Five-Year Follow Up after Catheter Ablation of Persistent Atrial Fibrillation using the “Stepwise Approach” and Prognostic Factors for Success

Running title: Schreiber et al.; 5y-outcome of persistent AF “stepwise” ablation

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Abstract:

**Background** - In the meantime, catheter ablation (CA) is widely used for the treatment of persistent (pers) atrial fibrillation (AF). There is a paucity of data regarding long-term outcomes. This study evaluates (1) 5 year-single and multiple procedure success and (2) prognostic factors for arrhythmia recurrences after CA of persAF using the “stepwise approach” aiming at AF termination.

**Methods and Results** - 549 patients (pts) with persAF underwent de novo CA using the “stepwise approach“ (2007-2009). 493 pts were included (holter-ecgs≥every 6 mo). Mean FU was 59±16 mo with 2.1±1.1 procedures/pt. Single and multiple procedure success rates were 20.1% and 55.9%, respectively (80% off AAD). AAD free multiple procedure success was 46%. Long-term recurrences (n=171) were paroxysmal AF in 48 pts (28%) and persAF/atrial tachycardia in 123 pts (72%). Multivariable recurrent event analysis revealed the following factors favoring arrhythmia recurrence: failure to terminate AF during index procedure (HR: 1.279; 95%CI [1.093-1.497]; p=0.002), number of procedures (HR: 1.154; 95% CI [1.051-1.267]; p=0.003), female sex (HR: 1.263; 95% CI [1.027 – 1.553]; p=0.027) and presence of a structural heart disease (HR: 1.236; 95% CI [1.003 – 1.524]; p=0.047. AF termination, was correlated with a higher rate of consecutive procedures due to AT recurrences (p=0.003, HR 1.71 95% CI [1.20-2.43]  

**Conclusions** - CA of persAF using the “stepwise approach“ provides limited long term freedom of arrhythmias often requiring multiple procedures. AF termination, the number of procedures, gender and the presence of structural heart disease correlate with outcome success. AF termination is associated with consecutive AT procedures.

**Key words:** catheter ablation, atrial fibrillation, arrhythmia (heart rhythm disorders), long-term outcome, success, stepwise approach, catheter ablation, atrial fibrillation
Introduction

Catheter ablation (CA) of paroxysmal AF (PAF) has been established as a standard treatment option with a class I recommendation as indicated in the current guidelines. Long-term success rates of pulmonary vein isolation (PVI) can be estimated as high as 70-80% after 5 years using 1.5 procedures per patient. On the other hand, the mechanisms underlying persistent atrial fibrillation (persAF) are more complex. Patients are being treated with various ablation approaches, linear lesions and/or electrogram-guided ablation targeting high-frequency complex fractionated electrograms (CFAEs). and clinical success rates of CA are limited. At present, no standard concept for CA of persAF has been established. In persAF, it seems reasonable to perform additional substrate modification beyond PVI in order to enhance clinical success rates. In contrast to ablation of PAF, in which the endpoint of electrical isolation of the pulmonary veins (PVs) is recommended by the guidelines, the optimal endpoint of CA in the setting of persAF is still under debate. The “stepwise ablation” approach aiming at procedural atrial fibrillation (AF) termination was introduced by Haissaguerre and co-workers in 2005. Long-term follow up (FU) data on any ablation approach for persAF are limited. 

In this study, we present 5-year FU data of patients with persAF undergoing “stepwise CA” aiming at AF termination.

Methods:

Study population

A total of 549 patients with persAF underwent catheter ablation using the “stepwise approach“ at our institution in 2007-2009. Of these, 493 patients with pers AF (long-standing persAF n= 119, 24.1%) were included in the study. Patients were eligible for study participation if AF episodes persisted for at least 1 month and required electrical cardioversion (CV) to restore sinus rhythm.
Additionally, a sufficient long-term-FU was required (see study protocol). Exclusion criteria were manifest hyperthyroidism, left atrium (LA) diameter >65mm, life-expectancy <1y and any previous ablation procedure.

**Study protocol**

The index procedure for persAF was uniformly performed using the “stepwise approach“ aiming at AF termination. Procedural success was defined as freedom from AT/AF with a duration >30 seconds in sequential holter-ecg, device interrogation or tele-ecgs. Only those patients (493/549) were included having a FU with repeat holter-ecg-recordings at least every 6 months (mo) after each procedure. In addition, documented arrhythmia on12-lead-ecgs or known electrical CV were also classified as procedural failure. After the ablation procedure, a blanking period of 3 mo was established according to the guidelines. The study was approved by the institutional review board. All subjects gave informed consent. FU was completed in October 2013.

