Repeat ablation strategies in atrial fibrillation patients with durably isolated pulmonary veins: insights on real-world practices from the Netherlands Heart Registration

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Abstract

Background and Aims: In 15-40% of patients undergoing repeat ablation for AF recurrence, all pulmonary veins (PVs) are durably isolated. Currently, there is limited evidence on the appropriate treatment strategy for these patients. Our aim was to characterize and compare the effectiveness of different re-ablation strategies. **Methods**: All patients referred for repeat AF ablation with all PVs durably isolated at 8 hospitals in the Netherlands were included [Netherlands-Heart-Registration (NHR); 2016-2019]. NHR data was used to determine the presence of PV-reconnection, ablation strategy used, and the outcome of ablation (atrial arrhythmia recurrence > 30 sec.). Effectiveness of ablation strategies were assessed with multivariable Cox models. **Results**: Of 2311 repeat AF ablations performed, 274 (11.9%) patients had all PVs durably isolated. Median age was 66 (IQR:58-70) years, 44.2% women, 45.6% had persistent/long-standing-persistent AF. In 33 (12.0%) patients no ablation was performed. Single ablation strategy was performed most often (41.2%). Posterior wall ablation (58.4%) was performed most often, followed by PV-antralization (26.3%). Over 2.0 (1.0-3.3) years, 147 (59.8%) patients had an atrial arrhythmia recurrence and 30 (12.7%) patients had another repeat AF ablation within 1 year. After multivariable adjustment, no difference in atrial-arrhythmia recurrences was detected between individual ablation strategies, number of strategies performed, and type of atrial-arrhythmia (p>0.05 for all). Left-atrial-size was associated with a higher recurrence-risk [aHR 1.03(95%CI 1.01-1.05)]. **Conclusion**: In patients with durably isolated PVs, a high proportion experienced recurrence of atrial-arrhythmias, with no difference in recurrence rates between different re-ablation strategies.

INTRODUCTION

Despite notable improvements in the efficacy of pulmonary vein isolation (PVI) through advancements of ablation strategies and technologies, recurrences of atrial fibrillation (AF) after PVI still persist in up to 25-50% of patients.(1–6) At repeat ablation procedures, pulmonary vein (PV) reconnection is often observed.(1,7–9) In these patients the primary objective of repeat ablation interventions remains re-isolation of the PVs.

Recent studies have shown that 15-40% of patients undergoing repeat ablation for AF recurrence appear to have all PVs durably isolated on electrophysiological mapping.(1,10–12) Despite the high incidence, limited evidence is available and no expert consensus exists on the optimal ablation strategy in patients with durably isolated PVs. This has led to a wide array of operator-dependent approaches such as linear ablation lesions, low-voltage area ablation and trigger ablation,.(10,13) Therefore, we conducted a nation-wide comparison of the effectiveness and safety of various real-world ablation strategies used during repeat AF ablation in patients with durably isolated PVs in the Netherlands, utilizing data from the Netherlands Heart Registration.

METHODS

Study design and patient population

The present study is an observational, retrospective, multicenter, real-world cohort study performed at 8 centers in the Netherlands. We identified all repeat ablations performed in these centers between 2016-2019 through the Netherlands Heart Registration (NHR). The NHR is a nationwide, non-voluntary, quality monitoring registry in the Netherlands dedicated to collecting comprehensive data on cardiovascular diseases and interventions, including all AF ablations performed in the Netherlands since 2013.(14) With regards to ablation procedures, the collected data include demographic characteristics, including medical history, and procedural data related to the ablation procedures (detailed overview of the variables included in the NHR ablation registry (15)). The study was approved by the institutional review board MEC-U (W19.270) and conducted in accordance with the principles of the Declaration of Helsinki. A waiver of informed consent was obtained for the analysis of data from the NHR data registry.

The inclusion criteria for the study were the following: (1) a history of paroxysmal or persistent AF (defined respectively as AF that terminates spontaneously or with intervention within 7 days of onset and AF that is sustained for more than 7 days, or less than 7 days but requires pharmacological or electrical cardioversion to terminate) treated with ablation procedure(s) consisting solely of PVI; (2) documented AF recurrence (12 lead ECG, Holter, ECG rhythm strips) after the 1st ablation procedure; (3) first repeat ablation performed between 2016 and 2019 during which all PVs were durably isolated on electrophysiological mapping.

