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Endocardial Device Leads in Patients with Patent Foramen Ovale: Echocardiographic Correlates of Stroke/TIA and Mortality

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Abstract

Background—Echocardiographically detected patent foramen ovale (PFO) has been associated with stroke/transient ischemic attack (TIA) in patients with cardiac implantable electronic devices (CIED). We sought to evaluate the relationship between echocardiographic characteristics and risk of stroke/TIA and mortality in CIED patients with PFO.

Methods—In 6086 device patients, PFO was detected in 319 patients. A baseline echocardiogram was present in 250 patients, with 186 having a follow-up echocardiogram.

Results—Out of 250 patients with a baseline echocardiogram, 9.6% (n=24) had a stroke/TIA during mean follow-up of 5.3 ± 3.1 years; and 42% (n=105) died over 7.1 ± 3.7 years. Atrial septal aneurysm (ASA), prominent Eustachian valve (EV), visible shunting across PFO, baseline or

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change in estimated right ventricular systolic pressure (RVSP)/tricuspid regurgitation (TR) or maximum RVSP were not associated with post-implant stroke/TIA ($p>0.05$). An exploratory multivariate analysis using time-dependent cox models showed increased hazard of death in patients with increase in TR 2 grades (HR 1.780, 95% CI 1.447 – 2.189, $p<0.0001$) or increase in RVSP by >10 mmHg (HR 2.018, 95% CI 1.593 – 2.556, $p<0.0001$) or maximum RVSP in follow up (HR 1.432, 95% CI 1.351 – 1.516, $p<0.0001$). A significant increase (p -value <0.001) in TR was also noted during follow up.

Conclusions—In patients with CIED and PFO, structural and hemodynamic echocardiographic markers did not predict future stroke/TIA. However, a significantly higher TR or RVSP was associated with higher mortality.

Keywords

stroke; transient ischemic attack; defibrillator; pacemaker; leads; echocardiography; patent foramen ovale

Introduction

The proven safety and effectiveness of cardiovascular implantable electronic devices (CIEDs) has led to utilization of these devices for a variety of cardiovascular indications.¹ Platelets aggregates and mobile thrombi frequently form on the endovascularly implanted leads of these devices and have the potential to paradoxically embolize to the systemic circulation through a patent foramen ovale (PFO).^{2,3} Based on retrospective analysis, we have previously reported a strong independent association of PFO with stroke/transient ischemic attack (TIA) in the setting of implanted endocardial device leads, and also suggested that this increased risk is not dependent on the physical characteristics of the leads.^{2,4-7}

Several echocardiographic markers such as the presence of a hypermobile atrial septum (or atrial septal aneurysm [ASA])^{8,9}, prominent Eustachian valve (EV)^{10,11} and presence of a right-to-left shunt,¹² when present individually or together¹³ have been proposed as risk factors for paradoxical embolism and stroke in patients with PFO, though some studies have been inconclusive.^{14,15} Moreover, the relationship of these predictors with stroke and mortality outcomes has not been studied in patients with endocardial device leads, and their predictive utility in this patient population is yet to be investigated. We sought out to evaluate the association between these echocardiographic markers and stroke/TIA and mortality in our database of patients with endocardial device leads and echocardiographically confirmed PFO. We also evaluated if lead related anatomic or hemodynamic changes in tricuspid regurgitation (TR)¹⁶ or right ventricular systolic pressures (RVSP)³ would impact outcomes.

Methods

Patient population

We obtained patients for this study from the population of patients with CIEDs and endocardial device leads reported in earlier studies on risk of stroke/TIA^{2,6} and pulmonary

embolism (PE).¹⁷ Patients who underwent implantation of either transvenous ICD or pacemaker at the Mayo Clinic, Rochester, MN between January 1, 2000 and October 25, 2010 were included in this study if they were diagnosed with a definite PFO on echocardiography, and had a baseline (see below for definition of “baseline”) echocardiogram to obtain information on study predictors. The presence of a PFO was determined by reviewing all the available echocardiographic data. Detection of PFO was by transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE), utilizing 2D imaging, color-flow Doppler and/or intravenous injection of agitated saline. Patients with reported diagnoses of “possible” or “probable” PFO were not included.

