sustained arrhythmia lasting >7 days.

All redo procedures were performed due to recurrent arrhythmia at least 3 months after the index ablation.

In patients with recurrent AF reconnected PVs were reisolated similarly to the index procedure. Pharmacologic stimulation using isoproterenol infusion (3-20 ug/min) to disclose non-PV triggers and subsequent extra-PV ablation were executed mostly in cases where minimal PV reconnection was found, at the discretion of the operator. No empirical linear ablation was performed.

In case of documented, recurrent OAT if the patient presented in sinus rhythm, programmed atrial stimulation (with up to 3 extrastimuli and two drive cycle lengths, without isoproterenol) was performed for arrhythmia induction. Alternatively, if the ECG documentation of the clinical arrhythmia was characteristic for typical flutter (counterclockwise CTI dependent atrial flutter) empirical ablation of the CTI was performed in sinus rhythm and the induction protocol performed afterwards.

If the patient presented with ongoing OAT entrainment pacing was performed first at the CTI. If CTI dependent flutter was diagnosed, linear RF ablation of the CTI was carried out. When the atrial flutter terminated, and bidirectional CTI block was achieved induction was attempted by programmed stimulation to reveal further atrial arrhythmias. For non-CTI dependent flutter activation mapping with an electroanatomic (EA) mapping system (CARTO 3, Biosense Webster, Diamond Bar, CA, USA) and further entrainment mapping was used to delineate the arrhythmia circuit. A non-CTI dependent atrial flutter was defined as gap-related when activation mapping suggested an origin around PV ostia, entrainment pointed to participation of reconnected PV myocardial sleeves, at least two gaps in the previously placed PVI ring were demonstrated: one serving as an entrance, the other as exit to electrical activation and the flutter terminated during ablation of one of the gaps. Other non-CTI dependent flutters were targeted by linear RF lesions, connecting electrically silent regions (spontaneous or previous ablation scar or mitral annulus). Linear ablation was considered successful after termination of the ongoing arrhythmia and demonstration of conduction block across ablation lines by pacing

close to the line and observing an activation detour on the opposite side. The latter was the end point of empirical ablation in case of non-inducible OAT.

Follow-up after a redo procedure followed the same protocol as after the index PVI. The primary end point of this study was freedom from recurrent atrial arrhythmia and recurrence free survival time after the last redo ablation, without antiarrhythmic drugs (AAD). Secondary end point was successful rhythm control, defined as lack of recurrence on or off AADs.

After collecting the data, statistical analyses were performed. Baseline characteristics of the study population with discrete and continuous variables were compared with chi-square test and independent samples t-test, respectively. Recurrence rates in different groups of the study population were compared with chi-square test, while Kaplan-Meyer curve and log-rank analysis were applied to evaluate recurrence-free survival time.

6. Results

6.1.Quasi-randomized comparison of US- and palpation-guided puncture

Of 457 patients 199 were allocated to US-guided puncture group, while the conventional, palpation-based approach was performed in 258 cases. There was no difference in patients' baseline characteristics between the groups (Table 1).

	Conventional puncture group	**US-guided puncture group**	**p Value**
Number of patients	258	199	n.s.
Sex, male (%)	145 (56.2)	113 (56.8)	n.s.
Age (years)	63.5±9.4	62.8±10.7	n.s.
Hypertension (%)	190 (73.6)	158 (79.4)	n.s.
Diabetes mellitus (%)	46 (17.8)	39 (19.6)	n.s.
Heart failure with reduced EF (%)	18 (7.0)	14 (7.0)	n.s.
Body mass index	29.7±4.7	28.5±4.1	n.s.
DOAC use (%)	145 (56.2)	127 (68.8)	n.s.
INR in patients on VKA treatment	2.1±0.5	2.2±0.5	n.s.

Table 1 Clinical characteristics of study population in the quasi-randomized comparison of US- and palpation-guided puncture

Compared with the conventional technique, US guidance reduced the composite rate of minor and major vascular complications (11.63% vs. 2.01%, $p < .0001$). The use of US significantly reduced both major (4.26% vs. 1.01%, $p = .038$) and minor (7.36% vs.1.01%, $p = .001$) vascular complications. The absolute risk reduction of minor/major vascular complications was 9.62% equated to a relative risk reduction (RRR) of 82.71%, and a number needed to treat of 10 to prevent one bleeding event. The decrease in the rate of prolonged hospitalization was also statistically significant (5.04% vs. 1.01%, $p = .032$). Results are shown in Figure 2 and Table 2.

