Ablation Versus Medical Therapy for Atrial Fibrillation in the Elderly: A Propensity Score-Matched Comparison

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Background:
Whether ablation therapy reduces the risk of death and embolic events in elderly patients with atrial fibrillation (AF) remains unclear.

Material/Methods:
AF patients ≥65 years old receiving either catheter ablation or non-ablation therapy at 2 tertiary and 2 non-tertiary hospitals in Beijing from November 2009 to December 2012 were enrolled. Patients were followed up every 6 months for information on treatment and clinical event occurrence. A propensity score matching algorithm produced comparable 2 groups of patients treated with ablation or non-ablation. Rates of a composite of all-cause death, non-fatal stroke, and peripheral embolism were the primary outcomes. Each composite component and major bleeding were the secondary outcomes.

Results:
There were 596 ablated patients and 1144 patients with non-ablation therapy enrolled. Propensity score algorithm matched 347 comparable pairs of patients. Patient characteristics variables were well balanced. During 523.5 and 497.5 patient-years follow-up, respectively, ablation therapy was associated with a significant lower risk of experiencing the primary composite outcome (hazard ratio [HR]=0.40; 95% confidence interval [CI]: 0.19–0.85), all-cause death (HR=0.13 95% CI: 0.04–0.43), and major bleeding (HR=0.23; 95% CI: 0.12–0.67), without apparent heterogeneity by age, sex, and AF type, and for risk score subgroups.

Conclusions:
In this propensity-matched elderly sample, ablation therapy was associated with lower risk of composite outcome consisting of all-cause death, non-fatal stroke, and peripheral embolism, and therefore might be an alternative to conservative therapy.

MeSH Keywords:
Atrial Fibrillation • Catheter Ablation • China • Propensity Score

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Background

Atrial fibrillation (AF), presenting predominantly among the elderly, is a known risk factor for stroke and accounts for up to 15% of all strokes [1]. By 2050, as stated in recent reports, Asia would have more than 2 million AF patients, thus putting 2.9 million patients at risk of AF-associated stroke [2]. China was estimated to have 5.2 million men and 3.1 million women older than 60 years suffering from AF according to recent reported age-adjusted AF prevalence rates [3]. Asia has a much higher overall disease burden because of its proportionally larger aged population [3].

Catheter ablation is increasingly used for atrial fibrillation treatment, and its effectiveness and safety are a subject of active research [4–10]. However, patients recruited in most studies have been relatively young without structural heart disease. A clinical decision is more complicated, as compared to relatively younger patients, in the elderly by their increased susceptibility to side effects on antiarrhythmic drug treatment due to reduced metabolic ability, comorbidities and multiple drug treatment [11,12], and a much higher risk of complications and recurrence with ablation therapy [13].

This prospective observational study aims to compare the effectiveness of ablation and medical therapy in terms of a composite primary outcome of total mortality, non-fatal stroke and peripheral embolism in atrial fibrillation elderly patients matched by propensity score.

Material and Methods

Participating hospitals and patients

Two typical tertiary hospitals (i.e., highly specialized hospitals: Beijing Anzhen Hospital, Capital Medical University, and Peking Union Medical College Hospital) and 2 non-tertiary hospitals without invasive electrophysiology (EP) treatment capabilities (Beijing Luhe Hospital and Beijing Fangshan Hospital) in Beijing urban and suburban areas participated in this study.

All patients aged ≥65 years with evidence of AF episode on electrocardiogram (ECG), Holter monitoring or any other electronic recording methods, were referred to the cardiology departments at the participating hospitals for AF treatment were eligible and consecutively enrolled at each participating center. De-identified data, including patient demographic characteristics, initial assessment and diagnosis, investigations, comorbidity, and final diagnosis and treatment, were entered into a web-based case report form. Data were collected and entered by trained investigators, who were cardiologists and taking care of AF patients as part of their routine clinical work.

Data of 10% of randomly selected patients were validated with their clinical medical record.

Catheter ablation and periprocedural management

Catheter ablation procedures were performed at electrophysiologist's discretion, namely, pulmonary vein isolation (PVI) for paroxysmal AF, and 3 additional linear ablations at the left atrial roof, mitral isthmus between the mitral annulus and left inferior PV and cavotricuspid isthmus for persistent AF [14]. All patients underwent transesophageal echocardiography before the procedure to rule out intra-cardiac thrombus. All patients were anticoagulated for at least 3 months after the procedure, although it could be discontinued when the patient was free from AF.