Assessment of clinical and echocardiographic variables

Baseline clinical data was abstracted from the electronic medical records using diagnosis codes (ICD-9, HIDCA and Berkson Mayo Clinic coding system) for all clinical encounters until date of index device implantation.

A baseline echocardiogram was defined as the one that is performed closest to implantation date among all the echocardiographic studies done within 2 years prior to 1 year after lead implantation. A follow up echocardiogram was defined as one that was performed closest to 3 years but within 1 to 6 years after implantation.

In all TTEs, the right ventricular systolic pressures (RVSP) and the degree of TR were assessed from the TR color and continuous wave Doppler analysis.¹⁸ TR was graded as none (0), trace (1+), if < 10% of the right atrial area was occupied by the color flow Doppler jet; mild (2+), if 10% to 25% of the right atrial area was occupied by the color-flow Doppler jet; moderate (3+), if 25% to 50% of the right atrial area was occupied by the color-flow Doppler jet; and severe (4+), if > 50% of the right atrial area was occupied by the color-flow Doppler jet.^{19,20}

Assessment of outcomes

Data pertaining to the outcomes like the timing, mechanism and cause of stroke/TIA were obtained from a centralized electronic medical record that aggregates data for all outpatient encounters, emergency room visits, hospitalizations, and home/nursing home visits for patients treated and followed up at the Mayo Clinic and all its affiliate hospitals. Patients with possible stroke/TIA were first identified using diagnosis codes that suggested cerebrovascular events. A board-certified vascular neurologist (A.A.R.) then reviewed the medical record to confirm an ischemic event consistent with cardioembolic etiology, and excluded cases with alternative etiology like intracranial hemorrhage, severe ipsilateral cerebrovascular stenosis, or lacunar strokes. Occurrence and date of death were established through multiple sources including the Mayo Clinic database and Accurant (LexisNexis, Philadelphia, Pennsylvania), an institutionally approved fee-based Internet research and location service. A detailed description of the study methods has been previously published.^{2,6,17}

Statistical methods

Descriptive statistics as well as the echocardiographic data at baseline and follow up are provided as frequency (percentage) for discrete variables and mean $\pm$ standard deviation for continuous variables. Comparisons of echocardiographic parameters between baseline and follow-up measurements are made using a paired t-test for continuous variables like RVSP and EF and signed rank test was used for comparing ordinal variables like TR grade. Dichotomous categorical variables related to the shunt across the PFO were compared using the McNemar's test. Assessment of time-to-event outcomes adjusting for univariate predictors at baseline was made using a Cox proportional-hazards model. When assessing the association between baseline RVSP/TR and stroke/TIA and mortality, we constructed a univariate Cox Proportional Hazards model and included all the patients with available data. Positive change in either TR or RVSP was used as a covariate when analyzing this data. In addition, a multivariate Cox model was constructed using stepwise selection to determine the statistically significant parameters associated with time-to-death in all the patients with available TR and RVSP data (at both baseline and follow-up). A cox model with change of predictors from baseline to follow-up as covariates was used to assess the association over time between associated change in TR ($>2+$) and RVSP (>10 mm HG) as well as the maximum RVSP (obtained from data available at all follow up visits) and the incident risk of stroke/TIA and mortality. Results from the Cox models are presented as hazard ratios (HR) with 95% confidence intervals and p-values. Kaplan-Meier survival curves are used to assess long-term mortality, stratified by an increase in TR ($>2+$) and RVSP (>10 mm HG) at some point during follow-up. Differences in survival curves are evaluated using a log-rank test. Statistical significance is defined as a 2-tailed *P* value of less than 0.05. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, North Carolina).

This study was funded exclusively by Mayo Clinic as part of an implantable device quality practice review and was approved by the Mayo Clinic Institutional Review Board (IRB #10-007582). The authors were entirely responsible for study hypothesis development, study design, data collection, data analysis, and manuscript preparation.

