**The risk of dementia after catheter ablation for atrial fibrillation: a nationwide cohort study**

Daehoon Kim, MD\*;1 Pil-Sung Yang, MD\*;2 Jung-Hoon Sung, MD;2 Eunsun Jang, MS;1 Hee Tae Yu, MD;1 Tae-Hoon Kim, MD;1 Jae-Sun Uhm, MD;1 Jong-Youn Kim, MD;1 Hui-Nam Pak, MD;1 Moon-Hyoung Lee, MD;1 Gregory Y.H. Lip, MD†;3 Boyoung Joung, MD†1

1Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, 2Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea, and 3Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom.

[\*The first two authors contributed equally to this work]

[†Joint senior authors]

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**Address for Correspondence:**

Boyoung Joung, MD. Gregory Y.H. Lip, MD.

50-1 Yonseiro, Seodaemun-gu, Liverpool Centre for Cardiovascular Sciences,

Seoul, Republic of Korea 03722 University of Liverpool and Liverpool

Phone: +82-2-2228-8460 Heart & Chest Hospital,

Fax: +82-2-393-2041 Liverpool, United Kingdom

E-mail: cby6908@yuhs.ac E-mail: gregory.lip@liverpool.ac.uk

**Abstract**

**Background:** Accumulating evidence shows that atrial fibrillation (AF) is associated with increased risk of dementia. Catheter ablation for AF prolongs the duration of sinus rhythm, thereby improving the quality of life. We aimed to investigate the association of catheter ablation of AF with the occurrence of dementia.

**Methods:** From the Korean National Health Insurance Service database, 194,928 adult patients (≥18 years) with newly diagnosed AF were treated with ablation or medical therapy (antiarrhythmic or rate control drugs) between 1 January 2005 and 1 December 2015. Of patients without a history of dementia, we studied 9119 patients undergoing ablation and 17,978 patients managed with medical therapy. The time at risk was counted from the first medical therapy, and ablation was analyzed as time varying covariate. Propensity score matching was used to correct for differences between the groups.

**Results:** After propensity score matching, the ablation and medical therapy groups had similar background characteristics. During a median (25th, 75th percentiles) follow-up of 39 (16, 76) months, compared to medical therapy patients, ablated patients showed lower incidence and risk of overall dementia (5.1 and 8.0 per 1000 person-years, respectively; hazard ratio [HR] 0.66, 95% CI 0.54-0.79). Ablation was associated with a lower risk of overall dementia even after censoring for incident stroke (HR 2.8, 95% CI 1.7-4.0), regardless of age, heart failure, stroke history and risk of stroke. Ablation was also associated with lower risk of dementia subtypes including Alzheimer’s disease and vascular dementia, but this was non-significant after censoring for stroke.

**Conclusion:** In this nationwide cohort of AF patients treated with catheter ablation or medical therapy, ablation was associated with lower risks of overall dementia. This relationship was also evident after censoring for incident stroke, and adjusting for clinical confounders.

**Keywords:** atrial fibrillation, catheter ablation, dementia

**Introduction**

Atrial fibrillation (AF) is the most common type of sustained cardiac arrhythmia and is therefore a substantial economic and public health burden.[1-3](#_ENREF_1) The age distribution of AF among populations of developed countries is predicted to shift in coming years, with an expected increase in prevalence among the elderly. The fact that AF prevalence has progressively risen 2.10 fold over the past 10 years in Korea, an increase to 8.15% in patients ≥80 years of age, supports this predicted progression.[2](#_ENREF_2) Importantly, AF increases the risk of mortality and morbidity resulting from concurrently associated conditions including stroke, congestive heart failure, and hospitalization, and is associated with the occurrence of comorbid chronic diseases.[4](#_ENREF_4)

There are approximately 40 million people living with dementia worldwide, and this number is expected to increase with a rising aged population.[5](#_ENREF_5) Although the pathophysiological mechanisms of dementia are largely unknown, evidence is accumulating that AF may contribute to the development of cognitive dysfunction and dementia.[6](#_ENREF_6), [7](#_ENREF_7) The Rotterdam Study demonstrated that cognitive dysfunction was approximately twice as common in subjects with AF as in those without.[6](#_ENREF_6) Since then, several longitudinal studies have shown that AF is independently associated with an increased risk of cognitive decline or dementia.[7](#_ENREF_7), [8](#_ENREF_8)

