

# Stroke rates before and after ablation of atrial fibrillation and in propensity-matched controls in the UK

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**Background:** We sought to determine whether catheter ablation of atrial fibrillation (AF) is associated with reduced occurrence of ischemic cerebrovascular events.

**Methods and results:** Using routinely collected hospital data, ablation patients were matched to two control cohorts via direct and propensity score matching. A total of 4,991 ablation patients were matched 1:1 to general AF controls with no ablation, and 5,407 ablation patients were similarly matched to controls who underwent cardioversion. Yearly rates of ischemic stroke or transient ischemic attack (stroke/TIA) before and after an index date were compared between cohorts. Index date was defined as the first ablation, the first cardioversion, or the second AF event in the general AF cohort. Matched populations had very similar demographic and comorbidity profiles, including nearly identical CHA<sub>2</sub>DS<sub>2</sub>-VASc risk distribution (*p*-values 0.6948 and 0.8152 vs general AF and cardioversion cohorts). Statistical models of stroke/TIA risk in the preindex period showed no difference in annual event rates between cohorts (mean±standard error 0.30% ± 0.08% ablation vs 0.28% ± 0.07% general AF, *p*=0.8292; 0.37% ± 0.09% ablation vs 0.42% ± 0.08% cardioversion, *p*=0.5198). Postindex models showed significantly lower annual rates of stroke/TIA in ablation patients compared with each control group over 5 years (0.64% ± 0.11% ablation vs 1.84% ± 0.23% general AF, *p*<0.0001; 0.82% ± 0.15% ablation vs 1.37% ± 0.18% cardioversion, *p*=0.0222).

**Conclusion:** Matching resulted in cohorts having the same baseline risks and rates of ischemic cerebrovascular events. After the index date, there were significantly lower yearly event rates in the ablation cohort. These results suggest the divergence in outcome rates stems from variance in the treatment pathways beginning at the index date.

**Keywords:** atrial fibrillation, catheter ablation, cardioversion, ischemic stroke, repeated measure

## Introduction

Stroke is the second most common cause of death worldwide,<sup>1</sup> and its risk is increased five times with atrial fibrillation (AF).<sup>2</sup> While catheter ablation reduces the burden of AF compared with drug therapy,<sup>3,4</sup> it is not known whether this results in reduced stroke risk.<sup>5</sup> Large randomized trials on this subject – Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial and Early Treatment of Atrial Fibrillation for Stroke Prevention Trial – will not report for several years. Several retrospective cohort design studies have addressed the same question but are limited by potential confounding due to unmeasured risks.<sup>6–10</sup>

We sought to overcome this key limitation by examining trends over time within the same populations. Using routinely collected data, we examined rates of ischemic stroke or transient ischemic attack (stroke/TIA) in patients undergoing ablation and two

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matched control cohorts with AF, one having undergone direct current cardioversion. Comparing stroke/TIA rates across cohorts and over time, we hypothesized that there would be a difference in temporal trends after the intervention date.

## Methods

### Data source

The data source for this study was an anonymized dataset of predefined variables created from the Hospital Episode Statistics (HES) data warehouse, including records from 1996 to 2013. HES contains details of all hospital admissions, outpatient appointments, and accident and emergency attendances at National Health Service hospitals in England. HES records include clinical diagnoses and procedures; patient demographics; and administrative information from inpatient visits since 1989, outpatient visits since 2003, and accident and emergency visits since 2007. The records used for this study included all patients with a diagnosis of AF International Classification of Diseases, tenth edition (ICD-10 code I48) recorded at any time prior to the end of 2013.

### Patient selection

Patients included in the analysis population for this study were required to have at least one AF diagnosis (ICD-10 code I48) during or after 2008 to ensure capture of contemporary treatments. Patients with a record of AF prior to April 2005 were excluded to eliminate patients known to have very long-standing AF. In addition, patients were excluded for diagnoses or procedures denoting evidence of valvular heart disease, atrioventricular node ablation, pacemaker, implantable cardioverter defibrillator, or any operation on the heart conduction system at or prior to the cohort-specific index date (Table S1).

### Cohort selection

From the selected patients, a pulmonary vein ablation (PVA) treatment cohort was defined as those patients who had an AF ablation incorporating percutaneous transluminal pulmonary vein isolation (ICD-10 procedure code K621) as their primary procedure, simultaneously with a primary AF diagnosis. Exclusions for this cohort included any additional catheter or surgical ablation of the heart prior to the index PVA (Table S1). A general AF control cohort was defined as those patients with at least two hospital records and no catheter or surgical ablation of the heart at any time. Additionally, a cardioversion control cohort was defined as the subset of the general AF control cohort with a record of direct current cardioversion (ICD-10 procedure code X501 or X502) simultaneously with a primary AF diagnosis.