Results

Although 375 patients with definite PFO were identified among 6086 patients with endocardial device leads in our database, 56 of the 375 patients were excluded from the study due to lack of lead related data. Out of the remaining 319 patients with definite PFO, 159 patients were diagnosed by TEE while 160 patients were diagnosed by TTE. A baseline echocardiogram and research authorization was available only for 250 out of the 319 patients and the remaining 69 patients were excluded. Among the 250 patients with a qualifying baseline echocardiogram, only 186 had a follow up echocardiogram. All 186 patients had TR data available at both baseline and follow up, and only 107 patients had RVSP data available from both baseline and follow up echocardiogram reports. Maximum follow up RVSP (from any echocardiogram report between 1 to 6 years post lead implantation) was available for 177 patients (Figure 1). Comparison of baseline characteristics as well as demographics of patients in the study population with (N=186) and without follow up data (N=64) are presented in Table 1.

Echocardiographic data at baseline and follow up (n=186) is presented in Table 2. On follow up echocardiogram, mean RVSP and mean LVEF were similar to baseline (p-value 0.6 and 0.2 respectively) (Table 2). Proportion of patients with trivial TR decreased to 31%, and 32% patients had mild TR at follow up. A greater proportion of patients had mild-moderate (11%), moderate (11%), moderate-severe (8%) and severe (8%) tricuspid regurgitation at follow up (p<0.001, Figure 2).

Stroke/TIA and mortality outcome

Out of the 250 patients with endocardial device leads and documented definite PFO, 9.6% (n=24) had a stroke/TIA during mean follow up of 5.3 ± 3.1 years; and 42% (n=105) died over an average of 7.1 ± 3.7 years. Baseline echocardiographic parameters including RVSP, TR severity, presence of a shunt or direction of the shunt across PFO, presence of ASA at baseline were not associated with increased risk of stroke/TIA (all p>0.05) (Table 3 and Figure 3A). Baseline RVSP (HR 1.02, 95% CI 1.01 – 1.04, p=0.009) and a TR grade (>2+) at baseline (HR 1.19, 95% CI 1.03 – 1.37, p=0.016) were associated with increased risk of mortality in the initial univariate analysis (Table 3 and Figure 3B). But subsequent multivariate analysis to assess association of baseline RVSP (1.02, 95% CI 0.99, 1.04, p = 0.15) and TR (1.12, 95% CI 0.96, 1.31, p = 0.15) with mortality showed no significance after adjusting for known confounders. In the sub-group of patients with follow up echocardiographic data on TR (186 patients) and RVSP (107 patients), 74 deaths in the TR cohort and 46 deaths in the RVSP cohort were recorded during the follow up period.

Effect of significant increase in tricuspid regurgitation (> +2) on stroke/TIA and mortality

Among 186 patients with TR data available at both baseline and follow up, time-dependent and univariate models showed that significant increase (> +2) in TR during follow up was not associated with any significant increase in the risk of post implant stroke/TIA (Table 4). But again in a separate analysis using time-dependent cox proportional hazards models, significant increase in TR was associated with and increased risk of mortality in both univariate and multivariate models (HR 1.780, 95% CI 1.447 – 2.189, p < 0.0001) (Tables 4 and 5). Kaplan- Meier curves for mortality associated with significant increase in RVSP (>10 mm HG) and TR (>2+) are presented in Figures 4 and 5 respectively.

Effect of significant increase in right ventricular systolic pressure (>10 mm HG) on stroke/TIA and mortality

Among 107 patients with RVSP data available at both baseline and follow up, time dependent and univariate models assessing the association between significant increase (>10 mm HG) in RVSP and risk of post implant stroke/TIA showed no statistical significance (Table 4). Again a separate analysis using time-dependent cox proportional hazards models showed that significant increase in RVSP in the follow up was associated with an increased risk of mortality in the initial univariate analysis and the subsequent multivariate adjustment (HR 2.018, 95% CI 1.593 – 2.556, p < 0.0001) (Tables 4 and 5).

