Impact of Renal Dysfunction on Left Atrial Structural Remodeling and Recurrence After Catheter Ablation for Atrial Fibrillation
— A Propensity Score Matching Analysis —

Yuya Takahashi, MD; Takanori Yamaguchi, MD; Akira Fukui, MD, PhD; Toyokazu Otsubo, MD; Kei Hirota, MD; Yuki Kawano, MD; Kana Nakashima, MD; Mai Tahara, MD; Takayuki Kitai, MD; Atsushi Kawaguchi, PhD; Naohiko Takahashi, MD, PhD; Koichi Node, MD, PhD

Background: Renal dysfunction coexists with other known risk factors of left atrial (LA) structural remodeling, expressed as low-voltage zones (LVZs), and the recurrence of atrial fibrillation (AF) after ablation. This study aimed to determine whether renal dysfunction had an independent effect on the presence of LVZs and recurrence after AF ablation, using propensity score (PS) matching analysis.

Methods and Results: 448 consecutive patients who underwent their initial AF ablation were enrolled. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², with 126 (28%) patients having CKD. Using PS matching analysis, new subsets (CKD and non-CKD group, n=103 each) were obtained, matched for age, sex, AF type, and LA volume. The presence of LVZs defined as bipolar voltage <0.5 mV was higher in the CKD group than in the non-CKD group (31% vs. 17%, P=0.034). Multivariate analysis showed eGFR was an independent predictor of the presence of LVZs (odds ratio 1.31 per 10-mL/min/1.73 m² decrease, P=0.029). AF-free survival rate was significantly lower in the CKD patients during 20±9 months of follow-up (63% vs. 82%, P=0.019), and eGFR was shown to be an independent predictor of recurrence (hazard ratio 1.29 per 10-mL/min/1.73 m² decrease, P=0.006), but the presence of LVZs did not predict recurrence.

Conclusions: Renal dysfunction independently predicted not only the recurrence of AF after ablation but also the presence of LVZs.

Key Words: Atrial fibrillation; Catheter ablation; Chronic kidney disease; Fibrosis; Low-voltage zone

Catheter ablation is an established procedure for maintaining sinus rhythm (SR) in patients with atrial fibrillation (AF). However, its efficacy is still limited in some patients. The presence of low-voltage zones (LVZs), which represent structural remodeling of the left atrium (LA), is known to be a strong predictor for the recurrence of AF after ablation. It has been suggested that the primary mechanism of LVZs is atrial fibrosis associated with a slowing of conduction and shortening of the refractory period, which facilitate the development of AF.

Chronic kidney disease (CKD) is not only a risk factor for new onset of AF, but also a risk factor for recurrence of AF after ablation. Chao et al reported that a decreased estimated glomerular filtration rate (eGFR) was associated with a reduction in LA bipolar voltage and a high rate of recurrence after ablation in patients with paroxysmal AF (PAF). Recently, Matsuda et al also reported an association between renal dysfunction and the presence of LVZs in the LA of patients in both PAF and non-PAF populations. However, the association between renal dysfunction and the presence of LVZs and recurrence of AF after ablation generally coexists with other known risk factors such as age, female sex, LA volume, and non-PAF type. These cofounding factors were not fully adjusted and accounted for in previous studies.

In order to clarify the sole effect of renal dysfunction on the presence of LVZs and recurrence of AF after ablation...
we used propensity score (PS) matching, a method commonly used to adjust for confounding factors and reduce differences in the clinical characteristics between patients with and without a specific condition.

