ORIGINAL RESEARCH

Five-Year Change in the Renal Function After Catheter Ablation of Atrial Fibrillation

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***Background*—**Although it has been reported that renal function can improve after catheter ablation of atrial fibrillation (AF), long-term changes in renal function and its relationship to rhythm outcomes have not yet been evaluated. We explored the 5-year change in estimated glomerular filtration rate (eGFR) in AF patients depending on medical therapy and catheter ablation.

***Methods and Results*—**Among 1963 patients who underwent AF catheter ablation and 14 056 with AF under medical therapy in the National Health Insurance Service database, we compared 571 with AF catheter ablation (59±10 years old, 72.3% male, and 66.5% paroxysmal AF) and 1713 with medical therapy after 1:3 propensity-score matching. All participants had 5 years of serial eGFR data (Chronic Kidney Disease-Epidemiology Collaboration [CKD-EPI] method). Catheter ablation improved $eGFR_{5\ yrs}$ ($P<0.001$), but medical therapy did not. In 2284 matched patients, age (adjusted odds ratio [OR], 0.98 [0.97–0.99]; $P<0.001$) and AF catheter ablation (adjusted OR, 2.02 [1.67–2.46]; $P<0.001$) were independently associated with an improved $eGFR_{5\ yrs}$. Among 571 patients who underwent AF ablation, freedom from AF/atrial tachycardia recurrence after the last AF ablation procedure was independently associated with an improved $eGFR_{5\ yrs}$ (adjusted OR, 1.44 [1.01–2.04]; $P=0.043$), especially in patients without diabetes mellitus (adjusted OR, 1.78 [1.21–2.63]; $P=0.003$, P for interaction=0.012). Although underlying renal dysfunction (<60 mL/min/1.73m^2) was associated with atrial structural remodeling (adjusted OR, 1.05 [1.00–1.11]; $P=0.046$), it did not affect the AF ablation rhythm outcome.

***Conclusions*—**AF catheter ablation significantly improved renal function over a 5-year follow-up, especially in patients maintaining sinus rhythm without preexisting diabetes mellitus. **(*J Am Heart Assoc*. 2019;8:e013204. DOI: 10.1161/JAHA.119.013204.)**

Key Words: atrial fibrillation • catheter ablation • renal function

Atrial fibrillation (AF), a common arrhythmia that increases mortality by 2 to 3 times,[1] is a progressive degenerative disease[2] associated with strokes,[1] dementia,[1] and heart failure.[1] Chronic kidney disease (CKD) has a well-established association with cardiovascular disease, and all-cause mortality and cardiovascular mortality progressively increase as renal function declines.[3,4] It has been shown that 7% to 18% of patients with a CKD stage of ≥3 (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) have concomitant AF, and 10% to 15% of AF patients have CKD.[5–7] This relationship becomes more significant for those aged >70 years. Patients with both AF and CKD have an increased risk of bleeding and thromboembolisms.[7] Washam et al[8] reported that AF rhythm control by antiarrhythmic drugs did not affect all-cause mortality and risk of a stroke in patients in the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry data. In contrast, AF catheter ablation has been known to be a more-effective method of AF rhythm control than antiarrhythmic drugs,[9] and it is known to lower the heart failure mortality[10,11] and risk of cerebral infarctions[12] and improve the cognitive function.[13,14] However, studies on renal-function changes after AF rhythm control by catheter ablation have been limited thus far. Takahashi et al reported that maintenance of sinus rhythm after a single AF catheter ablation resulted in a positive effect on renal function.[15] After a successful AF ablation, left ventricular systolic function improves and mean heart rate increases because of autonomic nerve modulation.[16,17] As a result, cardiac output increases, and a positive effect on renal

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Accompanying Tables S1 through S4 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013204

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Clinical Perspective

What Is New?

- Atrial fibrillation (AF) catheter ablation improved renal function over the 5-year follow-up, whereas medical therapy did not.
- No recurrence after the last AF ablation procedure was independently associated with an improved long-term renal function, especially in patients without diabetes mellitus.
- Impaired renal function was associated with an atrial structural remodeling in AF patients, but did not affect the rhythm outcome of AF catheter ablation.

What Are the Clinical Implications?

- AF catheter ablation and reduction of AF burden can improve renal function over a long-term period, especially in patients without diabetes mellitus.

function is expected after a successful AF ablation. However, given that AF has a substantial long-term recurrence rate after catheter ablation, there are no data on changes in renal function over a 5-year long-term period or after repeated procedures. Therefore, we hypothesized that an optimal AF rhythm control, including a repeat ablation, may improve long-term renal function beyond 5 years. In this study, we compared the change in renal function in AF patients who underwent catheter ablation followed by a guideline-based regular rhythm follow-up (Yonsei AF ablation cohort) and those that underwent medical therapy alone (Korean National Health Insurance [NHIS] database) over a peirod of 5 years. We also explored the relationship of the change in long-term renal function after AF catheter ablation to rhythm outcome or degree of atrial remodeling.

Methods

The data, analytic methods, and study materials that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

This study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Yonsei University Health System. The medical therapy group was selected from the NHIS database (NHIS-2018-2-189), and the ablation therapy group was selected from the Yonsei AF Ablation cohort (registered at ClinicalTrials.gov Identifier: NCT02138695). Both groups were enrolled as nonvalvular AF patients with baseline and 5-year follow-up eGFR (estimated by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) data. In the AF ablation group, all patients provided written informed consent for inclusion in the Yonsei AF Ablation study. The informed consent requirement in the medical therapy group from the NHIS database was waived. Among 1963 patients who underwent AF catheter ablation (AFCA) for symptomatic drug-refractory AF, 571 patients (59±10 years, 72.3% male, and 66.5% paroxysmal AF) who had 5-year serial eGFR data after AF ablation were enrolled in this study. All patients stopped their antiarrhythmic drugs for a period of time corresponding to at least 5 half-lives before catheter ablation. During the 5-year follow-up period, 103 patients underwent a second ablation, and 3 underwent a third ablation for antiarrhythmic-resistant recurrent AF (Figure 1). In the medical therapy group, among 14 056 patients with nonvalvular AF who were not treated with catheter ablation in the NHIS database, 1713 patients (59±11 years, 73.2% male) who had both baseline and 5-year follow-up renal function data were enrolled in this study for the control group after propensity-score matching with the AF ablation group. Exclusion criteria were as follows: (1) permanent AF refractory to electrical cardioversion, (2) AF with rheumatic valvular disease, and (3) previous cardiac surgery with concomitant AF surgery or AF catheter ablation.

