



# **Predictors of Recurrence After Catheter Ablation** of Persistent Atrial Fibrillation

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# Abstract

Catheter ablation of atrial fibrillation (AF) has been increasingly used to treat symptomatic patients. Within the last years a growing interest in ablation of persistent AF forms has evolved. Factors that may influence outcome of these procedures to treat persistent AF may be patient-specific (pre-procedural), procedure-related or may involve different post-ablation follow-up strategies. In this review potential factors predicting recurrence of AF after ablation of persistent AF have been evaluated. In essence, data is limited mostly due to incongruent definitions of persistent AF. Left atrial dimensions, duration of continuous AF and AF cycle length may be patient-specific predictors of outcome. Intra-procedural parameters involved in recurrence prediction may be extent of ablation (effective pulmonary vein isolation appears mandatory) and termination of AF during ablation. Timing and number of cardioversion if persistent AF recurs may predict outcome, as well.

Many studies have identified strators for higher recurrence rates in rather small patient groups and need to be further evaluated in larger patient collectives.

# Introduction

Catheter ablation of atrial fibrillation (AF) has emerged as an effective tool to treat symptomatic patients with drug-refractory AF. Success is usually measured as stability of sinus rhythm (SR) in multiple holter-ECGs after an initial blanking period of up to 6 months. Success rates in patients with paroxysmal AF of up to 89% have been reported. In contrast, AF ablation in persistent AF has a sufficiently lower success rate after a single procedure and more procedures/patient are needed to achieve adequate rhythm control.<sup>1,2</sup>

In specialized centres the percentage of patients with persistent AF undergoing ablation procedures may be in the range of 30%. For these patients, ablation concepts may implement ablations additional to effective pulmonary vein isolation (PVI). Ablation of left atrial regions identified by the existence of complex fractionated electrograms (CFAE) may improve outcome in some patients, whereas in addition linear ablation (LIN) to compartmentalize the left atrium

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has been proposed in different studies. Success rates differ widely depending on patient selection, experience of the operators and follow-up. Also, persistent AF is poorly defined by 1. either AF lasting longer than 7 days or 2. AF undergoing conversion by either drugs or electrical cardioversion. This definition may include a wide variety of patients with different stages of AF disease and therefore, success rates may vary widely.<sup>1-14</sup>

Recurrences after ablation of persistent AF may include recurrent AF or atrial tachycardia either due to inconsistent left atrial lesions, reconnected pulmonary veins (PVs) or as tachycardia originating from previously not ablated areas of the right and left atrium.

So far, only a limited number of studies have looked into predictors of AF recurrence after ablation of persistent AF. It can be speculated that 1. pre-procedural markers indicating ablation failure may exist, 2. intra-procedural determinants of failure and 3. post-procedural predictors of poorer outcome may be identified. It is most likely, that there is not a single predictor but a combination of different factors influencing outcome in this inhomogeneous patient group. As always with multivariate prediction analysis the number of determinants included in such a model will have effects on outcome of these statistical methods. In addition, many factors are correlated with each other in a rather complex way and may therefore not be appropriately analyzed using simple statistical methodology. In different studies, persistent AF has been identified as a significant confounder for a 50 to 55% higher risk for recurrence mostly in univariate analysis. This can be explained by the assumption, that a persistent type of AF includes many confounding variables that may lead to different results in multivariate analyses. Again, different stages of atrial disease may affect success rates of ablation procedures.<sup>15 - 21</sup>

### **1. Pre-Procedural Factors**

Many variables that may affect outcome of ablation procedures for AF have been evaluated mostly in either paroxysmal AF patients or in a mixed population. Only a limited number of studies evaluated the effect of pre-procedural variables in a predefined subgroup including only patients with persistent AF.<sup>18-21</sup>

### 1.1. Left Atrial Dimensions

Left atrial dilation is often associated with AF and vice-versa. Patients with large left atrial dimensions may have substantial left atrial myopathy serving as a basis for the perpetuation of AF. Left atrial dilation results in anisotropic conduction and regional differences in refractory periods. The combination of electrical and substrate remodelling facilitates the onset and perpetuation of AF.

Left atrial dimensions are usually evaluated using pre-procedural transthoracic echocardiography and measurements may differ widely intraindividually and in between observers. Left atrial volume as a more concise parameter has so far not been consistently evaluated in ablation studies.

