University of Szeged

Albert Szent-Györgyi Medical School

Doctoral of Clinical Medicine

Vascular complications and recurrences after catheter ablation of atrial fibrillation

PhD thesis summary document

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1. Table of contents

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: Q3

3. Introduction

Atrial fibrillation (AF) is a highly prevalent arrhythmia, its global prevalence was 46.3 million individuals in 2016. Mechanisms of AF and Organized atrial tachycardia (OAT)AF can arise from ectopic electrical activity of the pulmonary veins (PVs) (paroxysmal phase) microreentrant circuits as a consequence of atrial fibrosis due to cardiac and extracardiac diseases (persistent AF). OAT encompasses a spectrum of arrhythmias characterized by regular atrial activation from an active foci (atrial tachycardia (AT)) or macroreentrant circuits around the tricuspid annulus (typical flutter) or other structures such as scars or mitral annulus (atypical flutter). The behavior of OATs remains variable: catheter ablation often yields favorable outcomes, but advanced atrial remodeling and portend a poorer prognosis.

3.1.Pulmonary vein isolation

Current guidelines recommend pulmonary vein ablation (PVI) with Class I indication as a therapeutic option for AF. Beside the advantages of reduced symptoms, persistent restoration of sinus rhythm via PVI promotes reverse remodeling. In patients with heart failure, AF is associated with increased mortality and stroke, therefore, PVI confers significant clinical benefits in this population.

3.2.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. The most frequent complications are related to vascular access. Traditionally, femoral vein puncture is guided by palpation of the femoral artery. However, the position of the femoral vessels in relation to each other is variable, that vascular ultrasound (US) guidance can clarify, and thereby decrease access-related complications. Routine use of US to guide femoral access has been advocated, however, its universal adoption has been hampered by the lack of supporting randomized-trial data, only meta-analyses demonstrated reduced the rate of major and minor vascular complications.

Despite advances in technology, arrhythmia recurrence after PVI remains common, often necessitating repeat procedures. 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 reentrant circuits, often involving anatomical structures or scars. These scars may result from prior damage of left atrial tissue or can be iatrogenic.

One frequent source of iatrogenic scars is modification of the extra-PV atrial substrate, that is frequently attempted in addition to PVI. Left atrial linear ablation (LALA) is an ablated roof line connecting superior PVs and/or a mitral line either posterior or anterior to the left atrial appendage. Incomplete or reconnected linear lesions may create the conditions for reentry and lead to OAT. We have performed a meta-analysis of several studies that have compared the results of AF ablation using PVI-only versus PVI + LALA, and the outcome was reported separately for recurrent AF and OAT.

There is a debate in the literature whether AF or OAT recurrence portends a better prognosis. Several authors reported a more favorable outcome after OAT recurrence although these and other studies also report the conflicting finding of more advanced left atrial (LA) remodeling that is associated with more recurrences. The explanation may lie in the fact that substrate modification was attempted in addition to PVI during the index procedure in the above studies, serving as a potential substrate of iatrogenic OAT; however, their utility in AF-suppression is limited, if any. Therefore, some of the patients who experienced this man-made OAT might have had their AF controlled by PVI, and the prognosis of its' redo procedure 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.

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 (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 was consecutive patients older than 18 years undergoing de novo PVI for AF with standard indications. They were on therapeutic anticoagulation according to the latest guidelines. Patients were grouped based on whether US or palpation guidance was used for femoral venous access. After local anesthesia, two punctures were performed on both left and right femoral veins, according to the international standards. PVI was performed using point-by-point radiofrequency ablation supported by CARTO electroanatomical mapping system. Heparin was administrated intravenously just before transseptal puncture. Activated clotting time (ACT) was targeted between 300 and 350 s during the procedure. 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, and the frequency of prolonged hospitalization was also compared. 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.

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. Studies or subgroups of studies were included if they compared PVI-only and PVI + LALA (roof and/or mitral lines) approaches.

Mantel–Haenszel odds ratios (MH-OR) with 95% confidence intervals (CI) were calculated. 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, and subgroup analyses 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 post-PVI redo ablation to treat recurrence of atrial arrhythmia. Baseline characteristics did not differ significantly from the examined groups. We excluded patients with linear ablation other than at the cavotricuspid isthmus (CTI) and those with electrograms-based ablation at the index procedure, but subgroups were created comprising those with or without a history of CTI ablation before or during the index procedure.

Spontaneously occurring non-PV triggers were targeted at the discretion of the treating physician. Radiofrequency (RF) energy was applied with a deflectable, open-irrigated catheter, using a point-by-point technique, around ipsilateral PVs.

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. OAT was defined by regular atrial activation and fixed or regularly irregular RR intervals. Patients who experienced both recurrent OAT and AF recurrence were enrolled in the AF recurrence group. 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.