Electrophysiological Mapping and Radiofrequency Catheter Ablation

3D electroanatomical mapping (NavX; St. Jude Medical, Inc, Minnetonka, MN) was generated using a circumferential pulmonary vein (PV)-mapping catheter (Lasso; Biosense-Webster Inc, Diamond Bar, CA) through a long sheath (Schwartz left 1; St. Jude Medical, Inc). Multiview pulmonary venograms were obtained after the trans-septal punctures. The 3D geometry of both the left atrium (LA) and PVs was generated using the NavX system and then merged with 3D spiral computed tomography images. Systemic anticoagulation with intravenous heparin was achieved to maintain an activated clotting time of 350 to 400 seconds during the procedure.

An open-irrigated tip catheter (Celsius; Johnson & Johnson Inc, Diamond Bar, CA; NaviStar ThermoCool, Biosense Webster Inc; ThermoCool SF, Biosense Webster Inc; ThermoCool SmartTouch, Biosense Webster Inc; Coolflex, St. Jude Medical Inc; 30–35 W; 47°C; FlexAbility, St Jude Medical Inc; ThermoCool SmartTouch, Biosense Webster Inc, and Tacti-Cath, St. Jude Medical Inc) was used for AFCA. All patients underwent a de novo procedure with a circumferential pulmonary vein isolation. The majority of the patients (94.2%) underwent a cavotricuspid isthmus block during the de novo procedure if there was no atrioventricular conduction disease. We conducted an additional linear ablation including a roof line, posterior inferior line (posterior box lesion), and

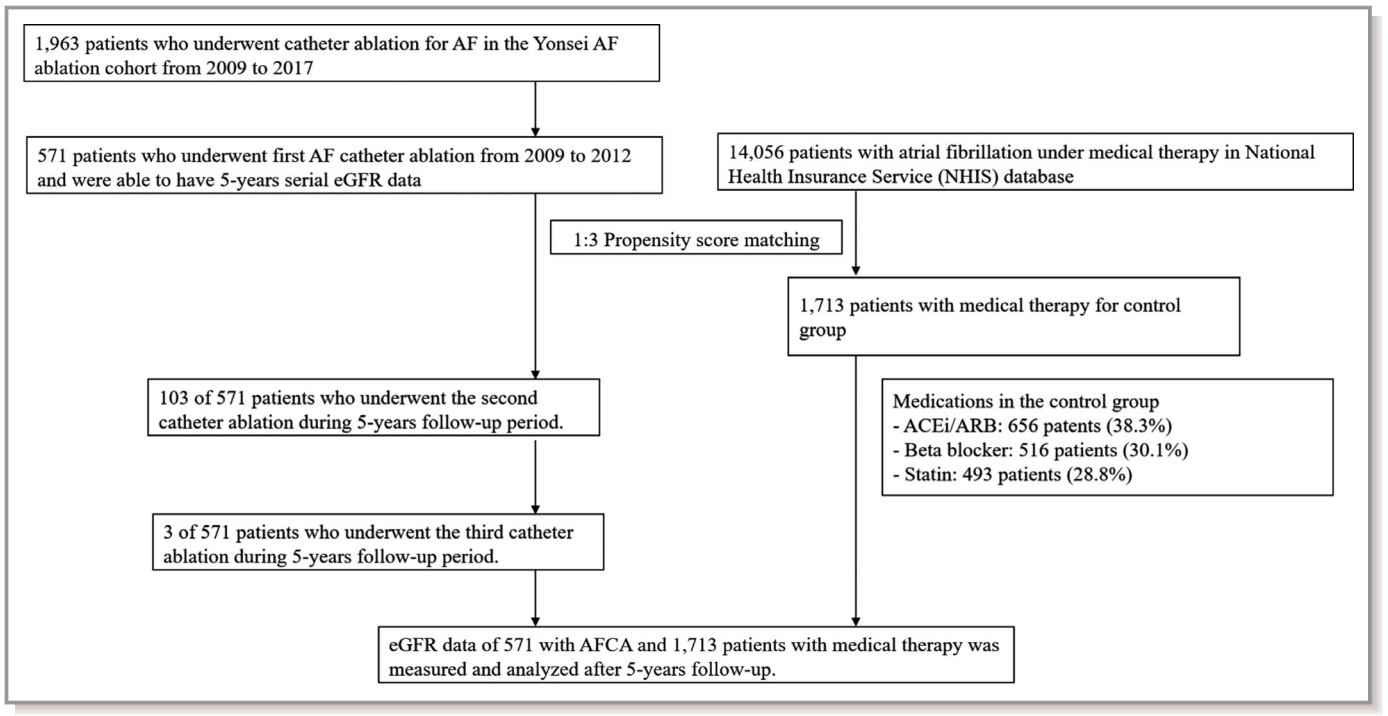

Figure 1. Study flow chart of the patient enrollment. ACEi indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; AFCA, AF catheter ablation; ARB, angiotensin type II receptor blocker; eGFR, estimated glomerular filtration rate.

anterior line, especially in patients with persistent AF. A left lateral isthmus ablation, right atrial ablation, and complex fractionated electrogram ablation were performed in a minority of the patients at the operator's discretion. The de novo procedure ended when there was no immediate recurrence of AF within 10 minutes after the cardioversion with an isoproterenol infusion (5–10 μg/min). In the case of mappable AF triggers or premature atrial beats, non-PV foci were carefully mapped and ablated as much as possible.

The detailed technique and strategy for the repeat ablation procedures were presented in a previous study.[18] If there were reconnections of PV potentials or a previous linear ablation, we completed the circumferential pulmonary vein isolation and accomplished bidirectional block of the circumferential pulmonary vein isolation, cavotricuspid isthmus, or linear ablation as much as possible. Then, we provoked extra-PV foci with an isoproterenol infusion (5–10 μg/min) and carefully mapped and ablated mappable AF triggers or frequent atrial premature beats. If there were multiple extra-PV triggers, we conducted an additional linear ablation or an electrogram-guided ablation at the operators' discretion.

Postablation Management and Follow-up

Patients visited the outpatient clinic at 1, 3, 6, and 12 months and every 6 months thereafter or whenever symptoms developed after the AFCA. ECG was performed at every visit. Twenty-four-hour Holter monitoring was performed at 3, 6, and 12 months and then every 6 months after the AFCA according to the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society expert consensus statement guidelines.[19] Patients underwent an annual laboratory examination (serum creatinine, blood urea nitrogen, urine hemoglobin, and dipstick urine protein). eGFR was estimated by the CKD-EPI equation. Patients who suffered from symptoms of palpitations underwent Holter/event-monitor examinations to investigate the possibility of an arrhythmia recurrence. We defined an AF recurrence as any episode of atrial tachycardia (AT) or AF lasting for 30 seconds or more. Any ECG documentation of an AF recurrence after a 3-month blanking period was classified as a clinical recurrence.