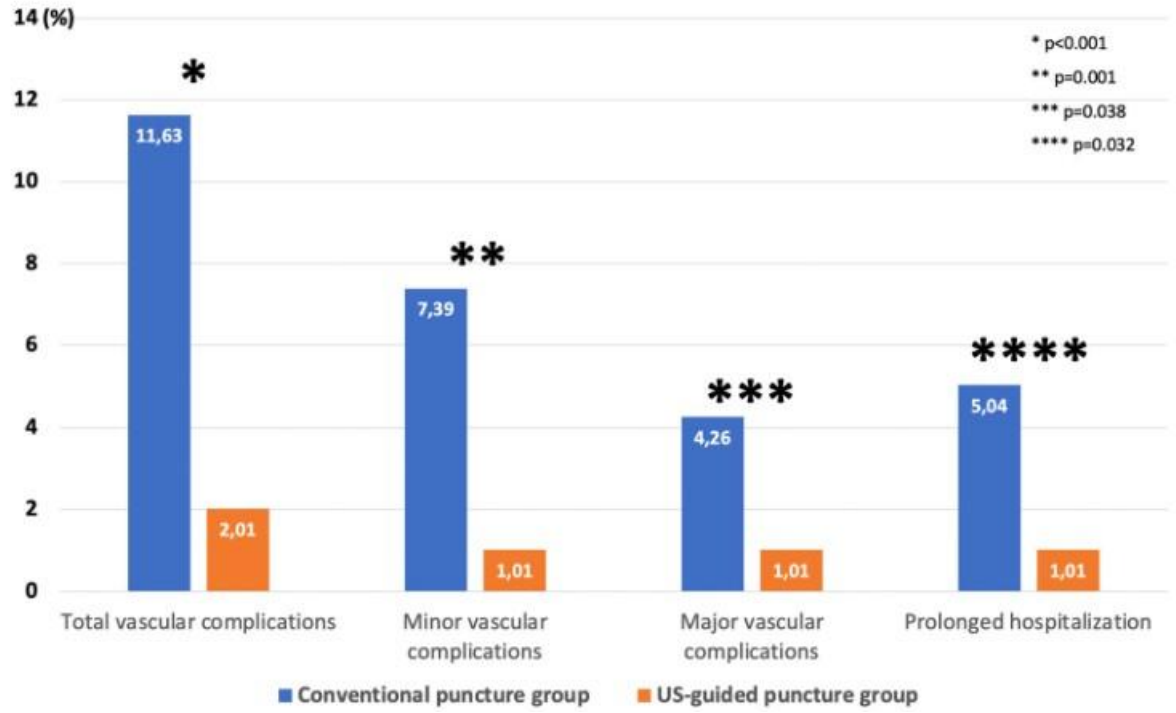


Figure 2 Comparison of major complications, minor complications, and prolonged hospitalization between conventional versus ultrasound (US)-guided femoral vein puncture group.

	Conventional puncture group	**US-guided puncture group**	**p Value**
Total vascular complications (%)	30 (11.63)	4 (2.01)	<0.001
Minor vascular complications (%)	19 (7.39)	2 (1.01)	0.001
Major vascular complications (%)	11 (4.26)	2 (1.01)	0.038
Prolonged hospitalization (%)	13 (5.04)	2 (1.01)	0.032

Table 2 Comparison of major complications, and prolonged hospitalization between conventional versus ultrasound-guided femoral vein puncture group.

Note: See Methods section for definitions. Abbreviations: US, ultrasound

6.2.Meta-analysis (PVI-only vs. PVI+LALA)

From 176 papers, two single-center, observational studies (41,42) and eight randomized, controlled trials (RCT) (40,43–49) met the inclusion criteria (Table 3). Only paroxysmal AF patients were included in three, while only persistent AF in two studies. The rest included both paroxysmal and persistent AF patients in different ratios. Regarding the LALA performed: only roof line was created in 2 studies, only mitral line in one, while both lines were performed in the remaining seven studies. Radiofrequency ablation was utilized in all studies.

Study	Design	AF type	LALA	Follow-up (months)	Iatrogenic OAT (mapped)	Other OAT (mapped)
Fassini 2005	RCT (single centre)	67% paroxysmal, 33% persistent	mitral line (posterior)	> 12		
Willems 2006	RCT (single centre)	100% persistent AF	roof line, mitral line (posterior)	16 (median)	2/2 - both perimitral with incomplete line	
Gaita 2008	RCT (single centre)	61% paroxysmal, 39% persistent	roof line, mitral line (posterior)	>36	7/13 - 6 perimitral, 1 roof-dependent	RA macroreentry, LA microreentry
Sawhney 2010	RCT (single centre)	100% paroxysmal	roof line, mitral line (posterior)	16 (mean)	6/9 - 4 perimitral, 2 roof dependent	LA ridge related
Mun 2012	RCT (single centre)	100% paroxysmal	roof line, mitral line (posterior)	16 (mean)		
Arbelo 2014	RCT (single centre)	100% paroxysmal	roof line	16 (mean)		
Verma 2015	RCT (single centre)	100% persistent AF	roof line, mitral line (posterior)	18		
Wynn 2016	RCT (single centre)	61% persistent, 39% sustained paroxysmal	roof line, mitral line (posterior)	12		
Ipek 2019	observational	59% paroxysmal, 41% persistent	roof line	28 (median)		
Lim 2024	observational	both (% not reported)	roof line, mitral line (anterior or posterior), CFAE (8,6%)	77 (mean)	29/36 - 25 perimitral, 7 roof-dependent	LA anterior, septal

Table 3 Studies evaluated in the meta-analysis and their most important parameters.

Out of the total 5536 patients, 4426 (80%) had PVI-only, while 1110 (20%) had PVI + LALA. After PVI-only 201 (4.5%) patients experienced recurrence of OAT, while after PVI + LALA recurrence of OAT occurred in 145 (13%). Seven studies reported the AF recurrence rates also, among the same patients. The pooled rates of AF recurrence in these studies after PVI-only and PVI + LALA were 41% and 38%, respectively.

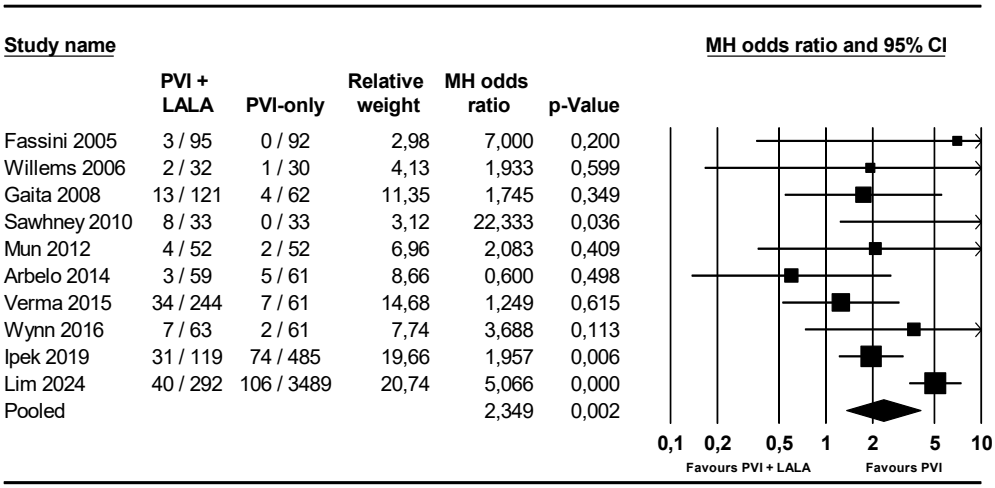


Figure 3: Studies examined in the meta-analysis. Number of OAT-recurrence were extracted from the studies in PVI + LALA and PVI-only patients, respectively.

