Stroke in patients with cardiovascular implantable electronic device infection undergoing transvenous lead removal

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BACKGROUND Stroke can be a devastating complication in patients with cardiovascular implantable electronic device (CIED) infection. Paradoxical septic embolism can occur in the presence of device leads and patent foramen ovale (PFO) via embolic dislodgement during transvenous lead removal (TLR).

OBJECTIVE The purpose of this study was to examine stroke and its associated factors in patients undergoing TLR for CIED infection.

METHODS We performed a retrospective analysis of all patients undergoing TLR for CIED infection from January 1, 2000, to July 30, 2017, from all 3 tertiary referral centers at the Mayo Clinic (Rochester, Phoenix, and Jacksonville). The primary outcome was stroke and was further categorized into preprocedural and postprocedural stroke. Associated risk factors were analyzed.

RESULTS A total of 774 patients (mean age 67.6 ± 14.9 years) underwent TLR for CIED infection. The stroke rate in this cohort was 1.9% (95% confidence interval [CI] 1.1%–3.2%). The preprocedural and postprocedural stroke rate was 0.9% (95% CI 0.4%–1.9%) and 1.0% (95% CI 0.4%–2.0%), respectively. PFOS were identified in 46.7% of patients with stroke and in 12.9% of patients without stroke, and were independently associated with stroke (P = .0002). This was especially in patients with right-sided vegetations with right-to-left shunting (odds ratio 6.4; 95% CI 1.3–31.0; P = .022).

CONCLUSION In patients with CIED infection undergoing TLR, the presence of PFO, especially with right-sided vegetation with right-to-left shunting, was associated with an increased risk of stroke. This finding suggests that PFO screening before TLR warrants meticulous attention.

KEYWORDS Cerebrovascular accident; Endocarditis; Outcomes; Patent foramen ovale; Transvenous lead extraction

Introduction
The incidence of cardiovascular implantable electronic device (CIED) infection is increasing.1,2 The mainstay of treatment of CIED infection is targeted antimicrobial therapy along with removal of device hardware, in most cases by transvenous lead removal (TLR). Unfortunately, among all procedures performed in the electrophysiology laboratory, TLR carries the highest risk of stroke.3 Patients with CIED infection often have more medical comorbidities,4 and stroke can be a devastating complication in this group of patients.

Previous studies have shown that pulmonary embolism may occur in patients with CIED infection before or after the TLR procedure.5,6
Stroke in patients with CIED infection undergoing TLR has not been evaluated in a systematic fashion. Therefore, we sought to assess all strokes in patients with CIED infection undergoing TLR and to further examine factors associated with stroke in this population.

Methods
We performed a retrospective cohort study of all patients undergoing TLR for CIED infection at the Mayo Clinic Enterprise Heart Rhythm Practice. The study included patients at the 3 academic campuses in Rochester, Minnesota; Phoenix, Arizona; and Jacksonville, Florida. The study was approved by the Mayo Clinic Institutional Review Board.

Study population
Adult patients (age ≥18 years) who underwent TLR for CIED infection between January 1, 2000, and July 30, 2017, were included in the study (Figure 1). CIED infection was defined using International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) codes for device infection, bacteremia, and endocarditis (Supplemental Table S1). These diagnostic codes were selected based on definitions of CIED infection in the Heart Rhythm Society expert consensus statement on CIED lead management and extraction.7 TLR procedures were identified using Current Procedural Terminology (CPT) codes 33234, 33235, and 33244, which identifies transvenous lead explant and extraction procedures.7 We excluded patients with concurrent procedural codes for orthotopic heart transplantation, ventricular assist device placement, or total artificial heart implantation, because these patients frequently have concomitant device removal procedural codes.

Data collection
Patient demographic parameters and comorbidities were collected. Comorbidities were identified using ICD-9 and ICD-10 codes (Supplemental Table S2).

All transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) reports were reviewed to collect predefined echocardiographic parameters (vegetation, patent foramen ovale [PFO], shunt direction). Two study personnel independently reviewed the echocardiographic reports. Data on vegetation and shunt direction were collected based on

![Figure 1](image_url)  
*Figure 1*  Patient inclusion and categorization CONSORT (Consolidated Standards of Reporting Trials) flow diagram. CIED = cardiovascular implantable electronic device; VAD = ventricular assist device.
echocardiogram performed before or during the TLR procedure during the same hospitalization. Presence of a PFO was determined by review of all echocardiogram reports within a time period of 6 months before to 6 months after the TLR procedure. Diagnosis of PFO used standard published criteria as used at our institution. Vegetations were identified based on visualization of mobile echodense masses and were further categorized into right-sided and left-sided vegetations.