Statistical Analysis

Continuous variables are expressed as mean±SD and were analyzed using a Student *t* test. Categorical variables are reported as numbers (percentages) and were analyzed using a chi-square or Fisher's exact test. We used a paired *t* test to investigate changes in $eGFR_{5\ yr}$ ($\Delta eGFR_{5\ yr}$) in both the AFCA group and control group. Also, we compared $\Delta eGFR_{5\ yr}$ after AFCA according to freedom from AF/AT recurrence by using a paired *t* test. A multivariate logistic regression analysis was used to investigate whether AF catheter ablation improved renal function and identify predictors associated with an improvement in renal function in patients who underwent AF

catheter ablation. The variables with a *P* value under 0.05 were included in the multivariate model. Furthermore, we did not use a step-wise selection model in multivariate regression analysis. A Kaplan–Meier analysis was used to analyze probability of freedom from AF/AT recurrence after AFCA according to a concomitant impaired renal function. Propensity matching was performed without a replacement and with a caliper of 0.01 at a 1: 3 ratio of the AF ablation group and medical therapy group based on the following variables: age, sex, body mass index, congestive heart failure, hypertension, diabetes mellitus, previous history of a stroke or transient ischemic attack, previous history of vascular disease, CHA_2DS_2VASc score, baseline eGFR, and medications, including angiotensin-converting enzyme inhibitors, angiotensin type II receptor blockers, β-blockers, and statins. $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS (version 23.0; SPSS, Inc, Chicago, IL) software for Windows.

Results

AF Catheter Ablation Versus Medical Therapy

Baseline characteristics in the AF catheter ablation group and propensity-score–matched control group are presented in Table 1. There were no significant differences in patient characteristics, medication use, and baseline eGFR between the AFCA group and medical therapy group. Nonetheless, eGFR measured at the 5-year follow-up in patients who underwent AFCA was significantly higher than that in patients with medical therapy (84.6±19.4 versus 82.4±18.1 mL/min/1.73 m^2; $P=0.014$; Figure 2A). $\Delta eGFR_{5\ yr}$ was also significantly higher in patients with AFCA as compared with patients with medical therapy (3.2±13.6 versus 0.7±16.8 mL/min/1.73 m^2; $P<0.001$; Figure 2B). Among the overall 2284 patients, a young age (adjusted odds ratio [OR], 0.98 [0.97–0.99]; $P<0.001$; Table 2) and AF catheter ablation (adjusted OR, 2.02 [1.67–2.46]; $P<0.001$; Table 2) were independently associated with an improved renal function ($\Delta eGFR_{5\ yr}$, >0 mL/min/1.73 m^2) after the 5-year follow-up after when adjusting for preexisting hypertension and angiotensin-converting enzyme inhibitor/angiotensin type II receptor blocker use. We tested the different thresholds of $\Delta eGFR_{5\ yr}$ based on previous studies,[15,20–22] and found that AFCA was a consistent variable of long-term improvement in renal function (Tables S1 through S3).

Patient Characteristics With a Renal Function Improvement After AFCA

Table 3 summarizes the comparison of baseline characteristics, including echocardiographic parameters and clinical rhythm outcome of 571 patients according to improvement in renal function ($\Delta eGFR_{5\ yr}$, >0 mL/min/1.73 m^2). Patients

Table 1. Comparison of the Baseline Characteristics and eGFR in AF Patients With AFCA or Medical Therapy

	Overall (n=2284)	AFCA (n=571)	Medical therapy (n=1713)	*P* Value	ASMD
Age, y	59±10	59±10	59±11.0	0.895	0.006
Male	1667 (73%)	413 (72.3%)	1254 (73.2%)	0.683	0.020
Body mass index	24.8±3.0	24.9±2.8	24.8±3.0	0.312	0.046
CHA_2DS_2VASc score	1.7±1.5	1.8±1.5	1.7±1.6	0.546	0.029
CHF	110 (4.8%)	30 (5.3%)	80 (4.7%)	0.573	0.027
Hypertension	1163 (50.9%)	290 (50.8%)	873 (51%)	0.942	0.004
Diabetes mellitus	394 (17.3%)	99 (17.3%)	295 (17.2%)	0.949	0.003
Stroke/TIA	263 (11.5%)	67 (11.7%)	196 (11.4%)	0.850	0.009
Vascular disease	336 (14.7%)	92 (16.1%)	244 (14.2%)	0.275	0.052
ACEi/ARB use	862 (37.8%)	206 (36.1%)	656 (38.3%)	0.358	0.046
Beta-blocker use	676 (29.6%)	160 (28.1%)	516 (30.1%)	0.353	0.046
Statin use	653 (28.6%)	160 (28.1%)	493 (28.8%)	0.745	0.017
Baseline eGFR	81.7±16.9	81.4±18.5	81.8±16.3	0.685	0.02

The patients under medical therapy were included in this study after propensity-score matching for the age, sex, body mass index, CHF, hypertension, diabetes mellitus, stroke/TIA, vascular disease, CHA_2DS_2VASc score, baseline eGFR, ACEi/ARB use, beta-blocker use, and statin use. ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AFCA, AF catheter ablation; ARB, angiotensin type II receptor blocker; ASMD, absolute standardized mean differences; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack.

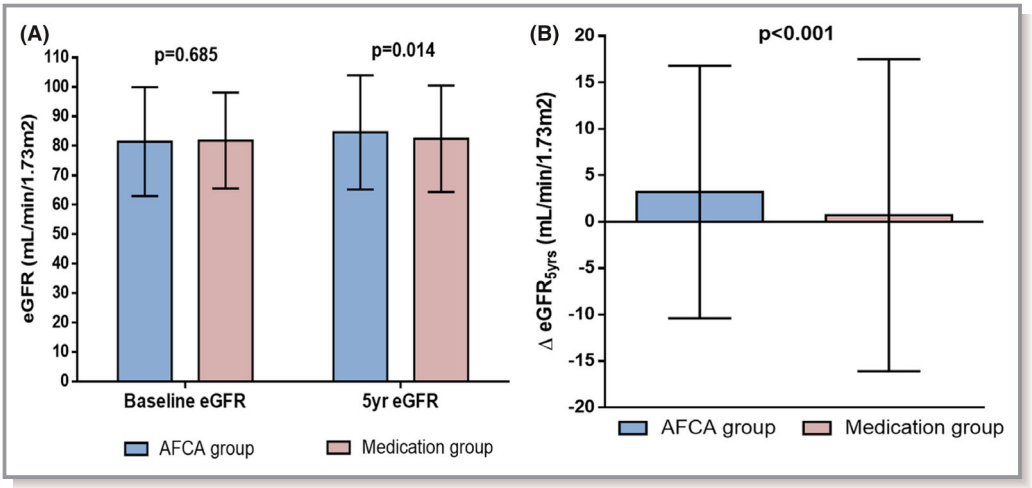

Figure 2. Mean estimated glomerular filtration rate (eGFR) measured at baseline and 5 years of follow-up between the AFCA and medication groups (**A**). Comparison of the increase in the eGFR from baseline to 5 years ($\triangle eGFR_{5\ yrs}$) between the AFCA and medication groups (**B**). AFCA indicates atrial fibrillation catheter ablation.

whose renal function improved during the 5-year follow-up were younger (*P*=0.008), had a lower CHA_2DS_2VASc score (*P*=0.015) and lower hypertension (*P*=0.003), took less angiotensin-converting enzyme inhibitors/angiotensin type II receptor blockers after the de novo ablation procedure (*P*=0.046), and were more likely to maintain sinus rhythm after the last ablation procedure (*P*=0.036) than those without renal function improvement.