The meta-analysis confirmed a significantly higher rate of OAT recurrence after PVI + LALA, compared to PVI-only (MH-OR 2.35, 95%CI 1.40-4.07, p=0.002) (Figure 3.). To explore the source of considerable heterogeneity (I^2=60%), a subgroup analysis was performed comparing studies in which only one (roof or mitral) line was created to those where both LALA were performed. In the three studies utilizing a single LALA there was no significant effect size in terms of OAT recurrence (MH-OR 1.43, 95%CI 0.39-5.23, p=0.590). The combination of the remaining seven studies where both lines were created showed a significantly higher rate of OAT recurrence with LALA (MH-OR 2.80, 95%CI 1.43-5.49, p=0.003). There was no significant difference in the pooled rate of AF recurrence after PVI + LALA and PVI-only strategies (MH-OR 0.59, 95%CI 0.28-1.21, p=0.146) (Figure 4).

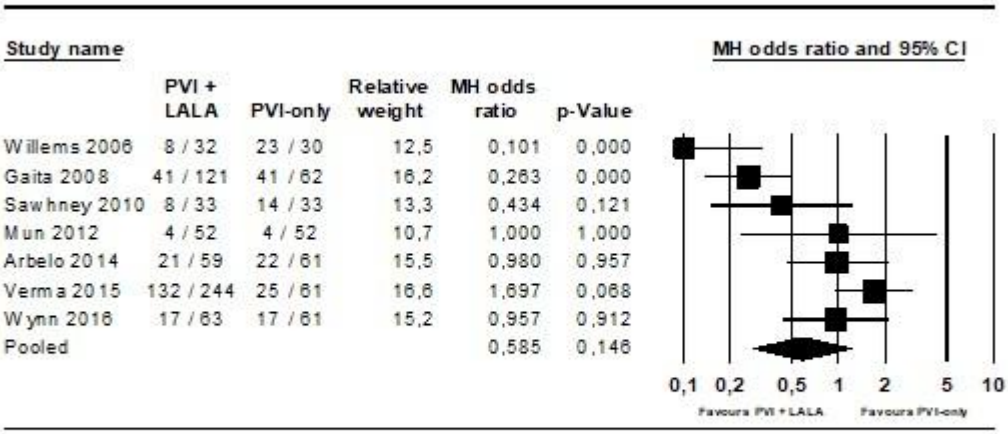


Figure 4: MH odds ratio of the examined studies, respectively, and the pooled MH odds ratio for AF recurrence.

Four studies reported the results of mapping of recurrent OAT during a redo procedure. The pooled frequency of the arrhythmia being related to gaps in previous LALA was 44/60 (73%).

6.3.Retrospective study (OAT vs. AF recurrence)

The indication for the index procedure was paroxysmal AF in 90 (48%) patients, and persistent AF in 95 (52%) patients. Twenty-two patients (12%) had a history of non-PV ablation before the index procedure (CTI in 15, AV nodal slow pathway in 4 and focal atrial tachycardia ablation in 2 patients).

During the index procedure only PVI was performed in 152 (82%) patients. All PVs were successfully isolated. Additional cavotricuspid isthmus (CTI) ablation was carried out in 30 (16%) cases, superior vena cava (SVC) isolation in 2 (1%), focal LA ablation in 3 (2%), AV nodal slow pathway ablation in 1 (0.5%) case.

Among the 185 patients, only OAT recurrence was recorded in 45 (24%), and AF in 140 (76%) cases. Patients who had recurrent AF and OAT as well were enrolled into the AF group. Recurrent AF was paroxysmal in 100 (71%), persistent in 40 (29%) patients (Table 4.). Recurrent arrhythmia was persistent and still ongoing at the beginning of the redo ablation in 27 of 45 (60%) patients in the OAT group.

type of initial atrial fibrillation	paroxysmal	persistent	p
number of patients	90	95	
male (%)	49	56	0.671
ejection fraction (%)	63.16±7.48	61.70±8.01	0.208
left atrial AP diameter (mm)	43.99±5.83	46.57±6.58	0.007
time to recurrence after index PVI (months)	16.44±15.02	17.11±12.93	0.742
follow up time after last redo (months)	40.97±26.72	32.97±21.14	0.026
age (years)	63.82±9.25	64.73±8.07	0.479
hypertension (%)	72	75	0.754
diabetes mellitus (%)	12	14	0.513
ischemic heart disease	11	11	0.309
CHADS-VASc score	1.80	1.81	0.957
recurrent OAT(%)/AF(%)	27/73	22/78	0.470
Gap-related OAT (%)	9	2	0.053

Table 4. Comparison of patients with paroxysmal and persistent AF before index PVI. OAT: organized atrial tachycardia, AF: atrial fibrillation, PVI: pulmonary vein isolation

Baseline parameters did not differ significantly between patients with OAT or AF recurrence, except OAT patients had a shorter time to recurrence after index PVI (Table 5). Minimum follow-up time was one year, mean follow-up time was 37±24 months.

