Journal of the American Heart Association

ORIGINAL RESEARCH

Catheter Ablation Improves Mortality and Other Outcomes in Real-World Patients With Atrial Fibrillation

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BACKGROUND: It is still controversial whether catheter ablation for atrial fibrillation (AF) improves survival and other outcomes in patients with AF. This study evaluated whether ablation reduces death and other events in nationwide real-world Asian patients with AF.

METHODS AND RESULTS: From the Korean National Health Insurance Service database, 194 928 adult patients (aged ≥18 years) with newly diagnosed AF were treated with ablation or medical therapy (antiarrhythmic or rate control drugs) between January 1, 2005, and December 1, 2015. Among these patients, this study included 9185 with ablation and 18 770 with medical therapy. The time at risk was counted from the first medical therapy, and ablation was analyzed as a time-varying covariate. Inverse probability of treatment weighting was used to correct for differences between the groups. After weighting, the 2 cohorts had similar background characteristics. During a median (25th, 75th percentiles) follow-up of 43 (19, 81) months, ablation of AF was associated with lower incidence and risk of composite outcome, including death, heart failure admission, and stroke/systemic embolism (2.5 and 6.4 per 100 person-years, respectively; hazard ratio [HR], 0.47; 95% CI, 0.43–0.52; $P<0.001$), all-cause death (1.0 and 3.6 per 100 person-years; HR, 0.41; 95% CI, 0.36–0.47; $P<0.001$), heart failure admission (0.7 and 1.9 per 100 person-years; HR, 0.43; 95% CI, 0.37–0.50), and ischemic stroke/systemic embolism (1.1 and 2.8 per 100 person-years; HR, 0.39; 95% CI, 0.34–0.44) than medical therapy.

CONCLUSIONS: Ablation may be associated with lower risk of death, heart failure admission, and ischemic stroke/systemic embolism in real-world Asian patients with AF.

Key Words: atrial fibrillation ■ catheter ablation ■ heart failure ■ mortality

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population.[1–4] AF has enormous socioeconomic implications because it increases the risk of mortality and morbidity resulting from stroke, congestive heart failure, dementia, and impaired quality of life.[1–3,5,6] However, it remains uncertain how much this risk can be mitigated by restoring sinus rhythm.

Catheter ablation for AF is superior to antiarrhythmic drugs in decreasing AF recurrences, prolonging the time in sinus rhythm, and improving the quality of life of patients.[7–10] However, its effects on other clinical outcomes are not well established. Some nonrandomized follow-up studies have reported favorable outcomes, such as the reduction of ischemic stroke and death, in ablated patients.[11–13] In a trial of ablation versus medical therapy in symptomatic patients with AF and heart failure, successful ablation may extend survival and reduce heart failure admission.[14] In contrast, in the recently performed

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015740

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For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In a nationwide real-world study of Korean patients with atrial fibrillation, ablation of atrial fibrillation was associated with a 53% lower risk of the composite outcome, including death, heart failure admission, and stroke/systemic embolism, compared with medical therapy.
- This trend was consistently observed in all subgroups regardless of sex, age, heart failure, hypertension, stroke, atrial fibrillation recurrence, and anticoagulation.

What Are the Clinical Implications?

- This study provides additional evidence of the potential role for ablation in real-world Asian patients with atrial fibrillation.
- The benefit for ablation might be related to the lower risk of heart failure and ischemic stroke/systemic embolism after ablation.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
CABANA	Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation
CASTLE AF	Catheter Ablation for Atrial Fibrillation With Heart Failure
CHA_2DS_2-VASc score	congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, age 65 to 74, female
HAS-BLED	hypertension, >65 years old, stroke history, bleeding history or predisposition, liable international normalized ratio, ethanol or drug abuse, drug predisposing to bleeding
HR	hazard ratio
NHIS	National Health Insurance Service
SE	systemic embolism

CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial,[15] catheter ablation for AF did not significantly reduce the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest, compared with medical therapy in general AF population. However, the estimated treatment effect of catheter ablation in this study was affected by the lower-than-expected event rates and treatment crossovers. In many studies, catheter ablation for AF consistently improved left ventricular ejection fraction and complication rates, including heart failure readmissions in heart failure patients with AF.[14,16–18] Therefore, the effects of AF ablation on the long-term incidence of mortality and other outcomes remain unknown.

The objective of this study was to compare the incidences of death, heart failure admission, and ischemic stroke/systemic embolism (SE) in real-world patients with AF. Moreover, we used "falsification analysis" to strengthen the results.

METHODS

All data and materials have been made publicly available at the National Health Insurance Service (NHIS) of Korea. The data can be accessed on the National Health Insurance Data Sharing Service homepage of the NHIS (http://nhiss.nhis.or.kr). Applications to use the NHIS data will be reviewed by the inquiry committee of research support and, once approved, raw data will be provided to the authorized researcher with a fee at several permitted sites. This study was a retrospective cohort analysis using the national health claims database (NHIS-2016-4-009) established by the NHIS of Korea. The NHIS is the single insurer managed by the Korean government. Most Korean citizens (97.1%) are mandatory subscribers to the NHIS, and the remaining 3% of the population are under the Medical Aid program. As the NHIS database contains the information of Medical Aid users, it is based on the entire Korean population.[1–3,6,19,20] This study was approved by the institutional review board of the Yonsei University Health System (4-2016-0179), and the requirement for informed consent was waived.

Study Population

From the Korean NHIS database covering a population 51.5 million inhabitants, 834 735 adult patients (aged ≥18 years) were newly diagnosed with AF from January 1, 2006, to December 31, 2015. Among these patients, the study population included those who were treated with ablation or medical therapy (antiarrhythmic drugs or rate control drugs). AF was diagnosed using the *International Classification of*

Diseases, Tenth Revision (*ICD-10*), code I48. To ensure diagnostic accuracy, AF was defined as present only when it was a discharge diagnosis or confirmed at least twice in the outpatient department. The AF diagnosis has previously been validated in the NHIS database with a positive predictive value of 94.1%.[1–3,6,19,20]

For both the ablated and the medical therapy patients, the time at risk was counted from index date of the first medical therapy. In patients who underwent AF ablation without medical therapy, the time at risk was counted from the index date of the first ablative procedure. Effect of ablation was analyzed as a time-varying exposure. The exclusion criteria for both groups were valvular AF, arrhythmia surgery (maze and similar procedures), implanted cardiac electric device, or heart failure admission. Among medical therapy patients, patients who had oral anticoagulants <30 days during the same period were additionally excluded. After exclusions, 9185 ablated and 18 770 medical therapy patients remained for the analysis (Figure 1).

Covariates

Information on comorbidity conditions was obtained from inpatient and outpatient hospital diagnoses. Baseline comorbidities were defined using medical claims and prescription medications before the index date. The patients were considered to have comorbidities when the condition was a discharge diagnosis or was confirmed at least twice in an outpatient setting, similar to previous studies using NHIS data (Table S1).[1–3,6,19,20] Baseline economic status was determined on the basis of the relative economic levels, categorized into 10 levels according to their health insurance premiums in the index year. Prescription medication use was verified by identifying NHIS database claims within 90 days before the index date.

Clinical Outcome Events and Assessments

The primary clinical outcome was a composite end point of all-cause death, heart failure, and ischemic stroke/SE. The secondary outcomes were each of these outcomes considered separately. Patients were followed up until the end of the study period (December 31, 2016) or death. Data on vital status and date of death were confirmed from the National Population Registry of the Korea National Statistical Office with the use of a unique personal identification number, in which central registration of death was conducted on the basis of death certificates.[1–3,6,19,20] This approach provides a complete event ascertainment, because the NHIS and National Statistical Office are national organizations covering all Korean subjects.

