

Ischemic Stroke or Systemic Embolism After Transseptal Ablation of Arrhythmias in Patients With Cardiac Implantable Electronic Devices

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Background—Incidental mobile thrombi are commonly found on endovascular leads of cardiac implantable electronic devices (CIEDs). Transseptal puncture for catheter ablation of arrhythmia poses a risk for paradoxical embolism. We examined risk of ischemic stroke, transient ischemic attack (TIA), or systemic embolism after transseptal ablation in patients with and without CIEDs.

Methods and Results—Using a national administrative claims database, 31 720 patients who underwent a transseptal catheter ablation between January 2004 and September 2014 were identified. Two propensity-matched cohorts were created by matching demographic variables, administrative variables, Charlson Comorbidity Index, CHA₂DS₂-Vasc score, and year and indication for ablation (5533 and 11 300 patients with and without CIEDs). Incidence rates and Cox proportional hazards models were used to estimate risk of ischemic stroke, TIA, or systemic embolism for patients with and without CIEDs. Impact of oral anticoagulation (OAC) use on the endpoint was examined. Over a mean follow-up of 2.1 years, the incidence of the combined endpoint was 1.9 per 100 person-years in patients with CIEDs and 1.5 per 100 person-years in patients without CIEDs ($P=0.03$). Among patients not on OAC, presence of a cardiac device was associated with an increased risk (hazard ratio [HR], 1.71 [1.24–2.35]; $P<0.01$), whereas there was no association noted among patients treated with OAC (HR, 0.98 [0.75–1.28]).

Conclusion—CIEDs are associated with an increased risk of stroke, TIA, or systemic embolism after transseptal ablation, but this risk is attenuated with postablation OAC use. Role of anticoagulation post-transseptal ablation in patients with CIED warrants further investigation. (*J Am Heart Assoc.* 2016;5:e003163 doi: 10.1161/JAHA.115.003163)

Key Words: atrial fibrillation • cardiac ablation • stroke • systemic embolism • transseptal puncture

Percutaneous catheter ablation has emerged as the mainstay for management of symptomatic, drug-refractory cardiac arrhythmias. Transseptal puncture has been increasingly used in the course of these ablation procedures when mapping or ablation is required in the left atrium or ventricle. Transseptal puncture is now standard of care during the course of ablation for atrial fibrillation (AF), a

common indication for ablation. Transseptal puncture using large bore sheaths is also increasingly used for structural interventions, such as percutaneous mitral valve repair and mitral valve annuloplasty. However, placement of sheaths and catheters across the interatrial septum creates an iatrogenic atrial septal defect (iASD) that may persist in 5% to 20% of patients 9 to 12 months postprocedure.^{1–5} The clinical relevance of a small persistent iASD in causing intracardiac shunting and systemic embolism is currently unknown.

Transvenous cardiac implantable electronic devices (CIEDs), including pacemakers and implantable cardioverter defibrillators, have proven efficacy in treating a number of cardiac arrhythmias and their use has increased over time.⁶ Intracardiac mobile thrombi are frequently found attached to endovascular leads and may embolize to the pulmonary circulation or less frequently to the systemic circulation through a right to left shunt.^{7–9} Elevated pulmonary artery pressure has also been reported in patients with CIED lead thrombus, although a cause-and-effect relationship has not been established.⁸ Many patients undergoing catheter

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ablation for arrhythmias also have transvenously placed CIEDs. However, the impact of the presence of a CIED on incidence of systemic embolism after transseptal puncture for ablation is unknown.

We hypothesized that the presence of a transvenous CIED increases the risk for stroke, transient ischemic attack (TIA), or systemic embolism after transseptal puncture for ablation of cardiac arrhythmias. To test this hypothesis, we retrospectively examined incidence of stroke, TIA, or systemic embolism in patients with and without a CIED after a percutaneous catheter ablation procedure that involved transseptal access in a large national administrative claims database.

Methods

Data Source

A retrospective analysis was conducted using medical and pharmacy administrative claims data from the Optum Labs Data Warehouse (OLDW). The database contains longitudinal health information on over 100 million privately insured and Medicare Advantage enrollees over the last 20 years, from geographically diverse regions across the United States, with greatest representation from the South and Midwest.¹⁰ The OLDW provides claims data for professional (eg, physician), facility (eg, hospital), and outpatient prescription medication services. Medical (professional and facility) claims include International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, ICD-9 procedure codes, Current Procedural Terminology, Version 4 (CPT) procedure codes, Healthcare Common Procedure Coding System procedure codes and the date of service. Pharmacy claims include fill date, generic names, brand names, and days of supply for each drug. Socioeconomic characteristics include income and race/ethnicity.

Study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996, and, because this study involved analysis of pre-existing, deidentified data, it was exempt from institutional review board approval.

