The optimal secondary prevention strategy in patients presenting with a cryptogenic stroke or transient ischemic attack (TIA) and a patent foramen ovale (PFO) is uncertain. In the United States, closure of a PFO using a percutaneous transcatheter device is currently considered investigational by the Food and Drug Administration. Nonetheless, many patients in this setting are treated off-label with devices that are approved for the closure of secundum atrial septal defects. There are also no definitive data about the use of medical therapy for secondary stroke prevention in this patient population. We evaluated the potential benefit of device closure of a PFO in this setting in CLOSURE I (evaluation of the STARFlex Septal Closure System in patients with a stroke and/or TIA because of presumed paradoxical embolism through a PFO).1

Methods
CLOSURE I was a prospective, multicenter, randomized, open-label, 2-arm superiority trial. The trial was sponsored by NMT Medical, Inc. The protocol was designed by the Executive Committee in consultation with the Food and Drug Administration, and was approved by the institutional review board at each participating site. Methodological details have been previously published.1,2

Study Subjects
Subjects were eligible for randomization if they were aged between 18 and 60 years, had had an ischemic stroke or TIA within the previous 6 months, and had evidence of a PFO with right to left shunting documented by a transesophageal echocardiogram. Exclusion criteria included any identified potential source of ischemic stroke or TIA other than the PFO.2

Study Procedures
Eligible patients were randomly assigned in a 1:1 ratio to either device therapy or medical therapy. Randomization was stratified by study site and by presence or absence of an atrial septal aneurysm.

Patients assigned to device therapy underwent percutaneous closure of their PFO with the STARFlex device (NMT Medical, Inc). After the procedure, all patients were prescribed clopidogrel 75 mg daily for 6 months and aspirin 81 or 325 mg daily for 2 years. Patients assigned to medical therapy were treated at the discretion of the site principal investigator with warfarin (target international normaliziation ratio, 2.0–3.0), aspirin (325 mg), or both.

Follow-up evaluations were planned at 1, 6, 12, and 24 months. A transesophageal echocardiogram was obtained at the 6-month visit for patients in the device arm.

The primary end point was a 2-year composite, including stroke, TIA, all-cause mortality for the first 30 days, and neurological mortality after 30 days. Secondary end points included major bleeding, all-cause mortality, stroke, TIA, and transient neurological events of uncertain etiology.

Primary Outcome
A total of 909 patients were enrolled in the trial. The Kaplan–Meier estimate of the cumulative incidence of the primary end point in the ITT analysis set after 2 years of follow-up was 5.5% in the device group and 6.8% in the medical group (adjusted hazard ratio, 0.78; 95% confidence interval, 0.45–1.35; P=0.37). The Kaplan–Meier estimates of 2-year rates of stroke were 2.9% and 3.1%, respectively (adjusted hazard ratio, 0.90; 95% confidence interval, 0.41–1.98), and for TIA they were 3.1% and 4.1% (adjusted hazard ratio, 0.75; 95% confidence interval, 0.36–1.55). No deaths had occurred at 30 days in either group and there were no neurological deaths during the 2-year follow-up. There was no evidence of heterogeneity of treatment effect by subgroup, including atrial septal aneurysm, or shunt size (Table; Figure).

Adverse Events
Protocol specified major procedural complications occurred in 3.2% of the device arm. Atrial fibrillation occurred significantly more frequently in the device arm (5.7% versus 0.7%; P<0.001). Atrial fibrillation occurred within 30 days of the procedure in 14 of 23 patients (61%). Atrial fibrillation was transient in 17 patients and persistent in 6 patients.

Pathogenesis of Recurrent Strokes and TIAs
Three TIAs occurred in the device arm after randomization but before device insertion and were included in the ITT analysis. Three of 12 strokes and 2 of 13 TIAs in the device arm occurred within 30 days of the procedure. In the medical arm, 2 strokes and 4 TIAs occurred within 30 days of randomization.

A possible alternative explanation for recurrent TIA or stroke was apparent in 20 of 23 patients in the device group and 22 of 29 patients in the medical group, including new onset atrial fibrillation, clot in the left atrium, subcortical lacunar infarction with risk factors, atheroma, complex migraine, and vasculitis. Three of the 12 strokes in the device arm were ascribed to atrial fibrillation, and 2 of these patients had device thrombus on transesophageal echocardiogram. One of the 13 strokes in the medical arm occurred in patients who had atrial fibrillation, which was documented subsequent to the event and after implantation of an off-study device.

Exploratory Analyses
Using Cox proportional hazard regression on both the intent-to-treat and the per-protocol populations and adjusting for related patient characteristics, including age, atrial septal aneurysm, prior TIA/stroke, smoking, hypertension, hypercholesterolemia, subcortical infarcts, we failed to identify any significant difference in the 2-year primary outcome between device and medical therapy for any subgroup.
Conclusions

There was no significant difference in the 2-year rate of recurrent stroke and TIA between device and medical therapy in this population of patients with cryptogenic TIA/stroke and a PFO. Major vascular complications occurred in 3% of patients in the device arm. Thrombus was found in the left atrium in 4 patients (1.1%) in the device arm, 2 of whom had a stroke.

