Long-Term Follow-Up after Catheter Ablation of Paroxysmal Atrial Fibrillation: The Incidence of Recurrence and Progression of Atrial Fibrillation

Running title: Takigawa et al.; Long-term Effect of CA on PAF

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Journal Subject Codes: [22] Ablation/ICD/surgery
Abstract:

Background - Although catheter ablation (CA) is a standard treatment for atrial fibrillation (AF), its long-term efficacy remains unclear. This study aimed to elucidate the incidences of AF-recurrence and of progression from paroxysmal to persistent AF, after CA, in paroxysmal AF (PAF) patients.

Methods and Results - We examined the incidence of AF-recurrence and AF-progression in 1220 consecutive patients (mean age, 61 years), with symptomatic PAF, undergoing CA, based on extensive pulmonary vein isolation and focal ablation for non-pulmonary vein foci. AF-recurrence-free survival probabilities at 5 years were 59.4% after the initial CA, and 81.1% after the final CA (average, 1.3 procedures). During a median follow-up period of 47.9 (range, 5.3–123.3) months after the initial CA, AF progressed from paroxysmal to persistent in 15 (1.2%) patients (0.3%/year). The duration of AF history (HR 1.03, P<0.0001), number of ineffective antiarrhythmics (HR 1.09, P=0.005), and left atrial diameter indexed by the body surface area (LADI; HR 1.05, P=0.001) were significant predictors of AF recurrence. Patient age (HR 1.12, P=0.0001) and LADI (HR 1.26, P=0.0006) were significantly associated with AF-progression. Patients aged ≤65 years and with a LADI of ≤24.0 mm/m² did not develop AF-progression for up to 10 years after the initial CA.

Conclusions - Although the long-term follow-up revealed the impact of CA on preventing AF-recurrence, repeated CA sessions might be required. The rate of progression from paroxysmal to persistent AF was 0.3%/year.

Key words: atrial fibrillation, catheter ablation, pulmonary vein isolation, recurrence, progression
Catheter ablation (CA) is a standard therapy for treating patients with atrial fibrillation (AF). However, its long-term outcomes, including the incidences of AF-recurrence and progression from paroxysmal to persistent AF, have not been fully elucidated.

Methods

Study population
A total of 1220 consecutive patients (mean age, 61 years; male, n=940) were enrolled in this study between February 2003 and October 2009. The patients were referred to our institution for an initial CA to treat paroxysmal AF (PAF) refractory to antiarrhythmic-drugs (AADs). AF was defined as paroxysmal when it terminated spontaneously within 7 days. All patients provided written, informed consent and our institutional review board approved the protocol.

Electrophysiological study
AADs were discontinued for >7 days (amiodarone was discontinued for >1 month) before the ablation; all patients were also effectively anticoagulated for >1 month. A 7-Fr, 20- or 14-pole, two-site mapping catheter (Irvine Biomedical, Irvine, CA, USA) was inserted through the right jugular vein and positioned in the coronary sinus for pacing, recording, and internal cardioversion.

CA technique
The strategy of extensive pulmonary vein isolation (EPVI) has been previously described. Briefly, after a transseptal puncture, pulmonary venography and contrast esophagography were performed to determine the anatomical relationships of the PV ostia, left atrium (LA), and esophagus. An activated clotting time of 250–350 s was maintained with a continuous infusion of heparin during the procedure. Two circular mapping catheters were placed in the superior and
inferior pulmonary veins (PVs), and the left and right ipsilateral PVs were circumferentially and extensively ablated under fluoroscopic and electrophysiological guidance. Radiofrequency current applications were delivered with an 8-mm tip ablation catheter (Japan Lifeline, Tokyo, Japan) in the temperature control mode, with a target temperature of 55°C (maximum power, 35W on the LA posterior wall; 40W at the anterior aspect of the PVs); esophageal temperature was measured during the application. The endpoint was the elimination or dissociation of PV potentials. After completing the EPVI, adenosine triphosphate (20–40 mg) was injected to unmask any dormant conductions, and those were disconnected. Thereafter, a cavo-tricuspid isthmus (CTI) line was created with an endpoint of bidirectional conduction block. Isoproterenol (5–20 μg/min) was intravenously injected before completing the procedure. If sustained or non-sustained AFs were reproducibly initiated from non-PV foci, they were focally ablated. When non-PV foci were located in the superior vena cava (SVC), the SVC was electrically isolated. If spontaneous AF did not occur, rapid atrial pacing was performed to induce AF. After an episode of pacing-induced AF was sustained, internal cardioversion was attempted to convert the AF to sinus rhythm (SR). If spontaneous reinitiation of AF occurred, the AF focus was subsequently ablated. Linear ablations (left atrial roof and/or bottom and/or mitral isthmus lines) were performed only when AFs from undetermined origins or macroreentrant atrial tachycardia spontaneously occurred, with an endpoint of a bidirectional conduction block. On completion of the procedure, the endpoints of EPVI, SVC isolation, and linear ablations were re-confirmed.