Patients were excluded if they underwent surgical ablation during prior procedures or other lesions were performed during the prior ablations (except for cavo-tricuspid isthmus ablation), or if the indication of the repeat procedure was for atrial tachycardia (AT) or atrial flutter (AFL).

Data Collection

The NHR data encompassed all ablation procedures. From the NHR database we obtained the data for the current analysis, including procedural data, demographic characteristics, medical history, and data related to prior ablation procedures. Starting from 2022, the ablation registry was expanded to include an additional set of variables related to baseline characteristics, procedural details, and follow-up data. This new variable set encompassed the following variables: hypertension, coronary artery disease (CAD), cerebrovascular accident/transient ischemic attack (CVA/TIA), diabetes mellitus, pulmonary vein reconnection status, ablation strategy used during repeat ablation, date of the last known follow-up, use of anti-arrhythmic drugs at the time of the last follow-up, date of recurrence after re-ablation, and type of atrial arrhythmia recurrence. This expanded dataset was collected by eight hospitals. Data regarding patients' follow-up were obtained, including recurrences after a 90-day blanking period, the use of antiarrhythmic drugs during last known cardiac follow-up, and additional repeat ablation procedures performed the first repeat procedure analyzed here. Follow-up was calculated starting from the date of the first repeat ablation. Follow-up occurred according to each center's standard protocol. Patients were usually scheduled for outpatient clinic visits at 3-, 6-, and 12-months, and every 12 months thereafter. During these visits, assessments were conducted for AF-related symptoms, adverse events, and ECG or 24-hour Holter monitoring to detect any recurrence of atrial arrhythmias, as determined by the physician's discretion. Patients were otherwise seen for emergency visits in case of symptomatic recurrence, during which 12-lead ECG would be performed. The last known follow-up was considered the end of the follow-up period for the survival analysis, which was impacted by the occurrence of recurrence and/or repeat ablation.

Repeat AF ablations

All centers participating in this study were using a multipolar mapping catheter during repeat procedures to confirm the durability of PVI. 3D electro-anatomical maps were created in all patients. Once isolation of the PVs was confirmed, the ablation strategy was determined by the operating electrophysiologist.

The ablation strategy adopted during the repeat procedure as detailed in the ablation report, was categorized as one of the following strategies or any combination of them (Figure 1): (1) No additional ablation; (2) PV antralization: a PV-based ablation consisting of an extension of the initial PVI lesion set to achieve a second, more antral PVI; (3) linear-based ablation lesions including: roof line, inferior line, posterior box ablation (as a combination of roof and inferior lines or full ablation of the posterior wall), mitral isthmus line (anterior or lateral line), cavo-tricuspid isthmus (CTI) line; (4) trigger ablation: focal RF at either superior vena cava ablation, left atrial appendage, coronary sinus ablation or other locations; (5) low voltage area ablation; (6) complex fractionated atrial electrogram ablation; (7) other ablation strategies: vein of Marshall ablation, rotor ablation. In case no additional ablation was performed once durably isolated PVs were confirmed, patients were categorized as having received no ablation.

Study End Points

The primary end point of the study was the atrial arrhythmia-free survival (AF, AT, or AFL) after the repeat ablation procedure. Any symptomatic or asymptomatic AF or AT/AFL was qualified as an arrhythmia recurrence if it lasted 30 seconds or longer and was documented by 12-lead ECG, surface ECG rhythm strips, or 24-hour Holter, after a blanking period of 90 days after the 1^{st} repeat ablation.

Statistical Analysis

Continuous variables were expressed as median and interquartile ranges and compared using Mann-Whitney U test. Patients were compared based on recurrence status (yes or no recurrence) and AF type, distinguishing between those with paroxysmal AF and persistent AF. Categorical variables were expressed as counts and percentages and were compared using the Chi-square test or exact Fisher test, as warranted.

