Atrial fibrillation ablation patients have long-term stroke rates similar to patients without atrial fibrillation regardless of CHADS2 score

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BACKGROUND Atrial fibrillation (AF) is a leading cause of total and fatal ischemic stroke. Stroke risk after AF ablation appears to be favorably affected; however, it is largely unknown whether the benefit extends to all stroke CHADS2 risk profiles of AF patients.

OBJECTIVE To determine if ablation of atrial fibrillation reduces stroke rates in all risk groups.

METHODS A total of 4212 consecutive patients who underwent AF ablation were compared (1:4) with 16,848 age-/sex-matched controls with AF (no ablation) and to 16,848 age-/sex-matched controls without AF. Patients were enrolled from the large ongoing prospective Intermountain Atrial Fibrillation Study and were followed for at least 3 years.

RESULTS Of the 37,908 patients, the mean age was 65.0 ± 13 years and 4.4% (no AF), 6.3% (AF, no ablation), and 4.5% (AF ablation) patients had a prior stroke ($P < .0001$). The profile of CHADS2 scores between comparative groups was similar: 0–1 (69.3%, no AF; 62.3%, AF, no ablation; 63.6%, AF ablation), 2–3 (26.5%, no AF; 29.7%, AF, no ablation; 28.7%, AF ablation), and ≥4 (4.3%, no AF; 8.0%, AF, no ablation; 7.7%, AF ablation). A total of 1296 (3.4%) patients had a stroke over the follow-up period. Across all CHADS2 profiles and ages, AF patients with ablation had a lower long-term risk of stroke compared to patients without ablation. Furthermore, AF ablation patients had similar long-term risks of stroke across all CHADS2 profiles and ages compared to patients with no history of AF.

CONCLUSIONS In our study populations, AF ablation patients have a significantly lower risk of stroke compared to AF patients who do not undergo ablation independent of baseline stroke risk score.

KEYWORDS Atrial fibrillation; Catheter ablation; Stroke; Risk factors; Atrium

ABBREVIATIONS **AF** = atrial fibrillation; **CVA** = cerebrovascular accident; ***ICD-9*** = *International Classification of Diseases, Ninth Revision*; **OR** = odds ratio

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Introduction

Atrial fibrillation (AF) is a leading cause of total and fatal ischemic stroke. It is estimated that AF accounts for 15% of all strokes.[1,2] Furthermore, in patients who have no immediate cause of stroke identified, AF is often documented subsequently with extended monitoring.[3] The finding of subsequent atrial tachyarrhythmias also conveys an additional risk of subsequent stroke.[4]

In AF patients, the CHADS2 risk score has reproducibly identified patients who have higher risks of stroke.[5,6] In addition, the CHADS2 score risk factor components have prognostic value for general cardiovascular morbidity and mortality risk.[6]

Recently, rhythm control strategies have emerged as possible tools to decrease stroke risk in AF patients. For example, in the ATHENA trial, dronedarone-treated patients had a lower stroke risk over the study follow-up compared to those who received placebo.[6] Regarding nonpharmacologic treatment, we examined stroke risk after ablation and found a lower overall risk compared to AF patients not treated with ablation. Furthermore, we found that the stroke risk over time of AF patients treated with ablation was similar to patients with no history of AF.[7] Also, AF patients after ablation with moderate to high risk CHADS2 scores in which warfarin was discontinued do not show a higher risk of stroke compared to those in which warfarin is continued.[8]

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In patients with low to moderate risk after ablation (CHADS2 score ≤2), the calculated stroke risk is 0.06% per year treated with long-term antiplatelet therapy only.[9]

Potential mechanisms of stroke reduction after ablation have not been elucidated. It is plausible that the observed benefit relates to lowering AF burden and favorable remodeling of the left atrium in those patients in which AF caused atrial myopathy.[10] However, it is also plausible that more fit patients or less risky patients are selected for ablation procedures that inherently have a lower stroke risk. In this regard, we would not anticipate a benefit in higher risk stroke patients after AF ablation. To further understand the effect of AF ablation on stroke risk, we examined the long-term risk of stroke after ablation compared to AF patients who did not undergo ablation and non-AF patients and specifically evaluated the potential benefit across all CHADS2 risk strata.