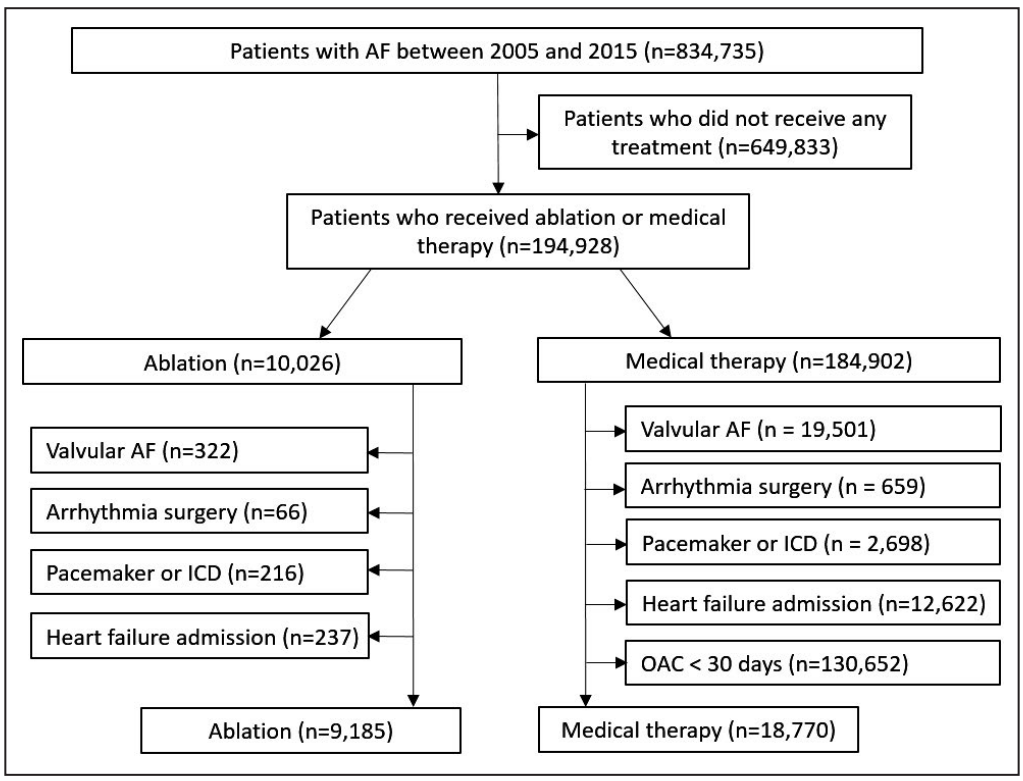

Figure 1. Flowchart of the enrollment and analysis of the study population.
AF indicates atrial fibrillation; ICD, implantable cardioverter-defibrillator; and OAC, oral anticoagulant.

Ischemic stroke was defined from any discharge diagnoses (*ICD-10* codes I63 and I64) with concomitant brain imaging studies. The accuracy of the diagnosis of an ischemic stroke in the NHIS claim data was previously validated.[1–3,6,19,20] The definitions of clinical outcomes are presented in Table S1. The same patient could have >1 study outcome during the study duration, but only the first event of each outcome was considered in the study.

Statistical Analysis

Baseline characteristics of participants with and without incident AF were compared using Student *t* test and Pearson's χ^2 test. Propensity score overlap weighting was used to account for the differences in baseline characteristics between patients who underwent ablation and those who were treated with medical therapy alone. A propensity score, the probability of undergoing ablation, was estimated using logistic regression based on sociodemographics, medical history, concurrent medication use, and AF duration (variables in Table 1). The overlap weight was calculated as 1-propensity score for the ablated patients, and the propensity score for the drug-treated patients. This weight is used to calculate the average treatment effect for the overlap population. The balance between the treatment populations was evaluated by standardized differences of all baseline covariates using a threshold of 0.1 to indicate imbalance.

Incidence rates of events were calculated by dividing the number of events by person-times at risk, with the 95% CIs estimated by exact Poisson distributions. We compared the incidences of death using the weighted log-rank test and plotted weighted failure curves. Cox proportional hazards regressions were used to compare those patients treated with ablation and medical therapy. The Fine and Gray method was used to consider death as a competing risk when assessing nonfatal outcomes (ie, heart failure and stroke/SE when considered separately).[21] The proportional hazards assumption was tested on the basis of Schoenfeld residuals.[22]

Sensitivity Analyses

First, we performed subgroup analyses for the primary composite end point and all-cause death stratified by sex, age, heart failure, hypertension, diabetes mellitus, stroke/transient ischemic attack, vascular disease, CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, aged 65 to 74 years, female), cardioversion or repeated ablation, and anticoagulation. Second, 1:1 propensity score matching was used instead of propensity score weighting. Third, we conducted a stratified analysis based on whether the drug-treated patients were treated with antiarrhythmic or with rate control drugs only. Fourth, we conducted an analysis between ablated patients and subjects without history of AF.

We used "falsification analysis" to determine whether ablation was associated with lower rates of urinary tract infections, varicella zoster, and fall accidents that should not be lower with ablation and would indicate that the population receiving ablation was different in ways that would result in reduced mortality or stroke that had nothing to do with ablation.[23]

A 2-sided $P<0.05$ was considered significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.3.2 (The R Foundation; http://www.R-project.org).

RESULTS

Differences Between Ablated and the Medical Therapy Patients

Compared with medical therapy patients, ablated patients were more often men, were healthy, and had an income in the highest quartile (Table 1). Ablated patients were on average 10 years younger and had less concomitant diseases. After inverse probability of treatment weighting, all baseline characteristics were similar between the 2 groups (Table 1). In multivariable analysis, the factors independently associated with the likelihood of undergoing catheter ablation were younger age, income in the highest quartile, and comorbidities, including heart failure, hypertension, and diabetes mellitus (Table S2).

Ablated patients were younger, were healthy, and had fewer comorbidities than antiarrhythmic drug-treated (Table S3) and rate control patients (Table S4). All baseline characteristics were similar between IPT weighted 2 groups.

Improved Primary Outcome in Ablated Patients

During a median (25^{th}, 75^{th} percentiles) follow-up of 43 (19, 81) months, 950 and 6818 cases had weighted primary outcome in the ablated and medical therapy group with weighted annualized rates of 2.5 and 6.4 per 100 person-years, respectively ($P<0.001$) (Table 2). The cumulative incidence of primary outcome was significantly lower in the ablated group compared with the medical group ($P<0.001$; Figure 2A). Compared with patients with medical therapy and after full adjustment of clinical variables, the risk of primary outcome was reduced by 53% in patients with ablations (hazard ratio