The maximum RVSP (assessed per 10 units change in maximum RVSP in 177 patients with available RVSP data at any point between 1 and 6 years post-implant) was also not significantly associated with increased risk of stroke/TIA but suggested increased mortality

in the initial univariate analysis that persisted despite multivariate adjustment (HR: 1.432, 95% CI 1.351 – 1.516, $p < 0.0001$) (Table 6) analyzed using time-dependent cox proportional hazards models.

Discussion

In this study, we found that variables such as ASA, prominent EV, presence of right to left shunt, baseline or significant increase in RVSP or TR grade and maximum RVSP during follow up were not associated with an increased risk of stroke/TIA among patients with endocardial device leads and PFO. But a separate multivariate analysis using time-dependent cox proportional hazards models showed that significant increases in RVSP and TR are associated with a higher risk of mortality in patients with endocardial device leads and PFO. Both initial univariate analysis and subsequent multivariate adjustment also suggested a significant association between maximum RVSP noted during follow up and subsequent increased risk of mortality. Although baseline RVSP and TR values were also shown to be associated with increased mortality in the initial univariate analysis, the association no longer persisted after adjusting for known confounders in the subsequent multivariate analysis.

In light of these findings, the increased incidence of stroke/TIA in patients with endocardial device leads and PFO reported earlier by our group² may be due to the mere juxtapositioning lead based thrombus to an open PFO leading to paradoxical embolism in certain patients rather than due to the influence of any anatomical or hemodynamic factors. Furthermore, patients with a pathological PFO and a high PFO-attributable fraction or high Risk of Paradoxical Embolism (RoPE) score²¹ could also have contributed to the increased stroke rate seen in our earlier reported study. The role of PFO (causal vs. innocent bystander) in the increased mortality found among our patients with significantly increased and maximum RVSP or significantly increased TR is unknown and may need further clarification through future studies. To date, this is the only study analyzing anatomic and hemodynamic echocardiographic risk markers and their ability to predict the risk of stroke/TIA and mortality in patients with PFO and endocardial device leads.

Right ventricular systolic pressure and stroke/TIA in patients with endocardial device leads and PFO

Earlier, Supple et al. detected lead based thrombi in about 30% of their patients undergoing ablation using an intra-cardiac echocardiogram (ICE) and also reported significantly higher pulmonary artery systolic pressures in them suggesting chronic pulmonary thromboembolism of these lead based thrombi.³ We hypothesized that in such patients with endocardial device leads and PFO, the higher RVSP may cause a right to left shunt across an open PFO and facilitate paradoxical embolism of the lead based thrombi leading to stroke/TIA. But in our univariate and time dependent models, we found no significant increase in the risk of stroke/TIA among endocardial device leads and PFO patients with respect to RVSP at baseline or in the follow up. Extremely low incidence (3 out of 186 patients) of right to left shunt visualized in our study and no significant paradoxical embolism of lead

based thrombi may explain the lack of association between increased RVSP and stroke in our study.

Tricuspid regurgitation and stroke/TIA in patients with endocardial device leads and PFO

Although there was a significant increase in the proportion of patients with greater degree of tricuspid regurgitation (TR) at follow up ($p < 0.001$), TR at baseline or its change over time during follow up was not predictive of future stroke/TIA in our cohort of patients with endocardial device leads and PFOs. The increase in TR over time seen in our patients is similar to the findings of a recently reported large retrospective study assessing the prevalence of TR after endocardial lead implantation.¹⁶ As discussed earlier, it is possible that the worsening TR noted at follow up may be the result of interference of the endocardial leads with tricuspid valve (TV) leaflet motion or due to TV structural injury from their placement, rather than due to increased RVSP caused from chronic pulmonary thromboembolism of the dislodged lead related thrombi and this is consistent with findings noted by Lin et al.