## Baseline definitions and data conventions

The index date (time zero) was defined as the date of the first PVA, the first cardioversion, and the second hospital record of any type in the dataset, for the PVA, cardioversion, and general AF cohorts, respectively.

Baseline risk factors were defined via diagnosis and procedure codes observed within 3 years prior to a patient's index date (Table S1). Risk factors included diagnoses of previous stroke or TIA, hypertension, diabetes mellitus, heart failure, peripheral vascular disease, coronary artery disease, sleep apnea, hemorrhagic stroke, cardiomyopathy, obesity, other arrhythmias or conduction disorders, chronic kidney disease, COPD, hyperlipidemia, and pulmonary disease, as well as procedures for coronary artery bypass graft and percutaneous coronary intervention. CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores<sup>11,12</sup> for stroke risk were also calculated.

## Cohort matching

In order to reduce selection bias and create cohorts of patients that were clinically well matched with respect to available risk information, a combination of propensity and direct matching was used to match ablation patients in a 1:1 ratio with patients in the general AF control cohort, and separately to patients in the cardioversion cohort.

Propensity scores, defined as the patients' probabilities of having PVA treatment based on their individual characteristics at or prior to their index date, were calculated separately for each control cohort from logistic regression models. Potential predictors in the propensity models included all baseline risk factors, as previously defined, with stepwise selection used to retain only those conditions that significantly impacted treatment cohort. The resulting propensity scores summarize patients' probabilities of being in the ablation cohort vs each control cohort given their unique baseline comorbidity profile.

The two sets of propensity score, one for each control group, were used simultaneously with additional metrics to match ablation patients with general AF controls and separately with cardioversion controls. A SAS macro called *gmatch*, developed by the Mayo Clinic Biomedical Statistics and Informatics Division, was used to match patients in a 1:1 ratio on age, sex, year of index date, time from AF diagnosis to index date, and the resulting comorbidity-based propensity scores.<sup>13</sup>

## Stroke endpoints

The primary outcomes of interest were occurrence of ischemic stroke/TIA (ICD-10 diagnosis codes I63-I64x, G45) within

1-year intervals over equal time spans before and after a patient's index date. The pre- and postindex analysis interval for each patient was equal to their follow-up from index date to last visit. Hospital and specialty care records were assumed to be comprehensive for all patients within this interval.

Binary stroke/TIA endpoints were created for each patient, for each year of their analysis interval, to indicate the occurrence of ischemic stroke or TIA events within the year. Patients with a stroke/TIA in a postindex year for which they did not have complete follow-up were included for that year to avoid bias from stroke mortality. Counts of patients with stroke/TIA and event rates for each year of follow-up were summarized by analysis cohort.

## Statistical modeling

Generalized estimating equations with binary distributions and log link functions were utilized to model stroke/TIA event rates by year for each set of matched cohorts. Repeated measures methodology with unstructured correlation was used to account for the lack of statistical independence among multiple endpoints for each patient.

Separate models were utilized to test for the impact of PVA treatment on stroke risk in the preindex period and the postindex period due to the expectation that treatment would change the pattern or slope of stroke/TIA rates over time. Two preindex models, one for each pair of matched analysis cohorts, were constructed to test the assumption that baseline stroke risks were similar in the risk-matched cohorts. They included cohort and year as predictors, with year as a categorical variable, and cohort-year interaction included only if significant at a level of  $\alpha = 0.05$ . Two similar postindex models were constructed to test whether the stroke risk patterns over time were similar or different after divergence in AF treatment pathways.

All statistical analyses in this study were performed using SAS software, Version 9.2 (SAS Institute, Inc., Cary, NC, USA). All data used to perform this analysis were deidentified and accessed in compliance with the Health Insurance Portability and Accountability Act. As a retrospective analysis of a deidentified database, the research was exempt from Independent Review Board review under 45 Code of Federal Regulations 46.101(b)(4).

## Results

A total of 1,409,106 patients had a diagnosis of AF, of which 6,356 met all inclusion and exclusion criteria for the PVA cohort. An additional 81,189 patients met the criteria for the cardioversion cohort, and 1,312,339 patients met the

criteria for the general AF cohort. These cohorts formed the eligible populations from which matched pairs of PVA and cardioversion patients, and separately matched pairs of PVA and general AF patients, were chosen.

## Matched populations

Of the 6,356 patients in the PVA cohort, 4,991 patients were matched to an equal number of general AF controls, and 5,407 patients were separately matched to cardioversion controls. CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score profiles were nearly identical between the two cohorts in each match (*p*-values 0.5588 and 0.6948, respectively, for PVA vs general AF; *p*-values 0.7428 and 0.8152 for PVA vs cardioversion). Age and sex distributions were also similar between cohorts, with the majority of patients 45–75 years of age and approximately 70% male. Since an AF diagnosis was required in 2008 or later and the data were only complete through 2013, most patients had index dates between 2008 and 2013, with nearly half of them in 2012 or 2013 (Table 1).