**Ablation procedure**

Details of the ablation procedure have been described previously. In brief, the first step of the ablation procedure was antral PVI with complete electrical isolation of the PVs proved by an elimination or dissociation of PV potentials recorded by a circumferential mapping catheter followed by ablation of complex fractionated electrograms. AF cycle length (CL) was continuously monitored inside the CS and inside the left atrial appendage (latter with a circumferential mapping catheter, mean over ten cycles measured). Targets for AF ablation consisted of CFAEs as well as areas of short CL activity and local bursts, temporal activation gradient between proximal and distal ablation bipoles or areas of local spatial centrifugal activation. The desired procedural endpoint was termination of AF, either directly to SR or via
atrial tachycardia (AT). Using the same criteria, mapping and ablation were carried out within
the coronary sinus (CS) and the right atrium if AF did not terminate. (figure 1) Subsequent ATs
were specifically targeted, whereas linear ablation was performed if a macroreentrant mechanism
was suspected. Linear lesions were always created with the endpoint of bidirectional block,
evaluated by differential pacing. If AF termination failed, external electrical CV was used to
restore SR after a 5l patient-fluid administration via catheter irrigation or lack of target regions.
The standard radiofrequency (RF) ablation setting consisted of a power output of 30 W using an
irrigation rate of 10 -30 mL/min (0.9% saline infused with the Cool Flow Pump, Biosense
Webster, Diamond Bar, CA) for PVIs and the right atrium. Along the LA posterior wall, the
maximum power was limited to 25W. Within the CS RF current was applied with a maximum of
25 W with a manually adjusted irrigation rate to keep the tip temperature below 42°C.

Repeat procedures
Indication for repeat procedure was put in place in case of symptomatic arrhythmia recurrences
and patients’ preferences. As a first step of repeat procedures, electrical isolation of the PVs was
evaluated and re-established if required. If patients presented in SR, induction of either AT or AF
according to the clinical recurrence was attempted using either programmed stimulation (AT) or
atrial burst pacing until loss of 1:1 capture (AF). AT was defined as an organized atrial activity
with CL of ≥180ms with monomorphic p-waves on ecgs and consistent endocardial activation
sequence. An AT with a stable CL was considered macroreentrant, when a consistent repeat
post-pacing interval (PPI) was observed and/or tachycardia CL could be demonstrated around the
presumed circuit. Focal AT was recognized as an atrial activation originating from a discrete site
activating the surrounding tissue centrifugally and demonstrating features consistent with a focal
mechanism (centrifugal activation pattern, variation in AT CL ≥ 15%, inconsistent PPI).
Localized reentry was defined as atrial activity confined to an area of continuous signals on the bipoles of the mapping catheter displaying ≥85% of tachycardia CL and showing consistent PPI ≤30 ms of the tachycardia CL after repeat entrainment pacing (at least twice at the same site). If patients presented with or were induced for AF, “stepwise ablation” was performed aiming at AF termination. If patients presented with AT or AT was induced, ablation was performed according to the above mentioned protocol, aiming at AT termination. In case of macroreentrant ATs ablation lines were created aiming for complete conduction block along the line.

Follow up

Patients were followed clinically every 3-6 mo with detailed symptom evaluation and a 12-lead ecg. Additionally, holter-ecgs were performed at least every three mo for the first year after CA and afterwards every six months. All patients received an additional questionnaire concerning arrhythmia symptoms and episode-duration, last known recurrence dates, current medications and were contacted by phone calls if documentation was incomplete or unclear. In case of symptoms suspicious for arrhythmia recurrences without previous documentation, external ecg event recording was accomplished. Patients with implanted pacemakers or defibrillators were eligible to be followed by device interrogation. Antiarrhythmic drug (AAD) treatment was continued for 1-3 mo after the procedure at the discretion of the operator. Long-term FU data were analyzed in the patients with complete FU only.

Statistical analysis

Continuous variables are summarized by mean ± SD or median {minimum – maximum} as appropriate. Categorical variables are represented by absolute and relative frequencies. To cope with censoring event-free survival was plotted and estimated by Kaplan-Meier curves. Two-group comparisons were performed using Student’s t-test. Recurrent events and covariate
associations were investigated with univariable and multivariable Anderson-Gill models \(^26\) with robust estimates and Efron tie handling. If covariates were missing multiple imputation was used to complete the dataset. For multiple imputation the FCS (fully conditional specification) method was used and 10 different imputed datasets were generated. Finally the pooled results are reported. For each of the variables, hazard ratios with corresponding 95% confidence limits and Wald test p-values of the respective univariable or multivariable model are reported.

Throughout all calculations, a two-tailed probability \(P\)-value of 0.05 indicated statistical significance. Statistics were calculated using SPSS version 20 (SPSS Inc., Cary, NC, USA) and Stata software version 13.0 (Stata, College Station, TX, USA).