**Lead removal protocol**

After CIED infection was confirmed, patients underwent transvenous lead explant or extraction. The procedures were performed under monitored anesthesia care or under general anesthesia, in the electrophysiology laboratory or the hybrid operating room, with cardiovascular surgery backup. In device leads that were extracted >1 year after implantation, specialized tools, such as locking stylets, mechanical sheaths, and laser sheaths, were used to extract the device. Use of intraprocedural TEE was based on the discretion of the operator. In patients who were on anticoagulation, international normalized ratio was permitted to return to normal and direct-acting oral anticoagulants were withheld per guidelines before the procedure. In patients who were bridged with therapeutic heparin, heparin was stopped 6 hours before the procedure. Anticoagulation was restarted after the procedure based on the patient’s underlying stroke risk, balanced against the bleeding risk from a débrided pocket.

**Assessment of outcomes**

The primary outcome was stroke during the period of illness (defined as 4 weeks before TLR procedure until hospital discharge). Stroke events were identified based on individual chart review to ensure that the diagnosis was made according to the standardized definition from the Valve Academic Research Consortium, which defined stroke based on occurrence of acute onset of a focal or global neurologic deficit with at least 1 neurologic sign or symptom consistent with stroke, lasting >24 hours (or less if available neuroimaging documented a new infarct, or the neurologic deficit resulted in death), no readily identifiable nonstroke cause for clinical presentation, and confirmation by either a neurology specialist or neuroimaging procedure. Transient ischemic attack was defined as focal or global neurologic deficit lasting <24 hours, with neuroimaging not demonstrating a new infarct. We did not include hemorrhagic stroke.

Strokes were adjudicated independently by 2 reviewers, with a third reviewer casting the deciding vote in cases of disagreements. Patients with possible stroke were initially identified using ICD-9 and ICD-10 codes (Supplemental Table S3) before individual chart review. Stroke was further categorized into preprocedural, if the event occurred within 4 weeks before the TLR procedure, and postprocedural, if the event occurred during or after the procedure until hospital discharge.

Secondary outcomes were duration of hospitalization and 30-day mortality, defined as death within 30 days of the TLR procedure.

**Statistical analysis**

Categorical variables are expressed as percentages, whereas continuous variables were expressed as mean ± SD. Baseline patient demographics were compared between stroke and nonstroke groups by using the χ² test for categorical variables and the Student t test for continuous variables. Wilcoxon rank sum test was used to compare median length of stay. Logistic regression was used to look at the association of various factors to stroke. Variables that showed a univariate relationship with stroke were also put into a multivariate model to assess their relative importance to stroke. All P values were 2-sided, and P < .05 was considered significant. In cases of multiple hypothesis testing, Bonferroni correction was used. Kappa was calculated to determine the degree of agreement between independent reviewers on stroke outcome. All statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

**Results**

The derivation of the patient cohort is summarized in Figure 1. A total of 774 patients (mean age 67.6 ± 14.9; 26% female) underwent TLR for CIED infection during the 17-year study period.

There were no significant differences in demographics and comorbidities between patients with and those without stroke (Table 1). However, patients who had a stroke were more likely to have a history of stroke (33.3% vs 7.4%; P = .0002).

Overall, the stroke rate associated with TLR in CIED infection was 1.9%. Among the 15 patients who experienced stroke events, 7 strokes (0.9%) occurred before the TLR procedure, and 8 strokes (1.0%) occurred after the TLR procedure (Figure 2). Among the postprocedural stroke group, 62.5% of strokes occurred within the first 2 days after TLR. Kappa for agreement on stroke outcomes was 0.96 (95% confidence interval [CI] 0.89–1.00).

Detailed demographic and clinical characteristics of each patient who experienced a stroke event are given in Supplemental Table S4. There were no occurrences of transient ischemic attack. All strokes seemed to be cardioembolic in nature, with neuroimaging findings ranging from acute infarct in a single focus to multiple bihemispheric foci. There were no strokes with a clear nonembolic cause, such as findings of severe ipsilateral carotid stenosis, small subcortical stroke with lacunar presentation, or severe intracranial stenosis in the relevant vessel.