Left atrial size was found to be a major determinant for recurrence of ablation for persistent AF in 2 studies. Freedom from AF decreases with increasing left atrial size up to 46mm but no change is identified in patients > 46mm left atrial dimensions <sup>7</sup>. In a second study by Lo et al.<sup>37</sup> left atrial size was greater in patients with failure of persistent AF ablation. As a cut-off value left atrial diameter > 43mm significantly influences 1- and 2-year AF free survival rates (54% at 1 year, 51% at 2 years compared to 91% for 1 and 2 year AF free survival in patients with left atrial diameters < 43mm).<sup>7, 37</sup>

In contrast, a large cohort analysis by Bhargava et al.<sup>19</sup> and a second study by Wokhlu et al. did not find left atrial size to be predictive of single procedure AF ablation success in persistent AF. These studies appeared to include mostly patients with shorter duration persistent AF which may explain some of the discrepancies.

Overall data is controversial and this may in some part be due to the insufficiency of echocardiographic measurement of correct left atrial dimensions in addition to differences in ablation strategies in different study groups. It can be concluded though, that increasing left atrial size may negatively affect rhythm success after ablation of persistent AF but no clear 2-dimensional cut-off value exists that may definitely predict failure of the ablation procedure.

### 1.2. Duration of Persistent AF

Data on duration of persistent AF prior to ablation is inconclusive. Bhargava et al.<sup>19</sup> identified a longer duration of persistent AF as predictor of failure after a single ablation procedure (hazard ratio 1.74; p=0.003). A recent study by Rostock et al.<sup>7</sup> documented duration of persistent AF longer than 6 months to be an independent predictor for AF recurrence in persistent AF ablation. McCready et al.<sup>18</sup> did not identify AF duration as predictive for recurrence of AF (hazard ratio 1.07; p=0.11) in the overall group of persistent AF. In the group of patients with a left atrial diameter above 43mm, duration of AF appeared as an independent predictor of AF recurrence. Specifically, patients with long-lasting persistent AF have poorer outcome after ablation emphasizing the importance of duration of AF prior to ablation. There does not appear to be a clear cut-off value for continuous AF duration indicating a relevant drop-down in efficacy (apart from 1 year consistent AF as indicated in the definition of long-lasting persistent AF). It needs to be stressed that pre-ablation AF duration in persistent AF cases should include only the time consistently in AF. In many centres, extent of ablation strategy is mainly based on duration of persistent AF prior to the ablation making multivariate analysis statistically challenging.

It can be concluded though, that long persistence of AF (> 6 months prior to ablation) negatively influences recurrence of AF after ablation. Again no clear cut-off value exists and ablation may be extended to additional areas in these patients.

### 1.3. Hypertension

Hypertensive heart disease is a major risk factor for the incidence of AF. In mixed populations with different types of AF hypertension appears to be a significant predictor of AF recurrence after ablation. 3 studies have evaluated hypertension as a strator of ablation outcome in persistent AF ablation in a multivariate model. Whereas hypertension was a predictor of ablation failure in patients with persistent AF in the study by Bhargava et al.<sup>19</sup> and for very late recurrence in the study by Wilber et al. (personal communication at Boston AF symposium 2011), it was not a relevant factor in the study by McCready et al.<sup>18</sup>

Data remains inconclusive on the predictive role of

hypertension on persistent AF ablation outcome.

### 1.4. Structural Heart Disease/Left Ventricular Function/Congestive Heart Failure

The presence of structural heart disease (mostly coronary artery disease) may affect AF ablation outcome. In addition, recent publications have highlighted the role of AF ablation in patients with left ventricular dysfunction or congestive heart failure. The prognostic relevance of underlying ventricular abnormalities on outcome of ablation strategies has not been clearly elucidated. One can speculate though, that severely impaired left ventricular function may lead to more aggressive ablation strategies to terminate AF. Most studies evaluating structural or valvular heart disease as a predictor did not identify a relevant relation to ablation outcome but 2 studies indicated a significant association in a mixed AF population. In a homogenous group of persistent AF, 2 studies documented contrary findings in relation to AF recurrence and structural heart disease/cardiomyopathy, Whereas McCready et al.<sup>18</sup> did not find any relation in 191 patients. Rostock et al.<sup>17</sup> identified a prognostic relevance of congestive heart failure in a multivariate regression analysis in 395 patients. Congestive heart failure involved a 10-fold risk for AF recurrence after the index procedure and after the final procedure. The existence of coronary artery disease also predicted a negative outcome after the final procedure in this study.

Congestive heart failure appears to be an independent predictor of AF recurrence in patients with persistent AF as indicated in a single study on nearly 400 patients undergoing ablation in a center with high expertise.