**Results**

Baseline characteristics of the study group are presented in Table 1. Known history of AF was 73 mo [median 48, 1-576] with a continuous AF episode duration of 14 mo [median 6, 1-240]. Patients had undergone 2 electrical CVs on average [0-21] and were treated with 1.7 AADs [0-5] prior initial procedure whereas 41% were on amiodarone. One third of patients showed a relevant structural heart disease (SHD) (CAD, cardiomyopathy or valvular heart disease).

**Index procedure**

The mean procedure time of the index procedure was 197 ± 56 min with a fluoroscopy time of 53 ± 21 minutes and 126034 ± 4410 Joule of RF energy application. Procedural details are summarized in Table 2. PVI was accomplished in all patients. The procedural endpoint of AF termination was achieved in 290/493 patients (59%). Of these, 46% converted directly to SR and 54% terminated into an AT. In 28 patients (5.7%), AF converted to SR with PVI. During index procedures, 148/493 patients (30%) showed ATs as consecutive arrhythmia (incl. right atrial
flutter). A total number of 146 ATs (max. 5 ATs) occurred. Of these, more than half were classified as typical macroreentrant ATs. Mitralisthmus-dependent flutter occurred in 5.5%, roof dependent ATs in 5.5% and right atrial cavo-tricuspid isthmus flutter in 9.5% of 493 patients. Ablation was continued until termination and achievement of complete block via the respective lines. Other ATs were identified in the anterior LA, the septum, CS and less frequently on other sites of both atria. In 52% of patients, electrical CV had to be performed to restore SR (either CV of AF or AT). After initial ablation, 44% of patients were discharged without specific AADs, 38% on amiodarone, 5% on propafenone and 13% on flecainide.

**Repeat procedures**

The predominant indication for the 2nd procedure was AF in 64% (n=206) and AT in 36% (n=115) of the cases. Of all 321 patients undergoing a second procedure 48% presented in SR to the first redo procedure. In 55% of patients, any AT was observed during 2nd procedure (n=1 in 26%, n=2 in 17%, n=3 in 8% and n>3 in 4% of the cases). During 2nd procedure, a mean of 2.3 ±1.3 PVs showed conduction recovery. The number of reconnected PVs declined with every repeat procedure (see table 2), Dominant indication for procedure 3 was AT in 53% of the cases (remaining AF), for procedure 4 in 76% of patients and in procedure 5, 6 and 7 in 91, 25 and 50% (figure 2).

We analyzed all 493 patients for clinical and procedural factors that are associated with repeat procedures due to AT recurrences. The hazard for AT is significantly associated with the application of lines in the foregoing procedure (p=0.014, HR 1.42 95% CI [1.07-1.88]), the amount of RF energy application (p=0.003, HR 1.005 95% CI [1.002-1.008]) and AF termination during the latter (p=0.003, HR 1.71 95% CI [1.20-2.43]). Also, the number of procedures (p<0.001, HR 1.69 95% CI [1.45-1.97]) was correlated with consecutive AT
procedures. No significant association could be shown for the clinical parameters age, sex and LA size (p= 0.636/0.557/0.584) respectively.

Linear lesions have been performed in 112/321 patients (34.9%) during the second procedure (in 191/493 (38.7%) during index procedure). Termination (either into SR or AT) was achieved in 81% of patients during 2nd procedure and in 87-98% during 3rd - 5th procedure. Only 4 patients underwent 6 or 7 procedures.

A detailed presentation of the repeat procedure periprocedural data is provided in table 2. In 5 patients with indication for cardiac surgery an endoscopical or open surgical AF ablation was performed as repeat procedure.

**Long-term follow up**

The mean FU duration was 59 ± 16 mo after the index procedure and 44 ± 22 mo after the last procedure. A total of 1042 procedures in 493 patients were analyzed (321 patients with ≥1 procedure) with a mean of 2.1 ± 1.1 procedures per patient. Five-year success rates were 20.1% after a single procedure and 55.9% after the last documented procedure, respectively. (Figure 3a, 3b). Based on holter-ecg results 171/493 patients (34.6%) showed recurrent arrhythmia in long-term outcome, which was classified as PAF in 48 patients (28.1%), and persAF/AT in 123 patients (71.9%) after one or multiple procedures (outcomes after each procedure depending on types of termination are shown in figure 2). At the end of FU, 42.8% of patients were off oral anticoagulation (OAC). Patients in stable SR presented off AADs in 79.8% of the cases at long term FU. If AADs were needed, patients received Class Ic AADs in 10.5% or Class III AADs in 9.7% of the cases. The Kaplan-Meier estimate of 60 mo arrhythmia and AAD free survival with multiple procedures is 45.6% (95% CI[40.4%-50.6%]) The 60-mo Kaplan-Meier curve and the distribution of AADs in the SR population are shown in figure 4.
Time to arrhythmia recurrence

