Stroke or Transient Ischemic Attack in Patients with Transvenous Pacemaker or Defibrillator and Echocardiographically Detected Patent Foramen Ovale

Running title: DeSimone et al.; Stroke/TIA with PFO and implanted devices

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Abstract:

Background—A patent foramen ovale (PFO) may permit arterial embolization of thrombi that accumulate on leads of cardiac implantable electronic devices (CIED) in the right-sided cardiac chambers. We sought to determine whether a PFO increases the risk of stroke/transient ischemic attack (TIA) in patients with endocardial leads.

Methods and Results—We retrospectively evaluated all patients who had endocardial leads implanted between January 1, 2000, and October 25, 2010, at Mayo Clinic Rochester. Echocardiography was used to establish definite PFO and non-PFO cohorts. The primary endpoint of stroke/TIA consistent with a cardioembolic etiology, and the secondary endpoint of mortality during post-implantation followup were compared in PFO vs. non-PFO patients using Cox proportional hazards models. We analyzed 6075 patients (364 with PFO) followed for mean 4.7 ± 3.1 years. The primary endpoint of stroke/TIA was met in 30/364 (8.2%) PFO vs. 117/5711 (2.0%) non-PFO patients (hazard ratio: 3.49, 95% CI 2.33-5.25, p<0.0001). The association of PFO with stroke/TIA remained significant after multivariable adjustment for age, sex, history of stroke/TIA, atrial fibrillation, and baseline aspirin/warfarin use (hazard ratio: 3.30, 95% CI 2.19-4.96, p<0.0001). There was no significant difference in all-cause mortality between PFO and non-PFO patients (hazard ratio: 0.91, 95% CI 0.77-1.07, p=0.25).

Conclusions—In patients with endocardial leads, the presence of a PFO on routine echocardiography is associated with a substantially increased risk of embolic stroke/TIA. This finding suggests a role of screening for PFOs in patients who require CIEDs, if detected, PFO closure, anticoagulation, or non-vascular lead placement may be considered.

Key words: pacemaker, defibrillation, stroke, transient ischemic attack, patent foramen ovale, ICD
Introduction

Transvenous cardiovascular implantable electronic devices (CIEDs) are widely used due to the effectiveness with which they treat cardiac arrhythmias and the relative ease and safety with which they are implanted.\textsuperscript{1, 2} However, an endovascular lead within the right atrium or ventricle represents a foreign body that can promote formation of mobile thrombi that may dislodge to the pulmonary circulation.\textsuperscript{3, 4} Although symptomatic pulmonary embolism after pacemaker or defibrillator implantation is uncommon, asymptomatic emboli may be present far more frequently,\textsuperscript{4-7} and endovascular lead-related thrombi are likely under-detected. Utilizing ventilation perfusion scanning, one study showed asymptomatic pulmonary emboli in 15% of patients within two weeks of device implantation without heparin prophylaxis,\textsuperscript{8} and at autopsy pulmonary emboli were present in 21% of patients with CIEDs.\textsuperscript{6} A study using intracardiac echocardiography at the time of a planned electrophysiologic procedure found mobile thrombi attached to leads in 30% of patients.\textsuperscript{9} These thrombi were rarely seen utilizing transthoracic echocardiography (TTE), reflecting their small size. Moreover, the presence of lead-related thrombi was associated with increased pulmonary artery systolic pressure, suggesting subclinical pulmonary embolic events.\textsuperscript{9} Elevated pulmonary artery pressures may in turn increase the likelihood of right-to-left shunting across a patent foramen ovale (PFO).