Study Population

We identified all patients who underwent a catheter ablation between January 1, 2004, and September 30, 2014, and were enrolled in medical and pharmacy health plan coverage at the time of and for at least 6 months before their ablation procedure. Ablation was defined using a procedure code on medical claims (ICD-9 procedure code 37.34 and/or Current Procedural Terminology, Version 4 [CPT-4] procedure codes 93651, 93656, and 93657). For individuals

with CPT code 93651 (general code for any ablation), an additional code for transseptal puncture (CPT 93621, 93622, 93642, 93462, or 93527) was required at the time of ablation. If a patient had more than 1 qualifying ablation over the study period, we considered the earliest ablation as their index procedure. Patients who underwent their first ablation in 2003 were excluded from the cohort. The algorithm used for selection of the study cohort is shown in Figure 1. The indication for ablation was identified using the primary arrhythmia diagnosis on the index ablation claim. Patients with a nonspecific arrhythmia diagnosis code were classified as “unspecified.”

Patient Characteristics

Demographics and socioeconomic characteristics at the time of the index procedure, including age, sex, race, household income, and residence region, were obtained. The Charlson Comorbidity Index (CCI) was used to assess patients' overall comorbidity burden.¹¹ The CHA₂DS₂-Vasc score was derived to measure patients' risk of stroke at baseline.^{12,13} All comorbidities were defined using ICD-9-CM codes from the primary or secondary diagnoses in any medical claim within the 6-month preablation period.

Exposure

Patients were considered to have a CIED if they had a primary or secondary diagnosis or procedure code (ICD-9-CM diagnosis, CPT, and ICD-9 procedure codes) that reflected health care use in relation to a CIED during the 6 months preablation or at time of ablation. Oral anticoagulant (OAC) use after ablation was identified based on prescription claims for dabigatran, rivaroxaban, apixaban, or warfarin from 3 months preceding to the index procedure until the end of follow-up, defined as the earliest date of the end of the enrollment in health plans, the end of study period, or the first event. OAC was assumed to be maintained until no residual days' supply were available. If patients ever received an OAC after the ablation and preceding end of follow-up, or had OAC in possession at time of ablation, they were considered using OAC.

Outcome

The primary outcome of interest was first occurrence of ischemic stroke (ICD-9-CM codes 433.x1, 434.x1, and 436), TIA (ICD-9-CM code 435.x), and systemic embolism (ICD-9-CM code 444.x). Diagnoses codes were obtained from inpatient claims, excluding those with a primary discharge code for rehabilitation (ICD-9-CM code V57) or any accompanying diagnoses of intracerebral hemorrhage (ICD-9-CM

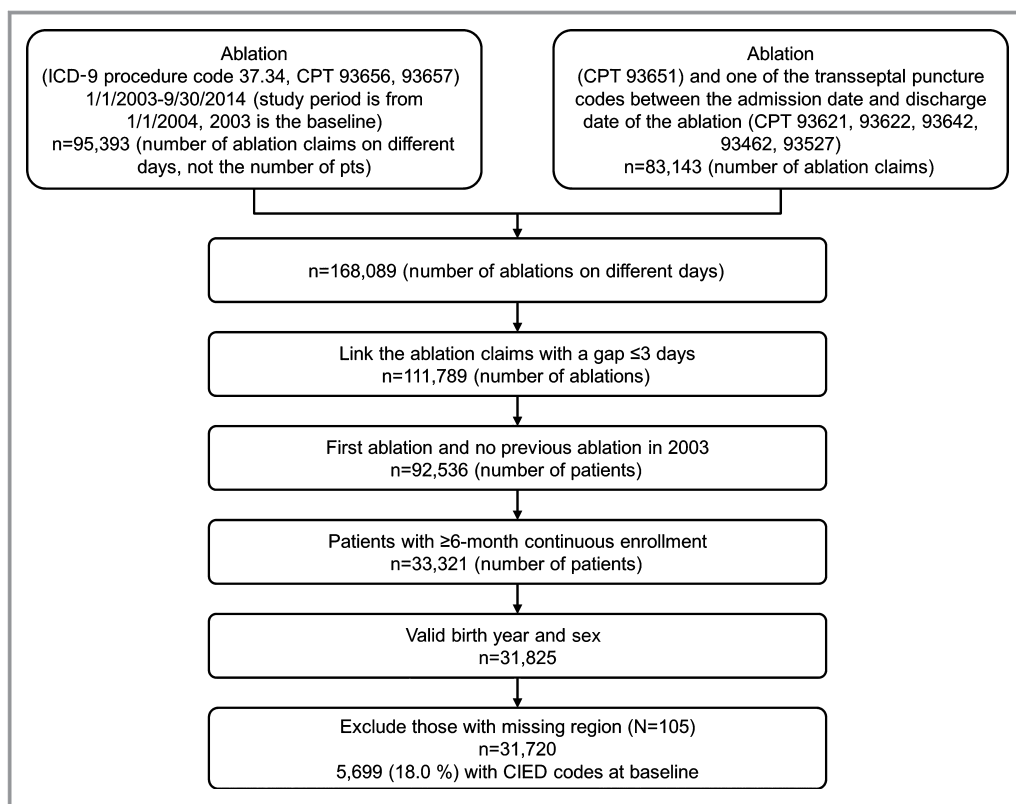


Figure 1. Algorithm used for selection of study cohort. CIED indicates cardiac implantable electronic device; CPT, Current Procedural Terminology; ICD-9, International Classification of Diseases, Ninth Revision; pts, patients.