Methods

Study Design and Patient Population
This study initially enrolled 448 consecutive Japanese patients who had undergone AF ablation for the first time between April 2014 and May 2017 after excluding the following: <20 years old; previous open-heart surgery; previous ablation in the LA; severe valvular heart disease; history of kidney transplantation; and hemodialysis (HD); 2 patients who failed SR restoration by external cardioversion were also excluded. CKD was defined as an eGFR <60 ml/min/1.73 m² for ≥3 months, irrespective of cause.12 Because all the patients in the study were Japanese, eGFR was calculated using an adapted equation: eGFR (mL/min/1.73 m²)=194×serum creatinine−1.094×age−0.287×0.739 (if female).14 eGFR was calculated using serum creatinine levels measured within 7 days before ablation. The original cohort included 126 patients with CKD (28%) and 322 patients who did not have CKD (72%). The PS for CKD was generated from a multivariate logistic regression model using 4 variables strongly associated with the presence of LVZs and recurrence of AF: age, sex, AF type (PAF or non-PAF), and LA volume measured by computed tomography (CT).2,5,11 Patients in the 2 groups were matched on a 1:1 basis using a 4-digit nearest neighbor algorithm, resulting in 103 patient pairs (CKD and non-CKD groups). For subanalysis, the patients in the CKD group were divided into subgroups that included CKD3a defined as eGFR ≥45 and <60 ml/min/1.73 m² (n=81) and CKD3b/4/5 defined as eGFR <45 ml/min/1.73 m² (n=22). Pre- and post-ablation eGFRs were calculated using the serum creatinine level measured within 7 days before ablation and 1 year after ablation, respectively. ∆seGFR was defined as the difference between pre- and post-eGFR. Written informed consent was obtained and the study was approved by the institutional ethical review board.

PAF and non-PAF, including persistent AF and long-standing persistent AF, were defined according to the HRS/EHRA/ECAS/APHRS/SOLAECE consensus report.14 Both transthoracic and transesophageal echocardiography was performed prior to ablation to examine LA diameter, left ventricular function, and to exclude LA thrombi. LA volume was also evaluated before ablation by an ECG-gated, contrast-enhanced CT scan. When the patient’s eGFR was <30 ml/min/1.73 m², the CT was performed without contrast medium. LA volume included the measurement of the LA body, LA appendage (LAA), and pulmonary vein (PV) volume from the ostium to the first bifurcation. Antiarrhythmic drugs, with the exception of amiodarone, were discontinued for at least 5 half-lives before the ablation.

Voltage Mapping and Ablation Strategy
Electrophysiological studies and catheter ablation were performed under general anesthesia.16 The details of voltage mapping and LA voltage-based ablation have been described elsewhere.4,5 Briefly, LA geometry and a voltage map were created during SR using a 20-pole circular mapping catheter with a 1-mm electrode length and 2-mm interelectrode spacing (Reflection HD™, Abbott) and a 3D-electroanatomical mapping system (EnSite NavX™, Abbott). The mapping catheter was manipulated through a SL0™ (Abbott) or Agilis™ sheath (Abbott) to prevent insufficient contact with the wall. Patients with AF at the beginning of the procedure had an external biphasic direct current cardioversion (DC) to restore SR. When restoration of SR failed even when delivering DC up to 270 J or SR could not be maintained because of frequent AF recurrence, PV isolation (PVI) was performed during on-going AF, and then DC was repeated.

A LVZ was defined as an area with a bipolar peak-to-peak voltage <0.5 mV that covered >5% of the LA surface area excluding the PV antrum and LAA.4,5,16 The %LVZ was defined as the total LVZ area divided by the LA surface area. PVI using an irrigated ablation catheter (CoolFlex™ or FlexAbility™, Abbott) was performed in all patients with an endpoint of entrance and exit block. No substrate modification was performed in patients without LVZs. For patients with LVZs, LVZ homogenization was performed with the endpoints set at ≥80% homogenization of the LVZs in a maximum 40% of the LA surface to prevent stiff LA syndrome.4,5,16 Patients with ≥40% of %LVZ underwent isolation of the LVZs and/or linear ablation across the LVZs.4,5 Superior vena cava isolation and cavotricuspid isthmus linear ablation were performed at the operator’s discretion. Finally, focal atrial tachycardia and non-PV ectopy triggering AF induced by isoproterenol infusion were also ablated.

To examine the distribution of the LVZs, the LA was divided into 6 regions: anterior, septum, roof, posterior, inferior, and lateral wall. Mean LA voltage was calculated as the average of the bipolar voltage of all the acquired points in the 6 LA regions.

