Current Status of Catheter Ablation for Atrial Fibrillation in Japan
A Claims Database Analysis of the Working-Age Population

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Summary
Catheter ablation for atrial fibrillation (AF) has been an established and frequently utilized approach in a variety of clinical settings. Nevertheless, real-world data about the clinical course of AF patients after initial catheter ablation remain limited, and these are mainly derived from particular registries or selected high-volume centers.

In this study, we used health check-ups and insurance claims database from a Japanese insurance organization. The study population was comprised of 1777 patients who underwent catheter ablation for AF before June 2016. During the 3-year follow-up period, 396 (22.3\%) patients underwent at least one repeated AF ablation, while 74 (4.2\%) underwent two or more repeated ablations. In multivariate Cox regression analysis, longer time after AF diagnosis (7-11 months and $\geq 12$ months versus 1-6 months) (HR, 1.05; 95\% CI, 1.01-1.08 and HR, 1.04; 95\% CI 1.02-1.07) was independently associated with repeated ablation. The discontinuation rates of OACs and AADs after the first ablation were 26.7\% and 63.0\% at 3 months and 75.2\% and 89.1\% at 1 year after the initial ablation, respectively. The former was independently associated with shorter time after AF diagnosis and lower diastolic blood pressure, whereas the latter was independently associated with older age, smaller CHADS\textsubscript{2} score, and shorter time after AF diagnosis.

We presented real-world data regarding the clinical course of young Japanese AF patients after initial catheter ablation based on a claims database in Japan.

Key words: AF ablation, Antiarrhythmic drugs, Claims data, Oral anticoagulants, Real-world

A number of clinical studies have already confirmed the effectiveness and safety of catheter ablation; in fact, this has become an established therapy for atrial fibrillation (AF).\textsuperscript{1,2} With the advances in catheter ablation techniques, the total number of catheter ablations has been increasing worldwide, including Japan.\textsuperscript{3} Most information on catheter ablation reported to date has been derived from clinical trials, registries, and/or experiences from selected high-volume centers, and Japan is no exception.\textsuperscript{4,5} These data were derived from studies arising from academic centers, regional databases, and national databases that are confined to outcomes after index ablation. Given that AF was initially diagnosed by referring physicians before AF ablation in specialized hospitals, and that follow-up of AF recurrence and medication therapy such as oral anticoagulants (OACs) or antiarrhythmic drugs (AADs) after ablation were sometimes continued at referring or related hospitals, comprehensive patient-based data would contribute to the evaluation of AF catheter ablation.

As health insurance claims data can be used in extensive research across multiple medical institutions, this study aimed to determine the current status of AF catheter ablation in Japan using patient-based data from a claims database. Here, we present real-world data about the time course of repeated catheter ablation procedures for AF and the use of OACs and AADs as post-procedural medications.

Methods

Data source: This is a real-world retrospective evaluation of data from a health check-up and claims database in Japan. We collected information from the JMDC Claims Database (JMDC Inc., Tokyo, Japan). Details of this database have been described elsewhere.\textsuperscript{6} Briefly, the JMDC database contains monthly claims submitted to multiple health insurance associations since 2005, with approximately 7.3 million insured individuals (as of April 2020), most of whom are employees of Japanese companies and their family members. Due to its nature, approximately 98\% of the patients are younger than 65 years. The database holds anonymized information about diagnoses (International Classification of Diseases, 10th revision [ICD-
10] codes), patient characteristics, drug prescriptions, medical procedures, and data on annual health check-ups for some patients. Patients can be continuously followed up, even if they were transferred to other hospitals or visited multiple medical institutions in this database. There was no requirement for informed consent because of the anonymized nature of the health insurance data used in this present study.

**Study population:** Patients who underwent their first catheter ablation for AF with and without atrial flutter (International Classification of Diseases, Tenth Revision [ICD-10]: I48) before June 2016, allocating a 3-year observation period until June 2019, were extracted from the database. Individuals who died or moved out of the health insurance society because of retirement or job change during the follow-up period were censored. This study was approved by the Institutional Review Board of the Cardiovascular Institute Hospital (Date of IRB approval, July 30, 2020; approval number, 399).