#### 1.5. Age and Sex

A recently published study by Rostock et al.<sup>17</sup> indicates a higher recurrence rate in female patients after ablation of persistent AF. A second study by Wilber et al. (personal communication at Boston AF symposium 2011) on 1404 patients with persistent or long-standing persistent AF also documented female gender to be a predictor of very late recurrence. Other studies have not identified a gender-specific success rate. In conclusion, there appears to be an effect of female gender on persistent AF ablation success specifically during late follow-up. The gender-specific mechanisms re-

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main unknown and need to be further evaluated.

There does not appear to be a relevant influence of ageonrecurrences of atrial tachy cardias after persistent AF ablation as indicated in different studies.<sup>17-19</sup> 1.6. Serum Markers

The extent of structural remodelling and brain natriuretic peptide (BNP) levels may be related and therefore higher pre-procedural BNP levels may indicate more extensive structural abnormalities. Baseline BNP levels appear to be higher in patients with persistent types versus paroxysmal AF types. Whereas baseline BNP levels are predictive of ablation outcome in patients with paroxysmal AF this has not been documented for patients with persistent and long-standing persistent AF.<sup>23</sup>

Higher baseline BNP levels do not appear to be a predictor of AF recurrence in patients with persistent form of AF but normalization after ablation may be.

#### 1.7. Atrial Fibrosis

Atrial structural remodelling leads to substrate formation for perpetuation of atrial fibrillation. Atrial myopathy in these cases includes different degrees of fibrotic replacement which appears to be related to the duration of ongoing AF. The amount of atrial fibrosis can be documented in delayed enhancement magnetic resonance imaging (DE-MRI). The percentage of fibrosis is related to the occurrence of embolic complications during AF and has been identified to be a predictor for failure of AF ablation in paroxysmal AF patients.<sup>24</sup> Staging atrial fibrosis into four categories has identified a higher proportion of patients with persistent AF to fall into the stages with more than 20% fibrosis. Higher stages of atrial fibrosis were related to higher recurrence rate independent to AF type. Identifying the degree of atrial fibrosis may help to select the appropriate ablation strategy and potentially predict AF recurrence in patients with extensive (or moderate) atrial fibrosis. Further studies need to evaluate the potential for pre-ablation DE-MRI to predict AF recurrence in a homogenous group of persistent or long-standing persistent AF. Whether areas of atrial fibrosis can be identified using intraprocedural bipolar voltage mapping needs further evaluation but may be a potential intraprocedurally evaluated factor to predict outcome if large areas of low voltage areas are documented.

#### 2. Intraprocedural Factors

Different procedural characteristics have been evaluated in their potential to affect outcome in ablation procedures for persistent AF. While, especially extent and type of left atrial ablation have been tested, also termination of AF during the ablation procedure may be a relevant marker.

#### 2.1. Extent of Ablation Procedure

There is evidence from 4 randomized trials<sup>3, 4,</sup>

Figure 1: Single procedure rhythm success rates 6 to 12 months after different ablation strategies for persistent AF presented in different trials (PVI + LIN: N = 417, PVI + CFAE: N= 256, PVI + LIN + CFAE: N = 341) (from 2, 3, 4, 15, 16, 17, 24, 25, 26, 27, 28, 29, 30, 31, 33, 34, 35, 36).



<sup>5, 25</sup> and 2 meta-analyses<sup>16, 26</sup> on the effect of different ablation strategies on outcome in persistent AF. Many studies have documented the necessity of PVI as a cornerstone of ablation procedures to treat AF. In addition, ablation of specific sites identified by unique appearance of local electrograms (complex fractionated atrial electrograms, CFAE) has been tested as a solitary approach or as an add-on to PVI. Other studies evaluated the usefulness of adding linear ablations (LIN) (mostly roof-line in between PVI boxes and left atrial isthmus line in between usually the left inferior PV and mitral annulus) to PVI. Triggered by the experience from the Bordeaux group, an extensive stepwise ablation approach including PVI, CFAE and linear ablation has been evaluated in 4 non-randomized trials.<sup>13, 14, 27, 28</sup> From the 4 randomized trials it can be concluded, that PVI is an essential component of ablation for persistent AF and that proven PVI (documenting entrance and (? exit block) is superior to PVablation without checking for efficacy.3, 4, 5, 25 CFAE ablation alone is inferior to PVI plus LIN and adding right atrial CFAE ablation to left atrial CFAE ablation does not provide additional benefit. One study<sup>25</sup> documented incremental benefit from adding CFAE ablation to PVI whereas a second<sup>3</sup> did not. A meta-analysis of these two trials revealed no evident treatment effect of adjunctive CFAE ablation.<sup>26</sup> Single procedure success rates in patients with longstanding persistent AF of 37 to 40% for effective (proven) PVI, of 38 to 57% for PVI plus LIN, of 24 to 63% for CFAE ablation alone, of 36 to 61% for effective PVI plus CFAE and of 38 to 62% for a stepwise ablation technique have been published (see figure 1).<sup>3 - 14, 16, 25, 26, 27,  $2\overline{8}$ </sup> It appears though, that results are comparable in between groups and that adding additional ablation strategies to PVI produces widely varying results. These differences may be due to experience of the operator and the not-clearly defined endpoint of CFAE or LIN ablation. Additional CFAE ablation may provide better results (as indicated in one randomized study) but only left atrial CFAE ablation seems mandatory. Again, the number of areas that need to be ablated in order to achieve superior results is not defined. From the presented studies it appears clear, that all patients ablated of persistent AF should undergo effective PVI.15, 16, 26