Factors Associated With Improvement in Renal Function in Patients That Underwent AFCA

Among the overall 571 patients, 465 underwent a single ablation procedure and the others underwent multiple procedures during the follow-up period. In the patients with a single procedure alone, 64.1% (298 of 465) were free from an AF/AT recurrence, and in the overall patients with single or multiple

Table 2. Logistic Regression Analysis for Variables Predicting an Improved Renal Function ($\Delta eGFR_{5\ yr} > 0$) After 5 Years of Follow-up (n=2284)

	Univariate		Multivariate Model	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	0.980 (0.972–0.987)	<0.001*	0.980 (0.972–0.989)	<0.001*
Male	0.915 (0.761–1.101)	0.347		
Body mass index	1.015 (0.988–1.044)	0.279		
CHA_2DS_2VASc score	0.946 (0.897–0.999)	0.044*		
CHF	0.746 (0.505–1.102)	0.141		
Hypertension	0.840 (0.712–0.990)	0.037*	1.005 (0.826–1.222)	0.961
Diabetes mellitus	0.888 (0.714–1.105)	0.288		
Stroke/TIA	0.914 (0.706–1.183)	0.494		
Vascular disease	1.037 (0.822–1.308)	0.759		
ACEi/ARB use	0.801 (0.675–0.949)	0.010*	0.871 (0.715–1.060)	0.169
BB use	0.855 (0.714–1.024)	0.089		
Statin use	0.985 (0.821–1.181)	0.870		
AFCA	2.021 (1.666–2.450)	<0.001*	2.023 (1.666–2.457)	<0.001*

The CHA_2DS_2VASC score was not included in multivariate model in Table 2 because the age and hypertension variables had already been considered to calculate the CHA_2DS_2VASc score. ACEi indicates angiotensin-converting enzyme inhibitor; AFCA, atrial fibrillation catheter ablation; ARB, angiotensin type II receptor blocker; BB, beta blocker; CHF, congestive heart failure; OR, odds radio; TIA, transient ischemic attack.
*Statistical significance.

Table 3. Comparison of the Baseline Characteristics, Catheter Ablation, and Clinical Rhythm Outcomes According to an Improved Renal Function ($\Delta eGFR_{5\ yr}$ >0) Among the Overall Patients With AFCA (n=571)

	Overall Patients With AFCA (n=571)	Improved Renal Function (n=342)	Nonimproved Renal Function (n=229)	*P* Value
Age, y	59±10	58±10	60±10	0.008*
Male	413 (72.3%)	245 (71.6%)	168 (73.4%)	0.652
PAF at procedure	380 (66.5%)	231 (67.5%)	149 (65.1%)	0.538
Body mass index	24.9±2.8	24.9±2.9	24.9±2.8	0.850
Body surface area	1.80±0.17	1.81±0.18	1.80±0.17	0.445
CHA_2DS_2VASc score	1.8±1.5	1.7±1.5	2.0±1.5	0.015*
Congestive heart failure	30 (5.3%)	13 (3.8%)	17 (7.4%)	0.057
Hypertension	290 (50.8%)	156 (45.6%)	134 (58.5%)	0.003*
Diabetes mellitus	99 (17.3%)	56 (16.4%)	43 (18.8%)	0.457
Stroke/TIA	67 (11.7%)	38 (11.1%)	29 (12.7%)	0.572
Vascular disease	92 (16.1%)	55 (16.1%)	37 (16.2%)	0.981
LA dimension, mm	41.9±6.1	41.9±6.1	41.9±6.1	0.911
LVEF, %	63.4±8.0	63.3±7.6	63.5±8.7	0.785
E/Em	10.6±5.0	10.6±5.3	10.6±4.5	0.999
Postablation ACEi/ARB use	206 (36.1%)	112 (32.8%)	94 (41.0%)	0.046*
Postablation BB use	160 (28.1%)	89 (26.1%)	71 (31%)	0.201
Postablation Statin use	160 (28.1%)	96 (28.2%)	64 (27.9%)	0.957
Postablation AAD use	128 (22.4%)	68 (19.9%)	60 (26.2%)	0.076
Advanced CKD at baseline	67 (11.7%)	33 (9.6%)	34 (14.8%)	0.059
Repeat ablations	106 (18.6%)	70 (20.5%)	36 (15.7%)	0.153
Freedom from AF/AT recurrence after last AFCA	366 (64.1%)	231 (67.5%)	135 (59%)	0.036*

$\Delta eGFR_{5\ yr}$ indicates the increase in the eGFR from baseline to 5 years after the AF ablation; AAD, antiarrhythmic drugs; ACEi, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; ARB, angiotensin type II receptor blocker; AT, atrial tachycardia; BB, beta blocker; CKD, chronic kidney disease; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early diastolic mitral annular velocity (Em); eGFR, estimated glomerular filtration rate; LA, left atrium; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; TIA, transient ischemic attack.
*Statistical significance.

procedures, 64.1% (366/571) were free from an AF/AT recurrence after the last ablation procedure during the 5-year follow-up period. Mean follow-up duration after the last ablation session in the 571 overall patients was 42.4±21.3 months, and in the 106 patients who underwent multiple procedures was 27.8±18.0 months. The 5-year follow-up eGFR was significantly higher than baseline eGFR in the patients without an AF/AT recurrence in both the overall ablation group (82.1±17.8–86.2±18.8 mL/min/1.73 m^2; $P<0.001$; Figure 3A) and single-procedure group (81.4±17.9–85.2±19.4 mL/min/1.73 m^2; $P<0.001$; Figure 3D). However, there was no significant improvement in 5-year follow-up eGFR in patients with an AF/AT recurrence (Figure 3B and 3E). Degree of eGFR increase ($\Delta eGFR_{5\ yrs}$) was significantly greater in patients who remained in sinus rhythm than in those with an AF/AT recurrence after the last ablation procedure (4.1±13.6 versus 1.5±13.4 mL/min/1.73 m^2; $P=0.029$; Figure 3C). After adjusting for the CHA_2DS_2VASc score and postablation angiotensin-converting enzyme inhibitor/angiotensin type II receptor blocker use, a multivariate logistic regression analysis demonstrated that freedom from an AF/AT recurrence after the last ablation procedure was independently associated with an improvement in renal function (adjusted OR, 1.44 [1.01–2.04]; $P=0.043$; Table 4).