**Echocardiographic characteristics**

Echocardiography with the use of agitated saline was performed in 326 patients (42.0%), and TEE was performed in 585 patients (75.6%). PFOs were found in 105 patients (13.6%). Most of the PFOs were only detected after TTE with agitated saline or TEE with or without agitated saline (Supplemental Figures S1 and S2), with no difference in types of echocardiography performed in stroke patients with and without PFO (Supplemental Table S5). Patients with stroke had higher rates of PFO than did patients without stroke.
Multivariable analysis revealed that PFO was independently associated with stroke (odds ratio [OR] 7.75; 95% CI 2.60–23.15; \(P = .0002\)) (Table 2). Among patients with PFO, a total of 7 strokes occurred. Two (28.6%) occurred before the TLR procedure, and 5 (71.4%) occurred after the TLR procedure. Patients with right-sided vegetation and right-to-left shunting had an overall stroke rate of 19% (OR 6.4; 95% CI 1.3–31.0; \(P = .022\)) (Table 3). All postprocedural strokes in patients with PFOs occurred within 2 days of the TLR procedure.

Patients with stroke also had a higher occurrence of left-sided vegetation than did patients without stroke (40% vs 10.5%; OR 5.7; 95% CI 2.0–16.3; \(P = .0016\)). Strokes in patients with left-sided vegetation were predominantly pre-procedural in nature, with 5 strokes (83.3%) occurring before the TLR procedure, and only 1 (16.7%) occurring after the TLR procedure (\(P = .04\)). Multivariable analysis revealed that left-sided vegetation was independently associated with stroke (OR 7.68; 95% CI 2.50–23.60; \(P = .0004\)) (Table 2). Among all postprocedural strokes, there were 3 patients who had a stroke but did not have a PFO or left-sided vegetation. All 3 strokes occurred late in the hospital course (3–11 days after lead extraction). Two patients had atrial fibrillation with dense spontaneous echocontrast in the left atrial appendage and were not undergoing anticoagulation before the stroke. One patient had atrial fibrillation and mechanical

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**Table 1** Characteristics of patients with CIED infections who underwent transvenous lead removal

<table>
<thead>
<tr>
<th></th>
<th>All stroke (n = 15)</th>
<th>Preprocedural stroke (n = 7)</th>
<th>Postprocedural stroke (n = 8)</th>
<th>No stroke (n = 759)</th>
<th>(P) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67.4 ± 15.8</td>
<td>62.7 ± 17.6</td>
<td>71.5 ± 13.8</td>
<td>67.6 ± 14.9</td>
<td>.9</td>
</tr>
<tr>
<td>Female</td>
<td>5 (33.3)</td>
<td>3 (42.9)</td>
<td>2 (25.0)</td>
<td>198 (26.1)</td>
<td>.56</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>53.1 ± 13.3</td>
<td>58 ± 6.2</td>
<td>48.3 ± 17.1</td>
<td>46.4 ± 16.5</td>
<td>.14</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.7 ± 7.1</td>
<td>29.6 ± 9.8</td>
<td>27.8 ± 3.5</td>
<td>29.5 ± 6.8</td>
<td>.52</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9 (60.0)</td>
<td>4 (57.1)</td>
<td>5 (62.5)</td>
<td>376 (49.5)</td>
<td>.45</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8 (53.3)</td>
<td>4 (57.1)</td>
<td>4 (50.0)</td>
<td>506 (66.7)</td>
<td>.28</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (66.7)</td>
<td>5 (71.4)</td>
<td>5 (62.5)</td>
<td>581 (76.5)</td>
<td>.36</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13 (86.7)</td>
<td>6 (85.7)</td>
<td>7 (87.5)</td>
<td>523 (68.9)</td>
<td>.17</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (20.0)</td>
<td>2 (28.6)</td>
<td>1 (12.5)</td>
<td>294 (38.7)</td>
<td>.18</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>4 (26.7)</td>
<td>1 (14.3)</td>
<td>3 (37.5)</td>
<td>292 (38.5)</td>
<td>.43</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3 (20.0)</td>
<td>2 (28.6)</td>
<td>1 (12.5)</td>
<td>64 (8.4)</td>
<td>.13</td>
</tr>
<tr>
<td>History of stroke</td>
<td>5 (33.3)</td>
<td>3 (42.9)</td>
<td>2 (25.0)</td>
<td>56 (7.4)</td>
<td>.0002</td>
</tr>
<tr>
<td>Echocardiographic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>7 (46.7)</td>
<td>2 (28.6)</td>
<td>5 (62.5)</td>
<td>98 (12.9)</td>
<td>.002</td>
</tr>
<tr>
<td>Right-sided vegetations</td>
<td>7 (46.7)</td>
<td>5 (71.4)</td>
<td>2 (25.0)</td>
<td>232 (30.6)</td>
<td>.29</td>
</tr>
<tr>
<td>Left-sided vegetations</td>
<td>6 (40.0)</td>
<td>5 (71.4)</td>
<td>1 (12.5)</td>
<td>80 (10.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hospitalization [median (IQR)]</td>
<td>19 days (10)</td>
<td>14 days (16)</td>
<td>20 days (11)</td>
<td>13 days (10)</td>
<td>.022</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>2 (13.3)</td>
<td>1 (14.3)</td>
<td>1 (12.5)</td>
<td>45 (5.9)</td>
<td>.23</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD or n (%) unless otherwise indicated.