Increased mortality associated with significant TR and significant/maximum RVSP in patients with endocardial device leads and PFO

Earlier studies suggested that LV systolic dysfunction and pulmonary hypertension are well-established markers of increased mortality.²² Nath et al. showed that moderate or greater TR is associated with increased mortality, independent of pulmonary artery pressure, LVEF, age, biventricular systolic function, RV size, and dilation of the inferior vena cava.²³ Another study suggested an increase in mortality in patients with endocardial device leads associated with both pre and post implantation TR independent of worsening LV function, but this study was not specific to patients with PFO.¹⁶

The long-term mortality associated with incremental changes in RVSP and TR in patients with endocardial device leads and PFO is unknown. So we evaluated the effect of incremental changes in TR ($>2+$) and RVSP (>10 mm HG) as well as maximum RVSP noted during follow up on mortality among patients with endocardial device leads and PFOs and found increased mortality in both our initial univariate analysis as well as in the subsequent multivariate mortality models. As expected, age and LVEF at baseline were also associated with increased mortality in patients with endocardial device leads and PFO. Additionally, the use of clopidogrel or warfarin and the presence of a prominent EV at baseline were also found to be associated with increased mortality in these patients. Where as the presence of peripheral vascular disease and diabetes were also associated with increased mortality in the maximum RVSP multivariate analysis. The increased mortality associated with the prominent EV may be due to statistical error of chance due to analysis on small number of patients (only 5 out of 186 patients had prominent EV identified at baseline) while the mortality associated with clopidogrel or warfarin use may just be a markers of a more sicker patient population with recent vascular events and with an overall increased risk of mortality. The cause of increased mortality associated with incremental increase in TR and RVSP/maximum RVSP seen during follow up and the role of PFO (causal vs. innocent bystander) in these patients is unknown. In our study group, the worsening TR and increased RVSP may have led to greater right to left shunting across the

PFO, causing increased left atrial pressures and more frequent episodes of pulmonary edema in these patients resulting in increased mortality. But this hypothesis may need to be further validated by future prospective trials in patients with endocardial device leads using a non-PFO control group.

Association of other baseline echocardiographic variables with stroke/TIA and mortality in patients with endocardial device leads and PFO

Right-to-left shunt, the presence of ASA or prominent EV was not associated with an increased risk of stroke/TIA or mortality in our cohort. This is consistent with the results of an earlier large prospective, multicenter, observational studies, CODICIA (right-to-left shunt in cryptogenic stroke)¹⁴ and the German Stroke Study,²⁴ which suggested that neither a right-to-left shunt nor its combination with ASA were independent risk factors for recurrence of stroke in general or younger stroke population.

The lack of association in our study may be due to the extremely low incidence of right to left shunt (3 of the 186 patients), ASA (10%) and prominent EV (3%) in our study group. Previous studies reported incidences up to 73% and 15% for prominent EV and ASA respectively using advance imaging techniques, such as intracardiac echocardiography (ICE) and TEE in selected patient groups.^{11,25} Interference from lead related artifacts on standard TTE images and the lack of clear consensus as to what constitutes a “prominent” EV might have contributed to this relatively lower detection rates seen in our study group. The low incidence of right to left shunt in our cohort may be explained by the dynamic nature of the shunt that is strongly dependent on the cardiac and hemodynamic changes occurring with each cardiac cycle and influencing the relationship between right and left atrial pressures across the PFO.²⁶

Limitations

Relatively small sample size may have led to inadequate power to detect weaker associations and impeded multivariable analysis to further test the association between TR or RVSP and mortality in patients with endocardial device leads and stroke/TIA. Incidence of AF and use of Coumadin in follow up is unknown and this could have led to attenuation or increase in stroke/TIA risk and/or mortality. Multiple operators were involved in measuring and interpreting the TEE and TTE data and inter and intra-operator variabilities were not calculated as a part of this study. Due to retrospective nature of this study and differing indications for the baseline or the follow up echocardiograms, the maneuvers and techniques used to accentuate or quantify the shunt during individual echocardiography were unavailable or highly variable. Some of the echocardiograms used in this study may have been obtained during hospitalization for unrelated terminal events like acute pulmonary embolism, pulmonary edema, severe pneumonia, etc., that can be associated with increased RVSP/TR independent of presence of endocardial device leads and could have influenced the positive correlation seen between mortality and increased RVSP/TR at follow up in our study. Defining baseline echocardiograms as those done 2 years prior to 1 year after implantation could have confounded the severity of TR measured in the follow up. As it could have resulted in missing the detection of early lead related TR in the 1st year of