Follow-up
Follow-up was performed at 1, 3, and 6 months, and thereafter every 6 months. A 12-lead ECG was performed at each follow-up visit. 24-h Holter monitoring was performed at 3 and 12 months, and 7-day Holter monitoring at 6 and 18 months. Thereafter, 24-h Holter monitoring was performed every 6-12 months. Any atrial tachyarrhythmia documented on the ECG recordings lasting ≥30 s after the 3-month blanking period was considered as a recurrence.14 When recurrence was suspected according to symptoms or a self-pulse check, 7-day Holter monitoring was performed. Antiarrhythmic drugs were discontinued 6 months after the procedure.

Statistical Analysis
Normally distributed data are expressed as the mean±standard deviation, and non-normally distributed data as the median and interquartile range (IQR). Continuous data were analyzed using the unpaired t-test or analysis of variance for normally distributed data, the Wilcoxon rank-sum test or Kruskal-Wallis for non-normally distributed data. Categorical data were analyzed using the χ² test or Fisher’s exact test as appropriate. Subgroup analysis was performed using trend tests to compare the characteristics of the patients and the electrophysiological data between the subgroups that included non-CKD, CKD3a, and CKD3b/4/5. The Jonckheere-Terpstra test was used for continuous data and the Cochran-Armitage test for categorical data. To identify the risk factors for the presence of LVZs, multivariate logistic regression analyses were performed using variables with a P-value <0.10 in the
univariate analysis. An atrial tachyrhythmia recurrence-free survival curve was generated by the Kaplan-Meier method and compared using a log-rank test between the CKD and non-CKD group, between the subgroups including non-CKD, CKD3a, and CKD3b/4/5, and between patients with PAF (3%) vs. 12% (P<0.001). Regarding underlying heart disease, 19 patients in the non-CKD group comprised 10 with non-ischemic cardiomyopathy, 4 with ischemic cardiomyopathy, and 5 with hypertrophic cardiomyopathy, and 24 patients in the CKD group respectively comprised 12, 8, and 4 cases. Amiodarone was prescribed in 22 patients. All patients underwent high-density mapping of the LA during SR (1.27±0.54 LA surface points) before (n=204) and after PVI (n=19). The characteristics of the patients in the subgroups are shown in Table 2.

### Differences in Structural Remodeling

Figure 1 shows examples of voltage maps in the LA. LVZs in the LA were more frequently identified in the CKD group compared with the non-CKD group (P<0.001). Both total LVZ area and %LVZ were significantly higher in the CKD group (Table 1), with subgroup analysis showing that total LVZ area increased as renal function deteriorated (Table 2). Although the difference in the LA mean voltage was not significant between the CKD and non-CKD groups (P=0.084, Table 1), subgroup analysis showed a trend of a decrease in LA mean voltage as renal function deteriorated (Table 2). The distribution of LVZs was similar in the non-CKD and CKD groups (Table 2).

### Results

#### Patients’ Characteristics

The patients’ characteristics before and after PS matching are shown in Table 1. Before matching, patients with CKD were significantly older, had larger LA size, lower EF, and a higher CHA2DS2-VASc score. After matching, no differences were observed in these variables between patients with and without CKD. We then compared the extent of structural remodeling and outcomes of ablation between the CKD and non-CKD groups. In the CKD group, 42 patients (41%) had persistent AF and 11 patients (11%) had long-standing persistent AF; in the non-CKD group, 36 patients (35%) had persistent AF and 10 patients (10%) had long-standing persistent AF (P=0.616). Regarding underlying heart disease, 19 patients in the non-CKD group comprised 10 with non-ischemic cardiomyopathy, 4 with ischemic cardiomyopathy, and 5 with hypertrophic cardiomyopathy, and 24 patients in the CKD group respectively comprised 12, 8, and 4 cases. Amiodarone was prescribed in 22 patients. All patients underwent high-density mapping of the LA during SR (1.27±0.54 LA surface points) before (n=204) and after PVI (n=19). The characteristics of the patients in the subgroups are shown in Table 2.