 Compared to antiarrhythmic drug therapy, catheter ablation for AF reduces the number of acute episodes and prolongs the duration of sinus rhythm, thereby improving the quality of life.[9-12](#_ENREF_9) The effect of ablation on the incidence of dementia has not been elucidated. Previous studies have reported that AF ablation was associated with declining cognitive function[13](#_ENREF_13), [14](#_ENREF_14) and acute brain lesions.[14](#_ENREF_14), [15](#_ENREF_15) Conversely, two recent studies demonstrated that cognitive function improved following ablation.[16](#_ENREF_16), [17](#_ENREF_17)

 Given the conflicting information available on the association of catheter ablation with cognitive function, we compared the development of dementia due to all-causes (including Alzheimer’s and vascular dementia) in patients with AF treated with or without ablation. Second, we assessed the relationship to stroke and long-term oral anticoagulation.

**Methods**

 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. The majority (97.1%) of Korean citizens 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](#_ENREF_1), [6](#_ENREF_6), [19](#_ENREF_19), [20](#_ENREF_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.

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.

*Study population*

 From the Korean NHIS database covering a population 51.5 million inhabitants, 834,735 adult patients (≥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 Disease 10th revision 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](#_ENREF_1), [6](#_ENREF_6), [19](#_ENREF_19), [20](#_ENREF_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, history of heart failure admission or dementia. Among medical therapy patients, patients who had oral anticoagulants less than 30 days or antiarrhythmic drugs less than 90 days during the same period were additionally excluded. After exclusions, 9119 patients with ablation and 17,978 patients with medical therapy remained for the analysis (Figure 1).

*Covariates*

Information regarding 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 (Supplementary Table 1).[1-3](#_ENREF_1), [6](#_ENREF_6), [19](#_ENREF_19), [20](#_ENREF_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. The Hospital Frailty Risk Score was calculated retrospectively using 109 ICD-10 diagnostic codes, which were found to be associated with frailty (Supplementary Table 2). [21](#_ENREF_21) Patients having the score of at least 5 were defined as frail.

*Clinical outcome events and assessments*

The primary clinical outcome was the initial occurrence of overall dementia. Secondary outcomes included development of dementia subtypes, including Alzheimer’s disease (AD) and vascular dementia (VaD). The Korean government covers medical expenditure for dementia patients. Diagnosis of dementia was defined using the following ICD-10 codes of dementia (F00 or G30 for AD, F01 for VaD, F02 for dementia with other diseases classified elsewhere, and F03 or G31 for unspecified dementia) and dementia drugs (rivastigmine, galantamine, memantine, or donepezil). To evaluate the accuracy of our definition of dementia, a validation study was conducted in two teaching hospitals with a total of 972 patients using patient medical records and results of cognitive function tests. The positive predictive value was 94.7%.[8](#_ENREF_8)

Ischemic stroke was defined from any discharge diagnoses (ICD-10: I63, 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](#_ENREF_1), [6](#_ENREF_6), [19](#_ENREF_19), [20](#_ENREF_20) The definitions of clinical outcomes are presented in Supplementary Table 1. It must be noted that the same patient could have more than one study outcome during the study duration, but only the first event of each outcome was considered in the study.

*Statistical methods*

Baseline characteristics of the participants with and without incident AF were compared using Student’s t-tests and Pearson’s chi-squared tests. One-to-two propensity score matching 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 socio-demographics, medical history, concurrent medication use, and AF duration (variables in Table 1).

Incidence rates of events were calculated by dividing the number of events by person-times at risk, with the 95% confidence intervals (CI) 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 dementia, Alzheimer’s disease and vascular dementia.[21](#_ENREF_21) The proportional hazards assumption was tested on the basis of Schoenfeld residuals.[22](#_ENREF_22)

*Sensitivity analyses*

First, we performed subgroup analyses for the primary outcome of dementia stratified by sex, age, heart failure, hypertension, diabetes, stroke/TIA, vascular disease, CHA2DS2-VASc, cardioversion or repeated ablation, and anticoagulation. Second, propensity score 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. The 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 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. Third, we conducted a stratified analysis based on whether the drug-treated patients were treated with antiarrhythmic or with rate control drugs only.