**Definition of explanatory variables:** Comorbidities that appeared within 1 year before the initial catheter ablation in the claims data were defined by ICD-10 codes with reference to the Charlson Comorbidity Index: hypertension, ICD-10 codes I10 to I15; hyperlipidemia, ICD-10 code E78; diabetes mellitus, ICD-10 codes E10 to E14; ischemic heart disease, ICD-10 codes I20 to I25; previous ischemic stroke/transient ischemic attack, ICD-10 codes G45 to G46 or I63 to I66; cardiomyopathy, ICD-10 codes I42 to I43; vascular disease, ICD-10 codes I70 to I77; congestive heart failure, ICD-10 code I50; and liver dysfunction, ICD-10 codes K70.4 or K72.7. The Charlson Comorbidity Index of each patient was calculated on the assumption that he/she was not infected with HIV because the JMDC database does not contain any AIDS-related information due to privacy policy. In addition, using the claims data, we identified the prescription of OACs, including warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban, and the use of AADs, including quinidine, procainamide, disopyramide, propafenone, sotalol, and amiodarone. The first seven of these drugs were classified as Class I drugs according to the Vaughan-Williams classification.

Finally, we calculated the CHADS2 and CHA2DS2-VASc scores using thromboembolic risk stratification schemes, including patients’ age and sex, presence of congestive heart failure (ICD-10 code I50), hypertension (ICD-10 codes I10 to I15, or systolic blood pressure level ≥ 160 mmHg), diabetes mellitus (ICD-10 codes E10 to E14), history of ischemic stroke/transient ischemic attack (ICD-10 codes G45 to G46 or I61 to I66), and/or vascular disease (ICD-10 codes I21 to I22). The risk of serious bleeding was assessed using modified HAS-BLED score, which was obtained by adding 1 point each for hypertension (ICD-10 codes I10 to I15, or systolic blood pressure level ≥ 160 mmHg), abnormal renal function (ICD-10 codes N17 to N19, or serum creatinine level > 2.26 mg/dL), abnormal liver function (ICD-10 codes K70.4 or K72), stroke (ICD-10 codes G45 to G46 or I61 to I66), previous bleeding, advanced age (aged ≥ 65), and drug consumption (history of prior alcohol or drug usage by ICD-10 codes F10.0 or F10.2 to F10.7, and medication usage predisposing to bleeding by EphMRA ATC codes B01 or M01A). This score ranged from 0 to 8 points as no information on labile international normalized ratio (INR) was available from the database.

Time after AF diagnosis was defined as the time period by months between the first appearance of AF in claims data and the initial catheter ablation.

**Outcome measures:** Participants were followed up from the initial catheter ablation of AF to the last visit during the 3-year study period. We defined the primary endpoint as admission to hospital because of repeated catheter ablation within 3 years after the initial ablation. We have also identified the discontinuation of OACs and AADs during the period as secondary endpoints.

Oral anticoagulation therapy and antiarrhythmic therapy after discharge following the initial catheter ablation were identified based on each drug received in the discharge prescription claims until the next prescription claim. Continuing medication was identified based on each drug received at prescription claims until the next prescription claim. Prescription analyses of those undergoing second ablation during the 3-year follow-up were censored at that time. The discontinuation of drugs was defined as the interruption of drug prescription for over 3 months.

**Statistical analysis:** All analyses were performed using the R statistical package (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria). In all analyses, P < 0.05 was determined to indicate statistical significance.

Prior to the present analysis, we conducted a validation study of our definitions of AF and catheter ablation, as recommended by the Guidelines for Epidemiological Studies for Safety Assessments of Medicines Using a Healthcare Database. To survey the positive and negative predictive value (PPV and NPV, respectively) of our definitions, 100 AF patients who underwent catheter ablation and 200 patients without these criteria visiting the Cardiovascular Institute Hospital were randomly extracted from the database, and their medical records were reviewed for validation. The number of extracted cases for validation was based on feasibility, not on statistical reasons.

Patients were divided into three groups according to ablation frequency, and baseline characteristics were compared between them. Categorical and consecutive data are presented as number (%) and mean ± standard deviation, respectively. The differences in categorical and consecutive variables were tested using chi-square test and one-way analysis of variance, respectively.