Follow-up

AADs were not prescribed after the procedure. Patients were prospectively followed-up at 2, 6, 10, 14, 24, 36, and 48 weeks after the procedure, with 12-lead electrocardiograms at each visit.
and Holter monitoring every 3 months. Thereafter, patients were followed-up every 1–3 months at our institution, or by a general physician. Symptomatic patients received a 1-month event recorder. Anticoagulation was discontinued after 3–6 months in AF-recurrence-free patients without risk factors of thromboembolisms. A one-month blanking period was set, during which atrial tachyarrhythmias were considered to be a transient phenomenon. After this period, the occurrence of atrial tachyarrhythmias lasting more than 30s, off AADs, was defined as AF-recurrence, and recurrent AFs persisting longer than 7 days were defined as AF-progression. Repeat ablation was recommended for patients experiencing AF-recurrence after the blanking period.

**Statistical analysis**

The data are expressed as mean (standard deviation) for continuous variables or frequencies and percentages for categorical variables. To clarify the clinical predictors of the outcomes, univariate Cox proportional analysis was first performed. Sequentially, all variables with P-values of <0.20 in the univariate analysis were included in a multivariate analysis, and hazard ratios (HRs) and 95% confidence intervals (CI) were calculated. LA diameter (LAD) indexed by the body surface area (LADI) strongly correlated with LAD ($r^2=0.59$), and both are predictors of AF-recurrence and AF-progression in the univariate analysis; LADI, with lower P-values, were included in the multivariate analysis. The follow-up period was calculated from the date of the procedure to that of the outcome (AF-recurrence, AF-progression) or censoring (death and end of follow-up) events. The estimated event-free survival probabilities were calculated using Kaplan-Meier analysis; log-rank statistics were used for group comparisons. P-values of <0.05 were considered statistically significant.
Results

Patient characteristics and clinical outcomes

Baseline characteristics of the 1220 patients are shown in Table 1. CA, based on EPVI, was successfully performed in all patients (Table 2A). Sixty-four (5.2%) procedure-related complications occurred in 1220 procedures (3.9% in 1596 procedures) (Table 2B); 55 (4.5%) occurred during the initial CA session, 9 (2.7%) occurred during the second session, and none occurred thereafter. No significant association was noted between the incidence of complications and the type or number of procedures.

Figure 1 shows a ladder diagram of the results of CA sessions. During a median follow-up period of 31.5 (range, 1.0–100.5) months, 449 (36.8%) had AF-recurrence; 328/449 (73.1%) patients with AF-recurrence after the initial CA and 42/109 (38.5%) with AF-recurrence after the second CA underwent further CA sessions. There were 376 repeat ablations in 328 patients; the 328 patients underwent a second ablation 2.2 (range, 0.1–78.7) months after the AF-recurrence occurred following the initial CA and 42 underwent a third ablation 3.8 (range, 0.1–32.6) months after the AF-recurrence occurred following the second CA. Ultimately, during a median follow-up period of 38.0 (range, 1.0–100.5) months, 892 (73.1%) patients had 1 CA, 286 (23.4%) had 2 CAs, 42 (3.4%) had 3 or more CAs. SR was maintained in 990/1220 (81.1%) and 1018/1220 (83.4%) of overall patients after the second and third CAs, respectively. Among the patients cured by the prior CA(s) and actually undergoing a subsequent CA if the prior session failed, SR was maintained in 990/1099 (90.1%) and 1018/1032 (98.6%) patients, after the second and third CA, respectively. The AF-free survival, 5-years after the CA in PAF patients was 59.4% (95%CI, 56.1–62.5%) after a single procedure, and 81.1% (95%CI, 78.4–83.7%) after multiple procedures (mean 1.3±0.6 procedures; median 1, range from 1 to 5)
EPVI quality and incidence of non-PV foci