BMI = body mass index; CIED = cardiovascular implantable electronic device; IQR = interquartile range; LVEF = left ventricular ejection fraction.

*Comparing all stroke and no stroke.

(46.7% vs 12.9%; \(P = .002\)). Multivariable analysis revealed that PFO was independently associated with stroke (odds ratio [OR] 7.75; 95% CI 2.60–23.15; \(P = .0002\)) (Table 2). Among patients with PFO, a total of 7 strokes occurred. Two (28.6%) occurred before the TLR procedure, and 5 (71.4%) occurred after the TLR procedure. Patients with right-sided vegetation and right-to-left shunting had an overall stroke rate of 19% (OR 6.4; 95% CI 1.3–31.0; \(P = .022\)) (Table 3). All postprocedural strokes in patients with PFOs occurred within 2 days of the TLR procedure.

Patients with stroke also had a higher occurrence of left-sided vegetation than did patients without stroke (40% vs 10.5%; OR 5.7; 95% CI 2.0–16.3; \(P = .0016\)). Strokes in patients with left-sided vegetation were predominantly pre-procedural in nature, with 5 strokes (83.3%) occurring before the TLR procedure, and only 1 (16.7%) occurring after the TLR procedure (\(P = .04\)). Multivariable analysis revealed that left-sided vegetation was independently associated with stroke (OR 7.68; 95% CI 2.50–23.60; \(P = .0004\)) (Table 2). Among all postprocedural strokes, there were 3 patients who had a stroke but did not have a PFO or left-sided vegetation. All 3 strokes occurred late in the hospital course (3–11 days after lead extraction). Two patients had atrial fibrillation with dense spontaneous echocontrast in the left atrial appendage and were not undergoing anticoagulation before the stroke. One patient had atrial fibrillation and mechanical

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**Figure 2** Timing of stroke in relation to transvenous lead removal procedure.
mitral valve, and was without anticoagulation for around 48 hours, with anticoagulation restarted 1 day before the stroke.

**Length of stay and 30-day mortality**

Median length of stay was 13 days (interquartile range 3–23). Patients who suffered from a stroke had a significantly increased length of hospital stay than did those who did not have a stroke (19 vs 13 days; \( P = .022 \)). Overall 30-day mortality was 6.2%. There was no statistical difference in 30-day mortality between patients with and those without a stroke (13.3% vs 5.9%; \( P = .23 \)).

**Discussion**

Our analysis of 774 patients with CIED infection who underwent TLR procedure showed that (1) there was an overall stroke rate of 1.9%; (2) PFO was identified in 105 patients (13.6%); (3) PFOs were independently associated with stroke, especially with the presence of right-sided vegetations with right-to-left shunting; and (4) left-sided vegetations were also independently associated with stroke.

Our data showed that the postprocedural stroke rate after TLR of infected CIED was 1.0%. Data on stroke rate specifically after TLR of patients with CIED infections are limited. Existing registry data of stroke rate after transvenous lead extraction procedures ranges from 0.07%–0.11%.\(^\text{11,12}\) Patients with CIED infection may have a higher stroke risk because of the risk of mobilization of right-sided vegetations during TLR leading to paradoxical embolism in the presence of a PFO (Figure 3), or because of the presence of concomitant left-sided vegetations, which itself carries the risk of embolic stroke.