type of recurrent arrhythmia	OAT	AF	p
number of patients	45	140	
male (%)	49	54	0.584
ejection fraction (%)	61.95±8.33	62.55±7.61	0.661
left atrial AP diameter (mm)	44.95±5.79	45.45±6.52	0.661
rate of persistent AF before index PVI (%)	53	47	0.470
time to recurrence after index PVI (months)	11.51±8.83	18.48±14.86	<0.001
follow up time after last redo (months)	44.45±27.55	34.39±22.70	0.029
age (years)	64.60±9.90	64.19±8.25	0.800
hypertension (%)	69	75	0.419
diabetes mellitus (%)	13	13	0.934
ischemic heart disease (%)	15	9	0.240
Mean CHADS-VASc score	1.73	1,48	0.677
PV-reconnections at 1. redo ablation (%)	82	94	0.022
Mean number of ablations	1.267	1.136	0.126

Table 5. Comparison of patients with OAT and AF recurrence. OAT: organized atrial tachycardia, AF: atrial fibrillation, PVI: pulmonary vein isolation

All patients had at least one redo and 23 (12%) underwent multiple repeat ablations after the initial PVI. The maximum number of redo procedures was 4. The first redo ablation was performed after 503.5±418.4 days from the initial procedure.

Reconnection of PVs was documented during the first redo ablation in 168 patients (90%), 37/45 (82%) in the OAT group and 131/140 (94%) in the AF group (p=0.022). Both left and right PVs were reconnected in 91 (54%), only left PVs in 25 (15%) and only right PVs in 52 (31%) cases. In the 23 patients who underwent a second redo ablation, reconnection was detected in 11 (48%); 4 out of 9 OAT patients (44%) and 7 out of 14 AF patients (50%) (p=0.79). In 8 patients, left and right PVs were both reconnected, in 2 cases reconnection was observed in the left, and in 1 patient in the right PVs. Recurrent PV reconnection was detected in only 2 of 8 (25%) subsequent redo procedures, in 1 case on both sides and in the other the left PVs were affected.

Among patients without PV reconnection, 8 (43%) were from the OAT group. In these cases ablation of the OAT was attempted. In 1 case, AV nodal reentry was also inducible, and the slow pathway was ablated. The remaining 9 patients without PV reconnection were from the AF group. The ablation targets were: ongoing (1 patient) or induced (2 patients) CTI dependent flutter, inducible left atrial OAT (2 patients), complex electrograms (in the rest).

No significant difference was observed in the success rate after the first redo ablation between OAT and AF groups (49% vs. 52%, p=0.72) (Figure 5.). Also, recurrence free survival time was not different between groups (51.08±6.66 vs. 53.37±4.75 months, p=0.54). Moreover, the majority of recurring patients after the first redo ablation had recurrent AF during further follow up in both groups (71% and 82% of recurrences in the OAT and AF groups, respectively, p=0.26).

Similarly, no significant difference was observed between OAT and AF groups in the rate of recurrence-free patients after the last redo procedure (60% vs. 58% p= 0.80), in the success of rhythm control (84% vs. 85%, p=0.93) and in mean recurrence-free survival time (63.2±7.04 vs. 61.2±5.32 months, p=0.23). (Figure 5. and 6a.).