During the second and third sessions, 254/328 (77.4%) and 15/42 (35.7%) patients, respectively, experienced LA-PV re-conductions, which were not identified in subsequent sessions (Table 2A).

A total of 524 non-PV foci were identified in 307 (25.2%) patients (median, 1; range, 1–7) throughout the procedures; 118 (9.7%) patients had 2 or more non-PV foci. Non-PV foci occurred in the SVC (150, 12.3%); coronary sinus (42, 3.4%); right atrial posterior wall (19, 1.6%); (right atrial) crista terminalis (55, 4.5%); right anterior wall, including the appendage (18, 1.5%); interatrial septum, including the foramen ovale (109, 8.9%); LA posterior wall (50, 4.1%); LA anterior wall, including the appendage (23, 1.9%); LA roof (23, 1.9%); and LA inferior wall (13, 1.1%).

Clinical predictors of AF-recurrence after the initial CA

A multivariate Cox proportional analysis revealed that the duration of AF history (HR, 1.03; 95%CI, 1.02–1.05; P<0.0001), number of ineffective AADs (HR, 1.09; 95%CI, 1.03–1.16; P=0.005), and LADI (HR, 1.05; 95%CI, 1.02–1.07; P=0.001) were significant predictors of AF-recurrence after the initial CA (Table 3).

AF-progression from paroxysmal to persistent AF

During a median follow-up period of 47.9 (range, 5.3–123.3) months after the initial CA, PAF progressed to persistent AF in 15 patients (1.2% of all patients; 7.5% of those with AF-recurrence; average AF-progression rate, 0.3%/year). Moreover, 11 of them eventually shifted to permanent AF. The AF-progression-free survival probabilities at 3, 5, and 7 years were 99.7%, 99.0%, and 96.0% (Figure 3A).
Clinical predictors of AF-progression

Multivariate Cox proportional analysis revealed that age (HR, 1.12; 95%CI, 1.04–1.22; P=0.001) and LADI (HR, 1.26; 95%CI, 1.11–1.44; P=0.0006) were significantly associated with AF-progression (Table 4).

A sensitivity-specificity analysis, utilizing a receiver-operating characteristic curve, identified the cut-off values for age (65 years) and LADI (24.0 mm/m²), to optimize the capability of predicting AF-progression. AF-progression was predicted by age (>65 years), with a sensitivity of 73% and specificity of 65%, and by LADI (>24.0 mm/m²), with a sensitivity of 87% and specificity of 73%. The areas under the curve for an age of 65 years and LADI of 24.0 mm/m² were 0.73 and 0.83, respectively. Patients were stratified by using these parameters (Figure 3B). Patients aged ≤65 years and with LADI of ≤24.0 mm/m² did not develop AF-progression for up to 10 years after the initial CA.

Discussion

Incidence of AF-recurrence

According to several studies of long-term AF ablation efficacy,2, 13-16 success rates usually drop within 1 year, and gradually decrease thereafter; this tendency was maintained after both initial (single) and final (multiple) procedures. In addition, repeat procedures usually improve the outcomes. A systematic review and meta-analysis demonstrated that the long-term success rates of CA in PAF patients were 54.1% (95%CI, 44.4–63.4%) after a single procedure, and 79.0% (95%CI, 67.6–87.1%) after multiple procedures (average, 1.45 procedures).16 The present study describes a similar incidence of AF-recurrence and the necessity of repeat ablation. From the findings of the present study, at least one repeat CA is required, and a third CA may be
acceptable for better outcomes. A discussion of CA outcomes should consider various clinical parameters, including the patient population, types of AF, CA strategies, ablation catheter types, AAD use after CA, follow-up frequencies and intensities, blanking period definitions, procedural success definitions, and the availability and timing of repeat procedures.2,13-17