The time from first AF diagnosis to index date was similar in the matched PVA vs general AF controls, as this requirement was added to the matching algorithm to ensure that controls were not matched prior to their first AF diagnosis (means: 15 months). The matched PVA vs cardioversion controls were less similar since this timing was not a matching requirement, resulting in the PVA cohort having AF of longer duration than the cardioversion control cohort (means: 21 months PVA, 5 months cardioversion; Table 1)

The average length of available follow-up after index through the end of the 2013 was over 2 years for all cohorts, with median durations close to 2 years (Table 1). The number of patients with sufficient follow-up through their last visit record to be included in each year of the statistical models is shown by cohort and year in Table 2. In addition, this table shows the number of patients who dropped out of the analysis population for each year due to having a record of death in a hospital setting or due to reaching the end of 2013. Deaths in a hospital setting after index were consistently higher in the control cohorts than in the PVA cohorts.

## Endpoint summary

In the PVA vs general AF matched cohorts, unadjusted stroke/TIA rates were similar between the cohorts in the year immediately prior to their index date, and both cohorts had increased stroke/TIA rates in the index year compared with prior years (Figure 1A). The increase in stroke rates during the index year was due in part to strokes occurring on the index date, which was a visit to the hospital system (including outpatient

**Table 1** Baseline patient characteristics

Characteristics	PVA vs AF match (N=4,991 per cohort)		PVA vs CV match (N=5,407 per cohort)	
	PVA	AF Control	PVA	CV Control
CHADS <sub>2</sub> risk score <sup>a</sup>				
0	62.8%	63.0%	58.7%	58.9%
1	29.2%	29.1%	32.6%	32.7%
2	6.9%	7.0%	7.4%	7.1%
3	1.0%	0.8%	1.1%	1.1%
4	0.1%	0.2%	0.1%	0.1%
≥5	0.0%	0.0%	0.0%	0.0%
CHA <sub>2</sub> DS <sub>2</sub> -VASc risk score <sup>a</sup>				
0	34.6%	33.8%	33.5%	33.5%
1	30.9%	31.7%	30.6%	30.8%
2	19.4%	19.9%	19.8%	20.0%
3	10.3%	10.1%	11.1%	10.9%
4	3.4%	3.4%	3.6%	3.8%
5	1.2%	0.9%	1.2%	0.9%
6	0.2%	0.1%	0.2%	0.1%
≥7	0.0%	0.0%	0.0%	0.0%
Age group at index date				
<35	3.0%	3.2%	2.6%	2.6%
35 to <45	9.1%	8.8%	8.1%	8.1%
45 to <55	22.6%	22.5%	21.5%	21.4%
55 to <65	35.9%	36.2%	37.3%	37.4%
65 to <75	25.4%	24.9%	26.4%	26.4%
75 to <85	4.0%	4.2%	4.0%	4.0%
85+	0.1%	0.2%	0.1%	0.1%
Sex				
Female	30.9%	30.9%	29.6%	29.6%
Male	69.1%	68.9%	70.4%	70.4%
Undetermined	0.0%	0.2%	0.0%	0.0%
Year of index date				
2007	2.0%	2.3%	2.0%	1.9%
2008	6.8%	6.5%	6.4%	6.7%
2009	10.2%	10.5%	9.7%	9.4%
2010	12.7%	13.9%	12.8%	12.8%
2011	17.8%	17.7%	17.5%	17.4%
2012	23.4%	23.2%	23.3%	23.4%
2013	24.9%	24.3%	26.3%	26.3%
2014	2.3%	1.6%	2.1%	2.1%
Months from first AF to index date <sup>b</sup>				
Mean	15	15	21	5
Median	9	9	13	0
Interquartile range	0–22	0–22	0–33	0–5
Months of follow-up after index date <sup>c</sup>				
Mean	28.1	28.9	27.5	27.8
Median	24.0	25.0	24.0	23.0
Interquartile range	11–42	12–44	11–41	11–42

**Notes:** <sup>a</sup>Based on diagnoses and procedures recorded within 3 years prior to the index date; <sup>b</sup>first AF is based on a diagnosis seen in a hospital setting; <sup>c</sup>follow-up is measured through the end of 2013.