The Kaplan-Meier method was used to estimate the cumulative incidence rates of repeated catheter ablation and discontinuation of OACs and AADs. Cox regression analysis was performed to determine which covariates in patient backgrounds were independently associated with repeated ablation (second ablation) and discontinuation of OACs or AADs. The multivariate model was adjusted for any covariates in patient backgrounds.

**Results**

**Validation study:** We conducted a validation study of our definition of AF with and without flutter with catheter ab-
was 7-11 months for 389 (21.9%) patients. The prevalence of heart failure was unexpectedly quite high, which may have been an overestimate due to the inherent limitations of the claims database. Its prevalence was highest in the ≥ 3 ablation frequency group. The mean CHADS2: and CHA2DS2-VASc scores were both low (1.6 and 1.8, respectively) and tended to increase with increasing ablation frequency.

Repeated ablations: The time after AF diagnosis tended to be longer with ablation frequency increased (Table I). Figure 1 shows the cumulative incidence of repeated catheter ablations. During the 3-year follow-up period, 396 (22.3%) of 1777 patients have reportedly experienced...
at least one repeated AF ablation. Of these patients, 74 (4.2\%) underwent two or more repeated ablations (64 with 3, 8 with 4, and 2 with 5 ablations). The average time period between the initial and repeated ablation were 12 months for second ablation, 18 months for third ablation, 18 months for fourth ablation, and 21 months for fifth ablation. The cumulative incidence rate of repeated ablations after the initial procedure determined by the Kaplan-Meier method was 14.9\% at 1 year and 20.4\% at 2 years.

In multivariate Cox regression analysis, male (HR, 0.52; 95\% CI, 0.27-1.00) and time after AF diagnosis (7-11 months and ≥12 months versus 1-6 months) (HR, 1.05; 95\% CI, 1.01-1.08 and HR, 1.04; 95\% CI 1.02-1.07) were independently associated with repeated (second) ablation (Table II).

**Anticoagulation after AF ablation:** Figure 2A shows the cumulative incidence of discontinuation of OACs as determined using Kaplan-Meier method. During the 3-year follow-up period, 804 (81.3\%) of 989 patients who did not experience a second ablation discontinued OACs. The discontinuation rate of OACs after the initial ablation determined by the Kaplan-Meier method was 26.7\% at 3 months and 75.2\% at 1 year in this study.

In a multivariate Cox regression analysis, diastolic blood pressure (HR, 0.99 [per mmHg]; 95\% CI, 0.98-1.00), CHADS2 score (HR, 0.83 [per point]; 95\% CI, 0.69-1.00), and time after AF diagnosis (7-11 months and ≥12 months versus 1-6 months) (HR, 0.97; 95\% CI, 0.95-0.99 and HR, 0.96; 95\% CI 0.95-0.97) were independently associated with discontinuation of OACs (Table II).

**Antiarrhythmic drugs after AF ablation:** Figure 2B shows the cumulative incidence of discontinuation of AADs using Kaplan-Meier method. During the 3-year follow-up period, 916 (92.6\%) of 989 patients who did not experience second ablation discontinued AADs. The discontinuation rates of AADs after the initial ablation determined by the Kaplan-Meier method were 63.0\% at 3 months and 89.1\% at 1 year in this study.

In multivariate Cox regression analysis, age (HR, 0.98 [per year]; 95\% CI, 0.97-0.99), CHADS2 score (HR, 0.64 [per point]; 95\% CI, 0.48-0.86), and time after AF diagnosis (7-11 months and ≥12 months versus 1-6 months) (HR, 0.98; 95\% CI, 0.96-1.00 and HR, 0.97; 95\% CI 0.95-0.98) were independently associated with discontinuation of AADs (Table II).

**Discussion**

**Main findings:** This present study aimed to determine the clinical course of AF patients undergoing initial catheter ablation in Japan based on a claims database. The major findings of the present study were as follows: (1) repeated ablation of AF was observed in 319 (24.4\%) of 1308 patients within 3 years, while cases with three or more repeated ablations were rare (4.8\%); (2) repeated ablation was independently associated with longer time (7-11 months and ≥12 months versus 1-6 months) after AF diagnosis; (3) the rates of discontinuation of OACs and AADs at 1 year were 75.2\% and 89.1\%, respectively—the former was significantly associated with diastolic blood pressure and shorter time after AF diagnosis, while the latter was reportedly associated with age, lower CHADS2 score, and shorter time after AF diagnosis.