Medical therapy in non-ablation patients

Medical therapy was at treating physician's discretion. According to current Chinese guidelines for AF management, warfarin use was recommended for all patients with $CHADS_2$ score ≥2 [15], and choice of antiarrhythmic agents included sotalol, amiodarone, or propafenone. For rate control, separate or combined treatments with β-blockers, calcium antagonist, or digitalis were recommended.

Follow-up

Patients were followed up every 6 months until June 30, 2014, by scheduled outpatient clinic visit or, if not possible, by telephone interview by nurses trained on data collection. Clinical information, including stroke and bleeding events, AF episode, AF treatment, and side effects of treatment, were collected at follow-up time points. During follow-up, patients were encouraged to undergo Holter monitoring every month and ECG tracing whenever they felt any symptoms of palpitation or fatigue. We only included patients with complete follow-up data for major clinical events in the analysis. All data collected were entered into the same electronic data capture system.

Outcomes

The primary study outcome was time to event for a composite of all-cause mortality, non-fatal stroke, and peripheral embolism. Incidence rates of each component of the primary outcome and major bleeding were considered as secondary outcomes. We define major bleeding as those requiring transfusion (at least 2 units of whole blood or erythrocytes), those requiring hospitalization or surgery, and those resulting in permanent disability, or involving a critical anatomic site; or any bleeding event that the physician characterizes as "major."

Statistical analyses

Among recruited patients, we calculated the propensity score for receiving a catheter ablation for each patient by using a multivariable logistic regression model [16]. We included those baseline characteristics, assumed to be associated with the probability of having a catheter ablation, in the model as independent variables, including sex, age, body mass index (BMI), type of insurance coverage, socioeconomic status (SES), smoking status, length of AF history, AF type, history of high blood pressure (HBP), diabetes mellitus (DM), coronary artery disease (CAD), stroke, carotid artery stenosis, intracranial hemorrhage, other hemorrhage, heart failure (HF), and use of aspirin or warfarin.

We matched patients receiving ablation and medical therapy patients on a 1: 1 basis by using the propensity scores (with a combination of nearest neighbor algorithm and caliper algorithm). For each patient receiving ablation, another patient receiving medical therapy with the smallest propensity score difference was matched. Patients that were not matched were excluded from the analysis.

We compared patients' characteristics between 2 treatment arms, including demographics, disease characteristics, socioeconomic status, and medication use variables. The 2-sample t-tests were used for continuous variables and χ^2 tests for categorical variables in the aforementioned comparison. Patient characteristics were first compared among the entire groups of patients meeting inclusion or exclusion criteria. They were then compared among the propensity-matched sub-sample, to ensure that the matching process resulted in well-balanced groups.

We used the Kaplan-Meier method and the log-rank test to compare the event rates of the composite primary outcome (i.e., the time to the first event of all-cause mortality, stroke or peripheral embolism) between 2 groups. We also calculated event rates for all-cause mortality, stroke, and peripheral embolism, respectively, by dividing total numbers of first events by the total number of patients for each group.

Ethics approval

The centralized Human Research Ethics Committee at Beijing Anzhen Hospital gave ethics approval for the study (approved date June 3, 2010), and other centers acknowledged this approval. All patients provided consent to be contacted for follow-up.

Results

Characteristics of study patients before and after propensity score matching

From November 2009 to December 2012, 596 consecutive catheter ablation patients, and 1144 consecutive medically treated patients that satisfied the inclusion criteria were included in this study. The propensity-matching algorithm produced 347 pairs of patients. Patient characteristics were summarized for both the overall patient population and the propensity-matched sample in Table 1. Significant differences were observed in demographic and clinical characteristics between the ablation and non-ablation cohorts before propensity score matching. Specifically, patients receiving ablation were relatively younger, more males, less likely to be with hypertension, coronary heart disease, stroke, and heart failure history, and hence a lower $CHADS_2$ score and CHA_2DS_2-VASc score, more likely to have paroxysmal atrial fibrillation and total medical insurance coverage. After matching, the 2 treatment groups had no significant difference for any covariate.