### 2.2. Termination of AF during ablation

Some centres perform ablation in persistent AF using termination by ablation as the endpoint of the procedure. This endpoint may include conversion of

AF to a regularized atrial tachycardia (AT) and effective ablation of these ATs. Termination of AF during ablation usually requires a stepwise ablation approach including PVI plus additional ablations (CFAE ablation, left and potentially right atrial lines) and may be achieved in up to 85% of patients with long-lasting persistent AF.<sup>27</sup> A recent analysis of sites of AF termination identified left atrial CFAE ablation as the part of the ablation procedure most commonly associated with AF termination (around 65%).<sup>27</sup> Especially ablation of CFAE sites within the coronary sinus and at the left atrial appendage were anatomical regions where ablation led to termination of AF. Rostock et al.28 document a biatrial component of persistent AF and the need for right atrial ablation to terminate AF in approximately 1/4 of patients. In a study on patients undergoing concomitant surgical AF ablation Deneke et al.<sup>29</sup> have identified no beneficial effect of right atrial ablation on rhythm success.28, 29 There still remains controversy on extending ablation to the right atrium, which may be needed for AF termination but may not affect rhythm outcome.

In two studies AF recurrence was significantly more often in patients without termination during the ablation procedure but atrial tachycardias were more common. In the studies by O'Neill et al.<sup>27</sup> and Rostock et al.<sup>28</sup> AF termination during ablation was a prognostic important factor, whereas a third study by Elayi et al.<sup>25</sup> did not find differences in regard to SR maintenance. Interestingly, ablation termination of AF can be predicted by pre-interventional measures like AF cycle length, which can also be determined on surface ECG.<sup>30</sup>

Overall, the role of AF termination during ablation procedures of persistent AF remains unclear but may be a good endpoint specifically for patients with duration of continuous AF shorter than 21 months and AF cycle length longer than 142ms.<sup>30</sup> AF cycle length may be an indicator for a more severely damaged left atrium. On the other hand, 40% of patients with long-lasting episodes of AF may remain in stable SR after multiple AF procedures targeting only PV isolation.<sup>31</sup> Drewitz et al.<sup>32</sup> present in their recent publication that AF cycle length was the only independent predictor of AF termination directly into SR whereas a shorter AF

cycle length was indicative of converting AF into regularized atrial tachycardias before terminating.

Data is conflicting but termination of AF if achieved in a reasonable time of ablation may be a good indicator for SR persistence during follow-up.

### 3. Post-procedural Factors

No studies comparing the effect of different management strategies during follow-up of patients after ablation of persistent AF exist. Early recurrence of AF during the initial phase of follow-up, antiarrhythmic medication and cardioversion in cases of persistent AF recurrence may have effects on long-term rhythm outcome.

#### 3.1. Early recurrence of AF (ERAF)

Early recurrence of atrial arrhythmia (ERAF) after ablation of AF may occur in 35% to 46% of patients and may be due to the transient unstable atrial remodelling processes after left atrial ablation including inflammatory response.33, 34, 35 Although ERAF is a common finding, around 50% of these patients do not have AF recurrences during longer follow-up. Therefore, most centres have established a " blanking period" after ablation acknowledging the transient pro-arrhythmogenic phenomena in the early phase after ablation (up to 3 months). On the other hand, early recurrence may be due to recovery of conduction over left atrial ablation sites and therefore may be an indicator for later ablation failure. Different studies identified ERAF as a highly significant predictor of later recurrence of AF and ablation failure in mixed paroxysmal and persistent AF patient groups. In a study by Themistoclakis et al.33 recurrences within the first 2 months appeared to implement transient left atrial instability and were not related to later recurrence, whereas recurrences of atrial tachycardias after 2 months were associated with AF recurrences after the blanking period. In the STAR-AF trial<sup>36</sup> ERAF also was significantly predicting failure of ablation, although no decisive data on the subgroup of patients with persistent AF was made.