We performed a “falsification analysis” to determine whether ablation was associated with lower rates of urinary tract infections, influenza, 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](#_ENREF_23)

A two-sided P-values of < 0.05 were considered significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA) and R version 3.3.2 (The R Foundation, www.R-project.org).

**Results**

Compared with medical therapy patients, ablated patients were more often male, healthy, and with an income in the highest quartile (Table 1). Ablated patients were on average 10 years younger, and had less concomitant diseases. After propensity score matching, all baseline characteristics were similar between the two 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 (Supplementary Table 2).

Ablated patients were younger, healthy and had less comorbidities than antiarrhythmic drug treated (Supplementary Table 3) and rate control patients (Supplementary Table 4). All baseline characteristics were similar between the two propensity score matched groups.

*Risk of dementia*

During a median (25th, 75th percentiles) follow-up of 39 (16, 76) months, 160 and 389 cases had dementia in the propensity score matched ablated and medical therapy group with annualized rates of 5.1 and 8.0 per 1000 person-years, respectively (P<0.001) (Table 2). The cumulative incidence of dementia 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 and competing risk of mortality, the risk of primary outcome was reduced by 34% in patients with ablations (hazard ratio [HR] 0.66, 95% CI 0.54–0.79, P<0.001) (Table 2). The risk of dementia was reduced in the ablated group compared with antiarrhythmic drug treated (HR 0.71, 95% CI 0.59~0.586, P<0.001) and rate control groups (HR 0.59, 95% CI 0.48~0.72, P<0.001) (Table 2). Other factors associated with the increased risk of dementia included: older age (per 10 increase: HR 2.70, 95% CI 2.28–3.20, P<0.001), ischemic stroke (HR 1.55, 95% CI 1. 70–2.24, P=0.022), higher Charlson comorbidity indices (per 1 increase: HR 1.10, 95% CI 1.04–1.16, P<0.001), and higher Hospital Frailty Risk scores (per 1 increase: HR 1.05, 95% CI 1.03–1.07, P<0.001).

Subgroup analyses showed that the risk of primary outcome was reduced in subgroups regardless of age, heart failure, stroke history and risk of stroke. The association was more pronounced in those without cardioversion or repeated ablation (P for interaction<0.001) and those without optimal oral anticoagulation (< 80%) (P for interaction<0.001).

In the propensity score matched ablated and medical therapy group, annualized rates of ischemic stroke were 0.9 and 2.0 per 100 person-years, respectively (P<0.001). After additionally censoring for incident stroke, ablation was still associated with lower risk of overall dementia than medical therapy (HR 0.74, 95% CI 0.60-0.91, p=0.004), antiarrhythmic therapy (HR 0.78, 95% CI 0.63-0.97, p=0.025), and rate control only groups (HR 0.68, 95% CI 0.54-0.86, p=0.001).

*Risks of Alzheimer’s disease and vascular dementia*

Ablation was related with lower incidence and risk of Alzheimer’s disease (3.8 and 5.2 per 1000 person-years, HR 0.76, 95% CI 0.61­–0.96, P=0.018) and vascular dementia (1.1 and 2.0 per 1000 person-years, HR 0.55, 95% CI 0.37–0.82, P=0.003) compared with the medical therapy (Table 2). The cumulative incidence of Alzheimer’s disease (P<0.001, Figure 4A) and vascular dementia (P<0.001, Figure 4B) was significantly lower in the ablated group compared with the medical therapy group. The risks of Alzheimer’s disease (HR 0.75, 95% CI 0.59~0.96, P=0.024) and vascular dementia (HR 0.46, 95% CI 0.30~0.71, P<0.001) were reduced in the ablated group compared with rate control group (Table 2).

After censoring for incident stroke, ablation was associated with consistent but non-significant trends for lower risks of Alzheimer disease and vascular dementia (Table 2, right panels of Figure 4A and Figure 4B).