The median event-free time after index procedure was 12.8 mo (95% CI [10.6-14.9]). The recurrence-rate during the first 12 mo after index procedure was 47.8% (95% CI [43.5-52.3]), whereas further 22.8% of patients experienced a late recurrence later than 12 mo and up to 36 mo after the index procedure (event-rate after 36 mo 70.6% (95% CI [66.5-74.6])). Similar values for the median event-free times were found after 1st and 2nd redo-procedure with 15.1 mo (95% CI [11.9-18.2]) and 12.6 mo (95% CI [7.9-17.2]). The median event-free times for the 3rd and 4th redo-procedure are 23.2 mo (95% CI [11.5-35.0]) and 8.3 mo (95% CI [4.8-11.8]), respectively.

Factors influencing arrhythmia outcome

Recurrent event analysis was performed for 1042 procedures of 493 patients. Univariable factors correlating with recurrence were failure to terminate AF during the index procedure irrespective to the mode of termination (direct SR vs. in subsequent AT), number of procedure, larger LA-diameter and presence of SHD. AF episode duration, age, CHA2DS2Vasc score or present arterial hypertension were not associated with procedural success. Multivariable recurrent event analysis revealed failure of AF termination (HR: 1.279; 95% CI [1.093-1.497]; p = 0.002), female sex (HR: 1.263; 95% CI [1.027-1.553]; p = 0.027), the number of procedures (HR: 1.154; 95% CI [1.051-1.267]; p=0.003) and the presence of SHD (HR: 1.236; 95% CI [1.003-1.524]; p = 0.047) as associated factors for arrhythmia recurrences (table 3). Arrhythmia termination during the index procedure was associated with a 22.8% reduced hazard of arrhythmia recurrence compared to termination failure (HR: 0.782 [95% CI: 0.668-0.915]; p = 0.002). Notably, the long-term arrhythmia free outcome declined with an increasing number of redo procedures. With every procedure, the hazard for arrhythmia recurrences increased by 15.4%. The hazard for arrhythmia recurrence for men is reduced by 20.8% compared to women. A
present SHD raises the hazard for arrhythmia recurrence by 23.6%. An additional periprocedural analysis showed no significant correlation between AFCL and arrhythmia free survival (HR 1.001 [95% CI 0.999-1.003], p=0.181, n=265).

There was also no association between the amount of RF energy applied during index procedure and long-term recurrences. However, the amount of RF during index procedure correlated with AF termination. Patients with AF termination showed a significantly lower amount of RF as compared to those in whom AF termination could not be achieved (mean difference RF termination vs. RF no-termination, 24982, 95% CI: 14813-35151, p<0.001).

Recurrent event analysis with the Anderson-Gill model for grouped episode durations (0-6, 6-12, 12-18, 18-24, >24 mo) revealed no correlation of episode duration and outcome (p=0.134). But patients with an episode duration < 6 mo showed a favorable multiple procedure outcome compared to those patients with an episode duration >6 mo p = 0.064; HR 0.853; 95% CI [0.721-1.010]).

**Procedural complications**

Overall, 4.9% (n=27) of 549 patients experienced procedure related complications during/after index procedure prolonging hospitalization. Of these, 2.7% (n=15) suffered from peripheral vascular complications such as AV-fistula, pseudoaneurysm or relevant groin hematoma (decrease in hemoglobin level >3g/dl). Pericardial tamponade occurred in 0.4% (n=2) requiring percutaneous pericardial drainage. Embolic stroke was seen in 0.4% (n=2). In one patient, all neurological deficits recovered without sequelae, the other one recovered from hemiplegia but still suffers from aphasia. In another 0.4% (n=2) acute heart failure occurred after the procedure requiring transient intensive care therapy and 0.9% (n=5) were documented to have post-interventional pneumonia, all of them recovered with antibiotic therapy. One patient (0.2%) with
a history of renal transplantation developed acute renal failure. No deaths, atrioesophageal fistulas or PV stenosis were observed. Overall, severe adverse events including embolic stroke and pericardial tamponade occurred in 4 patients (0.7%)

Discussion

Main findings

This study provides important information to the field of CA for persAF. First, termination of AF during ablation can be achieved in the majority of patients using the “stepwise approach”. Second, five-year FU results in limited freedom from AF/AT in 55.9% of patients with multiple procedures. Third, the effectiveness of a single procedure is insufficient. Furthermore, AF termination as a procedural parameter during the index ablation procedure, a lower number of procedures and the clinical absence of SHD and male gender are associated with a favorable outcome.