In the present study, similar to previous reports,2,13,16,18 electrical re-conduction between PVs and LA is considered the major mechanism of AF-recurrence; moreover, complete electrical disconnection between the PVs and LA is thought to be a minimal, but critical, requirement for the best outcomes of CA of paroxysmal AF. A careful and repetitive re-confirmation during the procedure may facilitate this outcome.

Clinical predictors of AF-recurrence after the initial CA
We focused on PAF to minimize the heterogeneity within the study population. Thus, we demonstrated that the duration of AF history, number of ineffective AADs, and LADI were significant predictors of AF-recurrence after the initial CA. The predictive value of the AF history duration on AF-recurrence remains controversial14,19,20 because the duration of a patient’s AF history may not always be equivalent to the actual length of the AF episode, and hence, might not reflect disease severity such as atrial remodeling. However, the larger population size and longer follow-up period of this study showed an affinitive association between the AF history duration and AF-recurrence. In the present study, the number of ineffective AADs was a significant predictor of AF-recurrence; very few other reports have examined this parameter as a predictor of AF outcome.21,22 Most patients were referred to our institution after the failure of intensive treatment involving a variety of AADs (median, 2; range, 1–8), suggesting that the number of ineffective AADs may have been an indicator of the disease severity. The significant association between LA size and AF-recurrence after CA is described in the literature,2,15 and is
in accordance with our findings. The use of LADI instead of LAD corrects for body size heterogeneity between individuals, which may provide a better correlation with atrial remodeling.

**Incidence of AF-progression**

In the present study, the AF-progression rate was as low (1.2% during the 48-month follow-up, 0.3%/year) as in previous studies describing AF-progression rates after CA therapy (1.5–3.0% during mid- to long-term follow-up). In contrast, other studies have indicated rates of 5.5–15%/year under pharmacological therapy, which is far worse than the current findings. Moreover, one report of a 6-year outcome after a single CA procedure demonstrated that AF progressed to permanent AF in 10 (9.8%) of 102 PAF patients during a mean follow-up of 50 months. These observations are nonrandomized and from separate trials, but do suggest that CA is better than pharmacologic therapy and repeat procedures are better than single procedures for preventing AF-progression, possibly because of the higher incidence of SR maintenance. An appropriate EPVI and focal ablation of non-PV foci, seems to play a primary role in maintaining SR, and consequently reducing AF-progression. A randomized study may help this issue to be elucidated.

**Clinical predictors of AF-progression**

In the current study, aging and increased LA size defined as LADI were found to be independent predictors of AF-progression. Aging and LA size are significantly associated with AF-progression in most relevant reports. In addition, several studies have documented that age and LA size are associated with atrial fibrosis, which may result in increased, non-uniform anisotropy and local conduction heterogeneity, thus playing a key role in promoting the perpetuation of AF. Additionally, we demonstrated that patients could be
stratified before the initial CA by combining these 2 parameters (age [65 years] and LADI [24.0 mm/m²]).

**Limitations**

This study was subject to limitations inherent in a retrospective design. However, the clinical and demographic characteristics, ablation data, and follow-up outcomes were prospectively collected, and the population number was large, helping to offset such limitations. Secondly, an 8-mm tip, non-irrigation catheter was used, instead of a 3.5-mm tip irrigation catheter, because of its availability in Japan during the study period. Thirdly, inducing non-PV AF foci under the burst pacing and isoproterenol infusion may be associated with a risk of inducing non-clinical AF foci or unmasking clinical AF foci. Fourthly, CTI was routinely ablated in all patients with PAF. However, this ablation was not performed for expected beneficial effects on preventing AF-recurrence. Fifthly, although all patients were strictly educated regarding the follow-up, surveillance might have varied according to the presence or absence of symptoms, the institution or physician where they were followed after 48 weeks, and the timing of their usual medical visits after 48 weeks (every 1–3 months). Finally, the survival curve after the "final CA" may include potential statistical limitations; it is a mixture of several curves with different start times; and the definition of "final" procedure will change as more patients undergo subsequent procedures, which depends on the length of follow-up.