Methods

Patient populations

Three cohorts of patients were studied: patients with AF who had undergone ablation, patients with AF who did not undergo ablation, and patients without a history of AF. Ablation patients were drawn from the large ongoing prospective Intermountain Atrial Fibrillation Study Registry, which comprises all health-care facilities within the Intermountain Healthcare network. Patients who underwent ablation from all Intermountain Healthcare facilities capable of performing AF ablation were included. The ablation approach, postablation anticoagulation strategy, and follow-up schedule were determined by the patient's electrophysiologist and not by a system-wide protocol. Control populations, patients with AF who did not undergo ablation, and a no AF population were matched 4:1 by age (±2 years) and sex to AF ablation patients. The latter patients were found to have no history of AF through the examination of all clinical notes, *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis codes, and the system-wide electrocardiogram database. These patients of whom we had at least 3 years of follow-up data comprise those previously studied in the general outcomes study report.[7] The enrollment periods for these patients were as follows: No AF: September 9, 1993, to November 24, 2009; AF, no ablation: January 12, 1984, to November 4, 2009; and AF, ablation: January 15, 1999, to November 2, 2009. The Intermountain Healthcare Urban Central Region Institutional Review Board approved this study.

Other risk factors, demographics, and patient follow-up and event assessment

In addition to age and sex, patient information collected included diabetes, hypertension, hyperlipidemia, heart failure, and renal failure. These risk factors were determined by using *ICD-9* diagnosis codes at or before the index date. Prior cerebrovascular accident (CVA), transient ischemic attack, and myocardial infarction were determined by using previous *ICD-9* discharge diagnosis codes.

Table 1 Baseline demographics of the study population

Characteristic	No AF (n = 16,848)	AF, no ablation (n = 16,848)	AF, ablation (n = 4212)
Age (y)	64.1 ± 13.0	66.0 ± 13.3	64.8 ± 12.7
Sex: male	60.8%	60.8%	60.8%
Hyperlipidemia	58.4%	37.3%	44.0%
Hypertension	41.2%	45.3%	47.8%
Diabetes	19.0%	21.1%	16.3%
Heart failure	14.5%	23.6%	29.5%
Renal failure	5.6%	7.8%	7.5%
MI history	10.0%	6.4%	6.4%
TIA history	4.0%	4.2%	4.6%
CVA history	4.4%	6.3%	4.5%
Valve history	10.9%	14.8%	27.7%
CHADS2 score			
0	41.0%	35.7%	38.7%
1	28.3%	26.6%	24.9%
2	17.9%	18.2%	16.5%
3	8.6%	11.5%	12.2%
4	2.9%	5.1%	5.2%
5	1.2%	2.3%	2.0%
6	0.2%	0.6%	0.5%
EF (n = 10,004)	60.0 ± 16.0	56.1 ± 15.9	51.3 ± 13.8

AF = atrial fibrillation; CVA = cerebrovascular accident; EF = ejection fraction; MI = myocardial infraction; TIA = transient ischemic attack.

The mean length of follow-up was 2.9 ± 2.9 years. The primary outcome of interest was CVA (referred to herein as stroke) and was determined through the examination of *ICD-9* diagnosis codes: 436*, 433._1*, and 434._1*.

Analysis

The Student *t* test and the χ^2 test were used to evaluate baseline and clinical characteristics among patients with and without AF. Multivariable Cox hazard regression analysis (SPSS, version 15.0) was used to evaluate the association of AF with the incidence of the study end point. For each CVA, a model was developed that included only confounding and significant covariables. Covariables included baseline risk factors, identified through *ICD-9* diagnosis codes, that were documented either at or before the index (baseline) date (Table 1). All comorbidities were baseline and predated the end points. For the ablation group, demographics were collected at the time of the first documented ablation procedure. Final models entered the significant ($P < .05$) and confounding (10% change in hazard ratio) covariables. Two-tailed P values of $<.05$ were designated to be nominally significant. A Bonferroni-adjusted P value of .025 (0.05/2) will be deemed as significant in the regression analyses to account for multiple comparisons (AF, no ablation vs no AF cohorts and AF, ablation vs no AF cohorts). We estimated survival free rates by using the Kaplan-Meier method for CVA. CVA rates were further compared by using CHADS2 strata.