Outcomes after persAF ablation

While different groups have presented data on outcomes after PVI for PAF, there remains a paucity of data regarding the long-term efficacy of CA of persAF. Different patient cohorts along with variable ablation strategies for persAF hinder comparability of existing outcome data. Furthermore, FU times vary considerably and are mostly mid-term so far. Multiple procedures (mean 2, 1-7 in our study) or AAD support are often required to maintain stable SR. We report a limited 5y-multiple procedure success rates of 59% (20% on AAD) using the „stepwise approach“ However, AF termination can be achieved and the majority of patients (65%) do present with AT as a recurrent arrhythmia indicating a first step towards SR. Furthermore, a significant number of patients (n=165, 33%) with recurrences did not undergo
repeat ablation due to AF regression to PAF (n=52) or symptom improvement (persAF, n=113) (figure 3). A higher rate of repeat CA may have resulted in improved outcomes. Tilz et al. reported on 5y outcome data using wide antral PVI alone for persAF (n=202) resulting in SR maintainance in 43.2% after multiple procedures (12% on AAD). Of note, PVI as the sole ablative strategy independently predicted arrhythmia recurrences favoring a supplemental substrate based ablation strategy. Very recently, 5y-outcome data of the “stepwise approach” (n=150) revealing AAD free single and multiple procedure success rates of 15.3% and 64.7% with a termination rate of 80% during index procedure have been published. The lower risk profile patient population (CHA2DS2Vasc ≥ 2 in 25% vs 65%) along with a slightly different follow up monitoring (89% holter vs. 100%) might explain deviating outcome results compared to our data.

Complication rates of our study are well in line with worldwide surveys. However, the periprocedural risks and the risk of cumulative radiation doses with multiple procedures have to be carefully considered while planning CA for patients with the “stepwise approach“.

Strategies for persAF ablation

Because the underlying mechanisms of persAF are poorly understood various approaches for the interventional treatment of persAF are being used. A metaanalysis of 32 studies evaluated the impact of different ablation techniques on the outcomes of persAF. The authors concluded that persAF could be effectively treated with a composite of (1) extensive index CA, (2) repeat procedures, and/or (3) adjunctive pharmacological therapy. It revealed favorable outcomes for the “stepwise approach”. Also, the current guidelines emphasize that in persAF, ablation strategies beyond PVI should be considered.

However, we are facing no more than limited outcomes, long procedure times and
multiple procedures per patient. Therefore, further research is needed to develop more effective and specific patient tailored AF ablation strategies. Experimental and animal models suggested that focal AF sources or drivers may maintain the fibrillatory process.\textsuperscript{28, 29} The CONFIRM trial compared conventional ablation with rotor and focus mapping guided ablation followed by conventional ablation and showed improved short-term outcomes for the latter.\textsuperscript{30} Also, panoramic non-contact mapping is aiming at identification of patient specific AF driving sources.\textsuperscript{31} Of note, these first data derive from small, mixed AF populations (PAF, persAF) with lack of clinical long term success so far. Moreover termination rates varied considerably from 66-82%.

In our study 66% of patients presented with AT as indication for repeat procedures. Linear lesions were created in 42% of procedures (n=438/1042) and clinical AT recurrences led to repeat ablation of the same line in up to 33% of repeat procedures. We showed that linear lesions, a high RF energy amount and AF termination in the foregoing procedure as well as a higher number of procedures were associated with consecutive procedures due to AT. It is well known that complete conduction block of lines remains challenging and conduction recovery is commonly observed.\textsuperscript{32} Regional differences in atrial cellular electrical properties due to conduction slowing or linear lesion gaps are considered to be pro-arrhythmic. Together with remodeling of atria, extended tissue ablation might therefore provide a favorable condition for the development of ATs but it also appears to result in a significant atrial substrate modulation avoiding perpetuation of AF. Additionally, AT recurrences (often based on macroreentrant mechanisms) can more easily be targeted during repeat procedures and are associated with favorable outcome as compared to CA for AF\textsuperscript{24, 33, 34} Therefore, occurrence of AT can be considered a step forward to SR.
Concerning LA transport function after CA of AF previous studies have shown that successful CA significantly decreases LA volumes and does not seem to adversely affect LA function. \(^{35}\) Latter was not only shown by echocardiography but also by MR imaging demonstrating recovery of active LA appendage emptying in the majority of patients \(^{36}\)

**Prognostic factors for long-term success**

Our data suggest that failure of AF termination during index procedure the number of procedures, and the clinical factors female gender and the presence of SHD are associated with an inferior long-term success.