implantation and misclassifying it as baseline TR. Data in regard to type of leads and their repositioning, removal/replacement or addition during the follow up was not analyzed and this could also influence the resultant TR. Lack of advanced imaging techniques to discern lead related artifacts and inability to review individual echocardiographic images may also have biased our study towards a null result. Our study may also have been biased towards patients with larger PFOs since smaller ones may have been missed or ambiguous ones might have been excluded. Also, PFOs with intermittent shunting or shunting with Valsalva may have been missed, as the initial echocardiograms obtained were not done with an intention to diagnose PFOs in these patients.

Conclusions

We found no association between the several anatomic and hemodynamic echocardiographic markers and stroke/TIA in patients with PFO and endocardial device leads but those with significantly increased TR and RVSP at follow up had a higher overall mortality. It is possible that “high risk” echocardiographic markers are not predictive of stroke/TIA in patients with leads because the mere presence of an endocardial lead thrombus juxtapositioned to a PFO large enough to be detected by transthoracic echocardiography may overwhelm all other hemodynamic risk factors for paradoxical thromboembolism. Larger prospective studies using a systematic imaging protocol (including TEE, ICE, agitated saline contrast and use of the Valsalva maneuver) to better identify PFO, lead based thrombi and other echocardiographic markers previously associated with higher stroke/TIA risk are necessary to further investigate this question.

Abbreviations

ASA	atrial septal aneurysm
CIED	cardiovascular implantable electronic device
CI	confidence interval
EV	eustachian valve
HR	hazard ratio
ICD	implantable cardioverter defibrillator
ICE	intracardiac echocardiography
LV	left ventricle
LVEF	left ventricular ejection fraction
PFO	patent foramen ovale
RV	right ventricle
RVSP	right ventricular systolic pressure
TEE	transesophageal echocardiography

TIA	transient ischemic attack
TR	tricuspid regurgitation
TTE	transthoracic echocardiography
TV	tricuspid valve

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Figure 1.
Flowchart of the study population

Figure 2. Severity of tricuspid regurgitation in patients with endocardial device leads and PFO at baseline and in follow-up. Baseline: echocardiograms done closest to implantation date and within 2 years prior or 1 year after lead implantation; Follow-up: echocardiogram done closest to 3 years after lead implantation and within 1 to 6 years after lead implantation.

Figure 3.

Panel A – Echocardiographic parameters at baseline and their association with stroke/TIA in patients with PFO and endocardial device leads – univariate analysis Forest plot*

Panel B – Echocardiographic parameters at baseline and their association with mortality in patients with PFO and endocardial device leads – univariate analysis Forest plot*

* Right to left and left to right shunt across PFO; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation; LVEF, left ventricular ejection fraction

Figure 4. Kaplan-Meier curve for mortality outcome among 186 patients with significant increase in tricuspid regurgitation (>2+) during follow-up.

Figure 5. Kaplan-Meier curve for mortality outcome among 107 patients with significant increase in right ventricular systolic pressure (>10 mm HG) during follow-up.