**Conclusions**

CA, based on an EPVI and non-PV focal ablation, is an effective strategy for preventing AF-recurrence and AF-progression over a long period. However, this may require repeat CA sessions. In addition, this study demonstrated that the duration of AF history, number of
ineffective AADs, and LADI were useful predictors of AF-recurrence, whereas age and LADI predicted AF-progression.

**Conflict of Interest Disclosures:** None

**References:**


Am Coll Cardiol. 2008;51:802-809.


Table 1. Baseline characteristics (N=1220)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, years</td>
<td>61 (10)</td>
</tr>
<tr>
<td>Gender, female (%)</td>
<td>280 (23.0)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.6 (2.9)</td>
</tr>
<tr>
<td>Duration of AF history, years</td>
<td>5.0 (5.4)</td>
</tr>
<tr>
<td>SHD, n (%)</td>
<td>220 (18.0)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>538 (44.1)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>130 (10.7)</td>
</tr>
<tr>
<td>CHF, n (%)</td>
<td>85 (7.0)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>93 (7.6)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>17 (1.4)</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>0.9 (1.0)</td>
</tr>
<tr>
<td>HATCH score</td>
<td>0.8 (1.0)</td>
</tr>
<tr>
<td>Number of ineffective AADs</td>
<td>1.8 (1.4)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
</tr>
<tr>
<td>LAD, mm</td>
<td>37.8 (5.1)</td>
</tr>
<tr>
<td>LADI, mm/mm²</td>
<td>22.2 (3.5)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>66.2 (7.3)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean (standard deviation). AADs, antiarrhythmic drugs; AF, atrial fibrillation; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LAD, left atrial dimension of end-systole; LADI, LAD index; LVEF, left ventricular ejection fraction; SHD, structural heart disease.
Table 2A. Details of multiple CA sessions

<table>
<thead>
<tr>
<th></th>
<th>1st CA (N=1220, 100%)</th>
<th>2nd CA (N=328, 26.9%)</th>
<th>3rd CA (N=42, 3.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>EPVI</td>
<td>1220 (100)</td>
<td>254 (77.4)</td>
<td>15 (35.7)</td>
</tr>
<tr>
<td>SVCI only</td>
<td>97 (8.0)</td>
<td>54 (16.5)</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td>Focal only</td>
<td>105 (8.6)</td>
<td>65 (19.8)</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>SVCI and Focal</td>
<td>23 (1.9)</td>
<td>31 (9.5)</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>Linear</td>
<td>12 (1.0)</td>
<td>35 (10.7)</td>
<td>15 (35.7)</td>
</tr>
</tbody>
</table>

A 4th CA was performed in 4 (0.3%) patients, 3 with focal and linear ablations and 1 with only linear ablation. A 5th CA was performed in 2 (0.2%) patients, both with focal and linear ablations.

AF, atrial fibrillation; CA, catheter ablation; EPVI, extensive pulmonary vein isolation; SVCI, superior vena cava isolation.
Table 2B. Incidence of procedure-related complications associated with CA