In case of documented, recurrent OAT if the patient presented in sinus rhythm, programmed atrial stimulation was performed. Alternatively, if the ECG documentation of the clinical

arrhythmia was characteristic for typical 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 and further entrainment mapping was used to delineate the arrhythmia circuit. A non-CTI dependent atrial flutter was defined as gap-related when testing maneuvers suggested an origin around PV ostia. Other non-CTI dependent flutters were targeted by linear RF lesions, connecting electrically silent regions. Linear ablation was considered successful after termination of the ongoing arrhythmia and demonstration of conduction block. 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.

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%. The decrease in the rate of prolonged hospitalization was also statistically significant (5.04% vs. 1.01%, p = .032). Results are shown in Figure 1.

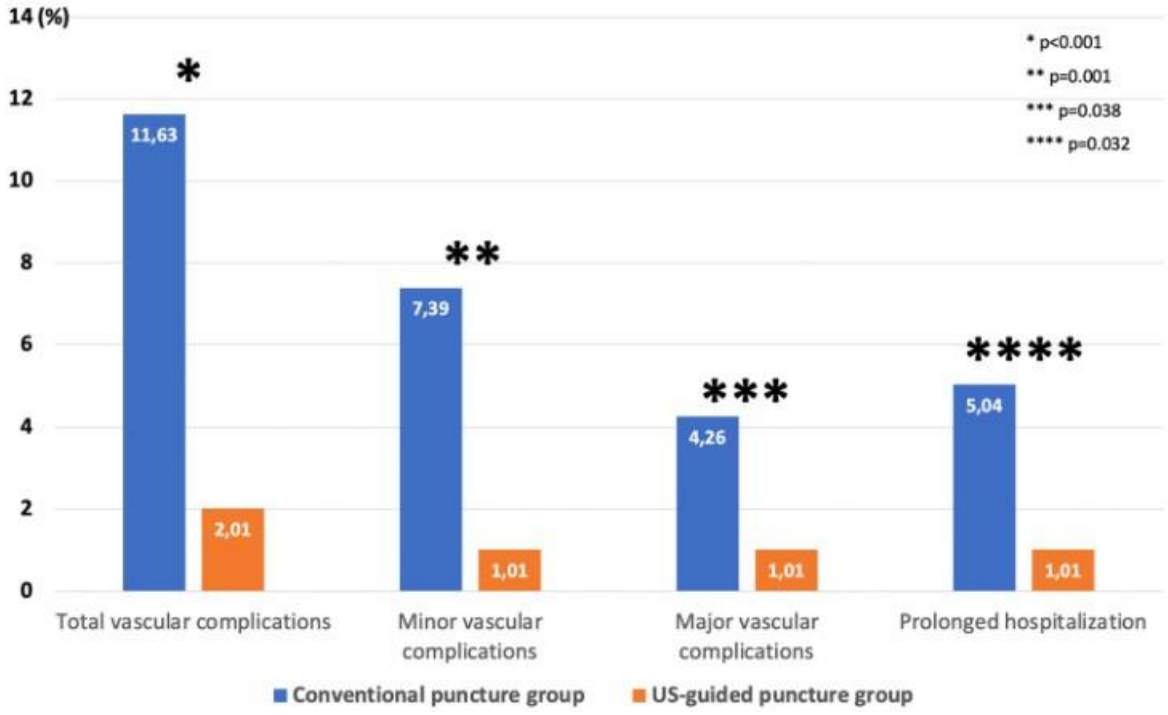

Figure 1 Comparison of major complications, minor complications, and prolonged hospitalization between conventional versus ultrasound (US)-guided femoral vein puncture group.

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

From 176 papers, two single-center, observational studies and eight randomized, controlled trials (RCT) met the inclusion criteria. 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.

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.