**Abbreviations:** AF, atrial fibrillation; CV, cardioversion; PVA, pulmonary vein ablation.

specialist visits). The stroke rates on this single day were 0.74% in the general AF cohort and 0.26% in the PVA cohort, leaving 1.02% and 0.39% stroke rates, respectively, occurring in the remainder of the first year. After the index date, the general AF cohort had consistently higher stroke/TIA rates than the PVA

cohort, rising steadily through 4 years postindex, while the rate in the PVA cohort steadily decreased until the rate was nearly nine times as high in the general AF control cohort. Stroke/TIA rates were then similar in the fifth year, at which time the combined population had decreased to just 469 patients.

**Table 2** Sample sizes and reasons for loss to follow-up by year

<b>PVA vs General AF match</b>						
Follow-up	Population size with utilization <sup>a</sup>		Died in hospital during the year		Data ended prior to end of year	
	AF control	PVA cohort	AF control	PVA cohort	AF control	PVA cohort
±1 year	2,444	3,083	60	7	1,289	1,355
±2 years	1,572	1,819	28	7	512	868
±3 years	963	1,072	29	5	384	521
±4 years	527	572	9	1	235	320
±5 years	227	242	9	0	213	240

<b>PVA vs CV match</b>						
Follow-up	Population size with utilization <sup>a</sup>		Died in hospital during the year		Data ended prior to end of year	
	CV control	PVA cohort	CV control	PVA cohort	CV control	PVA cohort
±1 year	3,049	3,319	16	10	1,533	1,534
±2 years	1,876	1,944	17	7	832	949
±3 years	1,137	1,147	9	4	521	562
±4 years	599	598	11	1	342	359
±5 years	275	254	3	0	228	250

**Notes:** <sup>a</sup>Follow-up is measured through the last date of hospital utilization only.

**Abbreviations:** AF, atrial fibrillation; CV, cardioversion; PVA, pulmonary vein ablation.

The PVA vs cardioversion control matched cohorts showed a pattern similar to the first match, although somewhat less regular (Figure 1B). Some notable differences were the higher stroke/TIA rates in this PVA cohort 1–4 years prior to the index date, and the higher stroke/TIA rates in the cardioversion control cohort for the year immediately prior to the index date. The index date accounted for 0.13% of the strokes in the cardioversion control cohort and 0.36% in the PVA cohort within the first year after treatment, leaving 0.66% and 0.51% rates, respectively, for the remainder of the first year. Since the cardioversion controls had a shorter duration of preceding AF, their higher stroke/TIA rate in the year before index suggests that a number of these events may have triggered the initial AF diagnosis.

Of the patients with stroke occurring on their index date, only a single PVA patient had another stroke in a subsequent year. This patient was represented in both matched populations and had a record of a second stroke in the second analysis year. No control patients in either the matched cardioversion cohort or the matched general AF cohort had strokes at index and also in a subsequent year. In addition, no patients with stroke occurring on their index date died in a hospital setting at any time through 2013.