Table 1. Baseline Characteristics Before and After Propensity Score Weighting

Characteristic	Ablation (N=9185)	Medical Therapy (N=18 770)	SMD, %	Ablation (N=9185)	Medical Therapy (N=18 770)	SMD, %
Demographic						
Age, y	57 (50, 65)	67 (59, 74)	83.6	61 (53, 68)	62 (53, 70)	8.0
Men	76.3	66.6	21.4	72.9	71.4	3.4
High-income status	54.9	45.5	19.0	50.7	49.6	2.3
AF duration, mo	24.4 (7.1, 56.7)	16.8 (2.5, 37.6)	25.8	14.8 (4.3, 42.3)	12.8 (1.1, 37.4)	3.5
Risk scores						
CHA_2DS_2-VASc score	2.0 (1.0, 3.0)	4.0 (2.0, 5.0)	76.7	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	7.6
mHAS-BLED score*	2.0 (2.0, 3.0)	3.0 (2.0, 4.0)	42.0	1.4 (0.9, 2.7)	2.5 (1.5, 3.4)	5.6
Charlson comorbidity index	3.0 (2.0, 5.0)	4.0 (2.0, 6.0)	43.4	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	4.2
Hospital frailty risk score	1.1 (0.0, 3.4)	1.8 (0.0, 6.3)	57.6	1.3 (0.0, 4.0)	0.8 (0.0, 4.2)	8.6
Comorbidities						
Heart failure	32.0	46.8	30.6	34.5	36.4	3.9
Hypertension	77.0	86.8	25.4	77.4	77.4	<0.1
Diabetes mellitus	13.8	26.4	31.8	19.1	19.7	1.6
Dyslipidemia	81.2	77.4	9.5	77.4	75.8	3.9
Ischemic stroke	15.7	34.4	44.3	21.7	24.0	5.5
TIA	7.8	9.6	6.3	8.3	8.2	0.2
Hemorrhagic stroke	1.3	3.1	12.3	1.9	2.1	1.9
Myocardial infarction	10.4	14.5	12.6	11.3	11.7	1.1
Peripheral arterial disease	10.5	15.3	14.2	11.9	12.3	1.1
Chronic kidney disease	4.0	6.8	12.4	5.3	5.2	0.4
End-stage renal disease	0.5	1.2	7.7	0.9	0.9	0.1
Proteinuria	4.9	6.0	4.7	5.3	5.3	0.2
Hyperthyroidism	18.6	14.4	11.1	15.8	15.2	1.6
Hypothyroidism	15.5	12.2	9.4	12.9	12.4	1.5
Malignancy	18.4	21.3	7.3	18.2	18.9	1.7
COPD	19.6	29.2	22.6	22.2	23.5	3.1
Liver disease	43.5	39.5	8.0	40.6	40.0	1.3
Hypertrophic cardiomyopathy	1.9	3.2	8.7	2.6	2.6	0.4
History of bleeding	28.8	30.7	4.2	28.4	28.3	0.2
Osteoporosis	15.5	25.2	24.4	19.1	19.9	2.0
Sleep apnea	2.0	0.7	11.4	1.2	1.0	1.7
Medication (treatment)						
OAC	59.1	71.5	26.3	52.8	54.1	2.6
Antiplatelet agents	73.4	64.4	19.6	63.4	62.0	2.8
ACE inhibitor/ARB	47.4	61.0	27.6	50.8	50.9	<0.1
Diuretics	33.3	56.1	47.0	41.3	42.9	3.3
K-sparing diuretics	6.6	16.4	30.9	9.8	10.8	3.5
Statin	38.6	40.2	3.4	37.1	36.2	1.8

Values are presented as median (quartile 1, quartile 3 [25th, 75th percentiles]) or percentage. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, female; COPD, chronic obstructive pulmonary disease; mHAS-BLED, modified HAS BLED (hypertension, >65 years old, stroke history, bleeding history or predisposition, liable international normalized ratio, ethanol or drug abuse, drug predisposing to bleeding); OAC, oral anticoagulant; SMD, standardized mean difference; and TIA, transient ischemic attack.

*mHAS-BLED=hypertension, 1 point; >65 years old, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; liable international normalized ratio, not assessed; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point.

[HR], 0.47; 95% CI, 0.43–0.52; *P*<0.001) (Table 2). The risk of primary outcome was reduced in the ablated group compared with antiarrhythmic drug-treated (HR, 0.51; 95% CI, 0.46~0.56; *P*<0.001) and rate control groups (HR, 0.43; 95% CI, 0.40~0.48; *P*<0.001) (Table 2). Subgroup analyses showed that the risk of

Table 2. Risk of Clinical Outcomes in Ablated and Nonablated Patients with Inverse Probability of Treatment Weighting

Variable	No. of Events	Person-Years	Event Rate (100 Person-Years)	No. of Events	Person-Years	Event Rate (100 Person-Years)	Absolute Reduction in Event Rate (95% CI)	Adjusted Hazard Ratio (95% CI)*	*P* Value
	Medical Therapy (N=18 770)			Ablation (N=9185)					
Ablation vs medical therapy									
Composite†	6818	107 277	6.4	950	38 009	2.5	3.9 (3.6–4.1)	0.47 (0.43–0.52)	<0.001
All-cause death	4357	122 235	3.6	420	40 636	1.0	1.2 (1.0–1.4)	0.41 (0.36–0.47)	<0.001
Heart failure	2134	115 032	1.9	265	39 238	0.7	1.2 (1.0–1.3)	0.43 (0.37–0.50)	<0.001
Stroke/SE	3163	111 494	2.8	420	38 925	1.1	1.8 (1.6–1.9)	0.39 (0.34–0.44)	<0.001
	Antiarrhythmic drug (N=13 117)			Ablation (N=9422)					
Ablation vs antiarrhythmic drug									
Composite†	4344	81 266	5.3	937	39 507	2.4	3.0 (2.7–3.2)	0.51 (0.46–0.56)	<0.001
All-cause death	2413	90 544	2.7	412	42 119	1.0	1.7 (1.5–1.9)	0.49 (0.42–0.56)	<0.001
Heart failure	1346	86 196	1.6	258	40 747	0.6	0.9 (0.8–1.1)	0.47 (0.39–0.56)	<0.001
Stroke/SE	2100	83 797	2.5	418	40 393	1.0	1.5 (1.3–1.6)	0.42 (0.38–0.48)	<0.001
	Rate control only (N=7368)			Ablation (N=9422)					
Ablation vs rate control only									
Composite†	3511	54 295	6.5	923	40 039	2.3	4.2 (3.9–4.4)	0.43 (0.40–0.48)	<0.001
All-cause death	2223	61 974	3.6	407	42 644	1.0	2.7 (2.4–2.8)	0.40 (0.35–0.46)	<0.001
Heart failure	1073	58 495	1.8	251	41 299	0.6	1.2 (1.1–1.4)	0.43 (0.37–0.51)	<0.001
Stroke/SE	1710	56 268	3.0	417	40 897	1.0	2.0 (1.8–2.2)	0.34 (0.30–0.39)	<0.001

SE indicates systemic embolism.

*Adjusted for age, sex, income, atrial fibrillation duration, CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, age 65 to 74 years, female), modified HAS-BLED (hypertension, >65 years old, stroke history, bleeding history or predisposition, liable international normalized ratio, ethanol or drug abuse, drug predisposing to bleeding) score, hospital frailty risk score, Charlson comorbidity index, hypertension, diabetes mellitus, ischemic stroke/transient ischemic attack, myocardial infarction, peripheral arterial disease, hypertrophic cardiomyopathy, chronic kidney disease, end-stage renal disease, liver disease, malignancy, hyperthyroidism, hypothyroidism, venous thromboembolism, chronic obstructive pulmonary disease, intracranial bleeding, cardioversion, history of bleeding, baseline use of warfarin, non–vitamin K antagonist oral anticoagulant, aspirin, clopidogrel, β blocker, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, dihydropyridine/nondihydropyridine calcium channel blocker, class Ic and III antiarrhythmic drug, statin, diuretics, digoxin, and oral anticoagulant coverage rate of time at risk.

†The primary clinical outcome was a composite end point of all-cause death, heart failure, and ischemic stroke/SE.

primary outcome was reduced in most subgroups (Figure 3).

Reduced Mortality in Ablated Patients

The cumulative incidence of all-cause death was significantly lower in the ablated group compared with the medical group (*P*<0.001; Figure 2B). Ablation was related with lower incidence and 59% lower risk of all-cause death (1.0 and 3.6 per 100 person-years; HR, 0.41; 95% CI, 0.36~0.47; *P*<0.001) compared with the medical therapy. Subgroup analyses showed that the risk of all-cause death was reduced in most subgroups (Figure 4). The risk of all-cause death was reduced in the ablated group compared with antiarrhythmic drug-treated (HR, 0.49; 95% CI, 0.42~0.56) and rate control groups (HR, 0.40; 95% CI, 0.35~0.46) (Table 2).