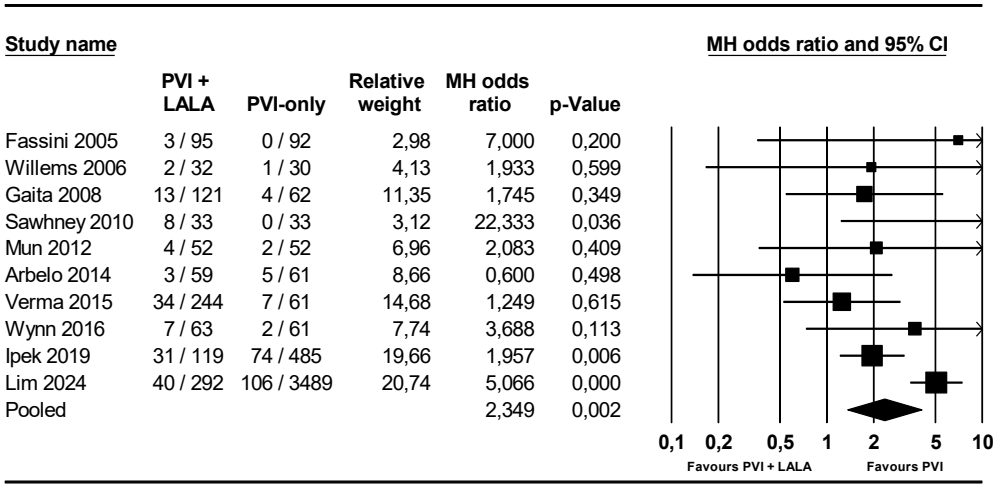

Figure 2: Studies examined in the meta-analysis. Number of OAT-recurrence were extracted from the studies in PVI + LALA and PVI-only patients, respectively.

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 2.). 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).

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 with twenty-two patients (12%) with non-PV ablation in their history. During the index procedure only PVI was performed in 152 (82%) patients. Additional non-LA ablation was carried out in 33 (18%) cases. 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.

Baseline parameters did not differ significantly between patients with OAT or AF recurrence. Minimum follow-up time was one year, mean follow-up time was 37±24 months.

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). Also, recurrence free survival time was not different between groups (51.08±6.66 vs. 53.37±4.75 months, p=0.54). 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 3. and 4.).

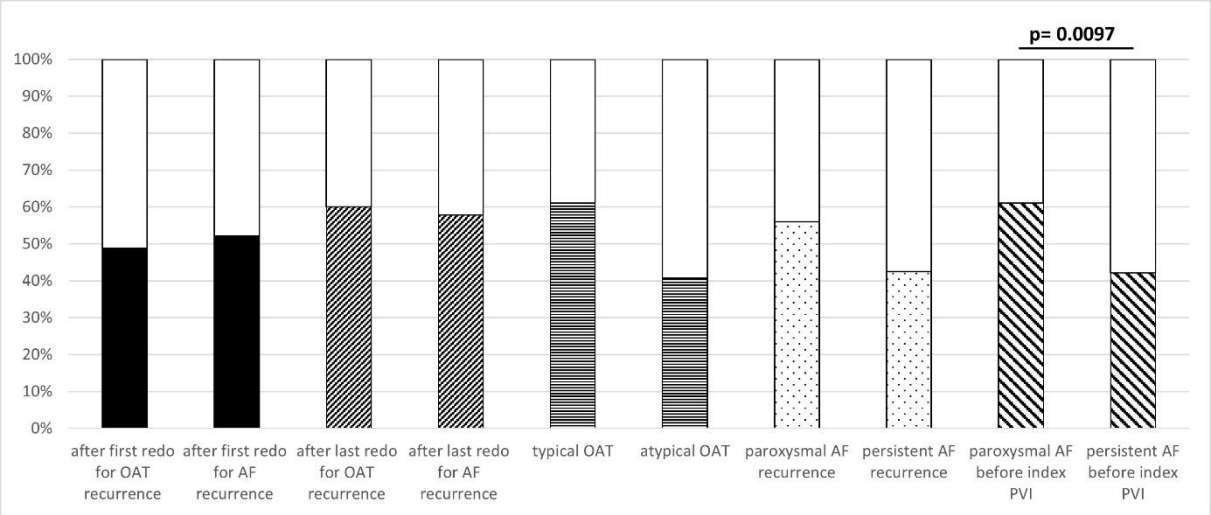

Figure 3: Rate of recurrence-free patients (shaded rectangles) in different groups. OAT: organized atrial tachycardia, AF: atrial fibrillation, PVI: pulmonary vein isolation

Separate analyses were conducted for patient groups with initially persistent and paroxysmal AF. Among patients with persistent AF, no significant difference was observed between those with OAT as compared to those with AF recurrence in the success rate after the first or last redo procedure, and the rate of successful rhythm control (all p>0.1). 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).