Up to 25% of the population may have a PFO detectable on autopsy, with persistence after birth of a connection between the right and left atria.\textsuperscript{10, 11} In patients with elevated right-sided pressures, flow through a PFO provides a mechanism of blood flow from the right heart to the left-sided circulation. In patients with a PFO, endovascular leads may pose a unique hazard since the thrombi that develop on leads may shunt across the PFO to the systemic circulation, resulting in ischemic cerebrovascular events or other systemic thromboembolism. We have
previously published two case-series on device lead mediated paradoxical thromboembolism\textsuperscript{12} and effective management of such high-risk CIED patients with PFO closure to prevent recurrent strokes.\textsuperscript{13} Transvenous pacing leads have also been associated with increased risk of systemic thromboembolism in patients with intracardiac shunts.\textsuperscript{14} Presently, when an intracardiac shunt, such as an atrial or ventricular septal defect is recognized, endocardial leads are not implanted, and patients are referred for either closure of the shunt or epicardial lead placement.\textsuperscript{14-16} However, whether the presence of a PFO in most CIED recipients increases the risk of clinical strokes or transient ischemic attacks (TIAs) is unknown. Therefore, screening for a PFO is not routinely performed at the time of CIED implantation, and the presence or absence of a PFO does not affect the implant decision or strategy in current clinical practice. In order to test the hypothesis that patients with PFO and right-sided CIED leads are at increased risk for stroke or TIA, we performed a large retrospective study.

**Methods**

**Patient population**

All patients who underwent transvenous implantation of an implantable cardioverter-defibrillator or pacemaker at Mayo Clinic, Rochester, Minnesota, between January 1, 2000, and October 25, 2010, were included in the study, and patients’ charts reviewed between the last quarter of 2010 and the first quarter of 2011. All patients had authorized review of their medical records for research purposes. Data were de-identified to protect patient confidentiality. Patients were excluded from the analysis if identified as sustaining a possible neurological event during followup but lacked sufficient details in the electronic medical record regarding the symptoms and timing of stroke/TIA, or had an inadequate evaluation to establish a diagnosis and cause of the event. Patients were also excluded if PFO was suspected on echocardiography but not
definitively confirmed, or the diagnosis of PFO was made within 30 days after the occurrence of a stroke/TIA event.

Assessment of PFO and clinical characteristics

All patients receiving implanted devices with endocardial leads at our center routinely have comprehensive TTE performed. Data are prospectively entered into a clinical database with predefined variables, including absence or presence of a PFO. PFO was detected as part of standard protocol for TTE and TEE at Mayo Clinic. This includes the routine use of 2-dimentional and color Doppler interrogation of the interatrial septum. We also attempt, in all TTEs, the measurement of right-sided pressures from the tricuspid regurgitant jet velocity. When necessary, use of agitated saline to evaluate for right to left shunting is performed, typically, based on the size of the right atrial chambers and whether there are doubts on the structural integrity of the interatrial septum. If a shunt is visualized or diagnosed but cannot be easily seen at the usual place of a PFO or primum or ASD (primum or secundum) then a TEE to exclude a sinus venosus type ASD is done.

For all study participants, all echocardiogram reports (transthoracic and transesophageal) were reviewed for the presence of a PFO either by color-flow Doppler and/or intravenous agitated saline “bubble study.” The study personnel reviewing echo reports for PFO diagnoses were blinded to the clinical outcomes. This allowed for delineation of the study population into two groups, those with and those without a PFO. Some reports were coded as “possible” or “probable” PFO; in the absence of additional studies that definitively included or excluded PFO, these patients were excluded from the study population. The use of aspirin, warfarin, and clopidogrel was obtained from the electronic medical record in all study patients at three points in time: (1) the date of device implantation, (2) the date of the index echocardiogram (at which
absence or presence of PFO was determined), and (3) the date of stroke or TIA (in those patients who had neurologic events). Clinical characteristics of the patient population including comorbidities and history of atrial fibrillation (AF) were obtained from the diagnosis codes (ICD-9, HICDA and Berkson Mayo Clinic coding system) for clinical encounters until the time of index device implantation.