*Sensitivity analyses*

The results using propensity score weighting (inverse probability of treatment weighting) were very similar to the primary results. For the primary outcome of overall dementia, the HR adjusted for clinical variables and competing risk of all-cause death was 0.52 (95% CI 0.44-0.61, p<0.001) for ablation vs. medical therapy, 0.58 (95% CI 0.49-0.69, p<0.001) for ablation vs. antiarrhythmic drug treated, and 0.47 (95% CI 0.40-0.57, p<0.001) for ablation vs. rate control. Ablation was also related to lower risks of Alzheimer’s disease and vascular dementia in the propensity score weighted ablated group compared to the medical therapy, antiarrhythmic drug treated and rate control groups. After additional censoring for ischemic stroke, these trends were consistently observed (Supplementary Table 5).

There were no significant relationships between ablation and any of the falsification endpoints (Supplementary Table 6).

**Discussion**

 In this study, our principal finding was that patients with AF undergoing catheter ablation were at a lower risk of dementia compared to drug-treated patients, even after adjusting for variations in background characteristics and competing risk of death. This association was consistently evident after censoring for stroke. Second, the lower risks of dementia associated with AF ablation were consistent across different sex, heart failure, stroke, vascular disease history, and CHA2DS2-VASc score.

Bunch et al. reported that patients ablated for AF have a significantly lower risk of dementia in comparison to age/gender matched AF patients without ablation.[7](#_ENREF_7) The present study extends prior observations by enrolling a larger number of ablated patients than the previous study and using both propensity score- matching and - weighting approaches. A recent prospective study demonstrated an improvement in cognitive function in well-anticoagulated AF ablated patients.[16](#_ENREF_16) Mild cognitive dysfunction was found in 30.4% of the patients at baseline, but at the end of follow-up, Montreal-Cognitive Assessment score increased by a median of +1.0 (-1.0, 2.0) unit and 7.2% fewer patients had mild cognitive impairment than those at baseline. In the present study, the lower risks of dementia associated with ablation were observed mainly in subgroups without optimal anticoagulation, suggesting the association might be attributable to possibly different levels of OAC use between the ablation and control groups. On the contrary, ablation therapy for AF has been associated with declining cognitive function at 90 days after the procedure.[13](#_ENREF_13), [14](#_ENREF_14) Furthermore, researchers have detected acute brain lesions without corresponding neurological symptoms in 25% of patients undergoing AF ablation using a high-resolution diffusion-weighted brain magnetic resonance imaging sequence that can identify acute cytotoxic brain edema.[14](#_ENREF_14), [15](#_ENREF_15), [26](#_ENREF_26), [27](#_ENREF_27) However, a direct association of silent cerebral embolism with a decline in neurocognitive function is unproven.[28](#_ENREF_28), [29](#_ENREF_29) The clinical significance of such asymptomatic cerebral embolic lesions is not known, and many will resolve to the point of being undetectable after weeks or months. These silent cerebral emboli are required to be distinguished from covert embolic strokes consequent to chronic AF. The latter have been linked with long-term cognitive decline and are much larger than the silent emboli observed peri-procedurally.[30](#_ENREF_30), [31](#_ENREF_31) The impact on cognitive function, if any, is uncertain.

Our study shows that catheter ablation for AF was associated with the lower risk of both Alzheimer’s disease and vascular dementia. Given the relationship between AF and stroke, vascular dementia, encompassing both multi-infarct and small vessel disease dementia, might be considered as an obvious contributory factor for cognitive decline in AF population.[6](#_ENREF_6), [34](#_ENREF_34) In general, the association of ablation with lower risk was more pronounced for vascular dementia than for Alzheimer’s disease. However, these results were not consistently observed after additionally censoring patients at the time of incident stroke suggesting that the reduction of overt stroke may account for the observed association of ablation with lower dementia risk.

Alzheimer’s disease is overall the most common type of dementia, and AF has been identified as a risk factor for Alzheimer’s disease.[7](#_ENREF_7), [8](#_ENREF_8) In the majority of cases, the brains of patients with Alzheimer’s disease show vascular microinfarcts, white matter lesions, or vessel wall alterations.[32](#_ENREF_32) Experimentally induced cerebral micro-emboli in aged rats have induced beta-amyloid accumulation and increased hyperphosphorylated tau reactivity in both the infarcted and adjacent regions of the brain,[33](#_ENREF_33) suggesting a possible association of the former with Alzheimer’s disease pathophysiology. Vascular risk factors have been correlated with a higher risk of Alzheimer’s dementia in many epidemiological studies.[32](#_ENREF_32) These vascular attributes might help explain the association between AF and the increased risk of Alzheimer’s disease, or between ablation and a decreased risk of Alzheimer’s disease.