CLOSURE I was designed to detect an ambitious two-thirds reduction in the risk of recurrent events. It thus did not have the power to detect a smaller reduction in the event rate. The insignificant trend favoring device for the primary outcome was driven by the lower rate of TIA in the device arm. We included strictly defined and independently adjudicated TIA as an end point because these events may be caused by

Table. Two-Year Primary End Point—Kaplan–Meier Event Rates

<table>
<thead>
<tr>
<th>Population</th>
<th>STARFlex* (n=447)</th>
<th>Medical* (n=462)</th>
<th>Hazard Ratio† (95% CI)</th>
<th>P-Value</th>
<th>P-Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Modified ITT</td>
<td>22/400 (5.6%)</td>
<td>29/451 (6.9%)</td>
<td>0.78 (0.44, 1.35)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7/208 (3.4%)</td>
<td>15/232 (6.8%)</td>
<td>0.50 (0.20, 1.22)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15/192 (7.9%)</td>
<td>14/219 (7.0%)</td>
<td>1.13 (0.55, 2.34)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Atrial Septal Aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15/249 (6.2%)</td>
<td>20/291 (7.4%)</td>
<td>0.81 (0.42, 1.59)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7/151 (4.6%)</td>
<td>9/160 (5.6%)</td>
<td>0.76 (0.30, 2.13)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Shunt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or Trace</td>
<td>8/118 (6.9%)</td>
<td>10/155 (6.8%)</td>
<td>0.99 (0.39, 2.52)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>7/144 (5.0%)</td>
<td>12/163 (7.4%)</td>
<td>0.61 (0.24, 1.55)</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Substantial</td>
<td>3/67 (3.5%)</td>
<td>5/85 (4.9%)</td>
<td>0.72 (0.15, 3.57)</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Entry Event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>15/300 (5.1%)</td>
<td>15/324 (5.1%)</td>
<td>1.01 (0.49, 2.07)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>7/100 (7.1%)</td>
<td>14/126 (11.6%)</td>
<td>0.60 (0.24, 1.49)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Baseline Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0/13 (0.0%)</td>
<td>2/38 (5.9%)</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Aspirin Alone</td>
<td>15/286 (5.3%)</td>
<td>16/252 (6.7%)</td>
<td>0.79 (0.39, 1.59)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Warfarin Alone</td>
<td>1/25 (4.2%)</td>
<td>8/111 (7.9%)</td>
<td>0.52 (0.06, 4.12)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Aspirin + Warfarin</td>
<td>6/72 (8.5%)</td>
<td>2/40 (5.4%)</td>
<td>1.59 (0.32, 7.99)</td>
<td>0.57</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ITT, intention-to-treat; MITT, modified intention-to-treat; and TIA, transient ischemic attack.

*Adjusting performed using Cox proportional hazard regression adjusting for patient characteristics, including age, atrial septal aneurysm, prior TIA/cerebrovascular accident, smoking, hypertension, hypercholesteremia.

†Hazard ratio calculated as STARFlex vs. Medical.

‡The n in parentheses represents number of patients experiencing a primary end point event. The number of patients experiencing each of stroke and TIA separately may sum to more than the number of patients experiencing the composite event because a patient may have experienced both the stroke and the TIA components of the composite event.
paradoxical embolism and the required sample size using stroke as the only end point would have been prohibitive.

The 2-year rate of stroke (≈3%) was low and virtually identical in the device and medical arms, suggesting that a much larger sample size would be required if stroke were the only end point and that a follow-up interval >2 years would be unlikely to show a significant difference in stroke outcomes. A recent propensity score observational study found no significant difference in stroke outcome between device and medical therapy with a median follow-up of 9 years.3

The Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS)4 found that the 2-year risk of recurrent stroke was the same in patients with cryptogenic stroke with and without PFO. This indicates that cryptogenic stroke comprises a heterogeneous group of pathogeneses and speaks to the difficulty of precisely diagnosing paradoxical embolism.5,6 Indeed, a key finding of our trial was that an alternative explanation for recurrent stroke or TIA, unrelated to paradoxical embolism, was usually apparent.

Of note, higher rate of atrial fibrillation was in the device arm. Atrial fibrillation has been previously reported in 5% to 20% of patients undergoing closure of a PFO with a variety of devices.7,8 Occult atrial fibrillation is common in patients with cryptogenic stroke or TIA.9 Atrial tachyarrhythmias have an unclear relationship, if any, to the presence of a PFO, but the higher frequency of atrial fibrillation in the device arm of CLOSURE I suggests the procedure itself may increase the risk of atrial fibrillation.

CLOSURE I does not preclude a possible role for device closure in highly selected patient populations. It is also possible that some patients may prefer device closure despite the small procedural risks and cost. Various clinical, neuroimaging, and anatomic criteria have been suggested to increase the likelihood that a stroke is because of paradoxical embolism through a PFO.5,6 We found no significant effect of atrial septal aneurysm or the degree of shunting on the outcome with respect to the primary trial end point. Selected subgroups, such as patients aged <45 years, with no risk factors and only cortical infarcts by MRI at baseline will likely have even lower recurrent event rates, requiring larger sample sizes or length of follow-up >2 years.

It is possible that adverse events and outcomes will vary by specific device. However, the primary results of CLOSURE I cannot be ascribed to device failure. The effective rate of PFO closure in the trial was 86%, which is consistent with previously reported results for the STARFlex implant and other transcatheter closure devices. Excluding periprocedural events, none of the patients in the device arm with recurrent stroke or TIA had residual leaking on transesophageal echocardiogram at 6 months.

Several potential reasons have been identified for the stark difference between the results of CLOSURE I and the numerous positive observational studies suggesting a benefit for device closure.10 It is likely that enrollment in CLOSURE I was hampered by the preference of some patients or physicians to elect device therapy rather than participation in the trial. We do not know how many potential patients underwent closure using another company’s device or how those patients differed, if at all, from the patients randomized into CLOSURE I. Aside from individual patient and physician bias, and although it may be possible to refine our neurologic, cardiac, and imaging criteria for paradoxical embolism, it remains to be proven that device closure is superior to medical therapy for stroke prevention in any PFO population.

Disclosures
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References
PFO Closure: CLOSURE
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