### 3.2. Type of recurrent arrhythmia

Arrhythmia recurring after persistent AF ablation may either be AF or regular macro-, micro-reentry of focal atrial tachycardia. These regular atrial tachycardias may account for 20 to up to 50% of recurrent arrhythmia<sup>6, 17, 25, 37</sup> and is more common with more extensive ablation approaches.<sup>26</sup> Recently, some studies identified, that the recurrence of AF is of different impact to the overall outcome compared to recurrent regular atrial tachycardia .17, 25, 37, 38 Ablation of subsequent atrial tachycardia occurring late after persistent AF ablation can be effectively treated in redo-procedures and the outcome is superior to ablation of recurrent persistent AF.<sup>39</sup> In a recent study by Ammar et al.<sup>38</sup>, regularized atrial tachycardia can be ablated with high efficacy and outcome is superior compared to repeat ablation procedures for recurrent persistent AF after an initial persistent AF ablation procedure. Recurrence of regular atrial tachycardia may be assumed to be one step towards effective rhythm control. It is interesting to note that regular atrial tachycardias are the dominant recurring arrhythmia in patients converting to regularized atrial tachycardia during persistent AF ablation.<sup>25</sup>

#### 3.3. Antiarrhythmic Drug Treatment After Ablation

Antiarrhythmic drug medication may affect outcome after AF ablation procedures. So far, no studies dedicated to this issue are available with concisive results. An analysis of patients after intraoperative concomitant AF ablation for long-standing persistent AF indicated no additive effects of sotalol compared to regular ß-blocker medication .40 Many other studies propose the use of antiarrhythmic drugs and indicate a higher rhythm success under antiarrhythmics compared to no use of rhythm effective drugs. In the recently published data from the 5A-Study<sup>41</sup> antiarrhythmic medication in the early phase after ablation may stabilize atrial rhythm in the early post-interventional phase but the long-term beneficial effect remains unclear.

#### 3.4. Cardioversion Strategy in Recurrent Persistent AF After Ablation

In patients with recurrent AF early cardioversion to restore SR may be advocated. Although no comparative studies are available time in SR may incur on left atrial re-remodelling and therefore rhythm stability over follow-up. One study indicates that cardioversion should be performed within 30 days after recurrence of AF after ablation. Of interest, in this study 1/3 of patients with cardioversion for recurrence of AF maintained SR during follow-up compared to only 15% of patients with cardioversion for regular atrial tachycardias. The study presents similar

Table 1

Pre-procedural factors indicated as having predictive value and number of reference indicating significant relation to recurrence of AF after persistent AF ablation

Predictor	References
Left atrial dimension	7, 41
Duration of AF	17, 19, (18 in subgroup)
Hypertension	19
Congestive heart failure, structural heart disease	17
Female gender	17
Amount of atrial fibrosis in DE-MRI	24

rates for maintaining SR if cardioversion was performed within 1 week or within the first month after onset of AF recurrence. Still, it remains unclear if earlier cardioversion may further affect outcome (low patient numbers in subgroups).<sup>42, 43</sup>

In addition, a second study evaluated the number of cardioversions needed indicating failure of an ablation procedure for persistent AF. More than 3 cardioversions within the initial 3 months were associated with low final success. Or in other words, recurrence of persistent atrial tachycardias more than 3 times within the first 3 months after ablation is highly associated with ablation failure.<sup>42, 43</sup>

As a conclusion, cardioversion may be used in the initial phase after ablation of persistent AF to restore SR. Cardioversion should be performed early after recurrence (at our institution usually within 3 days) and may still lead to rhythm success if performed up to 3 times within the first 3 months after ablation. Cardioversion may be more effective in patients with recurrence of AF compared to recurrent regular atrial tachycardia.

### Conclusions

Ablation of persistent AF is associated with a wide variety of success rates mostly due to the incongruent definition of persistent AF. Patient-specific pre-procedural factors, operator specific procedural factors and "institution"-specific factors during post-interventional follow-up may affect success or failure of persistent AF ablation. So far, the complex relation of many of the tested strators prevents decisive analysis of the statistical relation to outcome after AF ablation. Also, due

to the inhomogeneous patient groups included in many studies, the used statistical methodology may not adequately address the complexity of the problem. Identifying specific pre-procedural markers for higher recurrence rate after ablation procedures in patients with persistent AF would be most helpful to identify good candidates for ablation and may help to adapt the ablation strategy. Further studies on more homogenous patient subgroups and ablation strategies are needed for a definite individual risk of recurrence analysis.

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