Which Patients Exhibit a Significant Improvement in Renal Function After AF Ablation?

We performed subgroup analyses to assess whether maintaining sinus rhythm after the last ablation procedure in some groups of patients helped improve 5-year follow-up eGFR. The analyses showed that the beneficial effect of maintaining sinus rhythm proved to be more prominent in patients with a

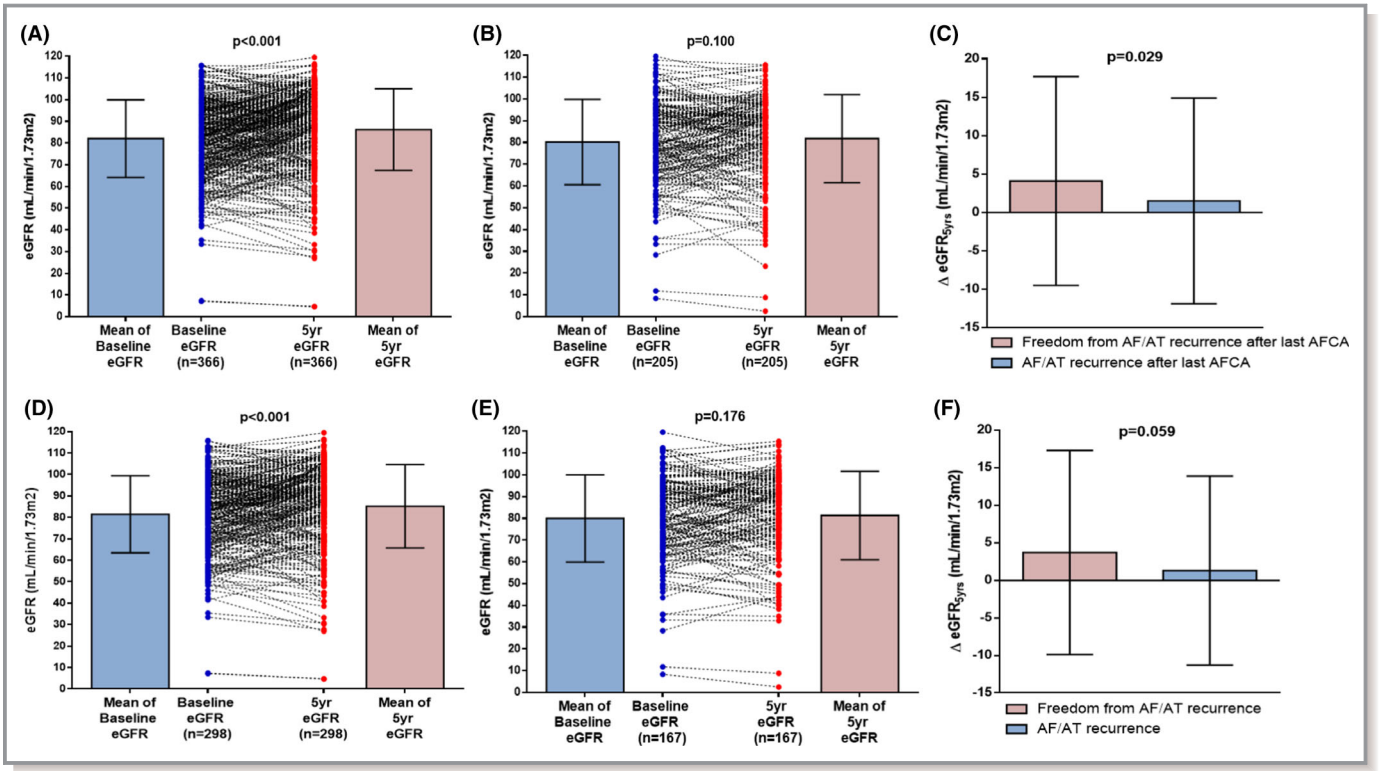

Figure 3. Scatter plot and mean changes in the estimated glomerular filtration rate (eGFR) from baseline to 5 years after AF ablation in the overall patients without an AF/AT recurrence (**A**) and those with an AF/AT recurrence (**B**), and in the single procedure alone group without an AF/AT recurrence (**D**) and those with an AF/AT recurrence (**E**). Comparison of the increase in the eGFR from baseline to 5 years ($\triangle eGFR_{5\ yrs}$) according to AF/AT recurrence after the AF ablation among the patients with repeat procedures (**C**) and a single procedure alone (**F**). ACEi indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; AFCA, AF catheter ablation; AT, atrial tachycardia.

CHA_2DS_2VASc score <2, left atrial diameter <45 mm, or left ventricular ejection fraction ≥50% and without preexisting comorbidities, including hypertension, diabetes mellitus, vascular disease, or advanced CKD (eGFR <60 mL/min/1.73 m^2; Figure 4). In particular, the positive effect of rhythm control on renal function improvement was more pronounced in patients without diabetes mellitus than in those with diabetes mellitus (*P* for interaction=0.012; Figure 4).

Baseline Renal Function and Long-Term Rhythm Outcome After AF Ablation

We compared advanced CKD (CKD stage ≥3; eGFR <60 mL/min/1.73 m^2) and early CKD (CKD stages 1 and 2; Table 5). Age, proportion with persistent AF at the de novo procedure, CHA_2DS_2VASc score, and proportion with a comorbid disease, including hypertension, diabetes mellitus, and vascular disease, and LA dimension, were significantly greater in AF patients with advanced CKD than in those with early CKD (Table 5). After adjusting for AF type during the de novo procedure, congestive heart failure, hypertension, diabetes mellitus, and a previous history of vascular disease, old age (adjusted OR, 1.11 [1.07–1.15]; *P*<0.001) and baseline LA dimension (adjusted OR, 1.05 [1.00–1.11]; *P*=0.046) were independently associated with baseline advanced CKD (Table S4). However, baseline CKD stage did not affect rhythm outcome of the AF catheter ablation after a single procedure (log rank, *P*=0.904) or after multiple procedures (log rank, *P*=0.381; Figure S1).

Discussion

Major Findings

In this study, we sought to determine how AF ablation contributed to long-term renal function as compared with medical therapy alone by comparing an AF ablation cohort database and an NHIS database after retrospective propensity-score matching. AF catheter ablation, but not medical therapy, significantly improved 5-year follow-up eGFR, and this improvement in long-term renal function was more significant in patients who remained in sinus rhythm after the last AF ablation session and in those without preexisting diabetes mellitus. We also found that preexisting CKD was associated with degree of atrial structural remodeling before the catheter ablation, but did not affect the rhythm outcome of the AF catheter ablation.