#### Table 1. Baseline Characteristics and Ablation Results of Pre- and Post-Propensity Score Matching Between Non-CKD and CKD Patients

|                      | Pre-propensity score matching | Post-propensity score matching |
|----------------------|------------------------------|--------------------------------|
|                      | Non-CKD (n=322)              | CKD (n=126)                    | P value |
|                      | Non-CKD (n=103)              | CKD (n=103)                    | P value |
| Age, years           | 63±10                        | 70±9                          | <0.001* |
| Female sex, n (%)    | 94 (29)                      | 38 (30)                       | 0.840   |
| LA volume, mL, median (IQR) | 125 (103–158)                | 144 (115–167)                 | 0.004*  |
| Non-PAF, n (%)       | 134 (42)                     | 64 (51)                       | 0.079   |
| BMI, kg/m²            | 24.0±3.7                     | 24.5±3.3                      | 0.253   |
| Underlying disease, n (%) | 43 (13)                      | 35 (28)                       | <0.001* |
| eGFR, mL/min/1.73 m², median (IQR) | 13.8 (9.5–21.0)               | 15.8 (7.5–26.2)               | 0.772   |
| Proc. time, min       | 153±35                       | 154±40                        | 0.867   |
| CTI ablation, n (%)   | 241 (75)                     | 94 (75)                       | 1.000   |
| SVC isolation, n (%)  | 197 (61)                     | 64 (51)                       | 0.055   |
| Non-PV foci ablation, n (%) | 45 (14)                     | 19 (15)                       | 0.765   |
| LA mean voltage, mV   | n/a                          | n/a                           | 1.32 (0.96–1.79) |
| Presence of LVZs, n (%) | 44 (14)                      | 36 (29)                       | <0.001* |
| LVZ area, cm², median (IQR) | 13.8 (9.5–21.0)               | 15.8 (7.5–26.2)               | 7.3 (4.0–17.2)  |
| %LVZ, %, median (IQR) | 15.8 (9.9–26.5)              | 16.8 (8.2–28.4)               | 3.7 (3.7–19.3)  |
| eGFR, ml/min,1.73 m², median (IQR) | 75 (67–84)                   | 52 (46–55)                    | 0.001*  |

*Significant value (P<0.05). %LVZ (%)=LVZ area/LA surface area. AF: atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; CTI, cavitricuspid isthmus; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LA, left atrium; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LA, left atrium; PAF, paroxysmal atrial fibrillation; PV, pulmonary vein; SVC, superior vena cava.
significant difference in the presence of LVZs between persistent and long-standing persistent AF (37% vs. 38%, P=0.939). Multivariate analyses showed that eGFR was independently associated with the presence of LVZs as well as age, female sex, LA volume, and non-PAF type (Table 3).

**Outcomes After Ablation**

All patients successfully completed PVI, and patients with LVZs underwent LVZ homogenization. Procedure-related complications were noted in 1 patient in the non-CKD group (1%) and 6 patients in the CKD group (6%): cardiac tamponade (n=1), PV stenosis (n=1), transient phrenic nerve injury (n=2), esophageal ulcer (n=1), and vascular-related complications (n=2). There was no significant difference in ∆eGFR between patients with (n=49) or without recurrence (n=157) at 1 year after ablation [0 (−5.3–6.5) vs. −0.3 (−6.0–5.8) mL/min/1.73 m², P=0.971]. However, in patients with non-PAF, eGFR did not tend to worsen in patients without recurrence (n=69) compared with those with recurrence (n=30) [∆eGFR, −2.2 (−8.0–2.2) vs. 4.0 (−4.4–7.5) mL/min/1.73 m², P=0.149]. This difference was not statistically significant. The atrial tachyarrhythmia recurrence-free survival rate was significantly lower in the