Comparative effectiveness of ablation strategies was evaluated with multivariable Cox proportional hazards models. Patients were followed from the index date of the first repeat AF ablation. Models were adjusted for age, sex, BMI, AF pattern (e.g. paroxysmal, persistent), diabetes, coronary artery disease, and hypertension. Cox models compared individual ablation strategies, number of ablation strategies performed, and presence of persistent AF. Kaplan-Meier estimates were utilized to generate time-to-first-arrhythmia recurrence curves, which were subsequently compared employing the log-rank test. In our models, we analyzed the effects of all strategies, irrespective of whether they were used alone or in combination with others. Interaction analyses between the primary ablative strategies were conducted to ensure the comprehensive evaluation of their impact. Results are presented as hazard ratios (HR) along with their corresponding 95% confidence intervals (CI). Effects estimates with 95% CI were used to determine statistical significance together with P value < 0.05. Statistical analyses were conducted using STATA version 18 (StataCorp LLC, College Station, TX, USA).

RESULTS

Patient population and prior ablation procedures

From January 2016 to December 2019, 2311 repeat ablation procedures were performed in the Netherlands across 8 centers, all using radiofrequency ablation (100%). Of these, 274 (12%) met the inclusion criteria of both AF recurrence and durably isolated PVs and were included in the analysis. See Figure 2 for a detailed flowchart of the study cohort.

The detailed baseline characteristics of the final population are presented in Table 1. The included patients had a median age of 66 years (IQR: 58-70), 44.2% were women, and the median CHA2DS2-VASc score was 2.0 (IQR: 1.0-3.0). Of all patients, 54.4% had paroxysmal AF and 45.6% had persistent forms of AF. Patients with paroxysmal and persistent AF exhibited similar characteristics, except for a significant difference in

the presence of coronary artery disease (CAD) (4.1% vs. 11.5%), weight [81 (72-96) vs. 89 (80-98)] and hypertension (45.5% vs. 62.1%) (for all: p<0.05; see Appendix Table 1A).

Ablation strategies for repeat ablation in patients with durably isolated PVs

Figure 3 provides an overview of distribution of individual strategies and number of strategies performed. In 12.0% of the 274 patients with durably isolated PVs no additional ablation was performed. A single ablation strategy was performed most often (41.2%), followed by two (32.1%), three (12.8%), and four (1.8%) strategies.

Posterior box ablation was the most frequently applied (58.4%) ablation strategy, followed by antralization of the PVs (26.3%). Roof line ablation alone was performed in 17 (6.2%) patients, while creation of an inferior line alone was performed in 1 (0.4%) patient. Posterior box creation through combined roof and inferior lines was performed in 34.3% of patients (58.8% of all posterior wall ablation cases). A mitral isthmus line was applied in 48 (17.6%) patients and CTI ablation in 72 (26.3%) patients. Trigger ablation was performed in 33 (12.0%) patients with the following triggers: superior vena cava in 14 (5.1%) patients, LAA in 4 (1.5%) patients, coronary sinus in 8 (2.9%) patients, other triggers in 10 (3.7%) patients. Low voltage area ablation was performed in 36 (13.1%) patients and CFAE ablation was performed in 43 (15.7%) patients. When comparing patients with paroxysmal AF to those with persistent AF, posterior box ablation was more commonly performed in the persistent AF group (p<0.05, see Appendix Table 1A). Additionally, persistent AF patients received more often a higher number of ablation strategies compared to patients with paroxysmal AF (p<0.05).

Follow-up and effectiveness

Patients were monitored after the first repeat ablation for a median of 2.0 (1.0-3.3) years. During follow-up 142 (52.8%) patients with durably isolated PVs had a recurrence of atrial arrhythmia >90 days post-procedure and 30 (12.7%) patients underwent subsequent repeat ablation within 12-months of the first repeat procedure (Table 2). At last known follow-up moment, 141 (57.3%) patients were still using anti-arrhythmic drugs.