Results

A total of 37,908 patients were included in the study. This included 4212 patients who underwent a catheter ablation for

symptomatic AF. A second 4:1 matched population was created of patients with AF who had a history of AF and did not undergo catheter ablation (n = 16,848). Finally, a third 4:1 matched population was created of patients with no clinical or electrocardiographic history of AF.

The baseline demographics of these 3 groups are listed in Table 1. The no AF group was younger and had lower rates of hypertension, heart failure, renal failure, and valve disease ($P < .05$) compared to the other 2 groups. The AF group who did not undergo ablation was slightly older and had a higher rate of diabetes and a prior stroke ($P < .05$). The AF ablation group had higher rates of hypertension, transient ischemic attack, and valvular heart disease ($P < .05$). The CHADS2 risk profiles were similar among groups; however, more patients with no history of AF had scores from 0 to 1.

At 1 year, 893 (2.4%) patients had a stroke. There was a significantly higher rate in those patients with AF who did not undergo ablation (3.5%, n = 590) compared to those with AF who underwent ablation (1.4%, n = 61) and those with no history of AF (1.4%, n = 242) (P trend <.0001). The rates between those who had ablation and those with no history of ablation were identical. The risk of stroke in AF patients not treated with ablation compared to those treated with ablation remained significant in univariate (odds ratio [OR] 2.49; $P < .0001$) and multivariate (OR 2.06; $P < .0001$) adjustment. The equivalence in this outcome between AF patients treated with ablation and those with no AF remained with both univariate (OR 1.01; $P = .95$) and multivariate (OR 0.95; $P = .74$) adjustment. The demographics of those patients who had a stroke during the first year of follow-up are listed in Table 2. The CHADS2 risk factors among the groups were relatively evenly distributed ($P = .20$). The no AF group was slightly younger than the other groups, and AF patients who underwent ablation more often were labeled as having valve disease.

We then examined long-term stroke by age among AF patients. The results are listed in Table 3. In all age group strata, there were lower stroke rates in AF patients who underwent ablation compared to those who did not. Finally, we sought to determine whether a benefit regarding long-term risk of stroke was observed not only across all age groups but also across the spectrum of CHADS2 risk profiles (Table 4). Figure 1 displays Kaplan-Meier survival curves of freedom from stroke based on AF status and treatment and CHADS2 risk score. Figure 2 displays the multivariate adjusted hazard ratios for the risk of stroke in patients with AF who underwent ablation, patients with AF who did not undergo ablation, and no AF patients. Figure 3 displays the multivariate adjusted hazard ratios for the risk of stroke in patients with AF who did not undergo ablation versus those without AF. In general, across all ages and risk profiles, there was a lower risk of stroke after catheter ablation. Of the baseline demographics in the AF ablation group, a history of stroke was the risk factor most associated with the future risk of stroke (OR 11.9; $P < .0001$). Figure 4 displays the multivariate adjusted hazard ratios for the risk of stroke in patients with AF who underwent ablation and in patients who had no history of AF. Across all age and risk strata, the risk of stroke was similar in these 2 groups.

Table 2 Baseline demographics of AF and non-AF patients who experienced a stroke at 1 y

Characteristic	No AF	AF, no ablation	AF, ablation	*P*
No. of patients	242	590	61	
Age (y)	67.0 ± 12.4	70.8 ± 11.0	70.0 ± 12.4	<.0001
Sex: male	53.3%	51.5%	47.5%	.71
Hyperlipidemia	59.1%	35.3%	50.8%	<.0001
Hypertension	56.6%	55.8%	65.6%	.34
Diabetes	29.3%	27.8%	23.0%	.61
Heart failure	23.1%	30.7%	45.9%	.002
Renal failure	7.4%	8.8%	11.5%	.58
MI history	9.5%	7.8%	16.4%	.07
TIA history	16.1%	11.9%	9.8%	.19
CVA history	40.9%	37.8%	31.1%	.35
Valve history	20.2%	19.8%	42.6%	<.0001
CHADS2 score				.20
0	16.9%	16.6%	19.7%	
1	16.5%	19.2%	19.7%	
2	21.1%	18.0%	4.9%	
3	23.1%	18.6%	24.6%	
4	12.0%	16..8%	19.7%	
5	9.5%	9.2%	8.2%	
6	0.8%	1.7%	3.3%	
EF (n = 148)	57.9 ± 16.0	51.0 ± 21.5	54.7 ± 10.5	.40