**Assessment of outcomes**

Outcomes data were obtained from a centralized system that contained complete records of all patients treated and followed at Mayo Clinic and its hospitals. These records provide a detailed history and diagnosis for all outpatient encounters, emergency room visits, home and nursing home visits, and inpatient care.\(^{17}\) We used the diagnosis codes consistent with cerebrovascular events to identify patients with possible stroke or TIA. The electronic medical records were reviewed, and in consultation with a board-certified vascular neurologist (A.A.R.), absence or presence of a documented ischemic stroke or TIA consistent with a cardioembolic etiology was determined and the date of events confirmed. We excluded those events from our stroke/TIA definition in which a definite non-cardioembolic cause for the stroke or TIA was documented, such as intracranial hemorrhage, proximal mobile aortic atheroma, severe ipsilateral carotid stenosis, radiologically proven small subcortical stroke with lacunar presentation, and severe intracranial stenosis in the relevant vessel. Mortality status and date of death were obtained from multiple sources including the Mayo Clinic registration database and Accurint (LexisNexis, Philadelphia, Pennsylvania), an institutionally approved fee-based Internet research and location service.

**Statistical methods**

Baseline patient demographics were compared between PFO and non-PFO groups using chi-
square tests for discrete variables and t-tests for continuous variables. The cumulative probabilities of stroke/TIA and of death following device implant among the two groups by PFO status were estimated using the Kaplan-Meier method. Potential confounders that attribute risk of stroke/TIA or mortality were evaluated using proportional-hazards regression models. Univariate and multivariate-adjusted Cox proportional-hazards models (adjusting for age, sex, prior history of stroke/TIA, and additionally adjusting for history of AF and use of aspirin and warfarin at time of implant) were used to determine differences in stroke/TIA and death between PFO and non-PFO patients during followup. Additional covariates were added to the Cox model using stepwise selection. A two-tailed \( \alpha \)-level 0.05 was considered the threshold for statistical significance for all tests. SAS version 9.3 (Cary, North Carolina) was used for statistical analysis.

The authors were entirely responsible for study hypothesis development, study design, data collection, data analysis, and manuscript preparation. The study was funded exclusively by Mayo Clinic as part of an implantable device quality practice review. There was no support or input from industry. This study was approved by the Mayo Clinic Institutional Review Board (IRB #10-007582).

**Results**

Our study included 6075 patients receiving CIED implantations with endocardial leads. The average followup after device implantation was 4.7 ± 3.1 years (range 0 - 12.3 years). There were 364 patients with definite PFO and 5711 patients without PFO. Transesophageal echocardiography (TEE) reports were available for 12.6% of patients and 108/364 (29.7%) PFO diagnoses were based on TEEs. We excluded 74 patients with probable/possible PFO on echocardiography that was not confirmed with further tests, and excluded 11 patients who had
the diagnosis of PFO made within 30 days after the index stroke/TIA event. Another 40 patients (5 in PFO group and 35 in non-PFO group) were excluded due to lack of sufficient followup data to confirm or refute diagnosis of stroke/TIA.

Baseline characteristics are presented in Table 1. There was no notable difference between PFO and non-PFO patients in terms of age, sex, history of stroke/TIA, diabetes, carotid artery disease, hyperlipidemia, hypertension, peripheral vascular disease, congestive heart failure, cerebral occlusion/stenosis, and CHA2DS2-VASc score. The PFO group was more likely to have a history of AF at baseline (49% in PFO vs. 44% in non-PFO group, p=0.03). The two groups were evenly matched for the distribution of CHA2DS2-VASc scores (mean 3.1 ± 2.0, p=0.58). Aspirin was used less often at the time of CIED implantation among patients with PFO (42% in PFO vs. 48% in non-PFO group, p=0.026) but warfarin use was similar (31% in PFO vs. 32% in non-PFO group, p=0.65).