Other factors associated with the increased risk of all-cause death included end-stage renal disease (HR, 2.94; 95% CI, 2.24–3.87; *P*<0.001), older age (per 10-year increase: HR, 1.89; 95% CI, 1.78–2.01; *P*<0.001), hypertrophic cardiomyopathy (HR, 1.34; 95% CI, 1.14–1.58; *P*<0.001), men (HR, 1.30; 95% CI, 1.10–1.53; *P*<0.001), higher CHA_2DS_2-VASc score (HR, 1.18; 95% CI, 1.10–1.25; *P*<0.001), higher Hospital Frailty Risk scores (per 1 increase: HR, 1.05; 95% CI, 1.05–1.06; *P*<0.001), and higher Charlson comorbidity indexes (per 1 increase: HR, 1.04; 95% CI, 1.02–1.06; *P*<0.001).

Heart Failure Admission and Stroke/SE

Ablation was related with lower incidence and risk of heart failure admission (0.7 and 1.9 per 100 person-years; HR, 0.43; 95% CI, 0.37–0.50; *P*<0.001) and stroke/SE (1.1 and 2.8 per 100 person-years; HR, 0.39; 95% CI, 0.34–0.44; *P*<0.001) compared with the medical therapy (Table 2). The cumulative incidence of heart failure admission (*P*<0.001; Figure 5A) and stroke/SE (*P*<0.001; Figure 5B) was significantly lower in the ablated group compared with the medical therapy group.

The risk of heart failure admission was reduced in the ablated group compared with antiarrhythmic drug-treated (HR, 0.47; 95% CI, 0.39~0.56; *P*<0.001) and rate control groups (HR, 0.43; 95% CI, 0.37~0.51; *P*<0.001). Ablation was also related with lower risks of ischemic stroke/SE in the ablated group compared

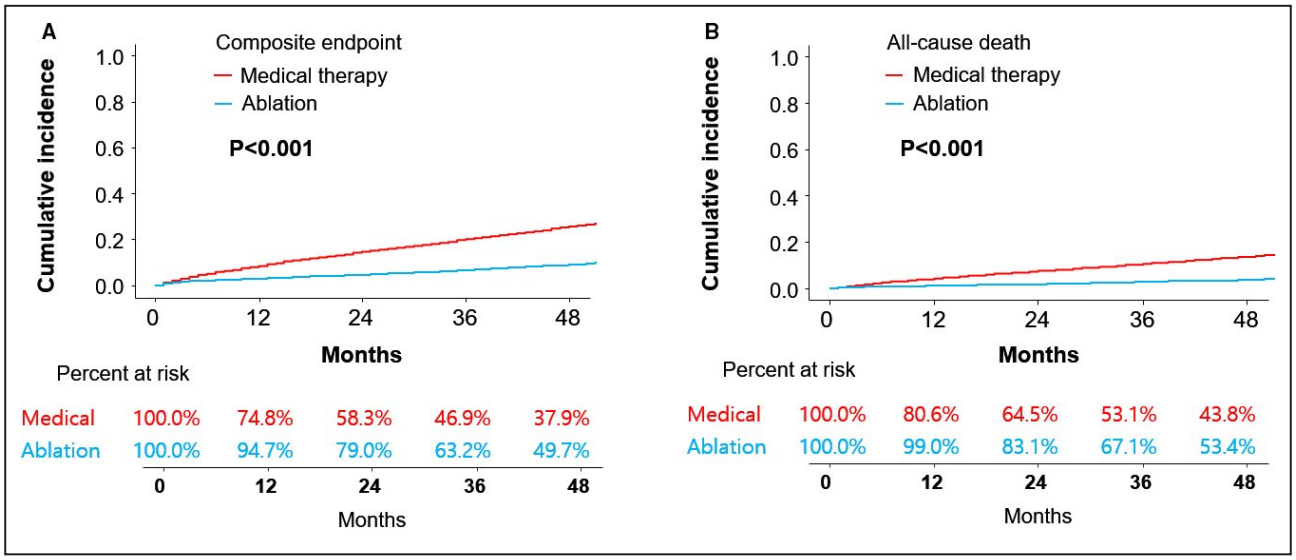

Figure 2. Weighted cumulative incidence curves of primary composite endpoint (A) and all-cause death (B) for ablated and medical therapy patients.

with antiarrhythmic drug-treated (HR, 0.42; 95% CI, 0.38–0.48; *P*<0.001) and rate control groups (HR, 0.34; 95% CI, 0.30–0.39; *P*<0.001) (Table 2).

Sensitivity Analyses

The results using 1:1 propensity score matching (instead of overlap weights) were similar to the primary results. For the primary outcome, the HR was 0.48 (95% CI, 0.44–0.53; *P*<0.001) for ablation versus medical therapy, 0.52 (95% CI, 0.48–0.58; *P*<0.001) for ablation versus antiarrhythmic drug treated, and 0.43 (95% CI, 0.39–0.48; *P*<0.001) for ablation versus rate control. Ablation was also related with lower risk of all-cause death, heart failure, and stroke/SE in 1:1 propensity score matched ablated group than medical therapy, antiarrhythmic drug-treated, and rate control groups (Table S5).

The comparison between AF ablation and a contemporary group of matched patients with no history of AF is presented in Table S6. Compared with IPT weighted patients without history of AF, the risks of primary outcome, all-cause death, heart failure, and stroke/SE were not significantly increased in ablated patients with AF (Table S6).

There were no significant relationships between ablation and any of the falsification end points, except varicella zoster virus infection, which had higher risk in ablated than rate control groups (Table S7).

DISCUSSION

The main finding of this study was that the risk of primary outcome was 53% lower in IPT weighted ablated patients than in medical therapy patients during a follow-up. Second, patients who underwent AF ablation had lower risks of all-cause death, heart failure, and ischemic stroke/SE than the medical therapy population. This finding suggests that the ablation is associated with the reduction of mortality in real-world Asian AF population, and this effect might be related with the reduction of heart failure and ischemic stroke/SE.

Reduction of Mortality and Heart Failure Admission by Ablation

In the intention-to-treat analysis of a recent randomized controlled trial (CABANA trial), catheter ablation did not significantly decrease the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest compared with drug therapy. However, in the treatment-received analyses, the HR for catheter ablation versus drug therapy with respect to the primary end point and all-cause mortality was 0.67 (95% CI, 0.50–0.89; *P*=0.006) and 0.60 (95% CI, 0.42–0.86; *P*=0.005), respectively.[15] In the current study, the better outcome of the ablation group relative to the non-ablation group was similar to the improved outcome of the "as-treated" ablation group compared with the drug therapy group in the CABANA trial. The apparent mortality benefit from AF ablation has been observed by other real-world studies, with a 54% to 61% reduction in mortality.[12,13,24]

In this study, catheter ablation was associated with a lower risk of heart failure admission. In many studies, including a randomized controlled study, catheter ablation for AF consistently improved left ventricular ejection fraction and complication rates, including heart failure readmissions in heart failure patients.[14,16–18] The recent CASTLE AF (Catheter Ablation for Atrial Fibrillation With Heart Failure) study