Table 4. Logistic Regression Analysis of the Variables Predicting an Improved Renal Function ($\Delta eGFR_{5\ yr} > 0$) After 5 Years of Follow-up Among the Overall Patients With AFCA (n=571)

	Univariate		Multivariate Model 1		Multivariate Model 2	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	0.977 (0.961–0.994)	0.008*	0.984 (0.966–1.001)	0.066		
Male	0.917 (0.630–1.335)	0.652				
PAF at procedure	1.117 (0.785–1.591)	0.539				
Body mass index	1.006 (0.948–1.067)	0.850				
Body surface area	1.462 (0.553–3.862)	0.444				
CHA_2DS_2VASc score	0.873 (0.781–0.975)	0.016*			0.898 (0.796–1.015)	0.084
Congestive heart failure	0.493 (0.235–1.035)	0.062				
Hypertension	0.595 (0.424–0.834)	0.003*	0.665 (0.421–1.050)	0.080		
Diabetes mellitus	0.847 (0.546–1.313)	0.458				
Stroke/TIA	0.862 (0.515–1.443)	0.572				
Vascular disease	0.994 (0.631–1.567)	0.981				
LA dimension	0.998 (0.971–1.026)	0.910				
LVEF	0.997 (0.976–1.018)	0.784				
E/Em	1.000 (0.966–1.035)	0.999				
Postablation ACEi/ARB use	0.702 (0.496–0.994)	0.046*	0.991 (0.626–1.569)	0.970	0.817 (0.558–1.196)	0.298
Postablation BB use	0.786 (0.543–1.138)	0.202				
Postablation stain use	1.010 (0.696–1.467)	0.957				
Postablation AAD use	0.699 (0.470–1.039)	0.077				
Advanced CKD at baseline	0.613 (0.367–1.021)	0.060				
Repeat ablations	1.380 (0.887–2.147)	0.154				
Freedom from AF/AT recurrence after last AFCA	1.449 (1.024–2.051)	0.036*	1.408 (0.990–2.002)	0.057	1.436 (1.012–2.037)	0.043*

$\Delta eGFR_{5\ yr}$ indicates the increase in the eGFR from baseline to 5 years after AF ablation; AAD, antiarrhythmic drugs; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; ARB, angiotensin type II receptor blocker; AT, atrial tachycardia; BB, beta blocker; CKD, chronic kidney disease; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early diastolic mitral annular velocity (Em); LA, left atrium; LVEF, left ventricular ejection fraction; OR, odds radio; PAF, paroxysmal atrial fibrillation; TIA, transient ischemic attack.
*Statistical significance.

AF and Renal Function

AF and CKD are both progressive degenerative diseases, and their prevalence increases with age. AF has been reported in ≈7% to 18% of CKD patients, and 12% to 25% of elderly individuals over 70 years of age with CKD have AF, which is 2 to 3 times that of the general population.[5,23,24] In contrast, CKD is also associated with 10% to 15% of AF patients.[25] Deterioration of renal function serves as an independent risk factor that increases AF prevalence, even in the early stages of CKD.[26] It may be because of the mechanistic association between an impaired renal function and AF. Both AF and CKD have several common pathophysiologies, including neurohormonal activation of the renin-angiotensin-aldosterone system,[27–30] inflammatory factors,[31,32] and oxidative stress.[33–35] Therefore, AF and renal dysfunction might adversely affect each other over time. In addition, CKD is important and clinically challenging in patients requiring anticoagulation, given that it simultaneously raises the thromboembolic and bleeding risks.[36] However, given that CKD has a very heterogeneous nature[37] and most major clinical trials related to AF management exclude advanced renal disease directly or indirectly,[38] it is hard to define a comprehensive treatment policy for AF patients with CKD.

Renal Function and AF Catheter Ablation

The irregular rhythm of AF reduces myocardial function[39] and microvascular function,[40] and a loss of atrial kick causes negative hemodynamic effects. Therefore, restoring sinus rhythm may improve renal function by changing the hemodynamics,[41–44] improving ventricular function,[16] raising mean heart rate,[17] and reducing inflammatory/oxidative

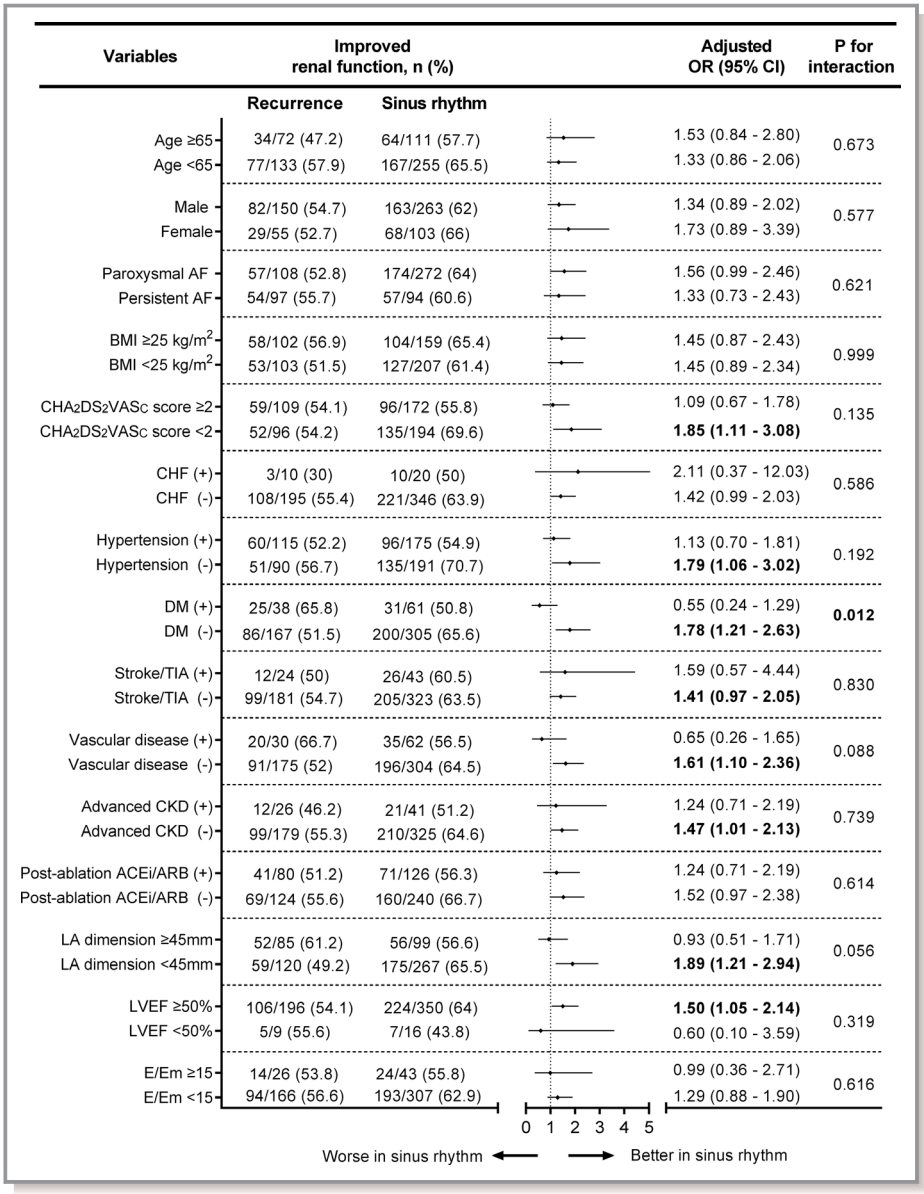

Figure 4. Efficacy of the freedom form AF/AT recurrence after the last AFCA in subgroup analyses. AF indicates atrial fibrillation; AFCA, AF catheter ablation; ARB, angiotensin type II receptor blocker; AT, atrial tachyarrhythmia; BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early diastolic mitral annular velocity (Em); LA, left atrium, LVEF, left ventricular ejection fraction; OR, odds ratio; TIA,transient ischemic attack.