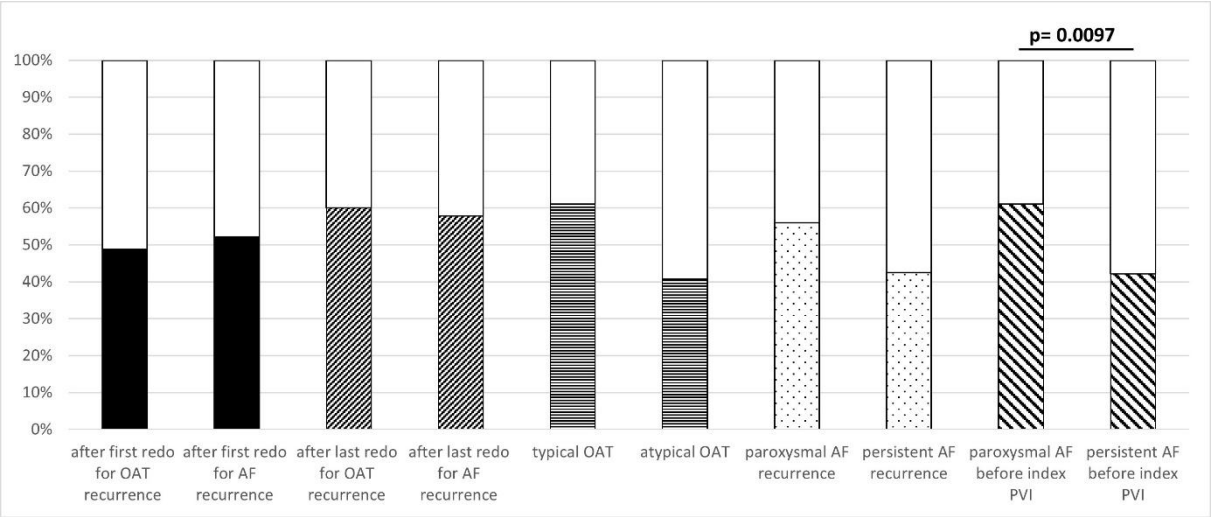
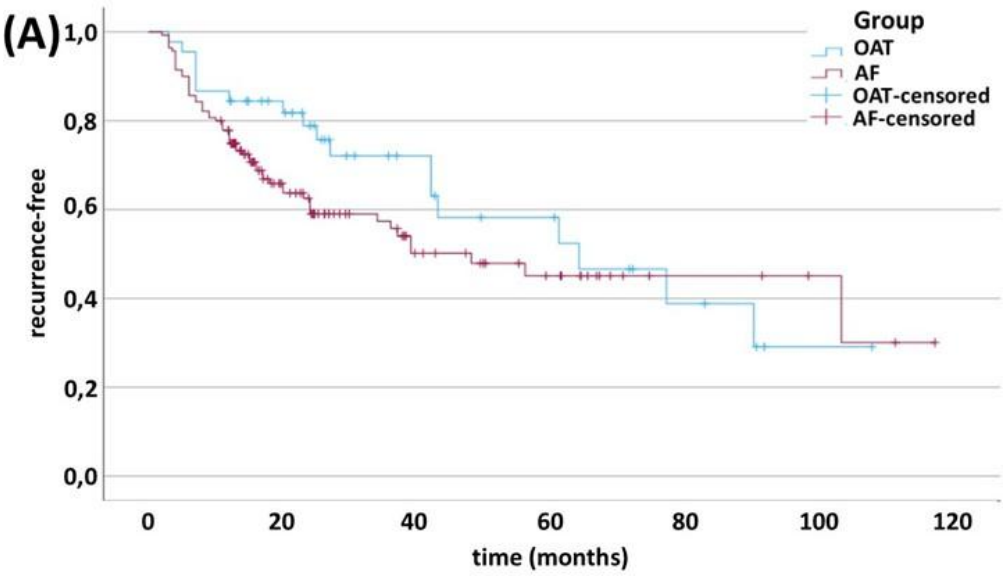
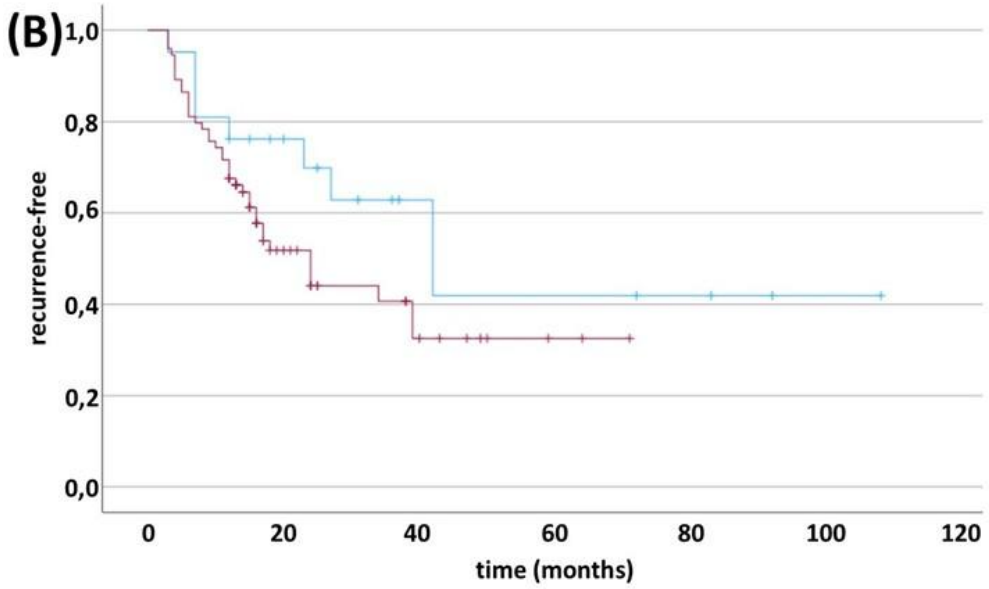


Figure 5: Rate of recurrence-free patients (shaded rectangles) in different groups. OAT: organized atrial tachycardia, AF: atrial fibrillation, PVI: pulmonary vein isolation

Recurring patients after the last procedure had AF in 95% and 92% in the OAT and AF groups, respectively (p=0.32).

Separate analyses were conducted for patient groups with initially persistent and paroxysmal AF. In the subgroup of 95 patients with persistent AF before the index PVI, recurrence was OAT in 21 (22%) cases, AF in 74 (78%) cases, with 34 (46%) having recurrent persistent AF among the latter. In this subgroup, no significant difference was observed between those with OAT as compared to those with AF recurrence in the success rate after the first (43% vs. 42%, respectively, p=0.94) or last redo procedure (57% vs. 47%, respectively, p=0.43), and the rate of successful rhythm control (81% vs. 76%, respectively, p=0.61) (Figure 6b). In the subgroup undergoing index PVI for paroxysmal AF there was also no difference in the primary or secondary outcome measures between patients with OAT vs. AF recurrence (all p>0.1) (Figure 6c).


(A)
Group
OAT
AF
OAT-censored
AF-censored
recurrence-free
1,0
0,8
0,6
0,4
0,2
0,0
0
20
40
60
80
100
120
time (months)


(B)
recurrence-free
1,0
0,8
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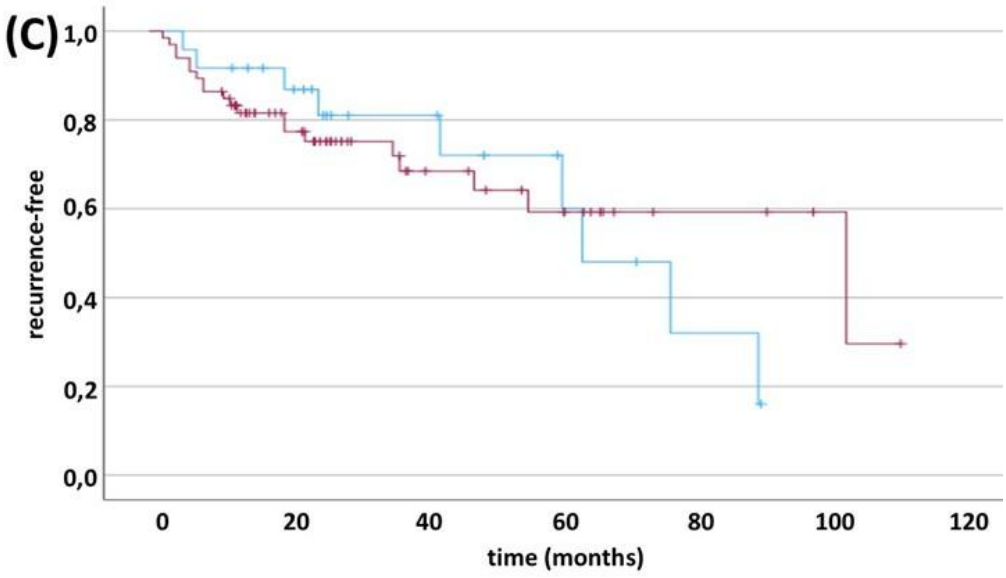
time (months)