**Diagnosis-to-ablation time:** There has been discussion regarding the optimal timing of catheter ablation for AF after first diagnosis. Multicenter analysis and a meta-analysis showed that a shorter duration between time of first AF diagnosis and AF ablation (≤1 year) was associated with lower rate of AF recurrence. In this present study, the diagnosis-to-ablation time was relatively short,
### Table II. Cox Regression Analysis for Endpoints

| Variable | Hazard ratio | 95% confidence interval | P-value |
|----------|--------------|-------------------------|---------|
| **Multivariate model for repeated (second) ablation** | | | |
| Age (per year) | 1.02 | 1.00–1.04 | 0.105 |
| Male | 0.52 | 0.27–1.00 | 0.049 |
| Body mass index (per kg/m²) | 1.02 | 0.98–1.07 | 0.272 |
| Systolic blood pressure (per mmHg) | 0.99 | 0.98–1.00 | 0.170 |
| Diastolic blood pressure (per mmHg) | 1.00 | 0.99–1.02 | 0.846 |
| Triglyceride (per mg/dL) | 1.00 | 1.00–1.00 | 0.156 |
| High-density lipoprotein cholesterol (per mg/dL) | 1.00 | 0.99–1.01 | 0.988 |
| Low-density lipoprotein cholesterol (per mg/dL) | 1.00 | 1.00–1.01 | 0.163 |
| HbA1c (per %) | 0.91 | 0.71–1.16 | 0.452 |
| CHADS₂ score* | 1.28 | 0.77–2.14 | 0.344 |
| HAS-BLED score** | 0.94 | 0.77–1.14 | 0.507 |
| Charlson Comorbidity Index | | | |
| High-very high (≥ 3) | Reference | | |
| Low-medium (0–2) | 1.02 | 0.72–1.44 | 0.911 |
| **Time after AF diagnosis (months)** | | | |
| 1–6 | Reference | | |
| 7–11 | 1.05 | 1.01–1.08 | 0.005 |
| ≥ 12 | 1.04 | 1.02–1.07 | 0.002 |
| **Multivariate model for OAC discontinuation** | | | |
| Age (per year) | 1.00 | 0.99–1.01 | 0.814 |
| Male | 1.09 | 0.77–1.54 | 0.634 |
| Body mass index (per kg/m²) | 0.99 | 0.97–1.02 | 0.553 |
| Systolic blood pressure (per mmHg) | 1.01 | 1.00–1.01 | 0.061 |
| Diastolic blood pressure (per mmHg) | 0.99 | 0.98–1.00 | 0.016 |
| Triglyceride (per mg/dL) | 1.00 | 1.00–1.00 | 0.373 |
| High-density lipoprotein cholesterol (per mg/dL) | 1.00 | 1.00–1.01 | 0.952 |
| Low-density lipoprotein cholesterol (per mg/dL) | 1.00 | 1.00–1.00 | 0.604 |
| HbA1c (per %) | 1.00 | 0.99–1.00 | 0.429 |
| CHADS₂ score* | 1.00 | 0.78–1.29 | 0.986 |
| HAS-BLED score** | 1.08 | 0.97–1.20 | 0.184 |
| Charlson Comorbidity Index | | | |
| High-very high (≥ 3) | Reference | | |
| Low-medium (0–2) | 0.83 | 0.69–1.00 | 0.049 |
| **Time after AF diagnosis (months)** | | | |
| 1–6 | Reference | | |
| 7–11 | 0.97 | 0.95–0.99 | < 0.001 |
| ≥ 12 | 0.96 | 0.95–0.97 | < 0.001 |
| **Multivariate model for AAD discontinuation** | | | |
| Age (per year) | 0.98 | 0.97–0.99 | < 0.001 |
| Male | 1.50 | 1.00–2.25 | 0.052 |
| Body mass index (per kg/m²) | 0.98 | 0.95–1.00 | 0.094 |
| Systolic blood pressure (per mmHg) | 1.01 | 1.00–1.01 | 0.107 |
| Diastolic blood pressure (per mmHg) | 0.99 | 0.98–1.00 | 0.160 |
| Triglyceride (per mg/dL) | 1.00 | 1.00–1.00 | 0.631 |
| High-density lipoprotein cholesterol (per mg/dL) | 1.00 | 1.00–1.01 | 0.429 |
| Low-density lipoprotein cholesterol (per mg/dL) | 1.00 | 1.00–1.00 | 0.833 |
| HbA1c (per %) | 1.02 | 0.88–1.19 | 0.753 |
| CHADS₂ score* | 0.64 | 0.48–0.86 | 0.003 |
| HAS-BLED score** | 0.94 | 0.83–1.07 | 0.356 |
| Charlson Comorbidity Index | | | |
| High-very high (≥ 3) | Reference | | |
| Low-medium (0–2) | 0.94 | 0.75–1.16 | 0.549 |
| **Time after AF diagnosis (months)** | | | |
| 1–6 | Reference | | |
| 7–11 | 0.98 | 0.96–1.00 | 0.043 |
| ≥ 12 | 0.97 | 0.95–0.98 | < 0.001 |