reactions,[20,33,35,45] especially after catheter ablation. Although there have been multiple clinical studies that evaluated renal function after AF catheter ablation within 1 to 2 years of follow-up,[15,20–22,46] renal function is hard to determine because eGFR declines by 0.5 to 1 mL/min/1.73 m^2 per year in the general population and 1 to 2.5 mL/min/1.73 m^2 per year in patients with CKD.[47] The present study included a longer-term follow-up of over 5 years in a higher number of patients, so we were able to more accurately evaluate the small differences in eGFR changes than in previous studies. We also conducted a consistent rhythm-monitoring and follow-up protocol based on the guidelines over 5 years.[19] We found that aggressive rhythm control and a reduction in AF burden through repeat ablation sessions were associated with an improved renal function during the long-term follow-up period. However, such beneficial effects of strict rhythm control by AF ablation were not shown in patients with preexisting diabetes mellitus. It might be because diabetes mellitus is associated with LA

Table 5. Comparison of the Baseline Characteristics Among the Overall Patients With or Without Concomitant Advanced CKD

	Advanced CKD (n=67)	Early CKD (n=504)	*P* Value
Age, y	66.6±7.6	58.1±10.0	<0.001*
Male	50 (74.6%)	363 (72.0%)	0.655
PAF at procedure	37 (55.2%)	343 (68.1%)	0.036*
Body mass index	25.2±2.7	24.9±2.9	0.318
Body surface area	1.81±0.15	1.80±0.18	0.790
CHA_2DS_2VASc score	2.8±1.6	1.7±1.5	<0.001*
Congestive heart failure	7 (10.4%)	23 (4.6%)	0.071
Hypertension	50 (74.6%)	240 (47.6%)	<0.001*
Diabetes mellitus	22 (32.8%)	77 (15.3%)	<0.001*
Stroke/TIA	10 (14.9%)	57 (11.3%)	0.388
Vascular disease	17 (25.4%)	75 (14.9%)	0.028*
LA dimension, mm	44.1±5.6	41.6±6.1	0.001*
LVEF, %	62.4±11.0	63.6±7.6	0.407
E/Em	11.6±4.4	10.5±5.1	0.099

CKD indicates chronic kidney disease; E/Em, the ratio of the early diastolic mitral inflow velocity (E) to the early diastolic mitral annular velocity (Em); LA, left atrium; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; TIA, transient ischemic attack.
*Statistical significance.

fibrosis and electroanatomical LA remodeling, which result in impairment of the LA reservoir and pump function.[48,49] Diabetes mellitus is also a well-known risk factor of CKD and progressive deterioration of renal function.[50] These adverse effects on the heart and kidneys of diabetes mellitus appear to have little effect on long-term renal function improvement, despite active AF rhythm control by AFCA.

Limitations

This study had several limitations. It was an observational cohort study from a single center, so highly selected patients referred for AF were included in this study. Because we considered that there was an improvement in renal function in patients whose $\Delta eGFR_{5\ yrs}$ was above 0 mL/min/1.73 m^2, this study might not be able to represent an improvement in CKD stage. Because many of the patients who underwent AFCA did not have advanced CKD, this study might not be able to represent a broad spectrum of patients with an impaired renal function. We could not investigate the mechanism of the association between renal function improvement and maintenance of sinus rhythm by comparing the change in hemodynamics and inflammatory markers; however, it was not the main subject of this study.

Conclusions

AF catheter ablation significantly improved renal function during the 5-year follow-up. Reduction in AF burden, even with repeat ablation sessions, was independently associated with an improvement in renal function in patients without preexisting diabetes mellitus as well as in the overall patients. However, patients with preexisting diabetes mellitus had no beneficial improvement in renal function; however, sinus rhythm was maintained after repeat ablation sessions.

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Disclosures

None.

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Supplemental Material

Table S1. Logistic regression analysis for variables predicting an improved renal function ($\Delta eGFR_{5yr} \geq 1$) after 5-years of follow-up (n=2,284).

	Univariate		Multivariate Model	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	0.979 (0.972-0.987)	**<0.001**	0.980 (0.972-0.989)	**<0.001**
Male	0.899 (0.747-1.082)	0.261		
Body mass index	1.016 (0.988-1.044)	0.264		
CHA_2DS_2VASc score	0.952 (0.902-1.004)	0.070		
CHF	0.717 (0.484-1.063)	0.098		
Hypertension	0.846 (0.718-0.998)	**0.047**	1.008 (0.829-1.226)	0.938
Diabetes	0.897 (0.721-1.116)	0.329		
Stroke/TIA	0.955 (0.737-1.236)	0.725		
Vascular disease	1.041 (0.825-1.312)	0.737		
ACEi/ARB use	0.814 (0.686-0.965)	**0.018**	0.885 (0.727-1.078)	0.224
BB use	0.865 (0.722-1.037)	0.118		
Statin use	0.996 (0.830-1.195)	0.965		
AFCA	1.844 (1.522-2.233)	**<0.001**	1.845 (1.521-2.237)	**<0.001**

OR = odd radio, CI = confidence interval, CHF = congestive heart failure, TIA = transient ischemic attack, ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin type II receptor blocker, BB = beta blocker, AFCA = atrial fibrillation catheter ablation.

Table S2. Logistic regression analysis for variables predicting an improved renal

function ($\Delta eGFR_{5yr}$>5) after 5-years of follow-up (n=2,284).