(C)
recurrence-free
1,0
0,8
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0,0
0
20
40
60
80
100
120
time (months)

Figure 6: Recurrence-free survival after last redo ablation. **a**: all patients **b:** patients with persistent AF at initial PVI **c:** patients with paroxysmal AF at initial PVI. OAT: organized atrial tachycardia, AF: atrial fibrillation

Subgroup analysis showed higher rate of OAT vs. AF recurrence in patients with a history of CTI ablation, compared to those without such a history (36% vs. 20%, p=0.024). However, OAT vs. AF recurrence was not predictive of the success of first or subsequent redo procedures in either of the subgroups (i.e. patients with and without a prior history of CTI ablation, all p>0.1).

Our work specifically focused on the impact of OAT and AF type on success of redo procedures

Among 45 patients with only OAT recurrence after index PVI, the arrhythmia was categorized as CTI-dependent flutter in 18 patients (40%). CTI ablation was successfully performed in all of them. The other 27 (60%) patients were diagnosed with atypical OAT. The most common arrhythmia mechanisms in this group were: roof-dependent left atrial flutter (25%), targeted by roof line ablation, perimitral flutter (21%), treated by anterior (50%) or posterior (50%) mitral line ablation, gap-related flutter (18%) treated by redo PVI. The acute success of non-CTI dependent flutter ablation was 80%. Five (18%) patients also had focal atrial tachycardia successfully ablated. Altogether 8 (17%) patients had multiple OATs targeted during the redo procedure.

Comparing only the successful recurrent OAT ablations with redo ablation for AF recurrence, success rate (56% vs. 51%, p=0.71, respectively) and rate of successful rhythm control (89% vs. 85%, p=0.36, respectively) did not show significant difference. On the other hand, when OAT ablation was acutely unsuccessful the prognosis tended to be worse than after successful OAT ablation (25% vs. 68% success, p=0.026 and 63% vs. 89% ultimate rhythm control, p=0.059).

There was no significant difference in the rate of recurrence-free patients and successful long-term rhythm control between CTI-dependent and atypical OAT (61% vs. 41%, p=0.18 and 78% vs. 89%, p=0.35, respectively). Recurrence-free survival time did not show difference either (50.55±8.37 vs. 47.9±9.4 months, respectively, p=0.717).

Gap-related OAT tended to be more common in patients with paroxysmal AF before index PVI (Table 4). In this subgroup the success rate after the last redo was numerically, but non-

significantly higher in patients with gap-related, compared to other OAT (83% vs. 56%, p=0.22).

The success of redo procedures was higher in patients who had undergone the index PVI for paroxysmal, as compared to persistent AF after the first (61% vs. 42%, p=0.01), and after the last redo ablation (68% vs. 48%, respectively, p=0.012). Ultimate rhythm control was also achieved more frequently (93% vs. 77%, p=0.002).

The difference in success rate of redo procedures and recurrence-free survival did not reach statistical significance between patients with paroxysmal vs. persistent AF recurrence after index PVI (56% vs. 43%, p=0.14 and 58.83±5.58 vs. 28.9±4.69 months, respectively, p=0.093), but paroxysmal AF recurrence was associated with a higher rate of successful rhythm control (92% vs 68%, p<0.0002) (Figure 5.).

7. Discussion

Our three studies focused on different steps of ablations in the "road to sinus rhythm". Our first prospective, quasi-randomized comparison of US- and palpation-guided femoral vein puncture enrolled patients undergoing initial PVI and examined the first step of ablations. The comparison supports that US-guidance improved the safety of AF ablation procedures compared with the conventional, palpation-based technique. US guidance was associated with lower composite, major and minor vascular complication rates. The most common complications of the EP procedures are related to the vascular access. (20,21) AF ablations carry the highest risk for these types of events, which can be explained by the use of large and multiple sheaths and uninterrupted, periprocedural anticoagulant treatment. (22,50,51) Vascular US guidance during femoral access provides real-time visualization of the inguinal vessels and the surrounding structures, identifying anatomical variations. (52) Additionally, it allows following of the needle during the puncture to guide and correct its course. (53) Several nonrandomized, observational studies showed the superiority of the US-guided technique in the rate of vascular complications of AF ablation, (54–56) however the only one RCT failed to meet its primary endpoint. (27) A retrospective trial involving 3420 patients undergoing PVI for AF showed, that US-guided femoral vein puncture improves the safety profile of PVI procedures by reducing total, major, and minor vascular complications. (54) Although the rate of these complications was low even in the non-US group (1.7%), the benefit from US guidance was clearly demonstrated by a 70.6% RRR. In the multicenter ULTRA-FAST RCT 320 patients, who underwent an AF ablation procedure were randomized to US-guided or conventional vein puncture.