### Table 2 Baseline Characteristics and Ablation Results of Subgroups

|                       | Non-CKD (n=103) | CKD3a (n=81) | CKD3b/4/5 (n=22) | P value CKD3a vs. CKD3b/4/5 | P for trend |
|-----------------------|-----------------|--------------|-----------------|----------------------------|-------------|
| Age, years            | 69±8            | 69±8         | 69±7            | 0.911                      | 0.969       |
| Female sex, n (%)     | 44 (43)         | 27 (33)      | 8 (36)          | 0.791                      | 0.293       |
| LA volume, mL, median (IQR) | 135 (109–170) | 135 (109–159) | 153 (124–183) | 0.019*                     | 0.375       |
| Non-PAF, n (%)        | 46 (45)         | 41 (51)      | 12 (55)         | 0.744                      | 0.307       |
| BMI, kg/m²             | 23.7±3.1        | 24.4±3.5     | 24.2±4.0        | 0.827                      | 0.166       |
| Underlying heart disease, n (%) | 19 (18)    | 16 (20)      | 8 (36)          | 0.115                      | 0.132       |
| CHA2DS2-VASc score, median (IQR) | 2 (1–3)          | 2 (1–3)      | 3 (2–4)         | 0.023*                     | 0.064       |
| LVEF, %, median (IQR) | 68 (60–71)      | 65 (60–71)   | 64 (46–68)      | 0.274                      | 0.072       |
| LVDD, mm, median (IQR) | 47 (43–51)     | 47 (44–50)   | 50 (45–55)      | 0.078                      | 0.088       |
| LA diameter, mm, median (IQR) | 41 (36–44)  | 41 (38–45)   | 44 (41–46)      | 0.005*                     | 0.025*      |
| Procedure time, min    | 154±35          | 154±39       | 152±45          | 0.824                      | 0.754       |
| CTI ablation, n (%)    | 81 (79)         | 59 (73)      | 19 (86)         | 0.169                      | 0.898       |
| SVC isolation, n (%)   | 65 (63)         | 40 (49)      | 12 (54)         | 0.667                      | 0.143       |
| Non-PV foci ablation, n (%) | 17 (16)      | 14 (17)      | 3 (14)          | 0.677                      | 0.860       |
| LA mean voltage, mV    | 1.32 (0.96–1.79)| 1.23 (0.88–1.69)| 1.11 (0.70–1.63)| 0.217                      | 0.044*      |
| Presence of LVZs, n (%)| 18 (17)         | 21 (26)      | 11 (50)         | 0.035*                     | 0.002*      |
| LVZ area, cm², median (IQR) | 7.3 (4.0–17.2) | 14.5 (5.9–25.7) | 15.2 (8.8–30.7) | 0.294                      | 0.001*      |
| %LVZ,†, median (IQR)   | 9.5 (4.9–19.3)  | 16.4 (6.7–27.9)| 16.2 (11.8–33.6)| 0.434                      | 0.001*      |
| eGFR, mL/min/1.73 m², median (IQR) | 70.6 (65.1–78.9) | 53.3 (49.9–56.6) | 36.8 (25.9–42.5) | <0.001*                    | <0.001*     |

*Significant value (P<0.05). †%LVZ (%)=LVZ area/LA surface area. Abbreviations as in Table 1.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Examples of a voltage map in patients without (A) and with (B) LVZs in the LA. LA, left atrium; LVZ, low-voltage zone.
Renal Function and AF Recurrence After Ablation

Recurrence-free rate decreased as the extent of LVZs increased (Figure 2C). Univariate and multivariate Cox regression analyses showed that eGFR was an independent predictor of recurrence (hazard ratio 1.29 per 10-mL/min/1.73 m² decrease, 95% confidence interval 1.08–1.56, P=0.006) as well as LA volume (Table 4). Interestingly, neither the presence of LVZs (multivariate model 1) nor CKD group during 20±9 months of follow-up (63% vs. 82%, P=0.019, Figure 2A). Subgroup analysis also showed trends of a decrease in recurrence-free survival rate as renal function deteriorated (Figure 2B). When the recurrence-free rate was compared between patients without LVZs (%LVZ <5%, n=156), with moderate LVZs (%LVZ ≥5%, <20%, n=29) and with extensive LVZs (%LVZ ≥20%, n=21), the recurrence-free rate decreased as the extent of LVZs increased (Figure 2C). Univariate and multivariate Cox regression analyses showed that eGFR was an independent predictor of recurrence (hazard ratio 1.29 per 10-mL/min/1.73 m² decrease, 95% confidence interval 1.08–1.56, P=0.006) as well as LA volume (Table 4). Interestingly, neither the presence of LVZs (multivariate model 1) nor