*CHADS₂ score: congestive heart failure, hypertension, age (75 years or older), diabetes mellitus, previous cerebral infarction/transient ischemic attack. **HAS-BLED score: hypertension, abnormal renal/liver function, stroke, previous bleeding, elderly (65 years or older), drugs/alcohol consumption. HbA1c indicates hemoglobin A1c; AF, atrial fibrillation; OACs, oral anticoagulants; and AADs, antiarrhythmic drugs.
and approximately half of the patients underwent catheter ablation for AF within 6 months after diagnosis. This short lag time may have led to the lower incidence of AF recurrence, thereby resulting in a lower incidence of repeated ablations in our study population. Moreover, shorter time (1-6 months) after AF diagnosis was also significantly associated with discontinuation of OACs/AADs in this present study. These results suggest the relatively early intervention for AF and continuing favorable clinical course after ablation in younger population in Japan. But as yet, we can only describe the apparent association between shorter time lag after AF diagnosis and favorable clinical course after ablation; therefore, we cannot refer to the causality. To clarify whether the early intervention after AF diagnosis produces favorable outcomes after ablation, further prospective studies are needed.

Repeated ablation of AF: In this present study, the rate of repeated catheter ablation procedures was 24.4% within 3 years. The 1-year recurrence rates of paroxysmal and non-paroxysmal AF were reported to be ~20% and >30%, respectively, and these rates increased gradually during long-term follow-up. In a Japanese multicenter retrospective registry, the AF recurrence rate at a median of 20.7 months was reported to be 30.3%. As not all of the patients with AF recurrence would undergo repeated procedures, the rates of repeated procedures in our study corresponded to the rates of AF recurrence described in previous studies.

There are two nationwide prospective registries of catheter ablation in Japan. The Japanese Catheter Ablation Registry for Atrial Fibrillation (J-CARAF) registered cases of ablation from not only high-volume but also from low-volume centers performed in September 2011, May 2012, and September 2012. In the J-CARAF registry, the 1-year rates of repeated AF ablation were reported to be 11.3% in paroxysmal AF and 17.3% in persistent AF, which were mostly consistent with that in this present study. The Japanese Catheter Ablation (J-AB) registry is an ongoing, nationwide prospective registry, which collects data on all cases performed in Japan. The incidence of repeated AF ablation has not been reported from the J-AB registry. In contrast to these registries, our findings were from patient-based health check-ups and a claims database. Both hospital-based and patient-based real-world data would contribute to the evaluation of AF catheter ablation because a recent report suggested that there may be a gap between them.

In our population, male gender was associated with less repeated ablation. To date, some studies have suggested that women may have higher rates of AF recurrence after ablation for AF than men, which may be partially explained by the higher prevalence of non-pulmonary vein triggers and more advanced atrial fibrosis in women compared to men.