The study was prematurely terminated before meeting its primary endpoint of reduction in vascular complications due to substantially lower-than-expected complication rates, which doubled the population size needed to maintain statistical power. (27) Only four major vascular complications occurred during the whole study period (1 [0.6%] in the US and 3 [1.9%] in the conventional arm). Nonetheless, beneficial intraprocedural outcomes — including shorter puncture time, fewer inadvertent arterial puncture, and higher first pass success rate — were associated with US guidance. In a prior meta-analysis by Sobolev et al. US-guided femoral vein puncture reduced the rate of major vascular complications in patients undergoing EP procedures. (25) Furthermore, another larger meta-analysis confirmed these findings and demonstrated 73% risk reduction in major vascular complications with US guidance in PVI procedures. (26) Interestingly, in one retrospective single-center trial including 4734 patients undergoing AF ablation procedures the benefit of US-guided femoral vein puncture was found in males only. (57) A most recently published retrospective analysis involving more than 10 000 and including 4356 AF patients also demonstrated, that major vascular complications are exceedingly rare with use of US for vascular access. (58) Vascular US for vessel puncture in EP procedures proved to be a cheap, easy-to-learn tool, (59) and is cost-effective. (60) In spite of the observational results the use of US to guide vascular access has still not been adopted by many EP centers worldwide. (58) While the lack of convincing RCT data supporting US use discourages these to change their practice, others are reluctant to omit US in any patient even for the sake of performing such an RCT. (61) Our quasi-randomized analysis may serve as a substitute for a true RCT. We prospectively collected data on patients who under-went PVI during the same period, by the same operators, but were randomly assigned to US guidance based on its availability. The results demonstrate a remarkable improvement in the risk of vascular complications and serve as a basis for a more widespread adaptation of the technique of US-guided femoral access for AF ablation. This quasi-randomized comparison strongly supports adapting routine use of US for AF ablation procedures.

In the second phase of our studies, we investigated factors influencing optimal patient selection for redo PVI. The primary objective was to define whether OAT recurrence differs in prognosis from AF recurrence. First, we sought to establish whether OAT recurrence is associated with not only patient-specific, but also procedural factors of AF ablation, specifically LALA added to PVI. Such an association would suggest that OAT recurrence following combined PVI+LALA may reflect an iatrogenic mechanism rather than a spontaneous recurrence pattern. The meta-analysis of available studies showed an increased rate of OAT recurrence after adjunctive linear ablation on top of PVI in the treatment of AF. This association was most

pronounced in case of studies employing a more extensive LALA lesion set. The increased rate of OAT recurrence was not offset by less AF recurrence after LALA in the meta-analysis. Furthermore, the OAT observed after LALA was related to gaps in the previously performed ablation line in more than 70% of the cases.

Empirical LALA is still employed in a considerable proportion of cases, despite the fact that it has not been shown to improve the outcome of AF ablation and it is not recommended by the latest guideline. (29) In addition to its limited effectiveness on top of PVI, LALA by contemporary RF technology leads to an increased rate of OAT recurrence. This proarrhythmic effect is probably related to incompleteness and low durability of linear lesions produced by legacy techniques. Slow conduction through gaps in the lines provides the requirement for the development of macroreentry. (30,31)

We can conclude that the findings of this meta-analysis question the utility of performing LALA in addition to PVI and point to the iatrogenic nature of OAT recurrence after linear ablation.

Several studies have examined prognostic implications of OAT and AF recurrence. However, these investigations predominantly included patients who had undergone PVI+LALA ablation. Consequently, the observed OAT recurrences likely originated from an iatrogenically modified left atrial substrate, potentially obscuring the accurate interpretation of their prognostic relevance.

In the retrospective, observational study we evaluated consecutive patients undergoing repeated catheter ablation after index PVI without LALA ablation and investigated the prognostic significance of recurrent organized atrial tachycardia (OAT) vs. recurrent AF. The main findings of this study are twofold:

1. Organized atrial tachycardia as recurrent arrhythmia after a PVI-only index procedure does not portend improved effectiveness of first and subsequent redo procedures, as compared to recurrent AF.

2. Further follow-up after redo procedures discloses AF in the majority of recurring patients, independently from whether they had OAT or AF recurrence after index PVI.

Our findings contradict previous studies that showed improved effectiveness of redo procedures in case of OAT. These reports themselves are in conflict with publications showing more advanced atrial remodeling in patients who experience OAT recurrence after PVI, as compared to those with recurrent AF. (36,41,62,63)

Is OAT recurrence after PVI “road to sinus rhythm”? (64)

Post-PVI OAT may seem a more attractive target for repeat ablation, due to the possibility of straight-forward characterization of the mechanism and selection of ablation strategy during redo procedures. In contrast recurrent AF after PVI may be more difficult to deal with - especially when PVs are found to be durably isolated - owing to the lack of an established ablation strategy beyond PVI. The question remains, however: do the above considerations translate into a more favorable outcome of redo procedures performed for recurrent OAT, compared to recurrent AF?

In a recent, large, retrospective study noninvasive measures of atrial remodeling were found to be strongly associated with incident OAT after AF ablation. (41) Magnetic resonance detection of advanced atrial cardiomyopathy was shown to be associated with OAT recurrence after AF ablation. (36) High-density voltage mapping studies have shown increased low-voltage areas in patients with OAT recurrence as compared to those with recurrent AF. (62,63) Adverse remodeling and scarring (manifest in low-voltage) are the most important predictors of failure of AF ablation. (65)

Surprisingly, however several studies have reported a better prognosis of post-AF ablation OAT, compared to recurrent AF. (32–35) This finding is even more unexpected in light of the fact that patients with recurrent OAT in the same studies were generally older and had more dilated LA and more persistent AF before index ablation, compared to those with recurrent AF. (34,35)

How can the contradiction be resolved?

Apart from advanced remodeling another consistent predictor of OAT recurrence after AF ablation is the performance of linear ablation at the index procedure. (33) It has been shown to be an independent predictor of atypical flutter recurrence. (36,39,41) More OAT recurrence was noted with linear ablation added to PVI in randomized studies. (66,67) Furthermore, mapping has shown that the majority of macroreentrant OAT after AF ablation involves gaps in prior ablation lines. (30,67,68) Recurrent atypical flutter may be considered an iatrogenic arrhythmia in this regard. (67,69) Our previous meta-analysis also suggested the proarrhythmic potential of linear ablation. In our retrospective series the only iatrogenic arrhythmia was related to PVI: gap-related flutter after PVI-only index procedures. This particular arrhythmia, seen primarily in paroxysmal AF patients, differs from remodeling-driven OAT and becomes less important with better technology producing durable PVI.