	Univariate		Multivariate Model	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	0.979 (0.971-0.987)	**<0.001**	0.980 (0.927-0.989)	**<0.001**
Male	0.840 (0.697-1.012)	0.067		
Body mass index	1.011 (0.983-1.039)	0.464		
CHA_2DS_2VASc score	0.949 (0.898-1.002)	0.060		
CHF	0.750 (0.502-1.121)	0.161		
Hypertension	0.825 (0.698-0.974)	**0.024**	1.033 (0.846-1.261)	0.750
Diabetes	0.758 (0.605-0.949)	**0.016**	0.838 (0.663-1.060)	0.140
Stroke/TIA	1.040 (0.802-1.350)	0.767		
Vascular disease	0.976 (0.771-1.235)	0.839		
ACEi/ARB use	0.784 (0.659-0.932)	**0.006**	0.857 (0.702-1.046)	0.129
BB use	0.853 (0.710-1.026)	0.091		
Statin use	0.959 (0.797-1.154)	0.657		
AFCA	1.223 (1.010-1.481)	**0.039**	1.225 (1.010-1.486)	**0.039**

OR = odd radio, CI = confidence interval, CHF = congestive heart failure, TIA = transient ischemic attack, ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin type II receptor blocker, BB = beta blocker, AFCA = atrial fibrillation catheter ablation.

Table S3. Linear regression analysis for variables predicting a change in eGFR ($\Delta eGFR_{5yr}$) after 5-years of follow-up (n=2,284).

	Univariate		Multivariate Model	
	B (95% CI)	P-value	B (95% CI)	P-value
Age	-0.200 (-0.263 to -0.136)	**<0.001**	-0.173 (-0.240 to -0.105)	**<0.001**
Male	-1.398 (-2.886 to 0.090)	0.066		
Body mass index	0.239 (0.016 to 0.461)	**0.035**	0.256 (0.028 to 0.485)	**0.028**
CHA_2DS_2VASc score	-0.713 (-1.141 to -0.285)	**0.001**		
CHF	-0.402 (-3.490 to 2.687)	0.799		
Hypertension	-1.658 (-2.978 to -0.337)	**0.014**	0.568 (-1.017 to 2.153)	0.482
Diabetes	-2.394 (-4.141 to -0.647)	**0.007**	-1.576 (-3.368 to 0.216)	0.085
Stroke/TIA	-1.387 (-3.458 to 0.683)	0.189		
Vascular disease	-0.471 (-2.338 to 1.395)	0.621		
ACEi/ARB use	-2.214 (-3.576 to -0.852)	**0.001**	-1.614 (-3.172 to -0.056)	**0.042**
BB use	-2.060 (-3.506 to -0.613)	**0.005**	-1.723 (-3.199 to -0.246)	**0.022**
Statin use	-0.945 (-2.408 to 0.519)	0.206		
AFCA	2.553 (1.030 to 4.077)	**0.001**	2.439 (0.929 to 3.949)	**0.002**

CI = confidence interval, CHF = congestive heart failure, TIA = transient ischemic attack, ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin type II receptor blocker, BB = beta blocker, AFCA = atrial fibrillation catheter ablation

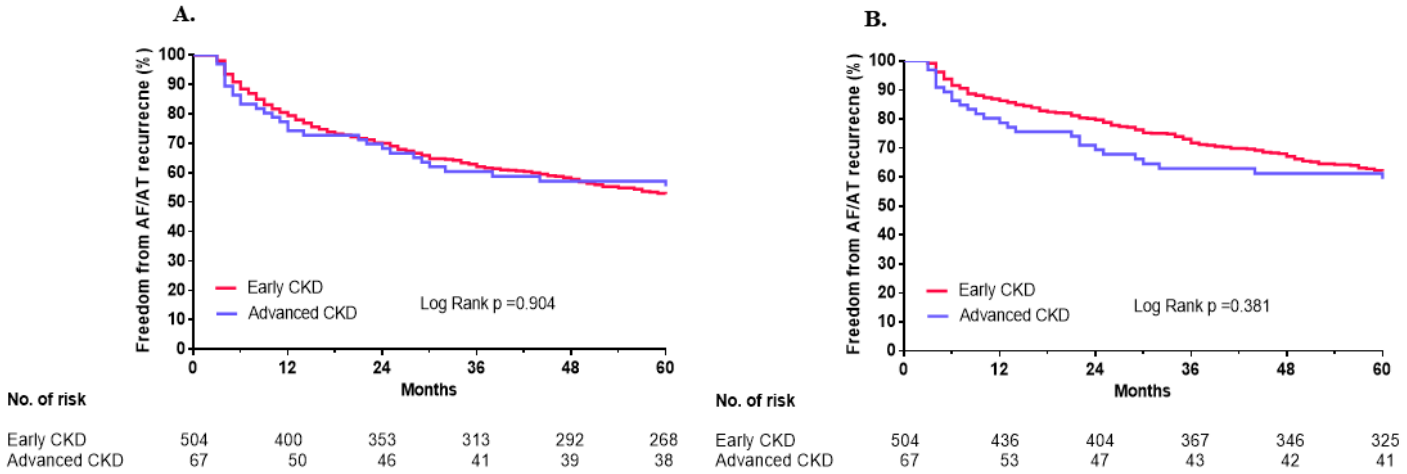
Table S4. Logistic regression analysis of the baseline risk factors predicting advanced CKD among the overall patients with AFCA (n=571).

	Univariate	Multivariate

	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.111 (1.074-1.149)	**<0.001**	1.105 (1.066-1.145)	**<0.001**
Male	1.142 (0.637-2.048)	0.655		
PAF at procedure	0.579 (0.345-0.970)	**0.038**	0.784 (0.427-1.440)	0.433
Body mass index	1.046 (0.958-1.142)	0.318		
Body surface area	1.222 (0.279-5.355)	0.790		
CHA_2DS_2VASc score	1.535 (1.308-1.800)	**<0.001**		
Congestive heart failure	2.440 (1.004-5.927)	**0.049**	2.057 (0.756-5.593)	0.158
Hypertension	3.235 (1.816-5.763)	**<0.001**	1.858 (0.987-3.497)	0.055
Diabetes	2.711 (1.541-4.769)	**0.001**	1.542 (0.817-2.910)	0.181
Stroke/TIA	1.376 (0.665-2.844)	0.389		
Vascular disease	1.945 (1.065-3.552)	**0.030**	0.952 (0.489-1.852)	0.885
LA dimension	1.070 (1.026-1.115)	**0.002**	1.054 (1.001-1.110)	**0.046**
LVEF	0.983 (0.954-1.013)	0.268		
E/Em	1.036 (0.992-1.081)	0.110		

CKD = chronic kidney disease, AFCA = atrial fibrillation catheter ablation, PAF = paroxysmal atrial fibrillation, TIA = transient ischemic attack, LA = left atrium, LVEF = left ventricular ejection fraction, E/Em = the ratio of the early diastolic mitral inflow velocity (E) to the early diastolic mitral annular velocity (Em)

Figure S1. Kaplan-Meier analysis of an AF/AT recurrence after a single AF ablation (A) and the last AF ablation (B) according to baseline advanced CKD.



AF = atrial fibrillation, AT = atrial tachycardia, CKD = chronic kidney disease.