Among patients with PFO, a total of 30 (8.2%) met the combined primary endpoint of ischemic stroke/TIA consistent with a cardioembolic etiology during followup as opposed to a total 117 (2.0%) among those without PFO (p<0.0001). Of these, 20/30 (66.7%) in PFO group and 80/117 (68.4%) in non-PFO group were classified as strokes as opposed to TIAs, thus an overall stroke rate of 5.2% vs. 1.4% (p<0.0001). At one-year post-implantation, the Kaplan-Meier cumulative incidence of stroke/TIA was higher in patients with PFO (1.4%) vs. non-PFO (0.6%). The cumulative difference progressed increasingly over time to 3.3% in PFO vs. 1.0% in non-PFO patients at two years, and 7.9% in PFO vs. 2.3% in non-PFO patients at five years (Figure 1).

On univariate time-to-event proportional-hazards estimation, the hazard rate of stroke/TIA in patients with PFO vs. non-PFO was 3.49 (97% CI 2.33-5.25, p<0.0001). This
strong association between PFO and stroke in patients with endocardial leads remained significant after multivariable adjustment for age, sex, and history of prior stroke/TIA (hazard ratio: 3.30, 95% CI 2.19-4.96, p<0.0001) and after additionally adjusting for history of AF and use of aspirin and warfarin at the time of index device implant (hazard ratio: 3.36, 95% CI 2.23-5.07, p<0.0001). No other covariates reached the statistical level for inclusion in the stepwise selection model (Table 2).

We performed further exploratory analyses to delineate possible subgroups with a different effect of PFO on stroke or TIA compared to the overall population. We stratified the analysis based on age (dichotomized at 65 years), gender, prior history of stroke/TIA, baseline history of AF, baseline aspirin and warfarin use, and thromboembolic risk as measured by CHA2DS2-VASc score (0 to 2 vs. 3 or more). The association between PFO and stroke/TIA was uniformly present in all subgroups as shown in the Kaplan-Meier curves in Figure 2.

There was no difference in unadjusted all-cause mortality among CIED patients with PFO (155/364; 46%) as compared to non-PFO (2200/5711; 39%), hazard ratio: 0.91 (95% CI 0.77-1.07, p=0.25, Figure 1). The absence of difference in mortality between groups persisted after adjusting for age, sex, and history of stroke/TIA (hazard ratio: 0.90, 95% CI 0.76-1.06, p=0.20), additional adjustment for history of AF and baseline aspirin and warfarin use (hazard ratio: 0.89, 95% CI 0.75-1.05, p=0.15), and further adjustment using stepwise selection of covariates (hazard ratio: 0.90, 95% CI 0.77-1.07, p=0.23, Table 2).

Discussion
In this large, retrospective analysis of endocardial pacemaker and defibrillator recipients, we found a more than 3-fold higher risk of stroke or TIA following device implantation in patients
with a PFO compared to those without a PFO. This dramatically increased risk remained after adjustment for age, sex, previous stroke or TIA, history of AF, and baseline use of aspirin and warfarin. Moreover, the elevated risk persisted over the course of follow-up. This finding contrasts population-based observational studies of PFO and thromboembolism, which failed to find an association between PFO and thromboembolism. However, these studies did not specifically include patients with endovascular pacemakers and defibrillators. The fact that endovascular leads are a nidus for thrombus development and adopt an intracardiac course that frequently is in juxtaposition to the interatrial septum likely accounts for the strong association we observed between PFO and stroke/TIA in device recipients (Figure 3). This is the first systematic evaluation of risk of systemic embolic events among patients with implanted endocardial pacemaker or defibrillator leads who have an incidentally identified PFO on echocardiography. In current practice, endocardial leads are avoided in patients with unclosed septal defects. Our findings suggest it may be reasonable to extend this strategy to patients with PFO, especially those with significant right-to-left shunt and easily identifiable on routine echocardiography.