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence in total 1220 patients</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; CA (N=1220)</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; CA (N=328)</th>
<th>Incidence in total 1596 procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac tamponade/effusion</td>
<td>23 (1.9%)</td>
<td>21 (1.7%)</td>
<td>2 (0.6%)</td>
<td>23 (1.4%)</td>
</tr>
<tr>
<td>Air embolism</td>
<td>7 (0.6%)</td>
<td>6 (0.5%)</td>
<td>1 (0.3%)</td>
<td>7 (0.4%)</td>
</tr>
<tr>
<td>TIA/CI</td>
<td>7 (0.6%)</td>
<td>4 (0.3%)</td>
<td>3 (0.9%)</td>
<td>7 (0.4%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>5 (0.4%)</td>
<td>5 (0.4%)</td>
<td>0 (0%)</td>
<td>5 (0.3%)</td>
</tr>
<tr>
<td>Phrenic nerve injury</td>
<td>8 (0.7%)</td>
<td>6 (0.5%)</td>
<td>2 (0.6%)</td>
<td>8 (0.5%)</td>
</tr>
<tr>
<td>Vagal nerve injury</td>
<td>5 (0.4%)</td>
<td>5 (0.4%)</td>
<td>0 (0%)</td>
<td>5 (0.3%)</td>
</tr>
<tr>
<td>Pulmonary vein injury/stenosis</td>
<td>3 (0.3%)</td>
<td>2 (0.2%)</td>
<td>1 (0.3%)</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2 (0.2%)</td>
<td>2 (0.2%)</td>
<td>0 (0%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td>Vascular injury</td>
<td>3 (0.3%)</td>
<td>3 (0.3%)</td>
<td>0 (0%)</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>64 (5.2%)</td>
<td>55 (4.5%)</td>
<td>9 (2.7%)</td>
<td>64 (3.9%)</td>
</tr>
</tbody>
</table>

No complications occurred during the 3<sup>rd</sup> (N=42), 4<sup>th</sup> (N=4), or 5<sup>th</sup> CA (N=2).

CA, catheter ablation; CI, cerebral infarction; DVT, deep vein thrombosis; PE, pulmonary embolism; PV, pulmonary vein; TIA, transient ischemic attacks.
Table 3. Clinical predictors of AF-recurrence after the initial CA session

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th></th>
<th>Multivariate*</th>
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<tbody>
<tr>
<td></td>
<td>P-values</td>
<td>HR</td>
<td>95%CI</td>
<td>P-values</td>
<td>HR</td>
<td>95%CI</td>
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<td>Patient age, year</td>
<td>0.61</td>
<td>1.00</td>
<td>0.99–1.01</td>
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<td></td>
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<tr>
<td>gender, female</td>
<td>0.31</td>
<td>1.12</td>
<td>0.90–1.38</td>
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<tr>
<td>BMI</td>
<td>0.45</td>
<td>0.99</td>
<td>0.96–1.02</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Duration of AF history, year</td>
<td>&lt;0.0001</td>
<td>1.03</td>
<td>1.02–1.05</td>
<td>&lt;0.0001</td>
<td>1.03</td>
<td>1.02–1.05</td>
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<tr>
<td>SHD</td>
<td>0.01</td>
<td>1.34</td>
<td>1.07–1.67</td>
<td>0.13</td>
<td>1.2</td>
<td>0.94–1.52</td>
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<td>Hypertension</td>
<td>0.75</td>
<td>0.97</td>
<td>0.90–1.17</td>
<td>0.09</td>
<td>1.29</td>
<td>0.96–1.70</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.06</td>
<td>1.32</td>
<td>0.99–1.73</td>
<td>0.09</td>
<td>1.29</td>
<td>0.96–1.70</td>
</tr>
<tr>
<td>CHF</td>
<td>0.23</td>
<td>1.23</td>
<td>0.87–1.70</td>
<td></td>
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</tr>
<tr>
<td>Stroke</td>
<td>0.59</td>
<td>1.10</td>
<td>0.77–1.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>0.3</td>
<td>0.65</td>
<td>0.23–1.40</td>
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<td></td>
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<tr>
<td>CHADS2 score</td>
<td>0.25</td>
<td>1.06</td>
<td>0.96–1.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HATCH score</td>
<td>0.46</td>
<td>1.03</td>
<td>0.94–1.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of ineffective AADs</td>
<td>0.0005</td>
<td>1.12</td>
<td>1.05–1.18</td>
<td>0.005</td>
<td>1.09</td>
<td>1.03–1.16</td>
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<tr>
<td>Echocardiography</td>
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</tr>
<tr>
<td>LAD, mm</td>
<td>0.005</td>
<td>1.03</td>
<td>1.01–1.04</td>
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<tr>
<td>LADI, mm/m²</td>
<td>0.0003</td>
<td>1.05</td>
<td>1.02–1.08</td>
<td>0.001</td>
<td>1.05</td>
<td>1.02–1.07</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.78</td>
<td>1.00</td>
<td>0.99–1.02</td>
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</tr>
</tbody>
</table>