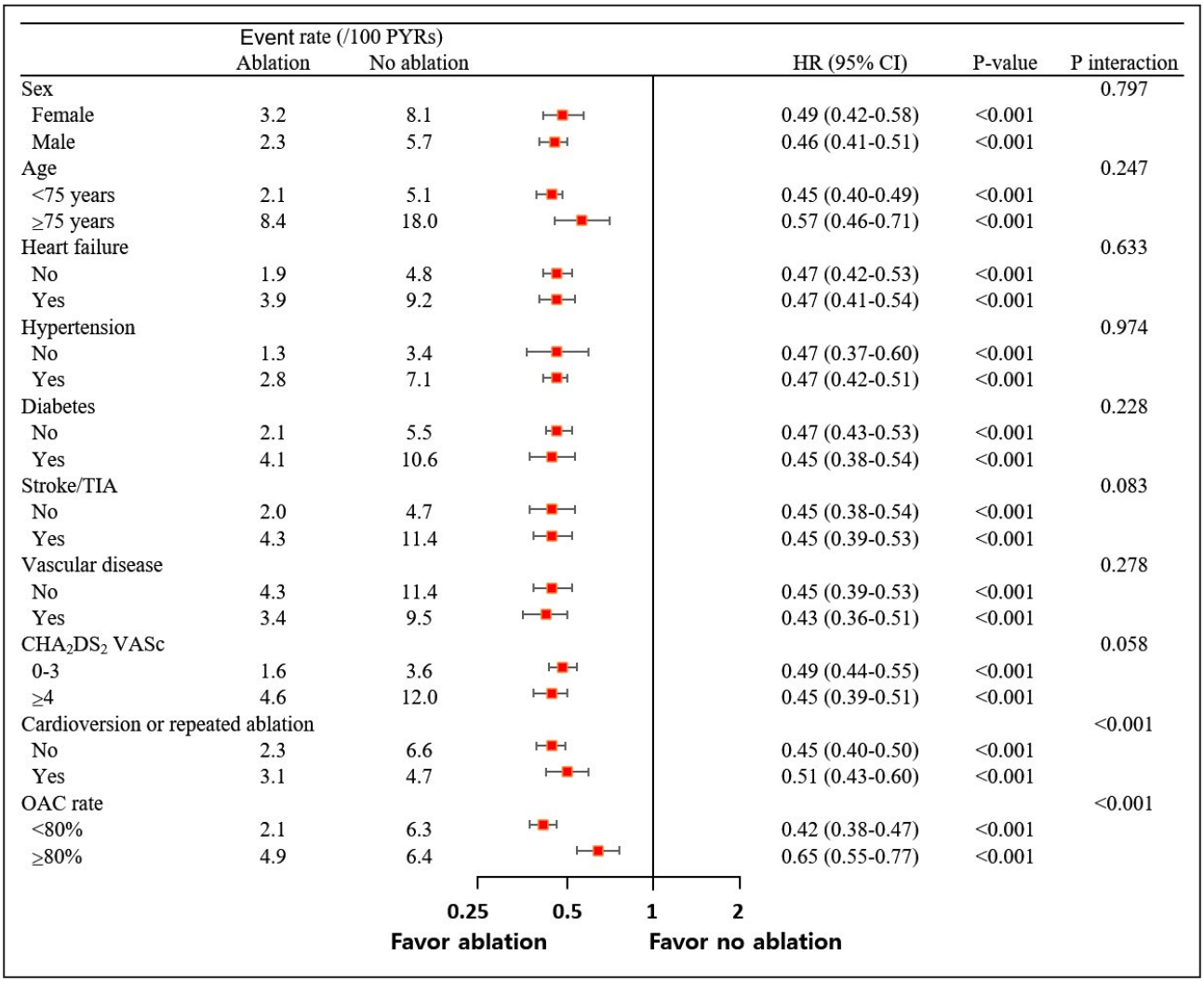

Figure 3. Subgroup analyses of the risk of primary composite outcome.
CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, female; HR, hazard ratio; OAC, oral anticoagulant; PYR, person-year; and TIA, transient ischemic attack.

showed that ablation improves outcome in patients with AF and heart failure.[14]

Other Outcomes

The risk of stroke was lower in ablated patients than in nonablated patients. Although the preventive effect of ablation against stroke in real-world patients has been reported,[11–13] it was not observed in the CABANA trial.[15] The loss of benefit of ablation in randomized controlled trials might be explained by the fact that the included populations are highly selected and do not represent typical real-world patients with AF. Trial participants tend to have better adherence to medical therapies (eg, oral anticoagulants) than patients in routine practice, and event rates are often lower in trials than in real-world practice. Therefore, it may be more difficult to detect further risk reduction from ablation on top of that from optimal medical therapy within a trial, compared with an observational study in which guideline-directed medical therapy is underused.

This study showed a strong association between ablation and survival. The cause of death was cardiovascular in patients with AF.[25] Theoretically, a reduction of cardiovascular mortality could be related to fewer strokes and cardiovascular events, as well as to reduced worsening of congestive heart failure associated with AF.[26]

Study Limitations

The present study has several limitations. First, studies using administrative databases might be susceptible to errors arising from coding inaccuracies. To minimize this problem, we applied the definition that has been previously validated in previous studies using the Korean

	Event rate (/100 PYRs) Ablation	No ablation	HR (95% CI)	P-value	P interaction
Sex					0.369
Female	1.1	4.3	0.40 (0.30-0.52)	<0.001	
Male	1.0	3.2	0.42 (0.36-0.49)	<0.001	
Age					0.177
<75 years	0.8	2.5	0.37 (0.32-0.44)	<0.001	
≥75 years	4.5	12.0	0.52 (0.39-0.69)	<0.001	
Heart failure					0.294
No	0.8	2.6	0.46 (0.38-0.55)	<0.001	
Yes	1.4	5.1	0.36 (0.29-0.46)	<0.001	
Hypertension					0.772
No	0.5	1.5	0.49 (0.32-0.77)	0.002	
Yes	1.2	4.1	0.40 (0.34-0.47)	<0.001	
Diabetes					0.108
No	0.9	2.9	0.47 (0.40-0.55)	<0.001	
Yes	1.6	6.5	0.31 (0.23-0.40)	<0.001	
Stroke/TIA					0.066
No	0.8	2.5	0.45 (0.38-0.53)	<0.001	
Yes	1.7	6.6	0.36 (0.28-0.45)	<0.001	
Vascular disease					0.004
No	1.0	3.0	0.48 (0.41-0.57)	<0.001	
Yes	1.2	5.8	0.28 (0.21-0.37)	<0.001	
CHA_2DS_2 VASc					0.003
0-3	0.6	1.6	0.51 (0.42-0.62)	<0.001	
≥4	1.9	7.1	0.35 (0.29-0.43)	<0.001	
Cardioversion or repeated ablation					<0.001
No	1.0	3.8	0.41 (0.35-0.48)	<0.001	
Yes	1.0	1.9	0.39 (0.28-0.55)	<0.001	
OAC rate					<0.001
<80%	0.8	4.1	0.31 (0.26-0.37)	<0.001	
≥80%	2.2	2.9	0.74 (0.57-0.95)	0.019	

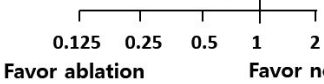

Figure 4. Subgroup analyses of the risk of death from any cause.
CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, female; HR, hazard ratio; OAC, oral anticoagulant; PYR, person-year; and TIA, transient ischemic attack.

NHIS sample cohort.[1–3,6,19,20] Second, causal relationships cannot be established by a retrospective registry study like ours, and only associations can be reported. Although inverse probability of treatment weighting and strict inclusion criteria for control group were used to match 2 groups, unknown confounding cannot be neutralized. Third, the information on type of AF and whether patients maintained stable sinus rhythm after ablation is insufficient. Finally, to indirectly evaluate the relationship between rhythm status on primary composite outcome or mortality, we added subgroup analysis according to "cardioversion or repeated ablation." However, the exact relationships between rhythm status on primary outcome or mortality were not evaluated.