code 431), subarachnoid hemorrhage (ICD-9-CM 430), or trauma (ICD-9-CM codes 800–804 and 850–854).^{14–16}

Statistical Analysis

One to 5 propensity score matching with replacement using a caliper of 0.001 was performed between patients with and without a CIED. Subjects were matched on age, sex, race, income, residence region, CCI, CHA₂DS₂-Vasc score, year of the index ablation, and indication for ablation. “With replacement matching” allows 1 control to be used multiple times. So, the sample size of the control (without CIEDs) is not 5 times of the CIED cohort and the control cohort had 11 300 unique patients. Because of the use of 1 to many matching, a weight was used in all analyses to account for the larger sample size of the control group, and the possibility that 1 control was used multiple times. The weighted sample size of the control cohort is 5533, the same as the cohort with CIEDs. The sample size in the control cohort in the Kaplan–Meier curves was also weighted. Standardized difference was used to assess the balance of covariates after matching. A standardized difference of less than 10% is considered balanced. All baseline characteristics were balanced after propensity score matching. Cox proportional hazard models

were used to assess patients’ risk of cardioembolic events during follow-up. The resulting hazard ratios (HRs), their 95% CIs and associated *P* values are reported. Interaction effects between presence of a CIED and use of OAC post ablation, as well as the interaction effects between the presence of CIED, OAC use and indication for ablation were tested. All analyses were conducted using SAS (version 9.3; SAS Institute Inc., Cary, NC) and Stata software (version 13.1; StataCorp LP, College Station, TX).

Results

Study Population

Between January 1, 2004, and October 30, 2014, we identified 31 720 patients who underwent percutaneous catheter ablation requiring transseptal puncture. Median (interquartile range; IQR) age was 60.0 (49.0–69.0) years and 58.8% were male. Ablation was performed for AF (36.3%), atrial flutter (19.2%), other supraventricular tachycardia (SVT; 21.0%), or ventricular tachycardia (VT; 4.4%). Indication for catheter ablation was not identifiable in 19.1% of patients who were grouped as “unspecified.” Mean follow-up after the index ablation procedure was 2.2 (±2.0) years.

An implanted CIED was present at time of ablation in 5699 (18.0%) patients. Baseline characteristics of the entire cohort and stratified by the presence of CIED are presented in Table 1. Patients with a CIED were older, more likely to be male, and had a higher median CHA₂DS₂-Vasc score (2.0 [IQR, 1.0–3.0] in patients without CIED and 4.0 [IQR, 3.0–5.0] in those with CIED, $P<0.0001$) and CCI score (1.0 [IQR, 0.0–2.0] in those without CIED and 3.0 [IQR, 2.0–5.0] in those with CIED; $P<0.0001$). Among patients with a diagnosis of AF, atrial flutter, SVT, VT, or a diagnosis of “unspecified” arrhythmia, a CIED was present in 19.1%, 17.7%, 4.9%, 47.0%, and 23.7%, respectively.

An OAC was prescribed to 16 075 (50.7%) patients in the *entire* cohort after index ablation. Whereas 82.3% of patients with AF and 67.8% of those with atrial flutter received an OAC, only 23.1%, 8.8%, and 26.1% of those with VT, SVT, and unspecified diagnosis, respectively, were on anticoagulation. Warfarin, apixaban, dabigatran and rivaroxaban were prescribed to 38.3%, 1.2%, 6.1%, and 5.0% of the cohort, respectively.

Table 2 compares characteristics of patients who did and did not receive an OAC in the *propensity-matched* cohort. Patients who were treated with an OAC were older, more likely to be male, and more likely to have CHA₂DS₂-VASc score ≥ 2 . Patients with a CIED were also more likely to be anticoagulated after ablation (OR, 1.3; $P<0.001$).

Ischemic Stroke, TIA, and Systemic Embolism After Transseptal Ablation

Outcomes in the *entire* cohort

The combined endpoint of ischemic stroke, TIA, or systemic embolism occurred in 636 of 31 720 (2.0%) patients in the *entire* cohort. Stroke and TIA accounted for 56.0% and 32.2% of the events, respectively. The majority of the events (52%) occurred within 1 year of the index ablation. The median (IQR) interval between the ablation and the embolic event was 0.92 (0.12–2.35) year. Twenty-nine percent of patients with an embolic event were on OAC before the event. The unadjusted event rate was 0.9, 1.1, 0.5, 1.2, and 1.3 per 100 person-years in patients with AF, atrial flutter, SVT, ventricular arrhythmia, and unspecified diagnosis, respectively. The rate of the combined endpoint was 1.9 per 100 person-years in patients with CIEDs, compared to 0.7 per 100 person-years in patients without CIEDs.