The multivariable Cox proportional hazards model, conducted following multivariable adjustment for age, sex, body-mass index, paroxysmal AF, diabetes, CAD, and hypertension, identified no individual ablation strategy as an independent predictor of AF recurrence (p > 0.05 for all; Figure 4). Subgroup analysis accounting for type of AF (paroxysmal AF or persistent AF), similarly demonstrated no discernible difference in AF recurrence for individual strategies between the two groups [HR 1.001 (95% CI 0.67-1.51)]. Furthermore, no significant associations were observed between the number of ablation strategies adopted and AF recurrence rates, when compared to no additional ablation (p>0.05; Figure 5). Sensitivity analyses confirmed the stability of these findings, reinforcing the conclusion that neither the choice of ablation strategy nor the cumulative number of strategies employed significantly influenced the recurrence of AF post-PVI.

In the multivariate Cox regression model, left atrial size appeared to be the only independent factor associated with an increased risk of atrial arrhythmia recurrence [adjusted HR 1.03 (95% CI 1.01-1.05); Figure 6].

Complications

Eight (3.5%) patients experienced a complication following repeat ablation. Table 3 displays the incidence of procedural complications. Two (0.9%) patients a cardiac tamponade. One patient experienced a major vascular complication and five (2.2%) patients experienced minor vascular complications (venous bleeding complication at the femoral puncture site).

DISCUSSION

Main findings

In the present multicenter NHR study we investigated the ablation strategies adopted in patients with durably isolated PVs at repeat AF ablation procedures. Several ablation strategies are being performed

ranging from no ablation to a single or multiple ablation strategies, with posterior wall ablation as the most prevalent approach. There was no difference in atrial arrhythmia recurrence after repeat ablation between the different strategies and compared to no re-ablation. Interestingly, these findings were observed irrespective of whether patients presented with paroxysmal or persistent AF.

Incidence of durably isolated PVs during repeat AF ablation

Previous studies have shown a variable incidence of durably isolated PVs in patients with AF recurrence presenting for repeat AF ablation. Reconnection rates may vary dependent on the study population, operator experience and the ablation technique. The chance of all veins being durably isolated increases with the number of previous PVI procedures.(16,17) A sub-analysis of the FIRE AND ICE trial examining findings at repeat ablation procedures, indicated a higher incidence of durably isolated PVs following cryoballoon ablation compared to radiofrequency ablation (21.9% vs. 17.3%).(18) Recent studies and meta-analyses have shown that incidence rates range between 15-40%.(1,10–12) However, a contemporary study by De Potter et al. reported a much higher incidence of 62%, potentially attributable to the CLOSE-guided ablation strategy used during the index ablation, which involves precise delivery of contact-force guided point-by-point radiofrequency ablation.(11) In the past years, novel ablation technologies such as pulsed field ablation have been introduced, which may lead to different lesion durability.(19) Data from two recently published large multicenter registries, the EU-PORIA registry and the MANIFEST registry, observed that 38% and 45.5% of patients, respectively, had durably isolated PVs at repeat ablation after initial PVI with pulsed field ablation.(20,21) Thus, with the development of novel ablation approaches and techniques the number of patients with durably isolated PVs during repeat procedures may increase.

Current ablation practices in patients with durably isolated PVs

The fact that a large portion of patients with recurrent AF have durably isolated PVs indicates that the source of AF must partially be located outside the PVs. The mechanisms of AF in this specific subset of patients are unknown. Although, ablation strategies targeting extra-pulmonary AF foci/triggers have been effective in certain sub-groups of patients, current evidence does not indicate that any individual strategy is more effective than PVI, whether used alone or in combination. This uncertainty explains the lack of consensus on the best ablation strategy for treating these patients, suggesting that an individualized approach may be necessary.

In the recent retrospective PARTY-PVI study, Benali et al. compared outcomes of various ablation strategies during repeat ablation for AF in 367 patients with durably isolated PVs from 39 centers.(10) The majority of patients were male (67%) with persistent AF as dominant recurrence type (56.4%). Most patients received only one ablation strategy (54.5%), followed by two or three (37.1% and 6.5%). Similar to our study, they observed no significant difference in AF-free survival across strategies, with LA size being the only independent predictor of recurrence. In their analyses Benali et al. clustered similar strategies to increase statistical power and therefore did not investigate the individual effect of ablation strategies. Additionally, they did not report data on the incidence of durably isolated PVs relative to all patients undergoing repeat ablation, nor did they specify how many patients received no additional ablation.