---

**Table 3. Predictors of the Presence of LVZs**

| Variables                           | Univariate | Multivariate |
|-------------------------------------|------------|--------------|
|                                     | OR (95% CI) | P value      | OR (95% CI) | P value      |
| Age (per 10-years increase)         | 1.99 (1.26–3.15) | 0.002*       | 2.25 (1.31–3.86) | 0.002*       |
| Female sex                          | 3.67 (1.89–7.13) | <0.001*      | 6.35 (2.69–15.00) | <0.001*      |
| LA volume (per 10-mL increase)      | 1.13 (1.04–1.22) | 0.002*       | 1.17 (1.04–1.31) | 0.006*       |
| Non-PAF                             | 4.31 (2.12–8.76) | <0.001*      | 3.30 (1.38–7.87) | 0.007*       |
| Underlying heart disease            | 2.14 (0.98–4.65) | 0.060        | 1.13 (0.43–2.97) | 0.810        |
| Hypertension                        | 0.90 (0.47–1.74) | 0.764        |               |              |
| Diabetes mellitus                   | 1.23 (0.50–3.03) | 0.655        |               |              |
| eGFR (per 10-mL/min decrease)       | 1.30 (1.06–1.60) | 0.010*       | 1.31 (1.02–1.69) | 0.029*       |
| AUC                                 |             |              | 0.827        |              |

*Significant value (P<0.05). AUC, area under the curve; CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

---

**Table 4. Predictors of Recurrence after AF Ablation**

| Variables                           | Univariate | Multivariate model 1 | Multivariate model 2 |
|-------------------------------------|------------|-----------------------|-----------------------|
|                                     | HR (95% CI) | P value               | HR (95% CI) | P value               | HR (95% CI) | P value               |
| Age (per 10-years increase)         | 0.89 (0.64–1.27) | 0.533                 |           |                        |           |                        |
| Female sex                          | 1.37 (0.76–2.55) | 0.296                 |           |                        |           |                        |
| LA volume (per 10-mL increase)      | 1.14 (1.07–1.21) | <0.001*               | 1.10 (1.03–1.17) | 0.007*               | 1.10 (1.03–1.18) | 0.003*               |
| Non-PAF                             | 1.85 (1.05–3.35) | 0.033*               | 1.08 (0.56–2.09) | 0.821               | 1.03 (0.50–2.14) | 0.924               |
| Underlying heart disease            | 1.75 (0.87–3.26) | 0.108                 |           |                        |           |                        |
| Hypertension                        | 1.37 (0.76–2.55) | 0.294                 |           |                        |           |                        |
| Diabetes mellitus                   | 2.20 (1.12–4.05) | 0.023*               | 1.73 (0.89–3.36) | 0.105               | 1.83 (0.86–3.61) | 0.110               |
| Presence of LVZs                    | 1.94 (1.08–3.47) | 0.025*               | 1.28 (0.67–2.41) | 0.452               |           |                        |
| LA mean voltage (per 0.1% decrease) | 1.07 (1.01–1.14) | 0.019*               | 1.02 (0.96–1.09) | 0.546               |           |                        |
| eGFR (per 10-mL/min/1.73 m² decrease) | 1.43 (1.19–1.71) | <0.001*               | 1.29 (1.08–1.56) | 0.006*               | 1.34 (1.10–1.62) | 0.003*               |

*Significant value (P<0.05). HR, hazard ratio. Other abbreviations as in Tables 1,3.
LA mean voltage (multivariate model 2) was shown to predict recurrence of AF.

**Discussion**

**Major Findings**

The present study used PS matched cohorts to show that renal dysfunction predicts the presence of LVZs and recurrence of AF after ablation. Interestingly, neither the presence of LVZs nor LA mean voltage was shown to predict recurrence of AF during 20±9 months of follow-up.

**Previous Study**

A population-based study that examined the association between ECG-documented AF and renal function in patients without HD dependency reported that the prevalence of AF increased in a dose-dependent fashion as renal function worsened. The prevalence of AF was 1.0% in adults without CKD and 2.8%, 2.7%, and 4.2% in adults with an eGFR ≥60 mL/min/1.73 m², albuminuria ≥30 and <60, or eGFR <30 mL/min/1.73 m², respectively. Matsuda et al reported recently on the relationship between CKD and AF. The study showed an independent effect of AF type. Previous studies have shown that LVZ was a strong independent predictor of recurrence, irrespective of AF type. However, in the present study the presence of LVZs was not a predictor of recurrence during long-term follow-up, whereas eGFR and LA size were shown to be independent predictors of recurrence. Additional LVZ ablation following PVI in patients with LVZs might have affected these results. Furthermore, in patients with a decreased eGFR and enlarged LA, fibrosis might have progressed over time independently of baseline fibrotic remodeling expressed as the presence of LVZs.