## Statistical modeling results

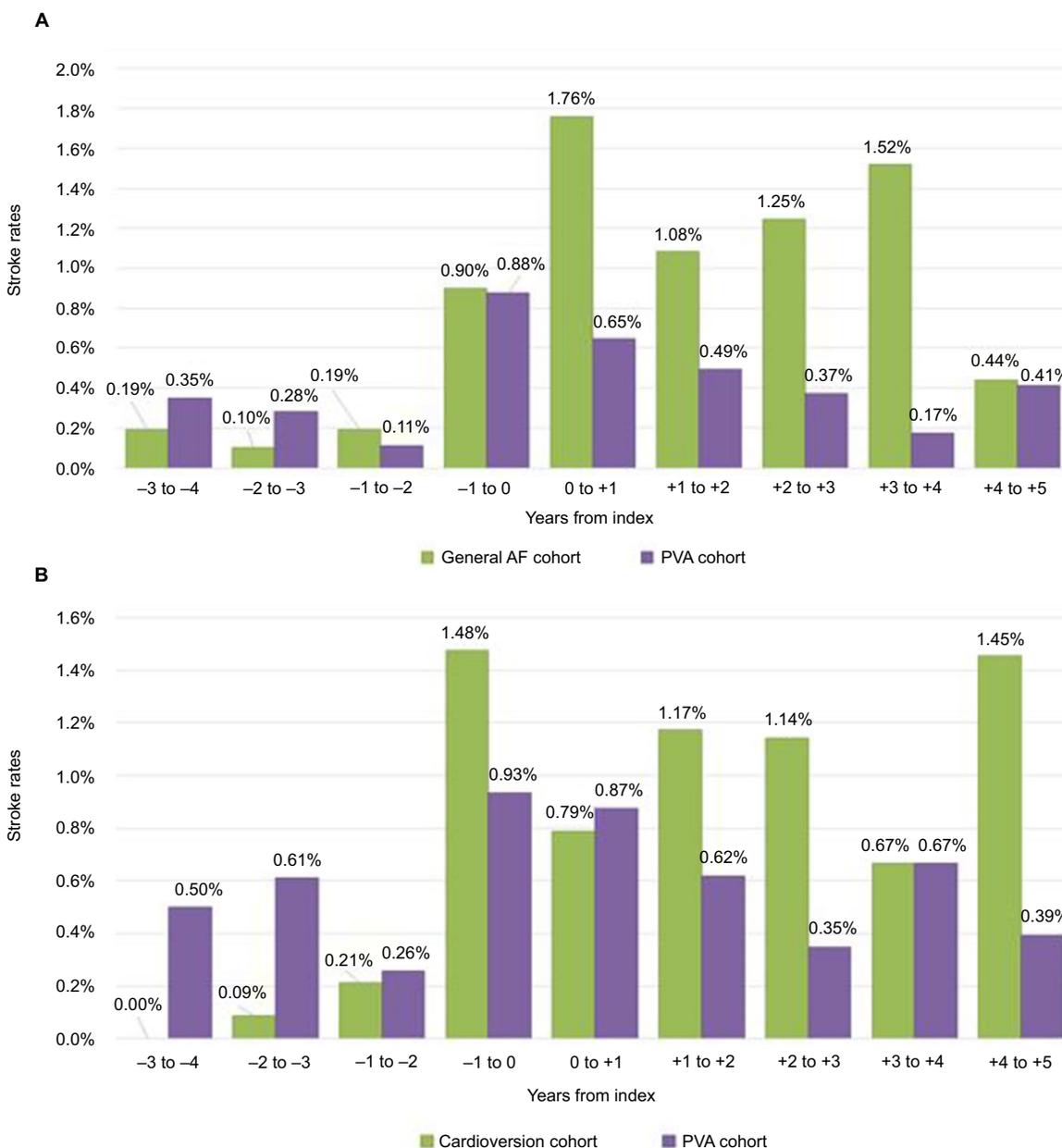
In both matched populations, statistical models of patient risk for stroke/TIA in the preindex time frame show similar event rates between cohorts ( $p=0.8292$  for PVA vs general AF

and 0.5198 for PVA vs cardioversion; Table 3). The similar preindex event rates indicate that cohort matching was successful in creating cohorts with similar baseline stroke risks.

Postindex model results are also consistent between the two matched populations, but these models show a significantly lower risk of stroke/TIA events in PVA patients vs matched control groups over 5 years postindex ( $p<0.0001$  for PVA vs general AF and 0.0222 for PVA vs cardioversion). Adjusted mean rates in PVA patients were 60% of the rates in matched cardioversion controls and 35% of the rates in general AF matches (0.82% PVA vs 1.37% cardioversion,  $p=0.0222$ ; 0.64% PVA vs 1.84% general AF;  $p<0.0001$ ). The large difference in postindex event rates and similar preindex rates suggests a divergence in outcomes stemming from the difference in treatment pathways beginning at the index date.

## Discussion

In this very large population, matching resulted in almost identical CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and stroke/TIA rates between cohorts prior to the index date. After the index date – on which ablation or cardioversion occurred – the adjusted rate of stroke/TIA was significantly lower in ablation patients than in either the cardioversion or the general AF control cohorts (40% and 65% lower, respectively). Repeated measures methodology, which observes the same patients before and after intervention, has not previously been utilized to determine whether catheter ablation of AF reduces stroke



**Figure 1** Yearly observed stroke rates in matched cohorts. (A) PVA vs matched general AF cohorts; (B) PVA vs matched cardioversion cohorts. **Abbreviations:** AF, atrial fibrillation; PVA, pulmonary vein ablation.

risk. The similarity in stroke risk between cohorts prior to the index date suggests that confounding by unmeasured variables is not responsible for subsequent differences, while the divergence following the index date suggests a treatment effect beginning on that date.

No studies have prospectively tested whether the superiority of catheter ablation over antiarrhythmic drugs in restoring sinus rhythm<sup>3,4</sup> results in a lower risk of stroke/TIA. Investigators have reported stroke/TIA rates <1%/year among patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc scores  $\geq 2$  and discontinued anticoagulation following AF ablation.<sup>14–17</sup> Registry data

have also shown that patients who maintain sinus rhythm following ablation have stroke/TIA rates similar to age- and sex-matched patients with no AF history.<sup>18</sup> Large randomized trials – Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial and Early Treatment of Atrial Fibrillation for Stroke Prevention Trial – are not expected to be completed until 2018–2019. Two retrospective cohort studies, each with 4,212 PVA patients, used age and sex matching,<sup>6</sup> and CHADS<sub>2</sub> score matching,<sup>7</sup> to show that stroke/TIA risk in the PVA patients was similar to patients without AF, and significantly lower than in patients with AF but