Table 1

Baseline characteristics: Comparing patients with and without follow-up data

Variable	Patients With Follow-Up (N=186)	Patients Without Follow-Up (N=64)	P Value
Age	67.2 (15.8)	67.6 (15.3)	0.85
Gender, n (%)			0.10
. Female	83 (45%)	21 (33%)	
. Male	103 (55%)	43 (67%)	
Comorbidities			
. Stroke/TIA, n (%)	18 (10%)	6 (9%)	0.94
. Diabetes, n (%)	47 (25%)	14 (22%)	0.59
. Carotid Artery Disease, n (%)	12 (6%)	5 (8%)	0.71
. Coronary Artery Disease, n (%)	97 (52%)	28 (44%)	0.25
. Hyperlipidemia, n (%)	117 (63%)	28 (44%)	0.007
. Hypertension, n (%)	128 (69%)	38 (59%)	0.17
. Atrial Fibrillation, n (%)	103 (55%)	35 (55%)	0.92
. Peripheral Vascular Disease, n (%)	25 (13%)	7 (11%)	0.61
. Congestive Heart Failure, n (%)	101 (54%)	29 (45%)	0.21
. Cerebrovascular Occlusion, n (%)	5 (3%)	3 (5%)	0.43
RVSP	41.8 (13.0)	41.1 (12.3)	0.78
TR Severity, n (%)			0.62
. Trivial	92 (49%)	28 (44%)	
. Mild	51 (27%)	23 (36%)	
. Mild-Moderate	17 (9%)	4 (6%)	
. Moderate	15 (8%)	4 (6%)	
. Moderate-Severe	7 (4%)	1 (2%)	
. Severe	4 (2%)	4 (6%)	
EF (%)	45.0 (18.0)	46.9 (16.1)	0.49
Shunt, n (%)	26 (14%)	9 (14%)	0.99
Shunt Direction, n (%)			0.45
. Left to Right	15 (63%)	4 (50%)	
. Right to Left	7 (29%)	4 (50%)	
. Bi-directional	2 (8%)	0 (0%)	
Atrial Septal Aneurysm, n (%)	18 (10%)	5 (8%)	0.66
Eustachian Valve, n (%)	5 (3%)	0 (0%)	0.19

TIA; Transient Ischemic Attack;

* Standard Deviation (SD)

Table 2

Echocardiographic parameters at baseline and follow up in patients with patent foramen ovale and endocardial leads

Variable	Baseline (N=250)	Follow up (N=186)	P-value
RVSP in mm HG	41.7 (12.8 [*])	42.1 (14.1 [*])	0.60
TR Severity, n (%)			<. 001
. Trivial	120 (48%)	58 (31%)	
. Mild	74 (30%)	59 (32%)	
. Mild-Moderate	21 (8%)	20 (11%)	
. Moderate	19 (8%)	20 (11%)	
. Moderate-Severe	8 (3%)	14 (8%)	
. Severe	8 (3%)	15 (8%)	
EF %	45.5 (17.6 [*])	46.4 (17.0 [*])	0.20
Shunt, n (%)	35 (14%)	14 (8%)	0.046
Shunt Direction, n (%)	32 (12.8%)	24 (12.9%)	
. Left to Right	19 (59%)	6 (43%)	
. Right to Left	11 (34%)	3 (21%)	
. Bi-directional	2 (6%)	5 (36%)	
Atrial Septal Aneurysm, n (%)	23 (9%)		
Eustachian Valve, n (%)	5 (2%)		

RVSP, Right Ventricular Systolic Pressure; TR, Tricuspid Regurgitation; EF, Left Ventricular Ejection Fraction;

^{*} Standard Deviation (SD)

Univariate analysis for stroke/TIA and mortality outcomes using echocardiographic parameters at baseline in patients with patent foramen ovale and endocardial leads

Table 3

Variable	Stroke/TIA Outcome			Mortality Outcome		
	HR	95% CI	P-value	HR	95% CI	P-value
Baseline RVSP (mm HG)	0.987	(0.946, 1.030)	0.55	1.024	(1.006, 1.043)	0.009
TR Severity (grade)	0.956	(0.681, 1.342)	0.79	1.187	(1.032, 1.366)	0.016
LVEF %	1.018	(0.993, 1.043)	0.15	0.991	(0.979, 1.003)	0.13
Shunt	1.370	(0.511, 3.674)	0.53	0.861	(0.509, 1.457)	0.58
Shunt Direction	0.366	(0.048, 2.781)	0.33	1.000	(0.421, 2.374)	1.0
Atrial Septal Aneurysm	0.392	(0.053, 2.906)	0.36	1.187	(0.650, 2.167)	0.58
Eustachian Valve	2.302	(0.310, 17.092)	0.42	2.319	(0.850, 6.325)	0.10