**Effect of Voltage-Based Ablation for CKD Patients**

Our study showed clearly that the recurrence rate for atrial tachyarrhythmia was higher as renal function deteriorated and that the %LVZ also increased. Of note, eGFR was shown to be an independent risk factor for recurrence, whereas neither the presence of LVZs nor LA mean voltage influenced recurrence. The outcomes of patients with %LVZ either <20% or ≥20% were similar during the long-term follow-up period even after additional LVZ homogenization, although in the early phase of follow-up there appeared to be a significant difference. These data suggest that LA fibrosis progresses over time, especially in patients with CKD, and eventually becomes the cause of the recurrence. Whether or not renal function itself or other factors that induce renal dysfunction are the cause of LA fibrosis progression and recurrence has yet to be determined.

**Effect of AF Type on the Outcomes**

The presence of LVZs was higher in non-PAF than in PAF (37% vs. 12%, P<0.001), with the non-PAF type being an independent predictor of the presence of LVZs, in addition to eGFR, LA size, age, and female sex. However, there was no significant difference in the presence of LVZs between persistent and long-standing persistent AF (37% vs. 38%, P=0.939). This suggests that the presence of LVZs, the primary mechanism of which is considered to be fibrosis, is associated with whether or not AF can persist, although it may not necessarily be associated with the duration of AF.

**Study Limitations**

This study was a retrospective cohort study. PS matching was performed for patient characteristics including sex, age, AF type, and LA volume, which are known predictors for LVZs, although it is possible other confounding factors may have also affected the development of this condition. Voltage mapping and voltage-based catheter ablation has several limitations as previously described in detail. The follow-up methodology after catheter ablation was not stringent, although 7-day Holter monitoring was carried out at 6 and 18 months. Thus, some cases of asymptomatic recurrence might have been missed.
Conclusions
Renal dysfunction is an independent predictor for both the presence of LVZs and recurrence after AF ablation. Renal dysfunction is a stronger risk factor for recurrence after AF ablation than the presence of LVZs in the LA.

Acknowledgments
None.

Data Availability
The deidentified participant data will not be shared.

Disclosures
T.Y. received remuneration and scholarship funds from Abbott Medical Japan. T.Y. and T.O. are also affiliated with the Department of Advanced Management of Cardiac Arrhythmia, Saga University, sponsored by Abbott Medical Japan, Nihon Kohden Corporation, Japan Medtronic, Japan Lifeline, Boston Scientific Japan, and Fides-ONE Corporation. The other authors declare that they have no conflict of interest. This research did not receive a grant from any funding agency in the public, commercial, or not-for-profit sectors. N.T. and K. Node are members of Circulation Journal’s Editorial Team.

IRB Information
Ethical Review Board of Saga-ken Medical Center Koseikan, Reference no. 18-09-02-02.