Recently, preliminary findings from the ASTRO-AF study were presented.(13) This multicenter, prospective, randomized study compared substrate modification and left atrial appendage isolation in 161 patients with durably isolated PVs.(13) They found no statistically significant difference in AF/AT recurrence at one year between the two ablation strategies. Of note, more than half of the patients had undergone more than one prior ablation procedure. Due to futility, the study was prematurely terminated after randomizing 63% of the planned patient population.

In our study, posterior wall isolation was the predominant strategy (58.4%) employed in patients with durably isolated PVs. The posterior wall is widely accepted as a major extra-PV harbor for AF triggers and drivers, partly attributed to the shared embryological development with the PVs.(22,23) However, conclusive evidence regarding its efficacy beyond PVI alone remains inconsistent and inconclusive, with currently available data showing contrasting results.(24,25)

To date, few studies have reported on the outcomes of repeat ablation in patients with durably isolated PVs. We observed a high rate of atrial arrhythmia recurrence after ablation in these patients (52.8%). In the PARTY-PVI study, Benali et al. observed a recurrence rate of 43.3% at 2 years after repeat ablation, which did not differ significantly between different types of ablations or combinations of them.(10) In the ASTRO-AF study, the recurrence rates of atrial arrhythmias at 1 year were 48.3% for low-voltage area ablation and 44.5% for empirical left atrial appendage isolation, showing no significant difference between the two approaches.(13) De Pooter et al. observed a 39% recurrence rate at 1 year after repeat ablation in patients with durably isolated PVs.(11) During repeat ablation they performed either empirical trigger ablation, which involved isolating the superior vena cava and/or antralization of the PVI lesions, or substrate ablation, which included creating linear lesions at the roof, mitral isthmus, and/or anterior wall. Small single-center series showed similar recurrence rates, with patients undergoing diverse strategies, including extra-pulmonary trigger ablation, CFAE ablation, and linear ablation.(26,27) In contrast to our study, none of the afore-mentioned investigations included a control group of patients who did not undergo additional re-ablation. The lack of evidence so far supporting a particular ablation strategy highlights the importance of including such a control group in future research.

Limitations

The retrospective study design limits statistical power of our analysis and its multicenter nature introduces heterogeneity in both ablation performance and patient outcomes. Furthermore, our investigation explored a wide variety of ablation strategies in this patient population. Detailed information regarding the ablation procedures, including ablation settings and operator preferences, was not available. Therefore, we are likely be underpowered to detect true difference between AF ablation strategies and this analysis should be considered hypothesis-generating. Additionally, while the efficacy of ablation strategies was assessed, confirmation of lesion durability for each strategy (e.g., posterior wall isolation or mitral line block) was not systematically verified, which may have influenced the observed recurrence rates.

It should be emphasized that identification of these patients is only possible during repeat procedures, making the inclusion of large numbers of patients challenging. Nonetheless, despite the retrospective design, through the NHR we were still able to identify one of the largest series of patients with durably isolated PVs. Lastly, detection of AF recurrences was not standardized, possibly leading to under-detection of AF recurrence. Despite this, we still observed a high recurrence rate suggesting that AF recurrence is very common in this subset of patients.

Conclusion

In a large group of patients with AF recurrence despite durably isolated PVs we investigated current ablation practices during repeat AF ablation, in the Netherlands. We observed a diverse range of ablation strategies ranging from no ablation to various combinations, with no significant difference in effectiveness between strategies, also irrespective of whether patients presented with paroxysmal or persistent AF. Prospective, randomized studies are necessary to gain further insights into whether and which additional ablation strategies beyond PVI are beneficial in this patient population and to explore the potential advantages of tailoring treatment to individual patient characteristics.