AF = atrial fibrillation; CVA = cerebrovascular accident; EF = ejection fraction; MI = myocardial infraction; TIA = transient ischemic attack.

Discussion

AF ablation patients have a significantly lower risk of stroke compared to AF patients who do not undergo ablation. The lower risk spans across all age groups studied with the most significant benefit observed in younger patients. Furthermore, the observed reduction in stroke persists across all CHADS2 risk profiles.

More compelling are the data comparing AF patients who undergo ablation to patients with no identifiable history of AF. We previously found that AF increases risk of stroke across all CHADS2 risk profiles compared to patients with no history of AF.[6] In addition, among patients who present for AF ablation, the CHADS2 risk factors also increase the likelihood of echo-contrast sludge and clot in the left atrial appendage as well as reduction in the appendage emptying velocities: echocardiographic findings suggestive of a higher risk of stroke.[11] The age- and CHADS2 risk-profile data that compared patients who underwent ablation with patients with no history of AF found long-term risk of stroke were similar. These data in part suggest that ablation, and the process and subsequent care associated with ablation, can favorably affect the natural history and consequences of AF. However, it must be emphasized that since these data are derived from a multicenter observation design, we do not have accurate data on long-term success rates of AF recurrence, particularly, subclinical AF. As such, we continue to advocate long-term stroke prevention strategies based on the

Table 3 Age-based long-term stroke rates among AF patients who underwent ablation compared to those AF patients who did not underwent ablation

Age	AF, no ablation	AF, ablation	*P*	Univariate HR for ablation	Multivariate HR for ablation
<60, n = 5638	3.6%	1.3%	<.0001	0.38, *P* < .0001	0.38, *P* < .0001
60–69, n = 5804	5.6%	2.9%	<.0001	0.50, *P* < .0001	0.59, *P* = .005
70–79, n = 7082	8.7%	3.8%	<.0001	0.42, *P* < .0001	0.50, *P* < .0001
≥80, n = 2536	8.6%	5.8%	.07	0.55, *P* = .009	0.72, *P* = .17

AF = atrial fibrillation; HR = hazard ratio.

CHADS2 score, regardless of whether ablation was performed, until prospective data are available.

The compelling question remaining is how AF ablation changes the natural history of AF as it relates to CVA. Typically AF severity, most easily quantified as episodes and duration of AF, will increase over time.[12] The progression is not uniform, and not all patients who develop paroxysmal AF will progress to persistent/long-standing persistent AF.[13] As the atrium is repetitively exposed to AF, early atrial contractile remodeling occurs.[12] If AF persists, structural remodeling develops.[12] Permanent changes occur as focal and then regional fibrosis develop in the left atrium.[14] These structural, anatomic, and functional changes are all associated with stroke in patients with AF.[11,14] It is possible that ablation early in the disease process, by either maintaining sinus rhythm or significantly reducing AF burden, can stop the progression of the structural, anatomic, and functional changes in the atrium.[10] This postulate is supported by serial echocardiographic assessments of atrial function over time after ablaton.[10]

Clearly there are risks associated with AF ablation, which may also increase stroke risk. AF ablation causes intentional scar/fibrosis in the left atrium[15]; if the injury is significant, it can cause mechanical dysfunction.[16] Also, there is risk of periprocedural stroke, in particular subclinical stroke, which as of yet is not fully understood and quantified.[17] These risks are likely modifiable by limiting the extent of the ablation performed and by careful and continuous use of anticoagulation.