Outcomes in the *propensity-score-matched* cohort

In the *propensity-score-matched* cohort, the rate of the combined endpoint of stroke, TIA, or systemic embolism was 1.9 per 100 person-years in patients with CIED and 1.5 per 100 person years in patients without CIED ($P=0.03$). Kaplan–

Meier curves of the combined endpoint stratified by the presence or absence of CIED is presented in Figure 2. Among patients not on an OAC, the presence of a CIED was associated with a significantly increased risk of stroke or systemic embolism (HR, 1.71 [1.24–2.35]; $P<0.01$). However, this association was not observed among patients on OAC (0.98 [0.75–1.28]; $P=0.894$; Table 3). Kaplan–Meier analysis of survival free of ischemic stroke, TIA, or systemic embolism stratified by the presence of a CIED and use of an OAC is presented in Figure 3.

Interaction between the presence of CIED and OAC in determining the endpoint in each arrhythmia diagnosis was also studied. The HR for the combined endpoint in patients with a CIED stratified by OAC use and arrhythmia diagnosis is shown in Table 3. Among patients with AF or atrial flutter, the presence of a CIED with and without OAC use was not associated with an increased risk of the combined endpoint. Among patients with SVT, VT, and unspecified arrhythmia diagnoses, the presence of a CIED in the absence of OAC was associated with an increased risk of stroke, TIA, and systemic embolism. Risk of the combined endpoint in patients with SVT, VT, and unspecified diagnoses who were anticoagulated after ablation was similar among patients with and without a CIED (Table 3). The P value for interaction between OAC and CIED was 0.01 in the whole cohort. Interaction was not significant for patients with AF or atrial flutter, but significant for other indications: P values were 0.046, 0.035, and 0.038 for SVT, VT, and unspecified diagnosis, respectively. Kaplan–Meier analysis of survival free of the primary endpoint in patients with different arrhythmia diagnoses is presented in Figure 4.

Diagnosis of AF was identified in 77% of patients who underwent ablation for an indication other than AF or atrial flutter. To test the effect of AF on the risk for stroke, a sensitivity analysis was performed in patients who underwent transseptal ablation for SVT, VT, or unspecified diagnosis. Survival analysis after adjusting for diagnosis of AF showed similar results. CIED was associated with increased risk of primary endpoint in patients who were not anticoagulated (HR, 1.81 [1.21–2.70]; $P=0.004$), without a significant association in those who received an OAC (HR, 0.70 [0.43–1.15]; $P=0.16$).

Discussion

We present the first systematic retrospective analysis to assess risk for ischemic stroke, TIA, or systemic embolism after percutaneous catheter ablation involving transseptal puncture in patients with and without a CIED from a large administrative claims database. Patients with a CIED had a 70% increase in the rate of the combined endpoint of stroke, TIA, or systemic embolism after transseptal ablation compared to those without a CIED in the absence of

Table 1. Baseline Characteristics of the Entire Cohort Stratified by the Presence of CIED

	No CIED* (N=26 021)	CIED* (N=5699)	Total (N=31 720)
Age, y, median (IQR)	58 (48–67)	69 (60–77)	60 (49–69)
Male, N (%)	14 999 (57.6)	3638 (63.8)	18 637 (58.8)
Race, N (%)			
White	20 691 (79.5)	4470 (78.4)	25 161 (79.3)
Black	1672 (6.4)	540 (9.5)	2212 (7.0)
Hispanic	1269 (4.9)	233 (4.1)	1502 (4.7)
Asian	518 (2.0)	82 (1.4)	600 (1.9)
Unknown	1871 (7.2)	374 (6.6)	2245 (7.1)
Household income, N (%)			
<\$40 000	3625 (13.9)	1526 (26.8)	5151 (16.2)
\$40 000 to \$49 999	1466 (5.6)	473 (8.3)	1939 (6.1)
\$50 000 to \$59 999	1614 (6.2)	418 (7.3)	2032 (6.4)
\$60 000 to \$74 999	2256 (8.7)	500 (8.8)	2756 (8.7)
\$75 000 to \$69 999	3376 (13.0)	626 (11.0)	4002 (12.6)
≥\$100 000	8528 (32.8)	1090 (19.1)	9618 (30.3)
Unknown	5156 (19.8)	1066 (18.7)	6222 (19.6)
Region, N (%)			
Midwest	7527 (28.9)	1963 (34.4)	9490 (29.9)
Northeast	3388 (13.0)	864 (15.2)	4252 (13.4)
South	10 943 (42.1)	2254 (39.6)	13 197 (41.6)
West	4163 (16.0)	618 (10.8)	4781 (15.1)
Primary indication for ablation (%)			
Atrial fibrillation	9309 (35.8)	2194 (38.5)	11 503 (36.3)
Atrial flutter	5004 (19.2)	1079 (18.9)	6083 (19.2)
Supraventricular tachycardia	6338 (24.4)	326 (5.7)	6664 (21.0)
Ventricular arrhythmia	744 (2.9)	660 (11.6)	1404 (4.4)
Unspecified	4626 (17.8)	1440 (25.3)	6066 (19.1)
Risk factors for stroke (%)			
Hypertension	16 403 (63.0)	4762 (83.6)	21 165 (66.7)
Diabetes	5201 (20.0)	2094 (36.7)	7295 (23.0)
Congestive heart failure	4611 (17.7)	3694 (64.8)	8305 (26.2)
Vascular disease [†]	10 315 (39.6)	4086 (71.7)	14 401 (45.4)
Moderate/severe renal disease	1720 (6.6)	1310 (23.0)	3030 (9.6)
Prior ischemic stroke or TIA	1355 (5.2)	633 (11.1)	1988 (6.3)