*Variables with a P-value of <0.20 in the univariate Cox proportional analysis were included in the multivariate analysis. CI, confidence interval; HR, hazard ratio. The other abbreviations are as in Table 1.
Table 4. Clinical predictors of the AF-progression after the initial CA session

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th></th>
<th>Multivariate*</th>
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<tr>
<td></td>
<td>P-values</td>
<td>HR</td>
<td>95% CI</td>
<td>P-values</td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td>Patient age, year</td>
<td>0.0002</td>
<td>1.13</td>
<td>1.06–1.23</td>
<td>0.001</td>
<td>1.12</td>
<td>1.04–1.22</td>
</tr>
<tr>
<td>gender, female</td>
<td>0.35</td>
<td>1.70</td>
<td>0.53–4.83</td>
<td>0.23</td>
<td>0.89</td>
<td>0.73–1.08</td>
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<tr>
<td>BMI</td>
<td>0.02</td>
<td>0.80</td>
<td>0.66–0.96</td>
<td>0.89</td>
<td>0.93</td>
<td>0.43–1.72</td>
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<tr>
<td>Duration of AF history, year</td>
<td>0.76</td>
<td>0.98</td>
<td>0.87–1.07</td>
<td>0.12</td>
<td>1.45</td>
<td>0.90–2.18</td>
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<tr>
<td>SHD</td>
<td>0.49</td>
<td>1.55</td>
<td>0.43–4.57</td>
<td>0.89</td>
<td>1.15</td>
<td>0.14–9.96</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.74</td>
<td>0.84</td>
<td>0.28–2.33</td>
<td>0.83</td>
<td>0.93</td>
<td>0.43–1.72</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.67</td>
<td>0.66</td>
<td>0.04–3.30</td>
<td>0.74</td>
<td>0.84</td>
<td>0.28–2.33</td>
</tr>
<tr>
<td>CHF</td>
<td>0.15</td>
<td>2.91</td>
<td>0.64–9.50</td>
<td>0.98</td>
<td>1.03</td>
<td>0.06–5.17</td>
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<tr>
<td>Stroke</td>
<td>0.98</td>
<td>1.03</td>
<td>0.06–5.17</td>
<td>1.03</td>
<td>1.03</td>
<td>0.06–5.17</td>
</tr>
<tr>
<td>COPD</td>
<td>0.52</td>
<td>1.62*10^{-5}</td>
<td>0.06–10.32</td>
<td>0.84</td>
<td>1.15</td>
<td>0.14–9.96</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>0.28</td>
<td>1.31</td>
<td>0.78–2.03</td>
<td>0.83</td>
<td>0.93</td>
<td>0.43–1.72</td>
</tr>
<tr>
<td>HATCH score</td>
<td>0.12</td>
<td>1.45</td>
<td>0.90–2.18</td>
<td>0.83</td>
<td>0.93</td>
<td>0.43–1.72</td>
</tr>
<tr>
<td>Number of ineffective AADs</td>
<td>0.77</td>
<td>0.95</td>
<td>0.66–1.29</td>
<td>0.83</td>
<td>0.93</td>
<td>0.43–1.72</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD, mm</td>
<td>0.005</td>
<td>3.42</td>
<td>1.46–7.60</td>
<td>0.0006</td>
<td>1.26</td>
<td>1.11–1.44</td>
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<td>LADI, mm/m^2</td>
<td>&lt;0.0001</td>
<td>1.29</td>
<td>1.16–1.41</td>
<td>0.031</td>
<td>0.73</td>
<td>0.45–1.37</td>
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<tr>
<td>LVEF, %</td>
<td>0.31</td>
<td>0.73</td>
<td>0.45–1.37</td>
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</tbody>
</table>

*Variables with a P-value of <0.20 in the univariate Cox proportional analysis were included in the multivariate analysis. The abbreviations are as in Table 3.
Figure Legends:

**Figure 1:** A ladder diagram showing the catheter ablation (CA) sessions and outcomes. “Overall patient-outcomes” describes the number of patients out of the overall 1220 patients who maintained sinus rhythm. The sinus rhythm maintenance rate increases remarkably after the second CA, and slightly after the third CA.