Another potential advantage with catheter ablation is reducing dependency on antiarrhythmic medications for long-term rhythm control. Long-term pharmacologic management can be challenging, particularly as the patient ages.[18] There are changes in metabolism, drug clearance, and, with the acquisition of additional cardiovascular diseases, the potential for drug-to-drug interactions.[18] These changes can alter a patient's functional status and also the risk for, use of, and patient selection for anticoagulation. As such, although catheter ablation has significant risks, these risks typically are realized upfront with the procedure whereas those with medications are observed continually over time.

Another possibility is that patients who have ablation may be more aggressive about addressing their AF risk and as such are more likely to also receive treatment for other risk factors of stroke, such as hypertension, diabetes, and heart failure. For example, the presence of heart failure, a potentially modifiable risk factor, in patients with AF presenting for ablation was the most commonly associated variable that resulted in the presence of left atrial appendage mechanical dysfunction, appendage clot, and sludge.[11] This is likely not the only mechanism, as we observed a benefit with AF ablation across the entire spectrum of CHADS2 risk scores, including patients who had acquired many disease states.

There is also the possibility that more fit or healthy patients are chosen for AF ablation. As such, they are less likely to experience morbidity and mortality associated with the disease. For this reason, we performed this risk-stratified study and found that there was a pervasive stroke-related benefit across all risk factors that we assessed. Nonetheless, the observational study design used cannot completely exclude this possibility as a mechanism behind the observed outcomes.

Study limitations

Our study has several important limitations. The study is observational and may be subject to incomplete correction for important covariables and confounders. The study is

Table 4 CHADS-2 score based long-term stroke rates among AF patients who underwent ablation compared to those AF patients who did not undergo ablation

CHADS2	No AF	AF, no ablation	AF, ablation	*P* score
0	2.6% (178 of 6902)	3.7% (220 of 6017)	1.6% (26 of 1628)	<.0001
1	3.0% (144 of 4772)	5.4% (243 of 4477)	1.9% (20 of 1050)	<.0001
2	4.3% (129 of 3015)	7.1% (217 of 3072)	2.2% (15 of 696)	<.0001
3	7.4% (108 of 1452)	9.0% (174 of 1939)	6.1% (31of 512)	.06
4	10.7% (52 of 484)	17.6% (152 of 864)	9.1% (20 of 220)	<.0001
≥5	13.9% (31 of 223)	18.6% (89 of 479)	13.2% (14 of 106)	.18

AF = atrial fibrillation.

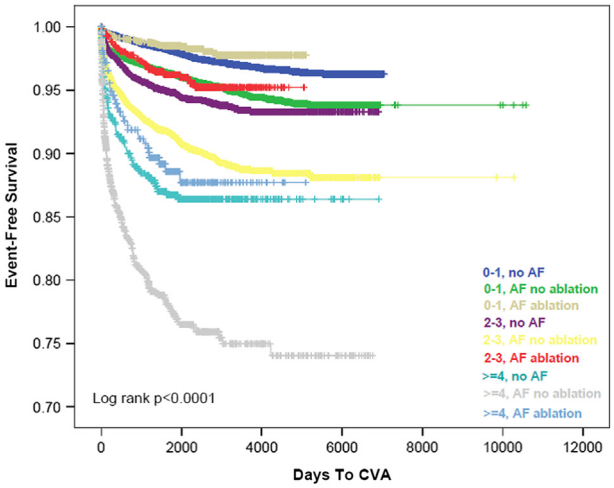

Figure 1 Kaplan-Meier survival estimates are displayed. The survival curves are displayed in 3 groups (atrial fibrillation [AF] no ablation, AF ablation, and no AF) and compared by CHADS2 risk score (0–1, 2–3, ≥4). In all comparisons, patients with AF who did not undergo ablation had early and persistent lower survival free of cerebral vascular accident (stroke) compared to AF ablation patients and patients without AF. AF ablation and no AF patients had similar survival curves. CVA = cerebrovascular accident.

derived from a large consecutive population of AF patients and no AF patients with long-term follow-up. In addition, the only inclusion criteria for the AF ablation population were that we had available long-term follow-up information. All other procedure variables and follow-up strategies were included, as we used patients from all multiple centers in which the procedure was performed. For the control population, attempts were made to match variables in a way that demographics were similar in order to allow a more specific