Continued

Table 1. Continued

	No CIED* (N=26 021)	CIED* (N=5699)	Total (N=31 720)
CHA ₂ DS ₂ -Vasc score (%)			
0 to 1	9773 (37.6)	483 (8.5)	10 256 (32.3)
2	5664 (21.8)	582 (10.2)	6246 (19.7)
3	4540 (17.4)	994 (17.4)	5534 (17.4)
≥4	6044 (23.2)	3640 (63.9)	9684 (30.5)
Charlson index, N (%)			
0	10 278 (39.5)	473 (8.3)	10 751 (33.9)
1	6441 (24.8)	932 (16.4)	7373 (23.2)
≥2	9302 (35.7)	4294 (75.3)	13 596 (42.9)

CIED indicates cardiac implantable electronic device; IQR, interquartile range; TIA, transient ischemic attack.

**P*<0.0001 for all comparisons between patients with and without CIED.

[†]Myocardial infarction, coronary artery disease, peripheral arterial disease, or aortic atherosclerotic disease.

postprocedural oral anticoagulation. In contrast, when an OAC was prescribed postprocedure, the risk was similar among patients with or without a CIED. Transseptal ablation of rhythms other than AF and atrial flutter were less likely to be followed by anticoagulation and showed a strong association between presence of CIED and occurrence of stroke, TIA, or systemic embolism. This underscores the need to investigate prospectively the role for anticoagulation post-transseptal ablation in those with CIED even in patients without AF or atrial flutter.

Transseptal catheterization of the left atrium is increasingly performed during the course of catheter ablation for arrhythmias and can be achieved with minimal periprocedural risks.¹⁷ The literature on complications of puncture of the interatrial septum has been focused on acute procedural complications. Placement of sheaths across the interatrial septum, however, has the potential to create an iASD, which has been reported to be as high as 95% at 1 day postcatheter ablation for AF.⁴ The iASD can persist in 5% to 20% of patients at 9 to 12 months after ablation.^{1–5} The lack of an intact interatrial septum may be associated with hemodynamic abnormalities and paradoxical systemic embolism in the presence of a right to left shunt. However, the clinical significance of iASD after ablation is largely unknown and previously published reports are limited to small case series with short duration of follow-up. We report, for the first time, an increased risk for stroke, TIA, and systemic embolism in patients who undergo transseptal catheter ablation in the presence of a CIED. This raises the possibility that postablation iASD may not be such a “benign” consequence of transseptal puncture as previously thought, particularly in patients with CIEDs in which device leads serve as a nidus for thrombus.

Table 2. Characteristics of Patients Who Were Prescribed OAC to Those Who Were Not Anticoagulated in the Propensity Score Matched Cohort

	No OAC, % (N=7026)	OAC, % (N=9807)
Age, yr		
18 to 54	19.5	12.0
55 to 64	18.9	25.2
65 to 74	26.8	31.8
≥75	34.8	30.9
Male	56.5	66.3
Charlson index		
0	11.4	7.2
1	17.1	16.1
≥2	71.5	76.7
CHA₂DS₂-VASc		
0 to 1	11.2	7.6
2	10.5	10.1
3	16.5	17.6
≥4	61.7	64.7
Risk factors for stroke		
Hypertension	81.2	87.1
Diabetes	35.3	40.0
Congestive heart failure	45.3	56.5
Vascular disease	67.7	70.5
Moderate/severe renal disease	19.6	19.7
Past ischemic stroke TIA	11.3	12.7

OAC indicates oral anticoagulant compared; TIA, transient ischemic attack.

The mechanism for an increased risk of embolism post-transseptal puncture in CIED patients cannot be definitively determined because of the retrospective observational nature of the study and these results should only be viewed as hypothesis generating. Mobile thrombi attached to CIED leads have been reported in 30% of patients imaged with intracardiac echocardiography in one series, with the majority occurring in the right atrium.⁸ We have previously shown an increased propensity for stroke or TIA in patients with a CIED and patent foramen ovale.¹⁸ We propose that the increased risk for systemic embolic events in the current study may be the result of paradoxical embolism of thrombi originating from CIED leads. Furthermore, higher pulmonary artery pressure has been reported in patients with CIED lead thrombus, increasing the likelihood of developing right to left shunts in these patients.⁸ The attenuation of risk with anticoagulation in this study provides further supportive evidence that the underlying mechanism is thrombotic. This hypothesis could not be verified using imaging for iASD at the time of the