Discontinuation of OACs: In this present study, discontinuation of OACs was observed in 26.7% of cases at 3 months and 75.2% of cases at 1 year after the initial ablation, which were higher than in a previous report based on data from cardiovascular centers in Japan (43.4% at 1 year and 56.2% at 2 years). In another report from Japan, OACs were discontinued in 44.9% of those who underwent an initial ablation for AF, during 28 months of follow-up. In our population, OACs tended to be discontinued earlier in patients with low CHADS2 score. The rate of OAC discontinuation beyond 3 months after ablation has been reported to range from 50% to 80%, and it seems to depend on multiple factors, including stroke risk before ablation, ablation success, and physicians' preferences. A previous study reported that the risk of OAC-associated bleeding after AF ablation may exceed the benefits of stroke prevention in patients with CHADS2 score ≤ 1 and that physicians rarely continued OACs beyond 1 year in patients with CHADS2 score ≤ 1 and no recurrent AF. Meanwhile, most specialists recommend OACs after AF ablation for patients with a score ≥ 2 regardless of AF elimination. Our patients were relatively young and had a mean CHADS2 score < 2. The high rate of discontinuation of OACs was associated with these patient characteristics, as expected and consistent with previous studies. In this present analysis, CHADS2 score was not associated with OAC discontinuation, probably because the database includes mostly young patients at low risk for stroke.
risk.

**Discontinuation of AADs:** In this present study, the discontinuation of AADs was concentrated within the first year, and it reached 89.1% at 1 year after the initial ablation. At 3 years, only 4.5% of patients continued to receive AADs. The discontinuation rate of AADs in our population was much higher than reported previously in Japan (67.7% at a median follow-up of 20.7 months).46 There seem to be no clear judgment criteria for discontinuation of AADs, and it mostly depends on ambiguous factors, including physicians’ preferences and the clinical course after ablation. In this present study, younger age and lower CHADS2 score were significantly associated with the discontinuation of AADs, which were characteristics that accounted for the majority of the population. Moreover, the incidence of repeated ablations was relatively low. The low-risk profiles and favorable clinical course would have affected the high rates of AAD discontinuation in the present study.

In the POWDER-AF study, the continuous use of AAD after ablation significantly reduced the rates of AF recurrence and repeat ablation in 1-year follow-up.11 Another study reported maintaining AAD therapy after the blanking period was associated with a long-term reduction in AF recurrence.40 However, the continuous use of AADs after the blanking period (3 months after ablation) remains to be a focus of discussion, as it may be regarded as a procedure failure. The non-uniformity between studies made it impossible to compare the outcomes;39 thus, further studies are needed to clarify whether the discontinuation of AAD during the blanking period after AF ablation reduces the recurrence of AF.

**Limitations:** Our study had several limitations inherent to the nature of a claims database. First, in terms of the diagnosis of AF, some variables and comorbidities used in this study may have been inaccurate because of the nature of the claims database that was not linked to the original medical records. Although some studies reported the validity of the Charlson Comorbidity Index or comorbidities based on claims data,39 some uncertainty remains. AF diagnosis was validated in this present study by improving PPV and NPV, that is, by adding the procedure of catheter ablation to AF. Second, clinical recurrence of AF could not be evaluated, and only capturing repeated AF ablations in the database was feasible. Third, only variables that were extracted from the database could be examined as risk factors. Therefore, some variables, such as type of AF and ablation strategies or protocols, which may be related to outcome, were not examined. Importantly, the database in the present study includes only relatively young patients (93% of patients are < 65 years old), mostly consisting of employees of Japanese companies and their family members. Therefore, data regarding older patients, most of whom are covered by public health insurance, are lacking and could not be analyzed.

Therefore, real-world data with a claims database should be interpreted cautiously at present and should be improved in quality and quantity in the near future. Regardless of these possible limitations, this present study, provided the first analysis of AF ablation with a real-world patient-based claims database, would further aid in evaluating the efficacy of AF catheter ablation in Japan.

**Conclusions**

In this large-scale observational study using real-world data from a claims database, we described the clinical course of Japanese AF patients after catheter ablation.

**Disclosure**

**Conflicts of interest:** Dr. Suzuki received research funding from Daiichi Sankyo and Mitsubishi Tanabe Pharma. JMDC had no role in the design of the study and interpretation of the data. Dr. Yamashita has received research funding and/or lecture fees from Daiichi Sankyo, Bayer Yakuhin, Bristol-Myers Squibb, Pfizer, Nippon Boehringer Ingelheim, Ono Pharmaceutical, and Toa Eiyo.

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