Follow-up

The patients receiving ablation had a total of 523.5 patient-years follow-ups, and 497.5 patient-years in the non-ablation group. During follow-up, 231 out of 293 patients (78.8%), 149 out of 217 patients (68.7%), 127 out of 195 patients (65.1%), 83 out of 139 patients (59.7%), 51 out of 92 patients (55.4%), and 25 out of 44 patients (56.8%) patients in the ablation group were in sinus rhythm at 6, 12, 18, 24, 30, and 36 months, respectively. Compared to non-ablation patients, those patients receiving ablation were less likely to use warfarin. The proportion of patients receiving warfarin in the ablation group were 21.7%, 18.9%, 15.5%,16.7%, 15.2%, and 22.7% of patients at each follow up time point, while the corresponding proportions were 23.0%, 40.1%, 43.3%, 39.6%, 30.6%, and 26.3% in the non-ablation group. The proportions of patients on anti-arrhythmia therapy at every 6 months of follow up were comparable between the 2 groups. The corresponding proportions were 13.0%, 17.4%, 15.6%, 16.0%, 8.7%, and 0% in the ablation group and 12.0%, 16.7%, 17.4%, 19.5%, 10.6%, and 5.3% in the non-ablation group.

Outcomes for matched patients

Figure 1 and Table 2 showed the long-term event rates according to the treatment groups in the matched patients. Patients in the ablation group were at significantly lower risk for the primary outcome composite of all-cause death, non-fatal stroke, and peripheral embolism compared with those treated conservatively (11 over 523.5 patient-years versus 32 over 497.5 patient-years; hazard ratio [HR]=0.40; 95% confidence interval

Table 1. Patient baseline characteristics before and after propensity score matching.

Variables	Before matching				After matching			
	Ablation therapy		Non-ablation therapy		P	Ablation therapy		Non-ablation therapy		P
Age, years	70.8	(4.3)	73.6	(5.5)	0.000	71.3	(4.3)	71.3	(4.2)	0.871
BMI, kg/m^2	25.7	(3.5)	24.7	(4.5)	<0.001	25.4	(3.2)	25.7	(4.5)	0.432
AF history, years	6.9	(6.8)	7.7	(7.1)	0.030	7.0	(7.1)	7.0	(6.2)	0.964
Female gender	225	(39.7%)	522	(46.1%)	0.012	142	(41.6%)	151	(44.3%)	0.486
Type of insurance coverage										
1	318	(66.4%)	882	(85.1%)	<0.001	252	(73.9%)	259	(76.0%)	0.536
2	161	(33.6%)	154	(14.9%)		89	(26.1%)	82	(24.0%)	
Socioeconomic status										
Low	390	(70.8%)	700	(67.4%)	0.164	236	(69.2%)	236	(69.2%)	1.000
High	161	(29.2%)	339	(32.6%)		105	(30.8%)	105	(30.8%)	
Current smoker	90	(16.1%)	100	(9.5%)	<0.001	38	(11.1%)	40	(11.7%)	0.810
AF type										
Paroxysmal	376	(66.2%)	598	(52.7%)	<0.001	217	(63.6%)	222	(65.1%)	0.689
Persistent	192	(33.8%)	536	(47.3%)		124	(36.4%)	119	(34.9%)	
History of HBP	365	(64.8%)	787	(70.5%)	0.019	230	(67.4%)	236	(69.2%)	0.621
History of DM	106	(18.7%)	233	(20.9%)	0.287	59	(17.3%)	70	(20.5%)	0.282
History of CAD	79	(14.0%)	226	(20.3%)	0.002	57	(16.7%)	50	(14.7%)	0.461
History of stroke	68	(12.0%)	250	(22.5%)	<0.001	44	(12.9%)	49	(14.4%)	0.577
History of ICH	4	(0.7%)	15	(1.4%)	0.242	3	(0.9%)	5	(1.5%)	0.477
History of other hemorrhage	3	(0.5%)	21	(1.9%)	0.026	3	(0.9%)	2	(0.6%)	0.654
History of HF	27	(4.8%)	121	(10.9%)	<0.001	21	(6.2%)	18	(5.3%)	0.621
Aspirin use	265	(48.0%)	656	(57.8%)	<0.001	180	(52.8%)	185	(54.3%)	0.701
Warfarin use	188	(33.7%)	268	(23.6%)	<0.001	99	(29.0%)	98	(28.7%)	0.933
CHA$_2$DS$_2$-VASc										
0 or 1	78	(13.7%)	83	(7.3%)	<0.001	40	(11.7%)	32	(9.4%)	0.319
≥2	490	(86.3%)	1051	(92.7%)		301	(88.3%)	309	(90.6%)	

BMI – body mass index; SES – socioeconomic status; AF – atrial fibrillation; HBP – high blood pressure; DM – diabetes mellitus; CAD – coronary artery disease; ICH – intracranial hemorrhage; HF – heart failure.