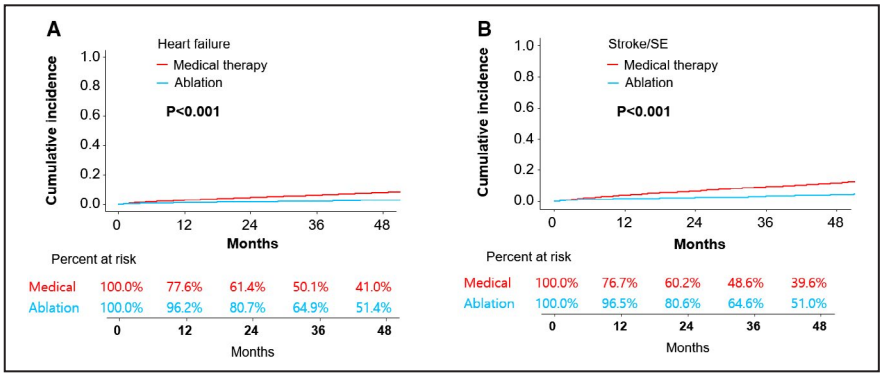

Figure 5. Weighted cumulative incidence curves of heart failure (A) and ischemic stroke/systemic embolism (SE) (B) for ablated and medical therapy patients.

CONCLUSIONS

Ablation may be associated with lower incidences and risk of all-cause death in real-world Asian patients with AF. This effect might be related with lower risk of heart failure and ischemic stroke/SE after ablation.

ARTICLE INFORMATION

Received December 30, 2019; accepted March 25, 2020.

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Acknowledgments

The National Health Information Database was provided by the National Health Insurance Service of Korea. The authors would like to thank the National Health Insurance Service for cooperation.

Sources of Funding

This study was supported by a research grant from the Korean Healthcare Technology R&D project, funded by The Ministry of Health and Welfare, Republic of Korea (HI15C1200, HC19C0130).

Disclosures

Dr Joung has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo; and has received research funds from Medtronic and Abbott. No fees are directly received personally. The remaining authors have no disclosures to report.

Supplementary Materials

Tables S1–S7

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Supplemental Material

Table S1. Definitions and ICD-10 codes used for defining the comorbidities and clinical outcomes.

	Definitions	ICD-10 codes or conditions
Comorbidities		
Atrial fibrillation	Defined from diagnosis*	ICD-10: I48
Heart failure	Defined from diagnosis*	ICD-10: I11.0, I50, I97.1
Hypertension	Defined from diagnosis*	ICD-10: I10, I11, I12, I13, I15 and antihypertensive medication
Diabetes mellitus	Defined from diagnosis* plus treatment	ICD-10: E10, E11, E12, E13, E14 Treatment: all kinds of oral antidiabetics and insulin.
Dyslipidemia	Defined from diagnosis*	ICD-10: E78
Ischemic stroke	Defined from diagnosis*	ICD-10: I63, I64
Transient ischemic attack	Defined from diagnosis*	ICD-10: G45
Hemorrhagic stroke	Defined from diagnosis*	ICD-10: I60, I61, I62
Myocardial infarction	Defined from diagnosis*	ICD-10: I21, I22, I25.2
Peripheral arterial disease	Defined from diagnosis*	ICD-10: I70.0, I70.1, I70.2, I70.8, I70.9
Chronic kidney disease	Defined from eGFR or diagnosis* (if laboratory value was not available, diagnosis code was used)	eGFR <60mL/min per 1.73 m^2 ICD-10: N18, N19
End-stage renal disease	Defined from national registry for severe illness.	Patients with end-stage renal disease undergoing chronic dialysis or received a kidney transplant.
Hypertrophic cardiomyopathy	Defined from at least one records of either inpatient or outpatient diagnoses	ICD-10: I42.1, I42.2
Sleep apnea	Defined from diagnosis*	ICD-10: G47.3
Proteinuria	Defined from laboratory data (if laboratory value was not available, diagnosis code was used)	Urine dipstick proteinuria 1+ or higher (ICD-10: N06, N391, N392, R80)
Osteoporosis	Defined from diagnosis*	ICD-10: M80, M81, M82 (except M82.0)
Hyperthyroidism	Defined from diagnosis*	ICD-10: E05
Hypothyroidism	Defined from diagnosis*	ICD-10: E03
Chronic Liver disease	Defined from diagnosis of chronic liver disease, cirrhosis, and hepatitis	ICD-10: B18, K70, K71, K72, K73, K74, K76.1

Chronic obstructive pulmonary disease	Defined from diagnosis* plus treatment	ICD-10: J42, J43(except J43.0), J44 Treatment: SABA, SAMA, LABA, LAMA, ICS, ICS+LABA, or methylxanthine (>1 months).
Malignancy	Defined from diagnoses of cancer (non-benign)	ICD-10: C00-C97
Clinical outcomes		
Ischemic stroke	Defined from any discharge diagnoses with concomitant imaging studies	ICD-10: I63, I64
Systemic embolism	Defined from admission diagnosis or related death	ICD-10: I74, N280 (including renal infarction)
Heart failure admission	Defined from admission diagnosis (including only main and first sub-diagnosis)	ICD-10: I11.0, I50, I97.1

*To ensure accuracy, comorbidities were established based on one inpatient or two outpatient records of ICD-10 codes in the database.
eGFR, estimated glomerular filtration rate; ICD-10, International Classification of Diseases-10th Revision.

Table S2. Preprocedural factors associated with a likelihood of undergoing catheter ablation.

	Multivariable adjustment	
	OR (95% CI)	**p-value**
Demographics		
Age (per 10-year increase)	0.68 (0.65-0.70)	<0.001
Male	0.78 (0.69-0.88)	<0.001
High economic status	1.50 (1.41-1.61)	<0.001
AF duration (per 1-year increase)	1.34 (1.32-1.36)	<0.001
Risk score (per 1 increase)		
CHA_2DS_2-VASc score	0.46 (0.42-0.51)	<0.001
mHAS-BLED score*	0.91 (0.86-0.97)	0.005
Hospital Frailty Risk Score	1.03 (1.02-1.04)	<0.001
Comorbidities		
Heart failure	2.19 (1.94-2.48)	<0.001
Hypertension	2.04 (1.82-2.29)	<0.001
Diabetes	1.59 (1.39-1.81)	<0.001
Ischemic stroke/TIA	7.35 (5.83-9.26)	<0.001
Myocardial infarction	1.32 (1.16-1.50)	<0.001
Peripheral arterial disease	2.06 (1.81-2.35)	<0.001
History of bleeding	0.80 (0.69-0.91)	0.001
Hyperthyroidism	1.21 (1.12-1.31)	<0.001
Hypothyroidism	1.35 (1.23-1.49)	<0.001
Venous thromboembolism	1.31 (1.13-1.51)	<0.001
Hemorrhagic stroke	0.72 (0.54-0.96)	0.024
COPD	0.91 (0.81-1.02)	0.094
Liver disease	1.46 (1.33-1.60)	<0.001

*Modified (m) HASBLED = hypertension, 1 point; >65 years old, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; liable international normalised ratio, not assessed; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point.
AF, atrial fibrillation; COPD, Chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; TIA, transient ischemic attack.

Table S3. Baseline characteristics of ablated and antiarrhythmic drug treated patients before and after IPT weighting.