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TABLES

Table 1. Baseline characteristics

Characteristic	n(%) / median(IQR)
Age, years	66 (58-70)
Women	121 (44.2%)
BMI (kg/m^2)	27.17 (24.41-29.77)
Type of AF Paroxysmal Persistent	124 (54.4%) 104 (45.6%)
Previous CVA/TIA	23 (8.4%)
Diabetes	16 (5.8%)
CAD (medication, PCI, or CABG)	19 (7.0%)
Hypertension	141 (51.8%)
Serum creatinine	82 (71-95)
LVEF (%)	55 (55-55)
LA size (ml/m2)	39 (31-46)
CHA_2DS_2-VAS_C score 0 1 2 3 [?]4	2 (1-3) 34 (15.0%) 44 (19.3%) 61 (26.9%) 54 (23.8%)
Preoperative mitral valve insufficiency None/Mild Moderate Severe	181 (89.6%) 21 (10.4%) 0 (0.0%)

[BMI = body mass index; AF = atrial fibrillation; CVA = cerebrovascular accident; TIA = transient ischemic accident; CAD = coronary artery disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; LA = left atrium]

Table 2. Repeat ablation outcomes

Outcome	Total (
AAD use at last known follow-up	141 (57

Outcome	Total (
Atrial arrhythmia recurrence (>3 months) AFL/AT Paroxysmal AF Persistent AF Median time to AF recurrence	142 (52
Repeat ablation with <1 year	30 (12.

[AAD = anti-arrhythmic drug; AF = atrial fibrillation; AFL/AT = atrial flutter or atrial tachycardia]

Table 3. Complications of repeat ablation procedures

Complication	N (%)
Cardiac tamponade	2 (0.87%)
Major vascular complications	1 (0.44%)
Minor vascular complications	5 (2.18%)

FIGURE LEGENDS

Figure 1. Overview of investigated ablation strategies.

Visual representation of the individual ablation strategies investigated in the study: 1) Durably isolated Pulmonary Veins (no additional ablation); 2) Pulmonary Vein Antralization; 3) Linear-Based Ablation: roof line, inferior line, posterior wall [both as box made using roof and inferior lines, as well as whole posterior wall (shaded red area)], cavo-tricuspid isthmus line, mitral isthmus line; 4) Trigger-Based Ablation: superior vena cava, coronary sinus, left atrial appendage, other triggers; 5) Low-Voltage Area Ablation; 6) CFAE (Complex Fractionated Atrial Electrograms) Ablation; 7) Other Strategies: vein of Marshall ablation, rotor ablation

Figure 2. Flowchart study population.

Overview of the included and excluded patients. This figure shows the selection process of patients undergoing repeat AF ablations from eight centers in the Netherlands (2016-2019; NHR). Out of 2311 patients, 1956 eligible patient were identified after excluding those with no AF (n=2) and those with surgical ablation, prior ablation outside the PVs, or an indication for atrial flutter/tachycardia (n=353). Among eligible patients, 1617 had reconnected pulmonary veins (PVs), 65 had missing PV reconnection data, and a total of 274 patients had all PVs isolated, which were included in the final analyses.

Figure 3. Distribution of individual ablation strategies and number of ablation strategies performed .

A) Visual representation of the percentage of patients who received each specific ablation strategy; B) Pie chart showing the percentage distribution of the number of ablation strategies/combinations performed among all included patients.

Figure 4. Forest plot for effectiveness of ablation methods.

Forest plot displaying the outcomes of a multivariate Cox regression analysis, comparing the hazard ratios (HR) on rates of atrial arrhythmia recurrence among different ablation strategies relative to performing no re-ablation at all. The cox regression analysis was conducted following multivariable adjustment for age, sex, body-mass index, paroxysmal AF, diabetes, CAD, and hypertension

Figure 5. Kaplan-Meier curve for number of strategies performed.

Kaplan-Meier survival curve illustrating the probability of atrial-arrhythmia-free survival over a 24-month follow-up period for patients with durably isolated pulmonary veins undergoing different numbers of ablation strategies during repeat ablation.

Figure 6. Forest plot for predictors of AF recurrence

Forest plot displaying the outcomes of a multivariate Cox regression analysis, comparing the hazard ratios (HR) for recurrence of atrial fibrillation between different factors, adjusted for ablation strategy.

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