**Table 3** Repeated measures logistic regression model results<sup>a</sup>

Model estimates of stroke rates	Adjusted overall mean	Standard error of mean	p-value for cohort comparison
PVA vs general AF match			
Preindex model			
PVA cohort	0.30%	0.08%	0.8292
Control cohort	0.28%	0.07%	
Postindex model			
PVA cohort	0.64%	0.11%	<0.0001
Control cohort	1.84%	0.23%	
PVA vs cardioversion match			
Preindex model			
PVA cohort	0.37%	0.09%	0.5198
Control cohort	0.42%	0.08%	
Postindex model			
PVA cohort	0.82%	0.15%	0.0222
Control cohort	1.37%	0.18%	

**Notes:** <sup>a</sup>Models included cohort and year as predictors, with year as a categorical variable and cohort–year interaction included only when statistically significant.

**Abbreviations:** AF, atrial fibrillation; PVA, pulmonary vein ablation.

without intervention. Two subsequent papers used propensity matching to compare populations of over 800 matched PVA and AF control pairs each, resulting in PVA groups with significantly lower stroke/TIA rates.<sup>8,9</sup> Propensity matching was also used to show a significantly lower stroke/TIA rate in 12,122 PVA patients compared with AF patients who had undergone cardioversion.<sup>10</sup>

While matching technologies can greatly reduce bias, they are still limited by the possibility of confounding due to unmeasured variables. The key strength of this study is the unique combination of tight matching and repeated measures methodology used to overcome this limitation. The tight matching of patient stroke risks ensures that stroke rates are similar among cohorts at baseline, while repeated measures methodology examines the effect of intervention over time in the same patients. Together, these provide confidence that the drop in stroke rates for the PVA cohorts after index is a consequence of treatment.

Until large randomized trials report, clinicians will need to judge from these data whether catheter ablation of AF reduces the risk of stroke. Previous cohort studies have been consistent in showing a large benefit toward PVA. The current study examines the modern era of PVA with >80% of procedures performed during or after 2010. Its results are consistent with previous studies, but greatly reduce the likelihood of selection bias by demonstrating equal stroke risks between cohorts prior to PVA.

These results, coupled with prior results suggesting that ablation prevents progression of paroxysmal to persistent AF<sup>19</sup> and its consequent morbidity and mortality,<sup>20,21</sup> raise important questions for clinicians. Current guidelines recommend catheter ablation be performed only in symptomatic

patients.<sup>22,23</sup> Additionally, they recommend that anticoagulation be continued late after ablation in patients with elevated CHA<sub>2</sub>DS<sub>2</sub>-VASc scores.<sup>24</sup> These recommendations are potentially impacted by the results of this study.

## Limitations

The primary limitation of this study is its reliance on routinely collected data, which may lack the sensitivity and specificity of prospectively collected data. Stroke/TIA rates may be underestimated, but this would be expected to affect all cohorts proportionately. The study could not differentiate types of AF, and thus the benefit of PVA may not be consistent across all stages of AF. Anticoagulation usage was unknown and could vary between groups, although the tight matching on CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores minimizes this risk, as does comparison to a cardioversion cohort. In previous studies where anticoagulation data were available, usage was similar between cohorts.<sup>8,9</sup> Recent adoption of continued oral anticoagulation at ablation could reduce the postindex stroke rate even further,<sup>25</sup> as might newer techniques that improve long-term maintenance of sinus rhythm.<sup>26</sup> It is important to note that despite the careful cohort matching combined with methodology that used patients as their own controls over time, residual confounding is still a possibility due to data limitations.

## Conclusion

Propensity matching of AF patients with PVA treatment to similar patients with cardioversion or with neither treatment resulted in cohorts with the same baseline rate of stroke/TIA. Following treatment, the stroke/TIA rate was significantly lower in the PVA cohort than in either control cohort.

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## Disclosure

TDH is an employee of CTI Clinical Trial & Consulting Services, Inc., which is a paid consultant to Biosense Webster. JLM is a paid employee of Biosense Webster. VM reports personal fees from Biosense Webster, outside the submitted work. The authors report no other conflicts of interest in this work.