Although we were able to observe an association between ablation and lower dementia risk across all subgroups, the association was accentuated especially in patients with prior cardioversion or repeated ablation, and those with optimal anticoagulation. This finding suggests the effect of reduction of dementia by ablation might be related with the maintenance of sinus rhythm, and the reduction of stroke in those with optimal anticoagulation.

*Study limitations*

The present study has several limitations. Although administrative databases are increasingly used for clinical research, such studies are potentially susceptible to inaccuracies arising from coding errors. To minimize this problem, we applied the definition that we had validated in previous studies using the Korean NHIS database [refs]. Second, our observational study findings cannot be used to establish causal relationships and residual confounding is likely to persist even after propensity score matching and weighting. Therefore, to check out the presence of confounding by indication, the falsification endpoints were assessed. No evidence of a hidden bias working in favor of ablation was found. Finally, level of education, baseline cognitive function, and quality of anticoagulation were not assessed and not included in our logistic regression models calculating propensity scores.

**Conclusions**

In this nationwide cohort of AF patients treated with catheter ablation or medical therapy, ablation was associated with lower risks of overall dementia. This relationship was also evident after censoring for incident stroke, and adjusting for clinical confounders.

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**Disclosures**

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**Table 1.** Baseline characteristics before and after propensity score matching.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Ablation(N=9,119) | Medical therapy (N=17,978) | SMD | Ablation(N=6,562) | Medical therapy (N=6,562) | SMD |
| **Demographic** |  |  |  |  |  |  |
| Age, years  | 57 (50, 65) | 67 (59, 73) | 80.9% | 60 (53, 67) | 60 (53, 67) | 1.5% |
|  <65 years | 44.0% | 49.0% | 71.0% | 47.0% | 47.0% | 1.5% |
|  65-74 year | 40.0% | 47.0% | 30.1% | 44.0% | 44.0% | 1.3% |
|  ≥75 years | 18.0% | 41.0% | 55.7% | 21.0% | 22.0% | 0.6% |
| Male | 42.0% | 47.0% | 20.1% | 44.0% | 43.0% | 1.6% |
| High income status | 50.0% | 50.0% | 19.5% | 50.0% | 50.0% | 2.1% |
| AF duration, months | 24.2 (7.1, 56.4) | 16.7 (2.5, 37.4) | 26.3% | 19.3 ( 5.9,48.0) | 19.6 (3.0, 44.7) | 1.1% |