HR, Hazard Ratio; RVSP, Right Ventricular Systolic Pressure; TR, Tricuspid Regurgitation; LVEF, Left Ventricular Ejection Fraction; CI, Confidence Intervals

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Univariate analysis of echocardiographic parameters (positive change in TR and RVSP) in patients with patent foramen ovale and endocardial leads:
Time-dependent univariate cox proportional hazards model for post-implant stroke/TIA and mortality

Table 4

Variable	Stroke/TIA Outcome			Mortality Outcome		
	HR	95% CI	P-value	HR	95% CI	P-value
Significant Increase in RVSP (> 10mm)	1.868	(0.626, 5.572)	0.2627	2.380	(1.889, 3.000)	< 0.0001
Significant Increase in TR (2+ category change)	1.750	(0.681, 4.493)	0.2451	2.171	(1.775, 2.654)	< 0.0001

HR, Hazard Ratio; RVSP, Right Ventricular Systolic Pressure; TR, Tricuspid Regurgitation; CI, Confidence Intervals;

Table 5

Multivariate analysis of echocardiographic parameters in patients with patent foramen ovale and endocardial leads: Time-dependent multivariate cox proportional hazards model for mortality adjusting for positive change in TR ad RVSP over time using * stepwise selection of covariates

Variable	Time-Dependent Multivariate Model for Mortality Adjusting for Positive Change in TR Over Time		Time-Dependent Multivariate Model for Mortality Adjusting for Positive Change in RVSP Over Time	
	HR	95% CI	P-value	P-value
Significant Increase in TR (2+ category change)	1.780	(1.447, 2.189)	<.0001	-
Significant increase in RVSP (> 10 mm HG)	-	-	-	<.0001
Age	1.057	(1.048, 1.067)	<.0001	<.0001
LVEF (%)	0.983	(0.978, 0.988)	<.0001	<.0001
Clopidogrel Use at Implant	4.445	(3.090, 6.394)	<.0001	<.0001
Eustachian Valve	1.662	(1.044, 2.646)	0.0321	0.0368
Warfarin Use at Implant	0.634	(0.517, 0.777)	<.0001	<.0001

HR, Hazard Ratio; RVSP, Right Ventricular Systolic Pressure; TR, Tricuspid Regurgitation; CI, Confidence Intervals;

* Stepwise Selection of Covariates: Prior Peripheral Vascular Disease, Prior Atrial Fibrillation, Prior Congestive Heart Failure, Ejection Fraction, Aspirin Use, Plavix Use and Warfarin Use

Table 6

Multivariate analysis of echocardiographic parameters in patients with patent foramen ovale and endocardial leads: Time-dependent multivariate cox proportional hazards model for mortality adjusting for maximum RVSP (per 10 units change) over time using * stepwise selection of covariates

Variable	HR	95% CI	P-value
Maximum RVSP	1.432	(1.351, 1.516)	<0.0001
Age	1.050	(1.041, 1.059)	<0.0001
Plavix Use at Implant	4.399	(3.047, 6.351)	<0.0001
Hx of Peripheral Vascular Disease	2.213	(1.783, 2.748)	<0.0001
Warfarin Use at Implant	0.510	(0.416, 0.625)	<0.0001
Gender (Male)	1.618	(1.347, 1.943)	<0.0001
Hx of Congestive Heart Failure	1.488	(1.223, 1.809)	<0.0001
Hx of Diabetes	1.276	(1.057, 1.540)	0.0111

HR, Hazard Ratio; RVSP, right ventricular systolic pressure; CI, Confidence Intervals; for Age, Gender, Prior Stroke/TIA, Prior Diabetes, Prior Coronary Artery Disease,

* Stepwise Selection of Covariates: Prior Peripheral Vascular Disease, Prior Atrial Fibrillation, Prior Congestive Heart Failure, Ejection Fraction, Aspirin Use, Plavix Use and Warfarin Use