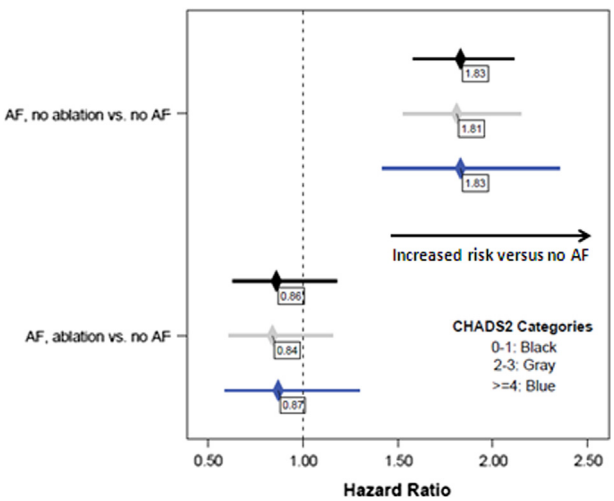

Figure 2 Multivariate hazard ratios (HRs) are displayed for patients with atrial fibrillation (AF) who did not undergo ablation (top 3) and AF patients who underwent ablation (bottom 3) versus patients with no known history of AF. An HR > 1.0 indicates an increased risk of stroke in AF patients not treated with ablation. HRs are displayed by CHADS2 risk scores. Across all categories and subcategories, HR >1.0 are noted in AF ablation patients who did not undergo ablation versus no AF patients. Across all categories and subcategories, HR crossed 1.0 in AF ablation patients versus no AF patients.

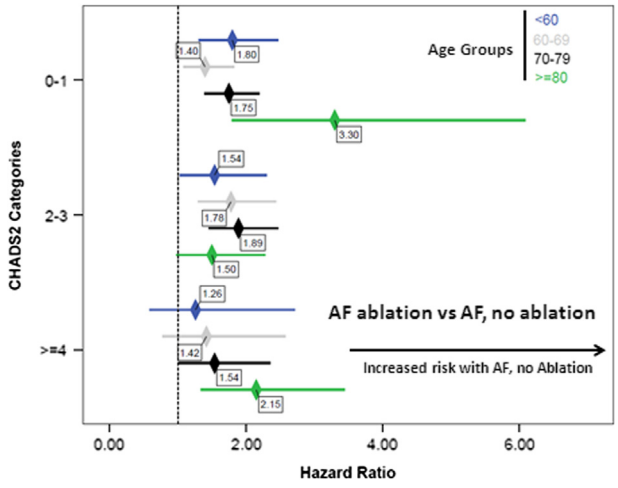

Figure 3 Multivariate hazard ratios (HRs) are displayed for patients with atrial fibrillation (AF) who did not undergo ablation versus patients with no known history of AF. An HR > 1.0 indicates an increased risk of stroke in AF patients not treated with ablation. HRs are displayed by age and CHADS2 risk scores. Across all categories and subcategories, HR >1.0 are noted in AF ablation patients who did not undergo ablation.

understanding of the role of AF treatment and outcomes. Another limitation is that we have no data available in the large population regarding anticoagulation strategy, compliance to anticoagulation, or physician adherence to guidelines regarding anticoagulation. It has been the general practice in these institutions to use warfarin or a similar anticoagulant long-term if the CHADS2 score is >2 regardless of the rhythm control strategy. Decisions to interrupt or change anticoagulation strategies outside the current guidelines should only be made on the basis of prospective randomized data when it becomes available. Finally, we used *ICD-9* diagnosis codes to determine CVA, and as such we recognize that this can be subject to occasional misdiagnosis. We