| **Risk scores** |  |  |  |  |  |  |
| CHA2DS2-VASc score |  2.0 (1.0, 3.0) |  4.0 (2.0, 5.0) | 73.1% |  2.0 (1.0, 4.0) |  2.0 (1.0, 4.0) | 1.2% |
| mHAS-BLED score\* |  2.0 (2.0, 3.0) |  3.0 (2.0, 4.0) | 38.2% |  2.0 (2.0, 3.0) |  3.0 (2.0, 3.0) | 2.8% |
| 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) | 1.6% |
| Hospital frailty risk score  |  1.1 (0.0, 3.4) |  1.6 (0.0, 5.6) | 32.6% |  1.1 (0.0, 3.7) |  0.8 (0.0, 3.6) | 1.5% |
| **Comorbidities** |  |  |  |  |  |  |
| Heart failure | 47.0% | 50.0% | 30.1% | 48.0% | 48.0% | 1.1% |
| Hypertension | 42.0% | 34.0% | 24.8% | 40.0% | 40.0% | 0.4% |
| Diabetes | 34.0% | 44.0% | 30.7% | 38.0% | 38.0% | 1.7% |
| Dyslipidemia | 39.0% | 42.0% | 10.5% | 40.0% | 40.0% | 1.7% |
| Ischemic stroke | 36.0% | 47.0% | 41.1% | 39.0% | 40.0% | 2.0% |
| TIA | 27.0% | 29.0% | 5.7% | 27.0% | 27.0% | 0.7% |
| Hemorrhagic stroke | 11.0% | 16.0% | 10.3% | 12.0% | 13.0% | 0.7% |
| Myocardial infarction | 30.0% | 35.0% | 12.3% | 31.0% | 31.0% | 1.1% |
| Peripheral arterial disease | 31.0% | 36.0% | 13.4% | 32.0% | 32.0% | 0.9% |
| Chronic kidney disease | 20.0% | 25.0% | 11.6% | 21.0% | 21.0% | 0.8% |
| End stage renal disease | 7.0% | 11.0% | 7.5% | 8.0% | 9.0% | 1.2% |
| Proteinuria | 22.0% | 24.0% | 4.7% | 23.0% | 23.0% | 0.5% |
| Hyperthyroidism | 39.0% | 35.0% | 11.3% | 37.0% | 37.0% | 0.2% |
| Hypothyroidism | 36.0% | 32.0% | 10.0% | 35.0% | 35.0% | 0.4% |
| Malignancy | 39.0% | 41.0% | 6.4% | 39.0% | 39.0% | 0.6% |
| COPD | 40.0% | 45.0% | 21.2% | 41.0% | 41.0% | 1.4% |
| Liver disease | 50.0% | 49.0% | 8.7% | 49.0% | 49.0% | 0.5% |
| Hypertrophic cardiomyopathy | 13.0% | 18.0% | 8.6% | 15.0% | 16.0% | 1.5% |
| History of bleeding  | 45.0% | 46.0% | 2.6% | 45.0% | 46.0% | 2.2% |
| Osteoporosis | 36.0% | 43.0% | 21.9% | 38.0% | 38.0% | 1.2% |
| Sleep apnea | 14.0% | 8.0% | 11.3% | 12.0% | 11.0% | 1.4% |
| **Medication (Treatment)** |  |  |  |  |  |  |
| OAC | 49.0% | 45.0% | 26.0% | 48.0% | 48.0% | 1.9% |
| Antiplatelet agents | 44.0% | 48.0% | 20.7% | 46.0% | 46.0% | <0.1% |
| ACE-inhibitor/ARB  | 50.0% | 49.0% | 26.8% | 50.0% | 50.0% | 0.5% |
| Diuretics | 47.0% | 50.0% | 46.2% | 49.0% | 49.0% | 0.4% |
| K sparing diuretics | 25.0% | 37.0% | 30.9% | 28.0% | 27.0% | 1.1% |
| Statin | 49.0% | 49.0% | 2.3% | 49.0% | 49.0% | 1.4% |
| Beta-blocker | 49.0% | 50.0% | 9.1% | 49.0% | 49.0% | 0.2% |
| CCB DHP | 45.0% | 49.0% | 28.7% | 47.0% | 47.0% | 0.7% |
| CCB Non-DHP | 42.0% | 39.0% | 13.3% | 41.0% | 41.0% | 0.5% |
| Digoxin | 32.0% | 44.0% | 37.8% | 35.0% | 35.0% | 0.8% |