[CI]: 0.19–0.85; P=0.016). Ablation patients experienced a significantly lower incidence of all-cause death (HR=0.13; 95% CI: 0.04–0.43, P=0.001) and major bleeding (HR=0.23; 95% CI: 0.12–0.67; P=0.004) during follow up, while difference of non-fatal stroke (HR=0.54; 95% CI: 0.23–1.29]; P=0.166) and peripheral embolism incidence did not reach statistical significance (HR=1.83; 95% CI: 0.17–20.13; P=0.623) (Table 2).

Outcomes for different subgroups

As shown in Figure 2, for different age groups (age <75 years or age 65–75 years), different sex, paroxysmal or persistent, higher or lower CHADS$_2$ score, on or off warfarin therapy, ablation therapy was favored over non-ablation therapy in reducing
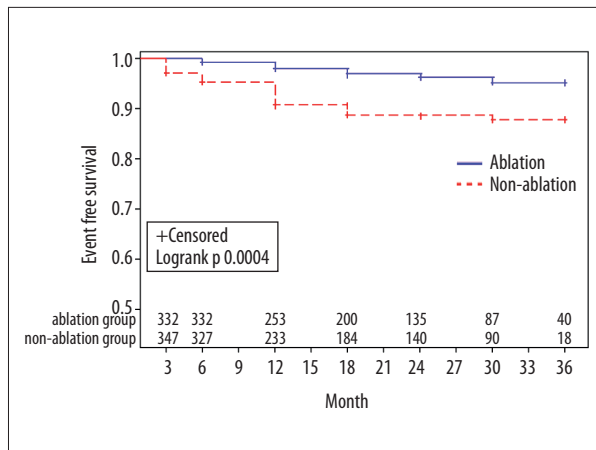
Figure 1. Composite event-free survival in the ablation group and non-ablation group. P-value was calculated using a univariate Cox model.

composite outcome of all-cause death, stroke and peripheral embolism (*P* for heterogeneity all >0.1).

Discussion

In this study, we compared the long-term outcomes of ablation therapy and non-ablation therapy in the present propensity-matched groups. This study showed that elderly AF patients receiving ablation therapy were associated with significantly lower risk in a composite outcome of death, non-fatal stroke, and peripheral embolism compared with those treated with non-ablation therapy, while an insignificant difference of non-fatal stroke and peripheral embolism incidence between the aforementioned 2 treatment strategies. The results were consistent across different subgroups, including patients 75 years or older or patients between 65–75 years old, male or female patients, paroxysmal or persistent AF, higher or lower CHADS$_2$ score, off or on warfarin therapy.

Our study was in line with previous studies, showing that sinus rhythm maintenance achieved by ablation strategy in AF patients is associated with a lower risk of stroke and death [17,18]. Ablation therapy wasn't more effective, as recently shown in the CABANA trial, in reducing composite events of death, disabling stroke, serious bleeding, or cardiac arrest, both in the main results and subgroup analysis of elderly patients, however, the CABANA trial failed to detect the difference between ablation and non-ablation in the elderly population [9]. Compared with previous studies, this study provided valuable information in several ways: First, this was a direct comparison between 2 treatment strategies rather than indirect comparison using administrative data or simulation study. Data reliability was strengthened by the more balanced comparison between

Table 2. Incidence of all-cause death, stroke, peripheral embolism, and major bleeding during follow-up.