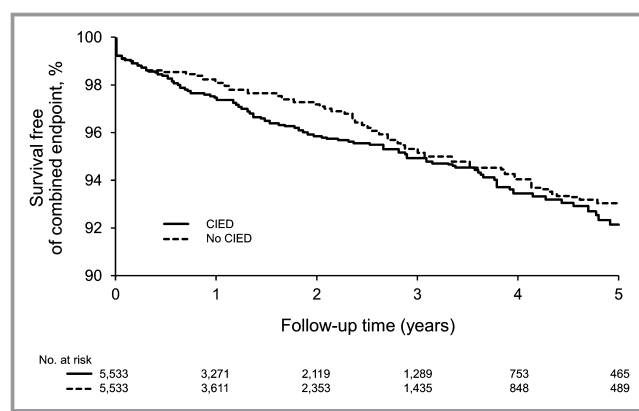


Figure 2. Kaplan–Meier survival free of combined endpoint of stroke, TIA, and systemic embolism in patients with and without CIED. CIED indicates cardiac implantable electronic device; TIA, transient ischemic attack.

embolic event in this retrospective study. Future studies should focus on the rate of persistence of iASD over time, its clinical and procedural correlates, and clinical relevance. Another potential explanation for these observations is the presence of unidentified comorbid conditions in patients with CIED that act as confounders in increasing the risk for stroke, but are incompletely accounted for in our propensity matching.

The increased risk of stroke was particularly notable in CIED patients who were not prescribed OAC after ablation. In contrast, the risk in CIED patients who were anticoagulated was comparable to that of patients without CIED. We further investigated the effect of OAC in patients with different arrhythmias. Incidence of the combined endpoint was comparable in patients with and without CIED after ablation for AF or atrial flutter, likely reflective of the high rate (77.3%) of OAC use after these procedures. This is consistent with the strong recommendations set forth by societal guidelines to anticoagulate patients with AF or atrial flutter who undergo left atrial ablation for a minimum of 2 months and indefinitely in patients with stroke risk factors.¹⁹ The number of subjects not anticoagulated after ablation for AF or atrial flutter may not have been sufficient to detect a significant trend toward increased incidence of the primary endpoint in this subgroup. Factors independent of OAC use and CIED presence that are not accounted for by our statistical methods may also serve as an alternative explanation for the presence of a significant increase in systemic embolism in patients undergoing ablation for certain arrhythmias, but not others. For example, structural heart disease in patients with VT may predispose to systemic embolism whereas this may not be a significant factor in those with AF or atrial flutter.

Our data show that ablation procedures for other arrhythmias, such as VT and SVT, were followed by anticoagulation in

Table 3. Risk for Ischemic Stroke, TIA, and Systemic Embolism in Patients With and Without CIED Grouped by Indication for Ablation

	HR (95% CI)	P Value
Entire cohort		
OAC initiated	0.98 (0.75–1.28)	0.894
OAC not initiated	1.71 (1.24–2.35)	0.001
Stratified by indication for ablation		
Atrial fibrillation/atrial flutter		
OAC initiated	1.12 (0.85–1.47)	0.431
OAC not initiated	1.09 (0.80–1.49)	0.587
Supraventricular tachycardia		
OAC initiated	1.22 (0.70–2.11)	0.488
OAC not initiated	1.44 (0.69–2.99)	0.334
Ventricular tachycardia		
OAC initiated	0.23 (0.03–1.93)	0.176
OAC not initiated	2.25 (1.01–5.01)	0.046
Unspecified diagnosis		
OAC initiated	1.65 (0.67–4.06)	0.273
OAC not initiated	0.45 (0.10–2.06)	0.301
SVT, VT and unspecified diagnosis		
OAC initiated	3.20 (1.13–9.04)	0.028
OAC not initiated	1.28 (0.90–1.83)	0.171
OAC initiated	0.84 (0.49–1.44)	0.522
OAC not initiated	1.81 (1.13–2.89)	0.014
SVT, VT and unspecified diagnosis		
OAC initiated	1.35 (1.00–1.84)	0.052
OAC not initiated	0.71 (0.43–1.17)	0.184
OAC not initiated	2.00 (1.36–2.95)	<0.001

CIED indicates cardiac implantable electronic device; HR, hazard ratio; OAC, oral anticoagulation; SVT, supraventricular tachycardia; TIA, transient ischemic attack; VT, ventricular tachycardia.

only 11.3% of patients. An increase in risk for stroke in the presence of CIED and the absence of anticoagulation was noted in these patients. The rate of stroke, TIA, or systemic embolism in patients with CIED who underwent transseptal SVT ablation was 1.5 per 100 person-years. These patients have typically been considered “low risk” for embolic events and guidelines currently do not recommend anticoagulation.²⁰ Similarly, whereas OAC is recommended after VT ablation in patients with structural heart disease, current expert consensus is to not routinely anticoagulate those with a structurally normal heart.²¹ Data on the presence of structural heart disease in VT ablation patients were not available in this study. Hence, the differential effects of structural heart disease on stroke in VT ablation patients with CIED is not known. The results of the current study would, however, suggest that OAC use may be a viable therapeutic strategy to reduce the risk of stroke after transseptal ablation for all arrhythmias, including SVT and VT, in patients with CIED. It is notable that OAC did not eliminate the risk of stroke or TIA, as evidenced by the fact that a significant number of patients who experienced an event were on OAC. This hypothesis,