PFO has long been postulated as a mechanism for cryptogenic stroke. Although numerous studies have suggested an association between cryptogenic stroke and PFO, an Olmsted county population-based study did not show an increased risk of stroke or TIA compared to age- and sex-matched controls. Similarly, the PFO in cryptogenic stroke study found no association between PFO and recurrent stroke among patients treated with aspirin or warfarin. The Closure I trial randomized patients with cryptogenic stroke to PFO closure and antiplatelet therapy or to medical therapy alone and found no difference in the rate of recurrent stroke or TIA. Several observations likely account for the lack of benefit of PFO closure in
Closure I as opposed to the strong association between stroke and PFO in our study. First, Closure I excluded patients with endovascular leads. PFO alone likely poses a significantly lower stroke risk without the concomitant presence of leads to seed thrombus formation in proximity to the interatrial septum. Second, the vast majority of patients with stroke or TIA after enrollment had mechanisms other than paradoxical embolism to account for the event, suggesting that in the device-free cryptogenic stroke population, paradoxical embolus is a relatively uncommon stroke mechanism. Third, Closure I compared an interventional to a medical strategy for stroke prevention; the finding that these had similar efficacy does not exonerate PFO from culpability in systemic embolism. The role of PFO in stroke or TIA is supported by a prospective, observational study that used propensity-score matched comparison groups to show fewer recurrent ischemic events after device closure of PFO. Patient followup was longer (median of 10 years) than in the Closure I trial (2 years).

Additional observations support the mechanistic role of PFO in thromboembolism in patients with endovascular leads. The cumulative incidence curve of stroke or TIA in patients with PFO only begins to diverge from that of non-PFO patients after 6 months post-device implantation (Figure 1A). This is consistent with a temporal delay as thrombi develop on the leads and right-sided cardiac pressures increase subsequent to subclinical pulmonary embolisms after device implantation, consequently promoting right-to-left blood flow shunting and paradoxical embolism. Previous studies have demonstrated increased pulmonary artery systolic pressure in patients with thrombi found on device leads using intracardiac echocardiography. The fact that these thrombi are small (and thus rarely seen with TTE) may account for the delay in pulmonary artery pressure elevation. Their small size may also account for the lack of increased mortality seen in patients with PFO. Small thrombi may be less likely to occlude a
sufficiently large vascular territory to cause fatal strokes. Other competing factors may also have accounted for the lack of mortality difference. The impact of the underlying cardiovascular disease that led to device implantation\(^{28-31}\) on mortality may have been sufficiently large as to overwhelm any influence of PFO-mediated thromboembolism.

Our findings have important clinical implications. They suggest it may be reasonable to screen patients undergoing endocardial lead placement to determine whether a PFO is present. In the presence of a significant PFO, concomitant anticoagulation, PFO closure, or epicardial or subcutaneous device placement should be considered. The clinical impact of these findings are large, given that an estimated 25\% of the general population has a PFO.\(^{10}\) In 2009, there were 1 million pacemakers and 328,000 defibrillators implanted worldwide, translating to approximately 332,000 devices in patients with PFOs that year alone. In our study, we found a 8\% risk of stroke/TIA at 5 years. Based on these numbers, this would translate to approximately 26,500 people annually with potentially preventable neurological events.

Our results are best interpreted in the context of study limitations. This was a retrospective study and is thus prone to all of the inherent biases associated with such study designs. Specifically, causality and evidence in favor of any clinical interventions cannot be provided. Moreover, any inferences are limited by the possibility of detection and classification biases, both in the clinical course and in the conduct of the study. We sampled antiplatelet and anticoagulant usage at limited points in time, although they varied only to a minor extent between the two groups. Surprisingly, we did not see any attenuation of the increased stroke/TIA risk among patients with PFO with baseline antiplatelet or anticoagulant use, and it is not clear if this was due to lack of efficacy of such therapies or methodological pitfalls like missing or time variable data, confounding, or ascertainment bias.
TEE is more sensitive than TTE for detection of PFOs. In our overall cohort of 6075 patients, independent of the study indication, the PFO detection rate was higher when TEE was performed (14.1% vs. 4.8% without TEE). We explored the possibility that patients who had a stroke/TIA outcome were more likely to have had a TEE that consequently would have biased towards a higher detection of PFOs. Extrapolating from the above detection rates and assuming no real association between PFO and stroke/TIA; merely due to a higher rate of TEEs among stroke/TIA patients (32.7% vs. 12.1% in those without stroke/TIA), we would expect detecting more PFOs among stroke/TIA patients (7.9% vs. 5.9% in those without stroke/TIA). This modest bias, however, cannot explain the actual discrepancy in PFO prevalence in the two outcome groups, 20.4% (30/147) in patients with stroke/TIA vs. 5.6% (334/5928) in those without stroke/TIA.