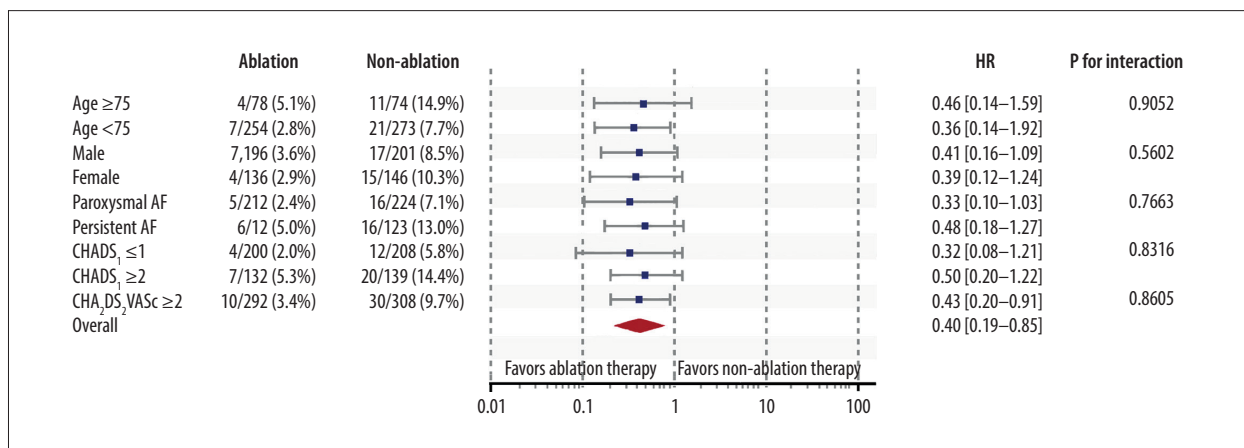|	Ablation		Non-ablation		Hazard ratio		*P*
Composite outcome	11	(3.1%)	32	(9.2%)	0.40	[0.19–0.85]	0.016
All-cause death	4	(1.2%)	20	(5.8%)	0.13	[0.04–0.43]	0.001
Stroke	8	(2.4%)	19	(5.6%)	0.54	[0.23–1.29]	0.166
Peripheral embolism	2	(0.6%)	4	(1.2%)	1.83	[0.17–20.13]	0.623
Major bleeding	7	(2.1%)	30	(8.6%)	0.23	[0.12–0.67]	0.004

Figure 2. The treatment effect of ablation therapy on composite endpoints in different subgroups.

2 propensity score-matched groups. Previous studies had suggested that matching according to the propensity score eliminates a greater proportion of baseline differences between 2 treatments than covariate adjustment [20]. Second, this was one of the largest case series comparing different strategies using real-world practice data. The components of the composite primary outcome of all-cause death, stroke, and peripheral embolism were all clinically relevant. This was an advantage compared with those studies using the maintenance of sinus rhythm *per se* as the primary endpoint. Third, all participating patients were Chinese, a subgroup of patients less represented in clinical trials and might have a different profile of stroke and bleeding risk [3]. Previous studies showed that Asian patients were at fourfold risk of major bleeding when taking oral anticoagulants while relative risk reduction in stroke was smaller [21,22]. Fourth, this study focused on elderly patients, for whom there were scant data on disease presentation and management. Elderly AF patients usually had more significant atrial fibrosis, and the success rate of ablation therapy may differ from that in younger patients [23,24]. Elderly patients also had more comorbidities and were less tolerant of antiarrhythmic drugs and anticoagulant therapy [11].

Limitations

The study is subject to several limitations. First, the study is an observational study. Although AF patients treated with ablation and non-ablation therapy were matched through a propensity score, which may minimize the patient selection biases. We are confident that known variables are well balanced between 2 groups, but unknown confounders can still affect results. Second, treatment was not optimal, with about 40% of patients in the non-ablation group receiving warfarin therapy during the follow-up. However, the underuse of anticoagulants is a common reality in many countries. For instance, in registry studies in Japan, anticoagulant therapy use rate was 53% patients [25] in a Swedish registry, 46% of AF patients received warfarin therapy [26], while in a worldwide registry study, which involved 540 sites in 19 countries, 38% of high-risk patients did not receive anticoagulant therapy [27]. Moreover, even in the best practice environment in clinical trials, as high as 20% of patients cannot tolerate long-term anticoagulant therapy [28]. Even we assume that all patients in the non-ablation group received anticoagulant therapy, the current results are less likely to be reverted because warfarin therapy reduces mortality by 26% and risk of stroke by two-thirds [29] while in this study, patients were at 3 times higher risk of experiencing an event under current treatment.

Conclusions

This study employed the registry method and used propensity score to match imbalanced groups, which was increasingly recognized as valuable, given that randomized clinical trials were cumbersome and onerous to conduct. Our results suggested that ablation therapy seemed to be associated with a significantly lower risk of composite outcome consisting of all-cause death, non-fatal stroke and peripheral embolism than medical therapy in managing elderly AF patients and could be considered as an alternative to medical therapy.

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