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## Supplementary material

**Table S1** Diagnosis or procedure codes

Diagnosis or procedure	Definition
Ablation – atrial flutter	Any of the following OPCS-4 codes appear in any procedure field: K622 – Percutaneous transluminal ablation of atrial wall for atrial flutter K623 – Percutaneous transluminal ablation of conducting system of heart for atrial flutter NEC (April 2007 onward)
Ablation – atrioventricular node	Any of the following OPCS-4 codes appear in any procedure field: K521 – Open ablation of atrioventricular node K571 – Percutaneous transluminal ablation of atrioventricular node
Ablation – other foci	Any of the following OPCS-4 codes appear in any procedure field: K574 – Percutaneous transluminal ablation of accessory pathway (April 2006 onward) K575 – Percutaneous transluminal ablation of atrial wall NEC (April 2006 onward) K578 – Other specified other therapeutic transluminal operations on heart
Ablation – pulmonary vein	Any of the following OPCS-4 codes appear in any procedure field: K621 – Percutaneous transluminal ablation of pulmonary vein to left atrium conducting system (April 2007 onward)
Atrial fibrillation or flutter	Any of the following ICD-10 codes appear in any diagnosis field: I48X – Atrial fibrillation or flutter
Cardiomyopathy	Any of the following ICD-10 codes appear in any diagnosis field: I42 – Cardiomyopathy I43 – Cardiomyopathy in diseases classified elsewhere I255 – Ischemic cardiomyopathy
Cardiomyopathy – hypertrophic	Any of the following ICD-10 codes appear in any diagnosis field: I421 – Obstructive hypertrophic cardiomyopathy I422 – Other hypertrophic cardiomyopathy
Cardioversion	Any of the following OPCS-4 codes appear in any procedure field: X501 – Direct current cardioversion X502 – External cardioversion NEC
Chronic kidney disease	Any of the following ICD-10 codes appear in any diagnosis field: I12 – Hypertensive renal disease I13 – Hypertensive heart and renal disease N18 – Chronic kidney disease
COPD	Any of the following ICD-10 codes appear in any diagnosis field: J439 – Emphysema, unspecified J44 – Other chronic obstructive pulmonary disease
Coronary artery bypass graft	Any of the following OPCS-4 codes appear in any procedure field: K40 – Saphenous vein graft replacement of coronary artery K41 – Other autograft replacement of coronary artery K42 – Allograft replacement of coronary artery K43 – Prosthetic replacement of coronary artery K44 – Other replacement of coronary artery K45 – Connection of thoracic artery to coronary artery K46 – Other bypass of coronary artery
Coronary artery disease	Any of the following ICD-10 codes appear in any diagnosis field: I20 – Angina pectoris I21 – Acute myocardial infarction I22 – Subsequent myocardial infarction I23 – Certain current complications following acute myocardial infarction I24 – Other acute ischemic heart diseases I25 – Chronic ischemic heart disease Z951 – Presence of aortocoronary bypass graft
Diabetes mellitus	Any of the following ICD-10 codes appear in any diagnosis field: E10 – Insulin-dependent diabetes mellitus E11 – Noninsulin-dependent diabetes mellitus E12 – Malnutrition-related diabetes mellitus E13 – Other specified diabetes mellitus E14 – Unspecified diabetes mellitus

(Continued)

**Table S1** (Continued)

Diagnosis or procedure	Definition
Heart failure	Any of the following ICD-10 codes appear in any diagnosis field: I110 – Hypertensive heart disease with (congestive) heart failure I130 – Hypertensive heart and renal disease with (congestive) heart failure I132 – Hypertensive heart and renal disease with both (congestive) heart failure and renal failure I50 – Heart failure
Hyperlipidemia	Any of the following ICD-10 codes appear in any diagnosis field: E780 – Pure hypercholesterolemia E781 – Pure hyperglyceridemia E782 – Mixed hyperlipidemia E783 – Hyperchylomicronemia E784 – Other hyperlipidemia E785 – Hyperlipidemia, unspecified
Hypertension	Any of the following ICD-10 codes appear in any diagnosis field: I10 – Essential (primary) hypertension I11 – Hypertensive heart disease I12 – Hypertensive renal disease I13 – Hypertensive heart and renal disease I15 – Secondary hypertension
Obesity	Any of the following ICD-10 codes appear in any diagnosis field: E66 – Obesity
Other arrhythmias/conduction disorders	Any of the following ICD-10 codes appear in any diagnosis field: I44 – Atrioventricular and left bundle-branch block I45 – Other conduction disorders I47 – Paroxysmal tachycardia I49 – Other cardiac arrhythmias
Other operations on the heart conduction system	Any of the following OPCS-4 codes appear in any procedure field: K522 – Epicardial excision of rhythmogenic focus K523 – Endocardial excision of rhythmogenic focus K524 – Open division of accessory pathway within heart K525 – Open division of conducting system of heart NEC K528 – Other specified open operations on conducting system of heart K529 – Unspecified open operations on conducting system of heart K572 – Percutaneous transluminal ablation of conducting system of heart NEC K573 – Percutaneous transluminal removal of foreign body from heart (April 2006 onward)
Pacemaker or implantable cardioverter defibrillator (ICD)	Any of the following OPCS-4 codes appear in any procedure field: K591 – Implantation of cardioverter defibrillator using one electrode lead K592 – Implantation of cardioverter defibrillator using two electrode leads K593 – Resiting of lead of cardioverter defibrillator K594 – Renewal of cardioverter defibrillator K595 – Removal of cardioverter defibrillator K596 – Implantation of cardioverter defibrillator using three electrode leads K598 – Other specified cardioverter defibrillator introduced through the vein K599 – Unspecified cardioverter defibrillator introduced through the vein K601 – Implantation of intravenous cardiac pacemaker system NEC K602 – Resiting of lead of intravenous cardiac pacemaker system K603 – Renewal of intravenous cardiac pacemaker system K604 – Removal of intravenous cardiac pacemaker system K605 – Implantation of intravenous single chamber cardiac pacemaker system K606 – Implantation of intravenous dual chamber cardiac pacemaker system K607 – Implantation of intravenous biventricular cardiac pacemaker system K608 – Other specified cardiac pacemaker system introduced through vein K609 – Unspecified cardiac pacemaker system introduced through vein K611 – Implantation of cardiac pacemaker system NEC K612 – Resiting of lead of cardiac pacemaker system NEC K613 – Renewal of cardiac pacemaker system NEC K614 – Removal of cardiac pacemaker system NEC K615 – Implantation of single chamber cardiac pacemaker system K616 – Implantation of dual chamber cardiac pacemaker system K617 – Implantation of biventricular cardiac pacemaker system