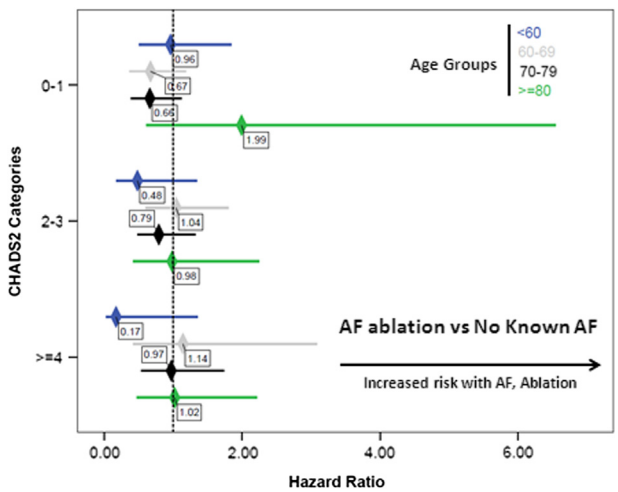

Figure 4 Multivariate hazard ratios (HRs) are displayed for patients with atrial fibrillation (AF) who underwent ablation versus patients with no known history of AF. An HR > 1.0 indicates an increased risk of stroke in AF patients treated with ablation. HRs are displayed by age and CHADS2 risk scores. Across all categories and subcategories, no significant increase in risk was found for transient ischemic attack or stroke despite the presence of AF in the ablation group.

attempted to minimize this by using *ICD-9* diagnosis codes of CVA that were associated with the primary diagnosis on an inpatient admission.

Conclusions

In our study populations, AF ablation patients have a significantly lower risk of stroke compared to AF patients who do not undergo ablation independent of baseline stroke risk. The lower risk persists across all age-related strata and is independent of the CHADS2 risk score. These long-term data coupled with the observation that risks are similar to patients without AF suggest that ablation treatment favorably affects stroke risk in AF.

References

1. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology 1978;28:973–977.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–988.
3. Seet RC, Friedman PA, Rabinstein AA. Prolonged rhythm monitoring for the detection of occult paroxysmal atrial fibrillation in ischemic stroke of unknown cause. Circulation 2011;124:477–486.
4. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. New Engl J Med 2012;366:120–129.
5. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–2870.
6. Crandall MA, Horne BD, Day JD, et al. Atrial fibrillation significantly increases total mortality and stroke risk beyond that conveyed by the CHADS2 risk factors. Pacing Clin Electrophysiol 2009;32:981–986.
7. Bunch TJ, Crandall BG, Weiss JP, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. J Cardiovasc Electrophysiol 2011;22:839–845.
8. Themistoclakis S, Corrado A, Marchlinski FE, et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. J Am Coll Cardiol 2010;55:735–743.
9. Hussein AA, Saliba WI, Martin DO, et al. Natural history and long-term outcomes of ablated atrial fibrillation. Circ Arrhythm Electrophysiol 2011;4:271–278.
10. Muller H, Noble S, Keller PF, et al. Biatrial anatomical reverse remodelling after radiofrequency catheter ablation for atrial fibrillation: evidence from real-time three-dimensional echocardiography. Europace 2008;10:1073–1078.
11. Puwanant S, Varr BC, Shrestha K, et al. Role of the CHADS2 score in the evaluation of thromboembolic risk in patients with atrial fibrillation undergoing transesophageal echocardiography before pulmonary vein isolation. J Am Coll Cardiol 2009;54:2032–2039.
12. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 2002;54:230–246.
13. Jahangir A, Lee V, Friedman PA, et al. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. Circulation 2007;115:3050–3056.
14. Daccarett M, Badger TJ, Akoum N, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. J Am Coll Cardiol 2011;57:831–838.
15. Badger TJ, Oakes RS, Daccarett M, et al. Temporal left atrial lesion formation after ablation of atrial fibrillation. Heart Rhythm 2009;6:161–168.
16. Gibson DN, Di Biase L, Mohanty P, et al. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors. Heart Rhythm 2011;8:1364–1371.
17. Haeusler KG, Koch L, Herm J, et al. 3 Tesla MRI-detected brain lesions after pulmonary vein isolation for atrial fibrillation: results of the MACPAF study. J Cardiovasc Electrophysiol 2013;24:14–21.
18. Chatap G, Giraud K, Vincent JP. Atrial fibrillation in the elderly: facts and management. Drugs Aging 2002;19:819–846.