	Ablation (N=9,185)	Antiarrhythmic drug treated (N=13,117)	SMD	Ablation (N=9,185)	Antiarrhythmic drug treated (N=13,117)	SMD
Demographic						
Age, years	57 (50, 65)	66 (58, 73)	76.2%	60 (52, 68)	61 (52, 69)	2.7%
Male	76.3%	67.8%	18.8%	73.3%	72.8%	1.3%
High income status	54.9%	46.1%	17.8%	51.3%	50.5%	1.6%
AF duration, months	24.4 (7.1, 56.7)	15.5 (2.6, 37.7)	26.4%	14.4 (4.2, 41.5)	11.4 (0.9, 37.5)	3.1%
Risk scores						
CHA_2DS_2-VASc score	2.0 (1.0, 3.0)	3.0 (2.0, 5.0)	68.4%	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	1.7%
mHAS-BLED score*	2.0 (2.0, 3.0)	3.0 (2.0, 4.0)	36.6%	1.6 (1.0, 2.7)	2.3 (1.1, 3.3)	5.5%
Charlson comorbidity index	3.0 (2.0, 5.0)	4.0 (2.0, 6.0)	38.5%	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	0.6%
Hospital frailty risk score	1.1 (0.0, 3.4)	1.5 (0.0, 5.6)	52.3%	1.2 (0.0, 3.8)	0.7 (0.0, 3.6)	3.0%
Comorbidities						
Heart failure	32.0%	44.9%	26.7%	33.4%	33.7%	0.8%
Hypertension	77.0%	85.7%	22.4%	76.3%	75.4%	2.1%
Diabetes	13.8%	24.9%	28.5%	18.0%	18.0%	0.2%
Dyslipidemia	81.2%	78.6%	6.5%	77.4%	76.0%	3.2%
Ischemic stroke	15.7%	32.5%	39.9%	20.5%	21.3%	2.2%
TIA	7.8%	9.5%	5.8%	8.1%	7.9%	0.7%
Hemorrhagic stroke	1.3%	2.7%	10.1%	1.7%	1.8%	0.4%
Myocardial infarction	10.4%	13.6%	9.8%	10.9%	10.8%	0.2%
Peripheral arterial disease	10.5%	14.3%	11.6%	11.4%	11.4%	0.2%
Chronic kidney disease	4.0%	6.3%	10.4%	5.0%	4.7%	1.3%
End stage renal disease	0.5%	1.1%	6.5%	0.8%	0.8%	0.8%
Proteinuria	4.9%	6.0%	4.6%	5.3%	5.2%	0.4%
Hyperthyroidism	18.6%	15.0%	9.4%	16.0%	15.7%	1.1%
Hypothyroidism	15.5%	12.4%	9.0%	13.0%	12.5%	1.3%
Malignancy	18.4%	20.9%	6.4%	17.9%	18.3%	1.0%
COPD	19.6%	28.1%	20.1%	21.6%	22.1%	1.0%
Liver disease	43.5%	39.8%	7.4%	40.8%	40.2%	1.1%

Hypertrophic cardiomyopathy	1.9%	3.3%	9.4%	2.6%	2.5%	0.4%
History of bleeding	28.8%	30.2%	3.1%	28.1%	27.7%	0.8%
Osteoporosis	15.5%	24.5%	22.8%	18.7%	18.7%	0.1%
Sleep apnea	2.0%	0.8%	9.9%	0.3%	1.3%	1.2%
Medication (Treatment)						
OAC	59.1%	70.4%	23.8%	50.4%	50.5%	0.3%
Antiplatelet agents	73.4%	63.5%	21.5%	63.0%	61.3%	3.5%
ACE-inhibitor/ARB	47.4%	59.6%	24.7%	49.4%	48.5%	1.8%
Diuretics	33.3%	54.1%	42.8%	39.7%	39.8%	0.1%
K sparing diuretics	6.6%	15.2%	27.8%	9.1%	9.4%	0.9%
Statin	38.6%	41.2%	5.3%	36.9%	36.0%	1.9%

Values are presented as median (Q1, Q3, quartiles [25th and 75th percentiles]) or %. *Modified HAS-BLED=hypertension, 1 point: >65 years old, 1 point: stroke history, 1 point: bleeding history or predisposition, 1 point: liable international normalized ratio, not assessed: ethanol or drug abuse, 1 point: drug predisposing to bleeding, 1 point.

ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; SMD, standardized mean difference; TIA, transient ischemic attack.

Table S4. Baseline characteristics of ablated and rate control only patients before and after propensity score weighting.

	Ablation (N=9,185)	Rate control only (N=7,368)	SMD	Ablation (N=9,185)	Rate control only (N=7,368)	SMD
Demographic						
Age, years	57 (50, 65)	68 (61, 75)	92.6%	60 (52, 68)	61 (52, 69)	2.7%
Male	76.3%	65.0%	24.8%	73.3%	72.8%	1.3%
High income status	54.9%	45.0%	19.9%	51.3%	50.5%	1.6%
AF duration, months	24.4 (7.1, 56.7)	20.0 (2.4, 37.5]	23.8%	14.4 (4.2, 41.5)	11.4 (0.9, 37.5)	3.1%
Risk scores						
CHA_2DS_2-VASc score	4.0 (2.0, 5.0)	2.0 (1.0, 3.0)	87.6%	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	1.7%
mHAS-BLED score	3.0 (2.0, 4.0)	2.0 (2.0, 3.0)	48.6%	1.6 (1.0, 2.6)	2.1 (0.9, 3.2)	7.1%
Charlson comorbidity index	4.0 (2.0, 7.0)	3.0 (2.0, 5.0)	49.9%	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	0.6%
Hospital frailty risk score	2.0 (0.0, 7.4)	1.1 (0.0, 3.4)	66.5%	1.2 (0.0, 3.8)	0.7 (0.0, 3.6)	3.0%
Comorbidities						
Heart failure	32.0%	49.8%	36.8%	33.4%	33.7%	0.8%
Hypertension	77.0%	88.2%	29.7%	76.3%	75.4%	2.1%
Diabetes	13.8%	28.1%	35.9%	18.0%	18.0%	0.2%
Dyslipidemia	81.2%	75.3%	14.5%	77.4%	76.0%	3.2%
Ischemic stroke	15.7%	36.8%	49.4%	20.5%	21.3%	2.2%
TIA	7.8%	9.7%	6.5%	8.1%	7.9%	0.7%
Hemorrhagic stroke	1.3%	3.8%	15.7%	1.7%	1.8%	0.4%
Myocardial infarction	10.4%	16.4%	17.7%	10.9%	10.8%	0.2%
Peripheral arterial disease	10.5%	16.4%	17.3%	11.4%	11.4%	0.2%
Chronic kidney disease	4.0%	7.6%	15.3%	5.0%	4.7%	1.3%
End stage renal disease	0.5%	1.4%	9.4%	0.8%	0.8%	0.8%
Proteinuria	4.9%	6.0%	4.6%	5.3%	5.2%	0.4%
Hyperthyroidism	18.6%	13.5%	13.7%	16.0%	15.7%	1.1%
Hypothyroidism	15.5%	12.3%	9.4%	13.0%	12.5%	1.3%
Malignancy	18.4%	21.9%	8.9%	17.9%	18.3%	1.0%
COPD	19.6%	31.1%	26.8%	21.6%	22.1%	1.0%
Liver disease	43.5%	38.8%	9.5%	40.8%	40.2%	1.1%
Hypertrophic cardiomyopathy	1.9%	3.0%	7.6%	2.6%	2.5%	0.4%

History of bleeding	28.8%	31.1%	5.1%	28.1%	27.7%	0.8%
Osteoporosis	15.5%	26.0%	26.2%	18.7%	18.7%	0.1%
Sleep apnea	2.0%	0.5%	13.8%	1.3%	1.2%	1.2%
Medication (Treatment)						
OAC	59.1%	73.2%	30.2%	50.4%	50.5%	0.3%
Antiplatelet agents	73.4%	65.6%	17.1%	63.0%	61.3%	3.5%
ACE-inhibitor/ARB	47.4%	62.4%	30.6%	49.4%	48.5%	1.8%
Diuretics	33.3%	58.7%	52.6%	39.7%	39.8%	0.1%
K sparing diuretics	6.6%	17.8%	34.6%	9.1%	9.4%	0.9%
Statin	38.6%	37.6%	2.0%	36.9%	36.0%	1.9%

Values are presented as median (Q1, Q3, quartiles [25th and 75th percentiles]) or %. *Modified HAS-BLED=hypertension, 1 point: >65 years old, 1 point: stroke history, 1 point: bleeding history or predisposition, 1 point: liable international normalized ratio, not assessed: ethanol or drug abuse, 1 point: drug predisposing to bleeding, 1 point.

ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; SMD, standardized mean difference; TIA, transient ischemic attack.

Table S5. Risk of clinical outcomes in 1:1 propensity score matched ablated and different control patients.

	Number of events	Person years	Event rate (100 PYs)	Number of events	Person years	Event rate (100 PYs)	Absolute reduction in event rate (95% CI)	Adjusted hazard ratio (95% CI) *	p-value
Ablation vs. Medical Therapy									
	Medical Therapy (N=6,621)			Ablation (N=6,621)					
Primary outcome†	1,977	46,129	4.3	643	29,707	2.2	2.1 (1.9-2.4)	0.48 (0.44-0.53)	<0.001
All-cause death	869	50,472	1.7	255	31,560	0.8	0.9 (0.7-1.1)	0.44 (0.38-0.51)	<0.001
Heart failure	567	48,725	1.2	172	30,573	0.6	0.6 (0.4-0.7)	0.46 (0.39-0.55)	<0.001
Stroke/SE	1071	46,902	2.3	280	30,311	0.9	1.4 (1.1-1.6)	0.40 (0.35-0.45)	<0.001
Ablation vs. Antiarrhythmic drug									
	Antiarrhythmic drug (N=6,065)			Ablation (N=6,065)					
Primary outcome†	1,695	41,581	4.1	601	27,034	2.2	1.9 (1.6-2.1)	0.52 (0.48-0.58)	<0.001
All-cause death	712	45,047	1.6	240	28,774	0.8	0.7 (0.6-0.9)	0.49 (0.42-0.57)	<0.001
Heart failure	496	43,629	1.1	164	27,824	0.6	0.6 (0.4-0.7)	0.50 (0.42-0.60)	<0.001
Stroke/SE	905	42,256	2.1	261	27,623	0.9	1.4 (1.2-1.6)	0.45 (0.39-0.51)	<0.001
Ablation vs. Rate control only									
	Rate control only (N=3,903)			Ablation (N=3,903)					
Primary outcome†	1,574	27,878	5.6	445	17,164	2.6	3.1 (2.7-3.5)	0.43 (0.39-0.48)	<0.001
All-cause death	827	31,462	2.6	192	18,447	1.0	1.6 (1.3-1.8)	0.38 (0.32-0.44)	<0.001
Heart failure	465	29,889	1.6	126	17,745	0.7	0.8 (0.6-1.1)	0.43 (0.35-0.52)	<0.001
Stroke/SE	828	28,692	2.9	188	17,611	1.1	1.8 (1.5-2.1)	0.35 (0.30-0.41)	<0.001

*Adjusted for age, sex, income, AF duration, CHA_2DS_2-VASc score, modified HAS-BLED score, hospital frailty risk score, Charlson comorbidity index, hypertension, diabetes, ischemic stroke/TIA, myocardial infarction, peripheral arterial disease, hypertrophic cardiomyopathy, chronic kidney disease, end stage renal disease, liver disease, malignancy, hyperthyroidism, hypothyroidism, venous thromboembolism, COPD, intracranial bleeding, cardioversion, history of bleeding, baseline use of warfarin, NOAC, aspirin, clopidogrel, beta-blocker, ACE-inhibitor/ARB, dihydropyridine/nondihydropyridine calcium channel blocker, Class Ic and III antiarrhythmic drug, statin, diuretics, and digoxin, and OAC coverage rate of time at risk.† The primary clinical outcome was a composite endpoint of all-cause death, heart failure and ischemic stroke/SE.

CI, confidence interval; PYs, person-years; SE, systemic embolism. Other abbreviations are same as table S3.

Table S6. Risk of clinical outcomes in IPT weighted ablated patients with AF and patients without AF.

	Number of events	Person years	Event rate (100 PYs)	Number of events	Person years	Event rate (100 PYs)	Absolute reduction in event rate (95% CI)	Adjusted Hazard ratio (95% CI)*	p-value
Ablation vs. Patients without AF									
	No AF (N= 439,128)			Ablation (N= 9,422)					
Primary outcome	31,925	3,125,245	1.0	5,886	313,579	1.9	-0.8 (-0.9 ~ -0.8)	1.66 (0.91-3.04)	0.099
All-cause death	19,070	3,172,406	0.6	2,306	329,211	0.7	-0.1 (-0.1 ~ -0.0)	1.77 (0.81-3.90)	0.154
Heart failure	2,730	3,164,886	0.1	814	321,969	0.3	-0.2 (-0.2 ~ -0.1)	2.10 (0.84-5.26)	0.115
Stroke/SE	11,696	3,137,176	0.4	2,684	317,214	0.8	-0.5 (-0.5 ~ -0.4)	2.18 (0.72-6.28)	0.071

* Adjusted for age, sex, income, AF duration, CHA_2DS_2-VASc score, modified HAS-BLED score, hospital frailty risk score, Charlson comorbidity index, hypertension, diabetes, ischemic stroke/TIA, myocardial infarction, peripheral arterial disease, hypertrophic cardiomyopathy, chronic kidney disease, end stage renal disease, liver disease, malignancy, hyperthyroidism, hypothyroidism, venous thromboembolism, COPD, intracranial bleeding, cardioversion, history of bleeding, baseline use of warfarin, NOAC, aspirin, clopidogrel, beta-blocker, ACE-inhibitor/ARB, dihydropyridine/nondihydropyridine calcium channel blocker, Class Ic and III antiarrhythmic drug, statin, diuretics, and digoxin, and OAC coverage rate of time at risk.

AF, atrial fibrillation; CI, confidence interval; IPT, inverse probability of treatment; PYs, person-years; SE, systemic embolism.

Table S7. Risk of falsification endpoints in propensity score weighted or 1:1 propensity score matched ablated and different control patients.

	Propensity score weighted		1:1 propensity score matched	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Urinary tract infection				
Ablation vs. Medical Therapy	0.99 (0.94-1.04)	0.583	0.99 (0.93-1.06)	0.819
Ablation vs. Antiarrhythmic drug	0.98 (0.93-1.03)	0.416	0.98 (0.92-1.05)	0.536
Ablation vs. Rate control only	0.95 (0.90-1.01)	0.096	0.94 (0.87-1.02)	0.141
Varicella-zoster virus infection				
Ablation vs. Medical Therapy	1.09 (1.01-1.18)	0.033	1.11 (1.01-1.22)	0.030
Ablation vs. Antiarrhythmic drug	1.06 (0.98-1.15)	0.157	1.02 (0.93-1.13)	0.625
Ablation vs. Rate control only	1.12 (1.02-1.22)	0.014	1.15 (1.02-1.29)	0.025
Fall accident				
Ablation vs. Medical Therapy	1.07 (0.59-1.93)	0.834	1.46 (0.63-3.39)	0.381
Ablation vs. Antiarrhythmic drug	1.25 (0.67-2.33)	0.486	1.76 (0.69-4.51)	0.237
Ablation vs. Rate control only	0.91 (0.48-1.74)	0.775	1.79 (0.78-4.13)	0.172

HR, hazard ratio; CI, confidence interval.