(Continued)

**Table S1** (Continued)

Diagnosis or procedure	Definition
	K618 – Other specified other cardiac pacemaker system
	K619 – Unspecified other cardiac pacemaker system
	U311 – Distant pacemaker test
	U318 – Other specified pacemaker testing
	U319 – Unspecified pacemaker testing
	OR
	Any of the following ICD-10 codes appear in any diagnosis field:
	Z450 – Adjustment and management of cardiac pacemaker
	Z950 – Presence of cardiac pacemaker
Percutaneous coronary intervention	Any of the following OPCS-4 codes appear in any procedure field:
	K49 – Transluminal balloon angioplasty of coronary artery
	K50 – Other therapeutic transluminal operations on coronary artery
	K75 – Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery (only available from April 2006)
Peripheral vascular disease (PVD)	Any of the following ICD-10 codes appear in any diagnosis field:
	I70 – Atherosclerosis
	I71 – Aortic aneurysm and dissection
	I72 – Other aneurysm and dissection
	I73 – Other peripheral vascular diseases
	I74 – Arterial embolism and thrombosis
	I798 – Other disorders of arteries, arterioles, and capillaries in diseases classified elsewhere
Pulmonary disease	Any of the following ICD-10 codes appear in any diagnosis field:
	I26 – Pulmonary embolism
	I27 – Other pulmonary heart diseases
	I28 – Other diseases of pulmonary vessels
Sleep apnea	Any of the following ICD-10 codes appear in any diagnosis field:
	G473 – Sleep apnea
Stroke – hemorrhagic	Any of the following ICD-10 codes appear in any diagnosis field:
	I60 – Subarachnoid hemorrhage
	I61 – Intracerebral hemorrhage
	I62 – Other nontraumatic intracranial hemorrhage
Stroke – ischemic	Any of the following ICD-10 codes appear in any diagnosis field:
	I63 – Cerebral infarction
	I64X – Stroke, not specified as hemorrhage or infarction
Transient ischemic attack	Any of the following ICD-10 codes appear in any diagnosis field:
	G45 – Transient cerebral ischemic attacks and related syndromes
Valvular disease	Any of the following OPCS-4 codes appear in any procedure field:
	K253 – Prosthetic replacement of mitral valve
	K263 – Prosthetic replacement of aortic valve
	OR
	Any of the following ICD-10 codes appear in any diagnosis field:
	I05 – Rheumatic mitral valve diseases
	I06 – Rheumatic aortic valve diseases
	I07 – Rheumatic tricuspid valve diseases
	I08 – Multiple valve diseases
	I091 – Rheumatic diseases of endocardium, valve unspecified
	I34 – Nonrheumatic mitral valve disorders
	I35 – Nonrheumatic aortic valve disorders
	I36 – Nonrheumatic tricuspid valve disorders
	I37 – Pulmonary valve disorders
	I38 – Endocarditis, valve unspecified
	I39 – Endocarditis and heart valve disorders in diseases classified elsewhere
	Z952 – Presence of prosthetic heart valve
	Z953 – Presence of xenogenic heart valve
Vascular disease	Any of the components in these fields:
	Coronary artery disease
	Peripheral vascular disease
	Coronary artery bypass graft
	Percutaneous coronary intervention

**Abbreviations:** NEC, not elsewhere classified; ICD, International Classification of Diseases; OPCS, Office of Population Censuses and Surveys.

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