Our data suggest that PFOs were associated with a higher occurrence of stroke in patients with CIED infection undergoing TLR. Subgroup analysis of patients with PFO revealed that the risk of stroke was highest in patients with both right-sided vegetations with right-to-left shunting. Embolization of vegetative material on endocardial leads is typically confined to the pulmonary circulation.\(^\text{5,6}\) However, in the presence of a PFO, there is a risk for paradoxical embolism. In a study of patients after endocardial lead implantation, PFOs have been shown to be associated with an increased risk of stroke.\(^\text{13}\) There have also been multiple case reports on paradoxical embolism in patients with CIED infection, as well as paradoxical embolism during TLR.\(^\text{14–16}\) During TLR procedure, there is a possibility of dislodgment of debris or vegetation that travels across the PFO because of right-to-left shunting, leading to paradoxical embolism (Figure 3).

Independently, right-sided vegetation or right-to-left shunting was not found to be significantly associated with an increased stroke rate. This is likely because of the small number of patients within each specific subgroup. More data will be needed to delineate their independent risk of stroke.

Within our cohort, there was no transient ischemic attack. This may suggest that cerebrovascular events occur due to a solid particulate embolus rather than a transient thrombus in a hypercoagulable state.

Strokes that occur after TLR could also be related to residual fibrous tissue called ghosts (Figure 3C).\(^\text{17}\) This is a remnant of a fibrous sheath that encapsulates a lead and may remain even after TLR. It has been shown to be an independent predictor of mid-term mortality after TLR.\(^\text{17}\) These ghosts may be a potential cause of persistent embolic risk even after TLR if vegetations are attached to it. Persistence of intracardiac vegetations despite TLR and the residual possibility for embolic phenomenon have previously been described in a case report but have not been systematically studied.\(^\text{18}\)

The risk of stroke in patients with CIED infection may also be due to concomitant presence of aortic or mitral valve vegetations and systemic embolism. Our study found that preprocedural stroke is mainly associated with left-sided vegetation, whereas postprocedural stroke is mainly associated with PFO. Stroke risk due to left-sided vegetation may decrease after TLR procedure because of the reduction of burden of infection after TLR as well as ongoing antibiotic therapy, which may have resulted in resolution of left-sided vegetations and reduction of risk of embolization.\(^\text{19}\)

The duration of hospital stay was longer in patients with stroke than in those without stroke, which may be an indirect indicator of the clinical impact of stroke. In all cases of stroke, there were neuroimaging findings of infarcts, more commonly in the distribution of the middle cerebral artery. Unfortunately, we were not able to obtain accurate objective data on the severity and persistence of neurologic deficits.

### Table 2

Multivariable analysis of risk factors associated with stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent foramen ovale</td>
<td>7.75 (2.60–23.15)</td>
<td>.0002</td>
</tr>
<tr>
<td>Left-sided vegetation</td>
<td>7.68 (2.50 – 23.60)</td>
<td>.0004</td>
</tr>
</tbody>
</table>

*Selected based on variables that were significant on univariate analysis.

### Table 3

Subgroup analysis of stroke rate in patients with patent foramen ovale

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Overall stroke n (%)</th>
<th>95% CI</th>
<th>Odds ratio (95% CI)</th>
<th>( P ) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right-sided vegetation ( n = 32 )</td>
<td>4 (12.5%)</td>
<td>3.5–28.9</td>
<td>3.3 (0.7–15.9)</td>
<td>.130</td>
</tr>
<tr>
<td>Right-to-left shunt ( n = 66 )</td>
<td>6 (9.1%)</td>
<td>3.4–18.7</td>
<td>3.8 (0.44–32.8)</td>
<td>.225</td>
</tr>
<tr>
<td>Right-sided vegetation and right-to-left shunt ( n = 21 )</td>
<td>4 (19.0%)</td>
<td>5.5–41.9</td>
<td>6.4 (1.3–31.0)</td>
<td>.022</td>
</tr>
</tbody>
</table>

\( \text{CI} = \text{confidence interval.} \)

*\( P < .025 \) was determined to be significant, based on Bonferroni correction for multiple hypothesis testing.
However, comparison of 30-day mortality between those with and those without stroke did not reveal any statistical difference. Our average 30-day mortality of 6.2% was similar to published 30-day mortality of 3.8%–10% for patients with lead-related infective endocarditis undergoing TLR.5,20

With the increased risk of stroke in patients with PFO, especially in those with right-sided vegetation and right-to-left shunting, preprocedural PFO screening may be beneficial. PFO may be screened with either TTE with agitated saline or TEE with or without agitated saline (Figure 4A).