We detected an overall lower prevalence of PFO in our study (364/6075, 6.0%) than has been reported by autopsy evaluations.10 This may reflect underreporting and reduced sensitivity of routine TTE for PFO detection, especially if done in patients with endocardial hardware and without an intravenous agitated saline “bubble study” with Valsalva maneuver. It is conceivable; however, that those PFOs that were detected were large or had high risk characteristics, accounting for the increased risk of stroke/TIA in patients with echocardiographically detected PFOs. Only a minority (32.7%) of our PFO diagnoses were based on the more sensitive TEE,32 and a minority of echocardiographic studies (28%) were requested specifically for PFO evaluation. We had a 14.1% PFO detection rate when TEE evaluations were performed. We further underestimate the prevalence by excluding 74 cases with probable/possible PFO, and another 11 PFO diagnoses made after the patient had a stroke or TIA. It is likely that a proportion of patients especially in the non-PFO group had undetected PFOs. Despite this
misclassification bias towards null, there was a significant difference in stroke or TIA during followup, further supporting the magnitude of the interaction between endocardial leads and PFO. In any case, our study shows that the “more apparent” PFOs that were identified without a protocolled method to evaluate for their presence were attributable towards a substantial increase in risk of embolic ischemic events.

In conclusion, in patients with endovascular pacemaker or defibrillator leads, the presence of a PFO is independently associated with a significantly increased risk of stroke or TIA, which persists during long-term followup. Lead thrombi and paradoxical embolism likely account for this observation. A confirmatory prospective cohort study to establish this association between PFO and stroke/TIA among recipients of endocardial CIED leads is warranted. If the association is confirmed, antithrombotic therapy, PFO closure, or non-vascular lead placement could be considered in patients with PFO undergoing placement of endocardial CIED leads.

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**Conflict of Interest Disclosures:** Dr. Friedman reports research support from Medtronic, Biotronik, and Cameron Health. Dr. Friedman owns intellectual property rights with Bard EP, Medical Positioning, Inc., Aegis Medical, NeoChord, and Preventice. Dr. Friedman has received Speaker and/or Consulting fees from Bard, Biotronik, Leadex, and Sorin. Dr. Ackerman reports consulting fees (<10K/year level) for Boston Scientific, Medtronic, and St. Jude Medical. Dr. Rabinstein reports being a member of the clinical event adjudication committee for the trial PREVAIL funded by Boston Scientific. Dr. Asirvatham reports Honoraria/Consulting Fees (none significant) for Abiomed, Atricure, Biotronik, Boston Scientific, Medtronic, Spectranetics, St.
Jude, Sanofi-Aventis, Wolters Kluwer, and Elsevier. Dr. Asirvatham is a co-patent holder and may receive future royalties from: Aegis (appendage ligation), ATP (atrial fibrillation ablation and coagulum reduction during ablation), Nevro (use of nerve signal modulation to treat central, autonomic, and peripheral nervous system disorders, including pain), Sanovas (lung ablation), Sorin Medical (tricuspid valve project). The other authors state that they have no disclosures.