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 2.** Risk of clinical outcomes in propensity score matched ablated and non-ablated patients.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Numberof events | Personyears | Event rate (1000 person-years)  | Numberof events | Personyears | Event rate (1000 person-years) | Absolute reductionin event rate(95% CI) | Adjusted hazard ratio(95% CI) \* | p-value |
| ***Ablation vs. Medical therapy*** |
|  | Medical Therapy (N= 6,562) | Ablation (N= 6,562) |  |  |  |
| *Including stroke* |  |  |  |  |  |
| Overall dementia | 389  | 48727  | 8.0  | 160  | 31153  | 5.1  | 2.8 (1.7-4.0) | 0.66 (0.54-0.79) | <0.001 |
| Alzheimer’s disease | 253  | 49093  | 5.2  | 118  | 31275  | 3.8  | 1.4 (0.4-2.3) | 0.76 (0.61-0.96) | 0.018 |
| Vascular dementia | 101  | 49516  | 2.0  | 35  | 31447  | 1.1  | 0.9 (0.3-1.5) | 0.55 (0.37-0.82) | 0.003 |
| *Censoring for stroke* |  |  |  |  |  |  |  |  |  |
| Overall dementia | 288  | 46570  | 6.2  | 137  | 30370  | 4.5  | 1.7 (0.6-2.7) | 0.74 (0.60-0.91) | 0.004 |
| Alzheimer’s disease | 200  | 46817  | 4.3  | 105  | 30466  | 3.4  | 0.8 (-0.1 to 1.7) | 0.83 (0.65-1.06) | 0.139 |
| Vascular dementia | 61  | 47221  | 1.3  | 26  | 30630  | 0.8  | 0.4 (-0.04 to 0.9) | 0.65 (0.41-1.05) | 0.076 |
| ***Ablation vs. Antiarrhythmic drug***  |
|  | Antiarrhythmic drug (N= 5,992) | Ablation (N= 5,992) |  |  |  |
| *Including stroke* |  |  |  |  |  |  |  |  |  |
| Overall dementia | 342  | 43907  | 7.8  | 159  | 28234  | 5.6  | 2.2 (0.9-3.4) | 0.71 (0.59-0.86) | <0.001 |
| Alzheimer’s disease | 221  | 44219  | 5.0  | 115  | 28368  | 4.1  | 0.9 (-0.1 to 2.0) | 0.83 (0.66-1.04) | 0.106 |
| Vascular dementia | 81  | 44534  | 1.8  | 37  | 28525  | 1.3  | 0.5 (-0.1 to 1.1) | 0.71 (0.48-1.06) | 0.093 |
| *Censoring for stroke* |  |  |  |  |  |  |  |  |  |
| Overall dementia | 261  | 42105  | 6.2  | 137  | 27515  | 5.0  | 1.2 (0.1-2.4) | 0.78 (0.63-0.97) | 0.025 |
| Alzheimer’s disease | 174  | 42325  | 4.1  | 104  | 27619  | 3.8  | 0.3 (-0.6 to 1.3) | 0.94 (0.73-1.20) | 0.601 |
| Vascular dementia | 58  | 42580  | 1.4  | 28  | 27771  | 1.0  | 0.4 (-0.2 to 0.9) | 0.71 (0.45-1.13) | 0.145 |
| ***Ablation vs. Rate control only*** |
|  | Rate control only (N= 3,829) | Ablation (N= 3,829) |  |  |  |
| *Including stroke* |  |  |  |  |  |  |  |  |  |
| Overall dementia | 358  | 29942  | 12.0  | 130  | 17933  | 7.2  | 4.7 (2.8-6.6) | 0.59 (0.48-0.72) | <0.001 |
| Alzheimer’s disease | 222  | 30351  | 7.3  | 96  | 18040  | 5.3  | 2.0 (0.5-3.5) | 0.75 (0.59-0.96) | 0.024 |
| Vascular dementia | 96  | 30685  | 3.1  | 28  | 18167  | 1.5  | 1.6 (0.7-2.5) | 0.46 (0.30-0.71) | <0.001 |
| *Censoring for stroke* |  |  |  |  |  |  |  |  |  |
| Overall dementia | 251  | 28107  | 8.9  | 110  | 17419  | 6.3  | 2.6 (0.9-4.3) | 0.68 (0.54-0.86) | 0.001 |
| Alzheimer’s disease | 167  | 28380  | 5.9  | 84  | 17503  | 4.8  | 1.1 (-0.3 to 2.5) | 0.84 (0.64-1.10) | 0.204 |
| Vascular dementia | 53  | 28689  | 1.8  | 21  | 17619  | 1.2  | 0.7 (-0.1 to 1.4) | 0.59 (0.35-0.99) | 0.044 |

\*Adjusted for clinical variables and competing risk of all-cause deaths. Clinical variables included age, sex, income, AF duration, CHA2DS2-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.

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; SE, systemic embolism NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

**Figure Legends**

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

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**Figure 2.** Cumulative incidence curves of overall dementia in propensity matched ablated or medical therapy patients. *Left panel*, Dementia including (not censoring) stroke. *Right panel*, Dementia after censoring for stroke.

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**Figure 3.** Subgroup analyses of the risk of primary composite outcome. CI: confidence interval, HR: hazard ratio, OAC: oral anticoagulant.

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**Figure 4.** Cumulative incidence curves of Alzheimer’s disease (A) and vascular dementia (B) in ablated or medical therapy patients. *Left panel*, including (not censoring) stroke. *Right panel*, after censoring for stroke.