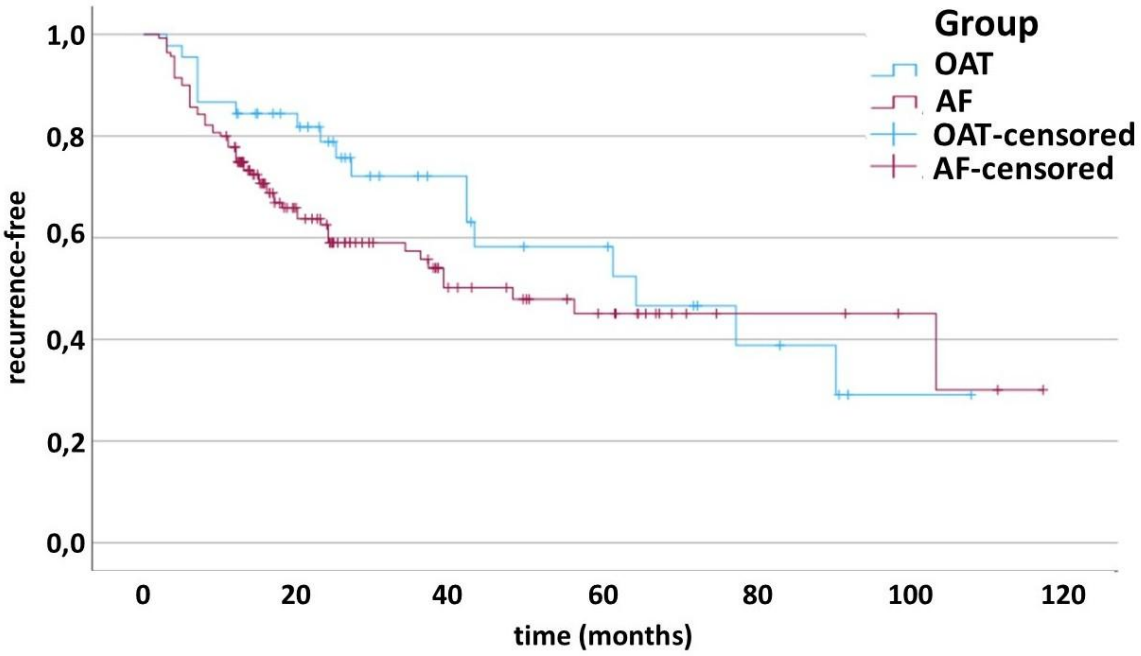

Figure 4: Recurrence-free survival after last redo ablation of all patients. OAT: organized atrial tachycardia, AF: atrial fibrillation

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.

Comparing only the successful recurrent OAT ablations with redo ablation for AF recurrence, success rate and rate of successful rhythm control did not show significant difference (all $p>0.1$). 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 ($p=0.18$ and $p=0.35$, respectively).

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%, $p=0.002$).

Although the success rate was not significantly different between paroxysmal vs. persistent AF recurrence, higher rate of successful rhythm control was achieved in the first group (92% vs 68%, $p<0.0002$) (Figure 3.).

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 supports that US guidance was associated with lower composite, major and minor vascular complication rates. Besides several nonrandomized, observational studies showed the superiority of the US-guided technique, the only one RCT failed to meet its primary endpoint. However, a retrospective trial involving 3420 patients undergoing PVI showed, that US-guided femoral vein puncture reduces total, major, and minor vascular complications. Meta-analyses have proved that US-guided femoral vein puncture reduced the rate of major vascular complications and demonstrated 73% risk reduction in major vascular complications with US guidance in PVI procedures. A most recently published retrospective analysis also demonstrated, that major vascular complications are exceedingly rare with use of US for vascular access. While the lack of convincing RCT data supporting US use discourages the adoption of US-guidance, others are reluctant to omit US in any patient even for the sake of performing such an RCT. Our quasi-randomized analysis may serve as a substitute for a true RCT. The results demonstrate a remarkable improvement in the risk of vascular complications and 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 procedural factors of AF ablation, specifically LALA added to PVI. 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, and it 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.

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.

For a repeat ablation, post-PVI OAT may seem a more attractive target, while it has been strongly associated with atrial remodeling. Our question was: can we expect a more favorable outcome of redo procedures performed for recurrent OAT, compared to recurrent AF?

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

1. OAT 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.

Two consistent predictors of OAT recurrence after AF ablation are advanced remodeling and performance of linear ablation at the index procedure. In our series the only iatrogenic arrhythmia was gap-related flutter after PVI-only index procedures, that differs from remodeling-driven OAT.

Thus, the discrepancy can be resolved by the following. A variable percentage (60-100%) of patients in previous studies underwent linear and/or electrogram-based ablation beyond PVI at the index procedure. These patients have been kept AF-free by PVI, and redo ablation had to treat only the iatrogenic OAT causing a better prognosis.

In the present 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 extra-PV ablation at the index procedure influenced the results of previous studies.

Persistent vs. paroxysmal AF patients

We found no difference in prognostic implications of OAT vs. AF recurrence between patients with persistent or paroxysmal AF. OAT recurrence may be more straightforward to target, but associated with advanced atrial remodeling.

Clinical implications

Although post-AF ablation OAT seemed to be an attractive target for redo ablation, data show more advanced atrial remodeling in these patients. This assumption questions serial redo procedures for patients with recurrent OAT

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. 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 that US-guidance offers substantial benefits.

One factor in the decision-making process of redo ablation is the morphology of arrhythmia recurrence, which remains a subject of debate in 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 have reported a more favorable prognosis for OAT-recurrence, but it appears to contradict the unfavorable prognosis of the advanced left atrial remodeling. 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 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 collect 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