**Structural heart disease**

One third of patients in our population had a relevant SHD (CAD, cardiomyopathy or valvular heart disease). Any kind of SHD may trigger a progressive process of structural remodelling in the atria imposing an increased LA afterload resulting in LA stretching, enlargement, and fibrosis. \(^{37,38}\) Heart failure and known SHD were shown to increase the incidence of AF recurrences. \(^{39}\)

**Female gender**

Although AF being significantly less common in females, latter have a higher prevalence of underlying heart disease, a lower quality of life and treatment aims are harder to achieve. Additionally, women have a higher risk of ischemic stroke. \(^{40}\) In our study female gender was associated with a worse outcome. Recently, some studies have examined the efficacy of CA for PAF in women but the findings have been inconsistent. \(^{41,42}\) Forleo et al. showed that gender had no effect on the outcome of CA for AF, while Patel et al. found lower success rates in females. Only one study evaluated the outcome for women after CA of persAF which revealed higher recurrence rates like shown in our study. \(^{43}\)
AF termination

The data of the present study indicate that procedural AF termination during CA of pers AF with the “stepwise approach” independently increases the likelihood of long-term freedom from arrhythmias.

There is an ongoing debate whether AF termination is a direct procedure related predictor for success and therefore termination is so far not incorporated or endorsed as an endpoint in the current guidelines. Several studies have shown that termination is predictive for long-term maintenance of SR. O’Neill et al reported lower recurrence rates in patients with AF termination during index procedure (5% vs. 39%). Termination to SR being associated with the highest single procedure success rate compared to AT or AF at the end of the procedure (42% vs. 13% and 25%) was shown by Ammar et al. In contrast, Elayi and colleagues noted no impact of termination on SR maintenance. It did, however, predict the mode of arrhythmia recurrence (AT vs. AF).

The question remains, whether failure to terminate AF is an epiphenomenon indicating a more pronounced atrial disease being less responsive to CA. Despite clear evidence based data, in practice, termination currently still is a commonly used endpoint for persAF ablation not only during conventional CFAE mapping, but also when novel approaches as mentioned above are applied.

Number of procedures

The fact that every repeat procedure lowered the long-term success rates may indicate a “point of no return” where AF may no longer be accessible for rhythm control by CA. AF progression might be a reason for the decreasing effect of CA. Previous studies indicated the presence of baseline comorbidities/cardiovascular diseases and the type of AF (persAF and long- standing persAF)
being independent predictors for progression.\textsuperscript{44}

**Risk prediction**

More clinical instead of procedural parameters including novel factors like sleep apnea, obesity or even MR imaging for detection of atrial fibrosis would be desirable to screen for long-term success patients prior decision making for or against CA. We were not able to create a clinical futility score identifying patients for whom ablation is not advised, but patients with SHD and an episode duration of >12 mo revealed very poor outcomes with 60 mo single and multiple procedure survival rates of 16\% and 28\%. It remains unclear if a clinical risk score would be able to estimate the extent of atrial remodeling, disease progression and response to CA therapy.

For now, clinical factors identifying a less favorable outcome along with acute CA results during initial procedure and the mode of arrhythmia recurrence (AT/AF) should be incorporated when weighing up the patients’ long-term benefit from CA, especially after a failed first or second procedure.

**Late AF relapse**

Although AF recurrences most often occur within the first 12 mo after ablation, previous studies and our data show a slow but steady decline in arrhythmia-free survival thereafter, even after more than 1 year of apparent arrhythmia control (figure 2).\textsuperscript{16,17,18} Failure of persAF ablation seems to be a combined consequence of inadequate trigger ablation, substrate modification or conduction recovery of previously ablated substrates. However, progression of the AF underlying atrial disease itself that may only partly be halted by SR restoration should be considered as an important factor. Facing very late recurrences in initially successfully treated patients, discontinuation of OAC should carefully be considered, especially since we found 14\% of patients with arrhythmias and a CHA\textsubscript{2}DS\textsubscript{2}Vasc score $\geq$1 being off OAC at time of long-term
FU.

**Study limitations**

Patients in this single center study were not randomized and the data analysis was retrospectively performed. Although the vast majority of patients presented with sustained forms of arrhythmias the potential for under-recognition of silent arrhythmia recurrences during FU exists. Because of discontinuous Holter ECG monitoring we are not able to provide data on AF burden prior and after CA.

**Conclusions**

The present data indicate that CA of persAF using the “stepwise approach“ provides limited long term freedom of arrhythmia recurrences often requiring multiple procedures. AF termination during index procedure, the number of procedures, sex and the presence of SHD are prognostic factors correlating with long-term outcome. AF termination is associated with consecutive AT procedures.