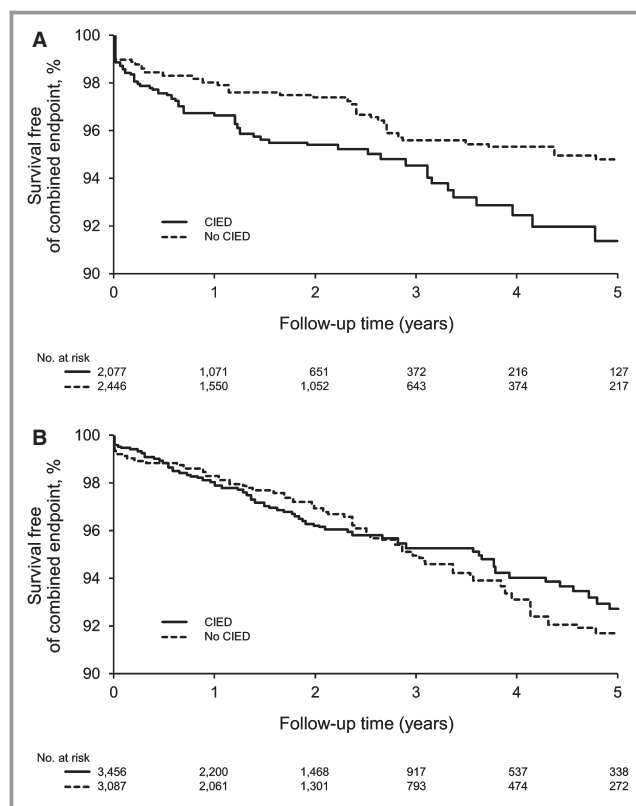


Figure 3. Kaplan–Meier survival free of combined endpoint of stroke, TIA, and systemic embolism in patients with and without CIED (A) in the presence of oral anticoagulation (OAC) postprocedure and (B) in the absence of oral anticoagulation. CIED indicates cardiac implantable electronic device; TIA, transient ischemic attack.

however, certainly merits further investigation in prospective studies.

The increased risk of systemic embolism in patients with CIED first appears several months after the ablation procedure, as seen in Figure 2. Subsequently, the cumulative incidence of the combined endpoint continues to diverge between patients with and without CIED until 2 to 3 years after ablation. This suggests that the increased risk is not attributed to a difference in acute procedure-related strokes. One potential explanation is that chronic presence of a CIED leads composed of thrombogenic material in juxtaposition to the iASD augments thromboembolic risk. The diminution of risk after 2 years may reflect iASD closure over time. Whereas iASDs have been known to persist up to 12 months after transseptal puncture in some patients, longer-term follow-up is not available and should be the subject of future studies.^{1–5} If iASDs are indeed shown to increase risk of paradoxical embolism in patients with CIED, transesophageal echocardiogram before discontinuation of anticoagulation to identify residual iASD and high-risk features, such as right to left shunt, may be used to guide

future anticoagulation therapy. The role of percutaneous device closure of iASD in high-risk individuals could also be investigated. The lack of significant difference in embolic risk in the first few months after ablation, when the risk for an

iASD is greatest, and persistent increase in risk beyond 2 years does raise the possibility of an alternative explanation, such as the presence of thromboembolic risk factors in CIED patients that are not well accounted for by the propensity matching.

The findings of this study raise additional clinically relevant questions that warrant prospective evaluation. Several patient and procedure related factors have been described to influence the incidence of iASD, including the size of the sheath used for transseptal access, single versus double transseptal puncture, ablation energy used (cryo vs radiofrequency ablation), length of procedure, as well as pulmonary arterial and left atrial pressure.^{2,3,22} These patient-level data were not available in this administrative database. Study of their influence on the risk for embolic events may identify additional targets to reduce risk of stroke in patients with a CIED. The clinical relevance of CIED lead thrombus in causing pulmonary and systemic emboli and the role of OAC in reducing the risk for CIED lead thrombus are not established and can only be determined by large, prospective studies with dedicated imaging. The efficacy of the novel oral anticoagulants in reducing thrombosis on foreign material in particular remains to be established.

Transseptal puncture is also a part of an increasing armamentarium of procedures for structural heart disease, such as mitral balloon valvuloplasty, percutaneous repair of mitral regurgitation, and left atrial appendage closure. These procedures have been associated with a significant incidence of iASD, and our study may also have implications for management in these patients.^{23–26} Additional studies involving embolism in these patients warrant further investigation to establish best postprocedural practices.