**Figure 2:** Atrial fibrillation (AF) recurrence-free survival probabilities and 95% confidence intervals after the initial (A) and final (B) catheter ablation (CA); AF-recurrence-free survival probabilities 5 years after the initial and the final CA were 59.4% and 81.1%, respectively; 73.1% had 1 CA, 23.4% had 2 CAs, 3.1% had 3 CAs, and 0.2% had 4 CAs, and the remaining 0.2% had 5 CAs. AF-recurrence-free survival probabilities after the second and third CA were demonstrated in supplemental figures.

**Figure 3:** Atrial fibrillation (AF) progression-free survival probabilities after the initial catheter ablation (A). Patients are stratified by age and left atrial diameter indexed by the body surface area (LADI); the optimized cut-off values for age (65 years) and LADI (24.0 mm/m²) are identified by a sensitivity-specificity analysis, by using a receiver-operating characteristic curve. (B).
Overall patient-outcomes

After the 1st CA

771/1220 (63.2%)

After the 2nd CA

990/1220 (81.1%)

After the 3rd CA

1018/1220 (83.4%)

After the 4th CA

1019/1220 (83.5%)

After the 5th CA

1021/1220 (83.7%)
Follow-up period: range 1-100.5 months
- First-quartile (25%); 5.8 months
- Median (50%); 31.5 months
- Third-quartile (75%); 51.6 months

1 year 72.0% (95% CI 69.4-74.5%)
3 year 65.4% (95% CI 62.6-68.1%)
5 year 59.4% (95% CI 56.1-62.5%)

Number at risk: 1220 878 827 638 461 319 214 127 75 45 4
Follow-up period: range 5.3-123.3 months

First-quartile (25%); 33.3 months

Median (50%); 47.9 months

Third-quartile (75%); 65.7 months

1 year 99.9%, 3 year 99.7%, 5 year 99.0%

7 years 96.0%, 10 year 84.8%
B

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**AF Progression-Free Survival Probability**

- **Age \( \leq 65 \) years and LADI \( \leq 24.0 \) mm/m² (\( N = 505 \))
- **Age > 65 years or LADI > 24.0 mm/m²** (\( N = 515 \))
- **Age > 65 years and LADI > 24.0 mm/m²** (\( N = 200 \))

**Time after the initial catheter ablation (months)**

- **P = 0.004**
- **P = 0.002**
Long-Term Follow-Up after Catheter Ablation of Paroxysmal Atrial Fibrillation: The Incidence of Recurrence and Progression of Atrial Fibrillation
Masateru Takigawa, Atsushi Takahashi, Taishi Kuwahara, Kenji Okubo, Yoshihide Takahashi, Yuji Watari, Katsumasa Takagi, Tadashi Fujino, Shigeki Kimura, Hiroyuki Hikita, Makoto Tomita, Kenzo Hirao and Mitsuaki Isobe

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Supplemental Figure: AF recurrence-free survival probability after the 2\textsuperscript{nd} CA

Follow-up period: range 1-97.7 months
- First-quartile (25%); 8.1 months
- Median (50%); 27.6 months
- Third-quartile (75%); 49.7 months

1 year  74.6% (95% CI 69.5-79.0%)
3 year  67.9% (95% CI 62.5-72.9%)
5 year  64.8% (95% CI 58.8-70.5%)

Time after the second catheter ablation (months)
Supplemental Figure: AF recurrence-free survival probability after the 3rd CA

Follow-up period: range 1-88.6 months

First quartile (25%); 5.3 months
Median (50%); 30.9 months
Third quartile (75%); 53.7 months

1 year 75.9% (95% CI 60.7-86.5%)
3 year 66.5% (95% CI 49.9-79.8%)
5 year 66.5% (95% CI 49.9-79.8%)

Time after the third catheter ablation (months)
AF Recurrence-Free Survival Probability
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0