Thus, the discrepancy in studies showing better outcome in case of OAT recurrence despite more advanced atrial remodeling may be resolved by the following. A variable percentage (60-100%) of patients in these studies underwent linear ablation and/or electrogram-based ablation beyond PVI at the index procedure. (32,33,35) Some of them would have done well with PVI-only, but developed iatrogenic OAT from extra-PV ablation. If those postablation OATs could be eliminated during a redo procedure, the patient – who has been kept AF-free by PVI - will be free of recurrence. From this scenario a better prognosis with postablation OAT might be erroneously inferred.

Also suggestive of the proarrhythmic potential of extra-PV substrate modification is the higher proportion of OAT recurrence in these studies (46-58 % (32,33) with typical flutter included, 30-38% atypical flutter only (34,35)), compared to ours (10 % typical, 15 % atypical flutter).

According to our retrospective study, when the index procedure is confined to PVI-only, recurrent OAT does not portend a better prognosis compared to recurrent AF, supporting the assumption that linear ablation and/or electrogram-based ablation at the index procedure influenced the results of previous studies.

Persistent vs. paroxysmal AF patients

We found no difference in terms of the prognostic implications of OAT vs. AF recurrence between patients with persistent or paroxysmal AF. OAT recurrence may be more straightforward to target during a redo procedure, but this is counteracted by its association with advanced atrial remodeling, especially in patients with persistent AF. In paroxysmal AF patients, structural remodeling may play less of a role, but recurrence of both OAT and AF after PVI is more commonly gap-related. (70) For them repeat PVI offers an equally effective treatment independent of whether their recurrence presents in the form of OAT or AF.

High rate of recurrent AF after redo

The other important finding of our study is that most recurring patients after redo ablation experience AF, even if the justification for the redo procedure was postablation OAT.

Our patients did not undergo empirical substrate modification during the index PVI or subsequent redo procedures and only clinical macroreentry was targeted. In this type of population – with less propensity for iatrogenic OAT - those that continue to have further recurrences after redo tend to have AF (also) during long-term follow up, even if they had only OAT after the index PVI.

Limited success in management of postablation OAT

Others have also shown a high rate of AF recurrence after left atrial macroreentrant tachycardia ablation. (71) On the other hand recurrent atrial tachycardia is also common after procedures targeting postablation OAT: despite using ultra-high-density mapping, a significant recurrence rate (26% and 46%) was registered in two contemporary studies. (72,73) As seen in our series, acute procedural failure of post-PVI OAT ablation further compromises the outcome of redo procedures. Technological progress likely will change this yet unfavorable prognosis.

Clinical implications

The view of post-AF ablation OAT being a “road to sinus rhythm” has developed over the years, (32,64) despite data showing more advanced atrial remodeling in these patients. (34,35,41,62,63) This assumption can lead to undue expectations and drive serial redo procedures for patients with recurrent OAT. When the index procedure is confined to PVI-only, our results show similar success rate compared to persistent AF recurrence and point to a possible iatrogenic nature of OAT in previous studies.

These findings have important implications for shared decision making with patients who experience recurrence after initial PVI.

8. Summary

In our studies, we focused on optimizing both the ablation procedure and patient selection to enhance the success of redo ablations while minimizing adverse events. Given that vascular complications are the most frequent adverse events during ablations, (74) we compared complication rates between traditional palpation-guided femoral puncture and novel US-guided approach. The US-guided technique demonstrated superior safety, significantly reducing the incidence of minor, major and composite complications. Our quasi-randomized study reinforces previous findings, showing that US-guidance offers substantial benefits – even when operators have limited experience with vascular US.

Despite high success rate of redo ablations and the established mortality benefit of maintaining sinus rhythm over AF, (19) multiple factors must be considered when determining the indication for a redo procedure. Personalized decision-making is essential to identify patients who are most likely to benefit. One such factor is the morphology of arrhythmia recurrence, which remains a subject of debate in the literature.

To investigate this, we conducted a meta-analysis examining the relationship between OAT recurrence and the use of PVI+LALA strategy. Our findings revealed a significant association between OAT recurrence and PVI+LALA strategy during initial PVI, suggesting that these arrhythmias frequently have iatrogenic origin.

Several studies (32–35) have reported a more favorable prognosis for OAT-recurrence, portraying it as a potential "road to sinus rhythm." This view appears to contradict the proarrhythmic effects and unfavorable prognosis of the advanced left atrial remodeling. (28) To further explore this, we retrospectively compared the success rates of redo ablation in patients with OAT vs. AF recurrence following a PVI-only strategy. No significant difference has been observed between the two groups.

These results suggest that PVI+LALA strategy may increase the risk of iatrogenic OAT recurrence, whereas OAT recurrence following a PVI-only approach may reflect a different pathophysiological mechanism and carries a prognosis comparable to AF recurrence.

Our work has several limitations. The US-guided puncture study was randomized but not blinded, and we did not collected data about subclinical events. The comparison of OAT and AF recurrence was based on a retrospective analysis, from an earlier era of ablation technology, which may have contributed to higher recurrence rates. Additionally, both investigations were conducted at a single center.

In conclusion, the major findings of this work are:

1. Ultrasound guidance during femoral vein puncture reduces local complications of AF ablation procedures.
2. Adding left atrial linear ablation to pulmonary vein isolation during AF ablation procedures increases the incidence of OAT recurrence
3. OAT recurrence following PVI-only ablation does not differ prognostically from AF recurrence

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