Limitations

This study is subject to all of the bias and limitations of a large, retrospective, observational study. Though propensity score matching was used to account for known confounders, unknown confounders may have affected the outcome. Administrative claims-based observational studies are inherently prone to errors attributed to under- or overcoding, and clinical diagnoses cannot be verified by direct chart review. Conclusions regarding causal relationship between

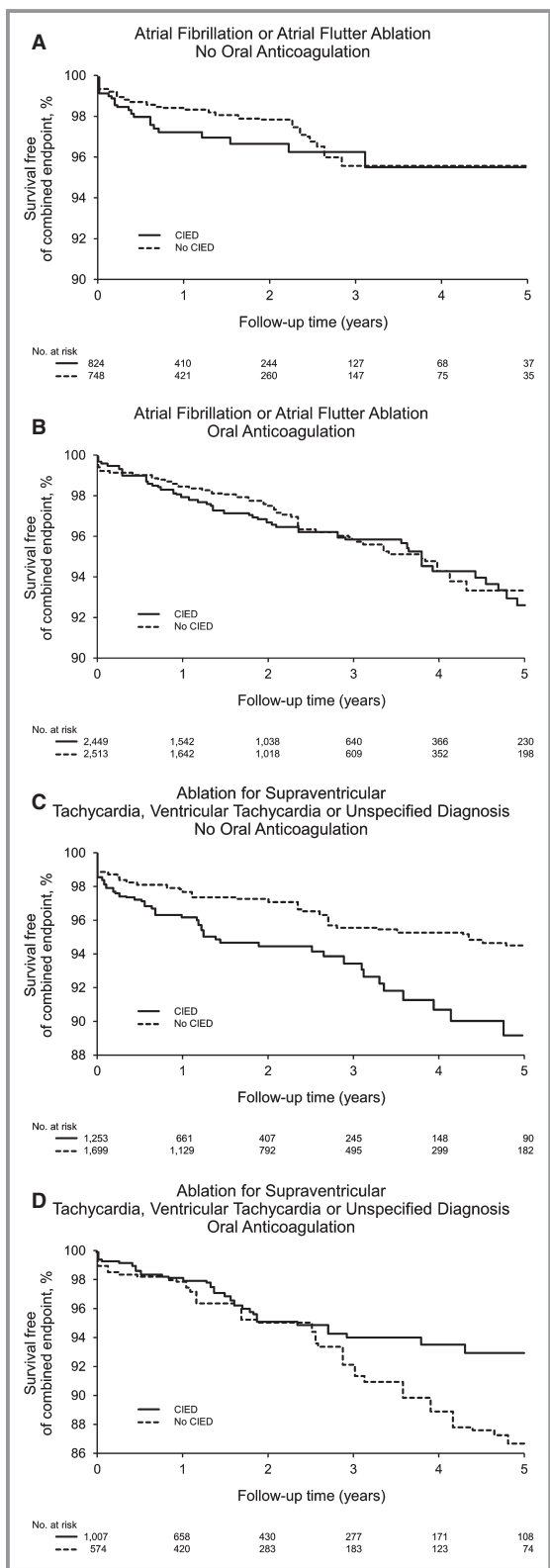


Figure 4. Kaplan–Meier survival free of combined endpoint of stroke, TIA, and systemic embolism in patients with and without cardiac implantable electronic device (CIED) in patients with (A) ablation for atrial fibrillation or atrial flutter not on oral anticoagulant (OAC), (B) ablation for atrial fibrillation or atrial flutter on OAC, (C) ablation for supraventricular tachycardia, ventricular tachycardia, or “unspecified” diagnosis not on OAC, and (D) ablation for supraventricular tachycardia, ventricular tachycardia, or “unspecified” diagnosis on OAC. TIA indicates transient ischemic attack.

transseptal puncture, presence of CIED, and occurrence of stroke cannot be inferred. Nearly 20% of the cohort has an ambiguous rhythm indication for the ablation and were classified as unspecified. Clinical and procedural characteristics of these patients, such as comorbidities, whether ablation was performed for AF, and extent of ablation, could have influenced the outcomes. Details regarding the ablation procedures (radiofrequency vs cryo energy, irrigated vs nonirrigated catheters) were not available, but could also influence stroke risk. Although OAC is recommended for all patients undergoing AF ablation, only 82% of this cohort was on OAC. Though this is likely attributed to a decision by the physician or patient to not initiate an OAC, we cannot rule out the possibility that the administrative database did not accurately reflect actual OAC use. These findings, however, correlate with our previous report of high rate of OAC discontinuation of 40% and 60% at 3 and 12 months after AF ablation, which correlated with increased risk of stroke.²⁷ The OLDW contains only privately insured and Medicare Advantage enrollees, so the conclusion may not necessarily be generalizable to Medicaid, Medicare fee-for-service, or uninsured populations.

Conclusions

Presence of a CIED significantly increases the risk of stroke, TIA, and systemic embolism after ablation procedures involving transseptal puncture. Use of concomitant oral anticoagulation may lead to a reduction in risk to levels noted in those without a CIED. Further prospective studies are necessary to determine the potential role of iatrogenic ASD in causing stroke and the role of anticoagulation in preventing embolic events in all patients with CIED undergoing transseptal puncture for ablation of arrhythmias.

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