References
1. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015; 372: 1812–1822.
2. Yamaguchi T, Tsuchiya T, Nagamoto Y, Miyamoto K, Muratori K, Okishige K, et al. Long-term results of pulmonary vein antrum isolation in patients with atrial fibrillation: An analysis in regards to substrates and pulmonary vein reconnections. Europace 2014; 16: 511 – 520.
3. Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: An independent predictor of procedural failure. J Am Coll Cardiol 2005; 45: 285 – 292.
4. Yamaguchi T, Tsuchiya T, Nakahara S, Fukui A, Nagamoto Y, Muratori K, et al. Efficacy of left atrial voltage-based catheter ablation of persistent atrial fibrillation. J Cardiovasc Electrophysiol 2016; 27: 1055 – 1063.
5. Yamaguchi T, Tsuchiya T, Fukui A, Kawano Y, Otsubo T, Takahashi Y, et al. Impact of the extent of low-voltage zone on outcomes after voltage-based catheter ablation for persistent atrial fibrillation. J Cardiol 2018; 72: 427 – 433.
6. McGann C, Akoum N, Patel A, Kholmovski E, Revelo P, Damal K, et al. Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. Circ Arrhythm Electrophysiol 2014; 7: 23 – 30.
7. Heijman J, Voigt N, Nattel S, Dobrev D. Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. Circ Res 2014; 114: 1483 – 1499.
8. Shang W, Li L, Huang S, Zeng R, Huang L, Ge S, et al. Chronic kidney disease and the risk of new-onset atrial fibrillation: A meta-analysis of prospective cohort studies. PLoS One 2016; 11: e0155581.
9. Diemerberger I, Genovesi S, Massaro G, Reggiani MLB, Frisoni J, Gorlato G, et al. Meta-analysis of clinical outcomes of electrical cardioversion and catheter ablation in patients with atrial fibrillation and chronic kidney disease. Cure Pharm Des 2016; 24: 2794 – 2801.
10. Chao TF, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, et al. Associations between renal function, atrial substrate properties and outcome of catheter ablation in patients with paroxysmal atrial fibrillation. Circ J 2011; 75: 2326 – 2332.
11. Matsuda Y, Masuda M, Asai M, Iida O, Okamoto S, Ishihara T, et al. Impact of renal dysfunction on left atrial low-voltage areas in patients with atrial fibrillation. Circ J 2019; 83: 985 – 990.
12. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013; 3: 1 – 150.
13. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53: 982 – 992.
14. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 RHR/ES/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. J Arrhythm 2017; 33: 369 – 409.
15. Yamaguchi T, Shimakawa Y, Mitsumizo S, Fukui A, Kawano Y, Otsubo T, et al. Feasibility of total intravenous anesthesia by cardiologists with the support of anesthesiologists during catheter ablation of atrial fibrillation. J Cardiol 2018; 72: 19 – 25.
16. Gibson DN, Di Biase L, Mohanty P, Patel JD, Bai R, Sanchez J, et al. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: Clinical characterization, prevalence, and predictors. Heart Rhythm 2011; 8: 1364 – 1371.
17. Baber U, Howard VJ, Halperin JL, Sollman EZ, Zhang X, McClellan W, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Circ Arrhythm Electrophysiol 2011; 4: 26 – 32.
18. Fukui A, Takahashi N, Nakada C, Masaki T, Kume O, Shinohara T, et al. Role of leptin signaling in the pathogenesis of angiotensin II-mediated atrial fibrosis and fibrillation. Circ Arrhythm Electrophysiol 2013; 6: 402 – 409.
19. Hung MJ, Yang NI, Wu IW, Cheng CW, Wu MS, Cheng WJ. Echocardiographic assessment of structural and functional cardiac remodeling in patients with predialysis chronic kidney disease. Echocardiography 2010; 27: 621 – 629.
20. Barbhaiya CR, Kumar S, Baldinger SH, Michaud GF, Stevenson WG, Falk R, et al. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. Heart Rhythm 2016; 13: 383 – 390.
21. Heiss A, DuChesne A, Denecke B, Grotzinger J, Yamamoto K, Renne T, et al. Structural basis of calcification inhibition by alpha 2-HS glycoprotein/ fetuin-A: Formation of colloidal calciprotein particles. J Biol Chem 2003; 278: 13333 – 13341.
22. Smith ER, Ford ML, Tomlinson LA, Rajkumar C, McMahon LP, Holt SG. Phosphorylated fetuin-A-containing calciprotein particles are associated with aortic stiffness and a procalcific milieu in patients with pre-dialysis CKD. Nephrol Dial Transplant 2012; 27: 1957 – 1966.
23. Nakaoka Y, Nishida K, Narimatsu M, Kamiya A, Minami T, Sawah H, et al. Gab family proteins are essential for postnatal maintenance of cardiac function via neuregulin-1/Erbb signaling. J Clin Invest 2007; 117: 1771 – 1781.
24. Seiler S, Cremers B, Rebリング NM, Hornof F, Jeken J, Kersting R, et al. The phosphatonin fibroblast growth factor 23 links calcium-phosphate metabolism with left-ventricular dysfunction and atrial fibrillation. Eur Heart J 2011; 32: 2688 – 2696.
25. Yamaguchi T, Fukui A, Node K. Bipolar voltage mapping for the evaluation of atrial substrate: Can we overcome the challenge of directionality? J Atr Fibrillatlon 2019; 11: 2116.