References:


**Table 1.** Baseline characteristics among the patent foramen ovale and non-patient foramen ovale groups.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFO (N=364)</th>
<th>No PFO (N=5711)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67.9 ± 15.3</td>
<td>66.8 ±17.0</td>
<td>0.22</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>219 (60%)</td>
<td>3672 (64%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Stroke/TIA, n (%)</td>
<td>53 (15%)</td>
<td>857 (15%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>81 (22%)</td>
<td>1327 (23%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Carotid artery disease, n (%)</td>
<td>26 (7%)</td>
<td>402 (7%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Cerebral occlusion/stenosis, n (%)</td>
<td>15 (4%)</td>
<td>188 (3%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>175 (48%)</td>
<td>2542 (45%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>191 (52%)</td>
<td>2928 (51%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>221 (61%)</td>
<td>3410 (60%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>180 (49%)</td>
<td>2492 (44%)</td>
<td>0.03</td>
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<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>41 (11%)</td>
<td>648 (11%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>171 (47%)</td>
<td>2640 (46%)</td>
<td>0.78</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>3.1 ± 2.0</td>
<td>3.1 ± 2.0</td>
<td>0.58</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ± standard deviation. PFO, patent foramen ovale.

**Table 2.** Cox proportional hazards models assessing association of patent foramen ovale amongst patients with endocardial device leads with outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stroke/TIA</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% confidence interval)</td>
<td>P-value*</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>3.49 (2.33, 5.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted for age, sex and history of stroke/TIA</td>
<td>3.30 (2.19, 4.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable adjusted†</td>
<td>3.36 (2.23, 5.07)‡</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* P-value testing for hypothesis hazard ratio = 1
† Adjusted for age, sex, prior stroke/TIA, history of atrial fibrillation, use of aspirin and warfarin at time of index device implant forced in the model, and additional covariates using stepwise selection with statistical level for inclusion in model p=0.05.
‡ No additional covariates reached statistical level for inclusion.
§ Additionally adjusted for diabetes, coronary artery disease, hyperlipidemia, hypertension, peripheral vascular disease, congestive heart failure and CHA2DS2-VASc score.
TIA, transient ischemic attack.
Figure Legends:

Figure 1. Kaplan-Meier survival curves for (A) stroke/transient ischemic attack and (B) mortality during followup, among patients with implanted endocardial leads. Solid line represents those with patent foramen ovale and dotted line those without patent foramen ovale. Time 0 is time of index lead implantation.

Figure 2. Kaplan-Meier survival curves for development of stroke/transient ischemic attack, in various subgroups of patients with implanted endocardial leads. Stratified by (A) age <65 vs. age ≥65 years, (B) sex, (C) without vs. with history of prior stroke/transient ischemic attack, (D) without vs. with history of atrial fibrillation, (E) not using vs. using aspirin at baseline, (F) not using vs. using warfarin at baseline, (G) CHA2DS2-VASc score 0-2 vs. ≥3. Solid line represents those with patent foramen ovale and dotted line those without patent foramen ovale.

Figure 3. Illustration of an endocardial lead thrombus embolizing through patent foramen ovale (PFO) to the left sided circulation and the brain. Panel A: Endocardial view of right atrial and right ventricular pacemaker leads. A PFO creating a communication between the right and left atria is also seen. Panel B: Thrombus formation on right atrial and right ventricular leads is shown. Also illustrated is a fragment of thrombus embolizing from the right atria across the PFO to the left-sided chambers and to the cerebral vasculature (yellow tracing). Panel C: Illustration of a PFO occluder device that closes the interatrial communication to prevent paradoxical embolization to the systemic circulation.
Figure 1

Panel A: Graph showing the relationship between post-implant stroke/TIA and time (Years) with lines for Device and PFO and Device and No PFO. The p-value is <0.001.

Panel B: Graph showing the relationship between death and time (Years) with lines for Device and PFO and Device and No PFO. The p-value is 0.25.
Figure 2
Figure 2, cont’d