**Conflict of Interest Disclosures:** None

**References:**


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Table 1: Baseline characteristics n=493

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<thead>
<tr>
<th>Baseline parameter</th>
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<tr>
<td>Age, y {min-max}</td>
<td>61 ± 10 {23-80}</td>
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<tr>
<td>Sex, m/f (m:w)</td>
<td>393/100(3.9:1)</td>
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<tr>
<td>BMI {min-max}</td>
<td>28 ± 4 {19-42}</td>
</tr>
<tr>
<td>Left atrial diameter, mm {min-max}</td>
<td>46 ± 6 {27-65}</td>
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<tr>
<td>Left ventricular ejection fraction</td>
<td>60 ± 10 {25-87}</td>
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<td>No. of cardioversions {min-max}</td>
<td>2 ± 2 {0-21}</td>
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<td>Hypertension, n (%)</td>
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<td>Structural heart disease n (%)</td>
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<tr>
<td>- CAD, n (%)</td>
<td>87 (18)</td>
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<tr>
<td>- Cardiomyopathy/Valvular HD, n (%)</td>
<td>80 (16)</td>
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<td>Diabetes mellitus</td>
<td>38 (8)</td>
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<td>Peripheral artery disease</td>
<td>25 (5)</td>
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<tr>
<td>Cardiac device (Pacemaker, ICD)</td>
<td>75 (16)</td>
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<tr>
<td>No AADs before ablation {min-max}</td>
<td>1.7 ± 0.9 {0-5}</td>
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<tr>
<td>Amiodarone, n (%)</td>
<td>192 (41)</td>
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<tr>
<td>Embolic events before ablation, n(%)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>CHA2DS2Vasc {min-max}</td>
<td>2 ± 1 {0-7}</td>
</tr>
<tr>
<td>OAC prior initial procedure n (%)</td>
<td>392 (85)</td>
</tr>
<tr>
<td>History of AF, mo {median, min-max}</td>
<td>73 ± 73 {48, 1-576}</td>
</tr>
<tr>
<td>Episode duration before index procedure, mo{median, min-max}</td>
<td>14 ± 27 {6, 1-240}</td>
</tr>
</tbody>
</table>
### Table 2: Procedural data for the index and redo procedures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P ≥1 (n=493)</th>
<th>P ≥2 (n=321)</th>
<th>P ≥3 (n=148)</th>
<th>P ≥4 (n=59)</th>
<th>P ≥5 (n=15)</th>
<th>P ≥6 (n=4)</th>
<th>P ≥7 (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration, min</td>
<td>197 ± 56</td>
<td>167 ± 68</td>
<td>157 ± 66</td>
<td>139 ± 58</td>
<td>134± 47</td>
<td>158 ± 56</td>
<td>153 ± 46</td>
</tr>
<tr>
<td>No. RF applications, n</td>
<td>50 ± 23</td>
<td>37 ± 27</td>
<td>34 ± 26</td>
<td>26 ± 23</td>
<td>25 ± 21</td>
<td>25 ± 18</td>
<td>23 ± 18</td>
</tr>
<tr>
<td>Energy application, J</td>
<td>126034 ± 44410</td>
<td>87645 ± 51791</td>
<td>67013 ± 45105</td>
<td>58694 ± 46442</td>
<td>45768 ± 35214</td>
<td>80714 ± 52589</td>
<td>71267 ± 70127</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>53± 21</td>
<td>41 ± 22</td>
<td>37 ± 21</td>
<td>35 ± 25</td>
<td>28 ± 19</td>
<td>37 ± 18</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>Mean area dose product per procedure (cGycm²)</td>
<td>6750 ± 9534</td>
<td>6204 ± 10221</td>
<td>5349 ± 7142</td>
<td>6028 ± 6836</td>
<td>4358 ± 3766</td>
<td>2964 ± 2499</td>
<td>4661 ± 1596</td>
</tr>
<tr>
<td>Mean cumulative dose/patient (cGycm²)</td>
<td>6808± 12519</td>
<td>11257 ± 10165</td>
<td>16734 ± 17771</td>
<td>23226 ± 16123</td>
<td>33250 ± 24623</td>
<td>25980 ± 19784</td>
<td>31455 ± 23965</td>
</tr>
<tr>
<td>No. reconducted PVs, n</td>
<td>-</td>
<td>2,3</td>
<td>1,0</td>
<td>0,6</td>
<td>0,5</td>
<td>0,7</td>
<td>0</td>
</tr>
<tr>
<td>Termination %</td>
<td>59</td>
<td>82</td>
<td>90</td>
<td>98</td>
<td>87</td>
<td>75</td>
<td>50</td>
</tr>
</tbody>
</table>

* incl. 5 surgical repeat procedures
Table 3: Univariable and multivariable analysis of associated factors of sinus rhythm maintenance