Further studies will be needed to evaluate the importance of management strategies in patients with PFO. The first option is surgical evacuation, either from conventional median sternotomy or via a limited atriotomy approach. However, because of the invasive nature of the surgical procedure, it is associated with postoperative mortality rates ranging from 9%–40%.21,22 Furthermore, the high doses of heparin needed during cardiopulmonary bypass surgery may be contraindicated if a patient already has an acute embolic stroke due to risk of hemorrhagic conversion. The second option is deployment of a PFO closure device before TLR (Figure 4B). However, because of the potential risk of infection of the PFO closure device, the procedure may have to be delayed until blood cultures are negative. The risk of infection of the PFO closure device will have to be balanced against the

Figure 3  A: Transvenous lead removal may lead to dislodgment of endocardial lead vegetation. B: Paradoxical embolism of vegetation across a patent foramen ovale into the systemic circulation. C: Even after removal of the pacemaker lead, a mobile cast may still remain, leading to persistent risk of embolization.
risk of delaying TLR. The third option is deployment of bilat-
eral carotid artery filters during TLR (Figure 4C). However,
heparinization would still be required during deployment of
the cerebral embolic protection device. The fourth option is
temporary occlusion of the PFO with a balloon during lead
extraction (Figure 4D). However, if the procedure is per-
formed without anticoagulation to reduce the risk of the
lead extraction procedure, there is a risk of development of
clot on the balloon, both on the right atrial side (Figure 4E)
and the left atrial side (Figure 4F) of the balloon.

Our study focused on the first 3 aspects of the public
health approach to problem-solving: (1) define the problem;
(2) measure the magnitude of the problem; and (3) develop a
conceptual framework for the key determinants of the prob-
lem.23 We anticipate that as more evidence accumulates,
the remaining aspects of the problem-solving methodology,
which includes identification and development of interven-
tion strategies, will be touched on.

Study limitations
Our results are best interpreted in the context of several lim-
itations. Some patients with PFO likely went undetected
because of the limitations of echocardiography. Within our
patient cohort, 13.6% of patients were found to have PFO.

This percentage was lower than data from autopsy series
that found PFO to be present in 25% of the population but
was similar to the 15% reported in a population-based study
with TTE and agitated saline.24,25 There is also variability in
the extent for which maneuvers for detection of shunting was
performed, such as agitated saline or Valsalva, which were
performed at the discretion of each operator. We also could
not analyze the relationship of stroke to the amount of
shunting across the PFO or the concomitant presence
of atrial septal aneurysm given the inconsistent reporting of
these occurrences during this retrospective study. Accuracy
detection of vegetations was also limited based on the
imaging technique used. Histologic and microbiological
analyses of the extracted leads were not performed
routinely. As a result, although only patients with
bacteremia, infective endocarditis, and device infections
were included in our study, it is possible that some of the
vegetations identified within our study were simply
thrombi or fibrin casts. The overall small absolute number
of stroke outcome events also limited further statistical
analysis on other procedural factors that may possibly be
associated with stroke.

Furthermore, this study was based on data from 3 tertiary
referral centers, and there may be limited extrapolation to
hospitals with a different patient population, procedural technique mix, and clinical expertise. We also excluded patients with CIED infection who did not undergo TLR; therefore, our results may only be applicable to patients with device infection who meet TLR criteria and did not have any contraindications to the procedure. However, we suspect that the number of patients who did not undergo TLR is small, with a previous study reporting that 98% of patients with CIED infection underwent complete device removal.26 Our study also did not include patients in whom the device was extracted via open heart surgery as the primary approach.

Finally, because our cerebrovascular outcome definition was based on standardized definitions, we did not include subclinical stroke. Also, no systematic neurocognitive testing was performed to detect more subtle central nervous system injury in patients without clinically apparent neurologic symptoms.

Conclusion
In patients with CIED infection undergoing TLR, the overall stroke risk was 1.9%. Our study revealed that the presence of a PFO was associated with an increased risk of stroke, which mostly occurred after the TLR procedure. This was especially so if there was a concomitant finding of right-sided vegetation and right-to-left shunting, which suggests that paradoxical embolism of lead vegetation may occur in patients with CIED infection undergoing TLR. This finding highlights the importance of preprocedural PFO screening in patients with CIED infections undergoing TLR. Further studies will be needed to assess management strategies in patients with PFO undergoing TLR for CIED infection, such as PFO closure or use of cerebral embolic protection devices.

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Appendix

Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2018.08.008.

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