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Hazard ratio</th>
<th>95% Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariable</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.859</td>
<td>0.711-1.039</td>
<td>0.117</td>
</tr>
<tr>
<td>Age</td>
<td>1.006</td>
<td>0.996-1.016</td>
<td>0.237</td>
</tr>
<tr>
<td>CHA2DS2Vasc</td>
<td>1.050</td>
<td>0.996-1.107</td>
<td>0.069</td>
</tr>
<tr>
<td>HTN</td>
<td>1.062</td>
<td>0.870-1.296</td>
<td>0.554</td>
</tr>
<tr>
<td>SHD</td>
<td>1.223</td>
<td>1.021-1.464</td>
<td>0.029</td>
</tr>
<tr>
<td>Episode duration</td>
<td>1.002</td>
<td>0.999-1.006</td>
<td>0.172</td>
</tr>
<tr>
<td>Termination (initial procedure)</td>
<td>0.756</td>
<td>0.643-0.888</td>
<td>0.001</td>
</tr>
<tr>
<td>LA diameter</td>
<td>1.020</td>
<td>1.005-1.037</td>
<td>0.012</td>
</tr>
<tr>
<td>Number of procedure</td>
<td>1.164</td>
<td>1.063-1.273</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Multivariable</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.792</td>
<td>0.644-0.974</td>
<td>0.027</td>
</tr>
<tr>
<td>Age</td>
<td>1.006</td>
<td>0.995-1.017</td>
<td>0.303</td>
</tr>
<tr>
<td>CHA2DS2Vasc</td>
<td>0.958</td>
<td>0.877-1.045</td>
<td>0.334</td>
</tr>
<tr>
<td>HTN</td>
<td>1.055</td>
<td>0.847-1.315</td>
<td>0.632</td>
</tr>
<tr>
<td>SHD</td>
<td>1.236</td>
<td>1.003-1.524</td>
<td>0.047</td>
</tr>
<tr>
<td>Episode duration</td>
<td>1.002</td>
<td>0.998-1.005</td>
<td>0.309</td>
</tr>
<tr>
<td>Termination (initial procedure)</td>
<td>0.782</td>
<td>0.668-0.915</td>
<td>0.002</td>
</tr>
<tr>
<td>LA diameter</td>
<td>1.012</td>
<td>0.996-1.029</td>
<td>0.146</td>
</tr>
<tr>
<td>Number of procedure</td>
<td>1.154</td>
<td>1.051-1.267</td>
<td>0.003</td>
</tr>
</tbody>
</table>

n=1042 procedures of 493 patients
SHD=Structural Heart disease
HTN=arterial hypertension
AFCL=atrial fibrillation cycle length (n=265)
Figure Legends:

Figure 1: “Stepwise approach” for catheter ablation of persAF. Left: Catheter ablation flow chart illustrating procedural course, right: Ensite Navx® 3D reconstruction of a patients’ biatrial anatomy with ablation targets (LA/RA=left/right atrium, CS=coronary sinus, LSPV=left superior pulmonary vein, LIPV=left inferior pulmonary vein, RSPV=right superior pulmonary vein, RIPV=right inferior pulmonary vein, RAA/LAA=right/left atrial appendage, yellow dots: pulmonary vein isolation, brown dots: spots of biatrial defragmentation)

Figure 2: Flow chart demonstrating arrhythmia outcomes after each procedure depending on mode of termination (termination to SR, termination to AT, no termination), in brackets we provide information on repeat procedure indication (AF or AT). Numbers in italic indicate patients undergoing repeat ablation. *patients treated with endoscopical/surgical ablation

Figure 3: Kaplan-Meier analyses demonstrating cumulative arrhythmia free survival and estimates of 60-mo arrhythmia free survival with CA of persAF using the “stepwise approach” after a) index procedure and b) last documented procedure (in braces: number of events observed in corresponding time interval).

Figure 4: a) AAD treatment at the time of last FU for patients in sinus rhythm. b) Cumulated AAD and event free survival and Kaplan-Meier estimate of 60-month survival after last documented procedure (in braces: number of events observed in corresponding time interval).
Atrial fibrillation

Step 1:
Pulmonary vein isolation

Step 2:
Defragmentation
LA CS RA

Atrial tachycardia

Step 3:
Specific AT-ablation

Sinus rhythm

Electric cardioversion

Termination
* epicardial surgical ablation: 5 pts (3 SR, 2 Pers, 1 pt with consecutive endocardial repeat procedure)
a

Arrhythmia and AAD free survival

45.6% (95% CI[40.4%;50.6%])

b

Number at risk

Follow up in months

493 (155) 332 (23) 273 (28) 203 (23) 149 (9) 84