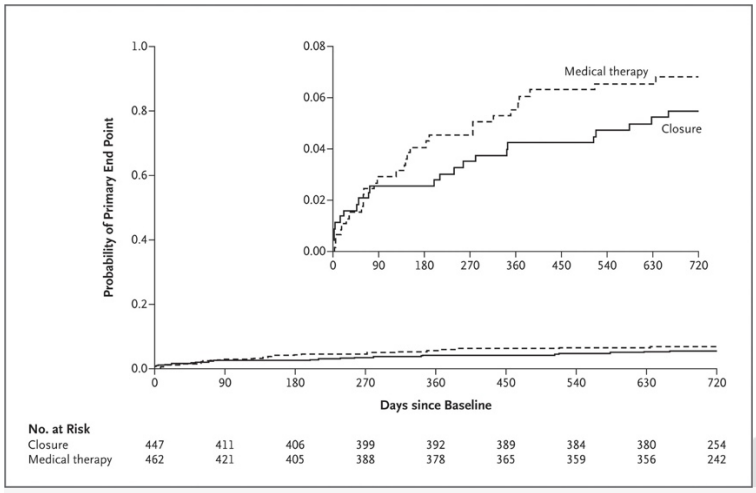
# Estudos de fechamento de forame oval patente

| CLOSURE I | CLOSE | PC TRIAL | RESPECT | RESPECT | REDUCE | DEFENSE |
|---|---|---|---|---|---|---|
| 2012<br>ECR, multicêntrico, aberto | 2017<br>ECR, multicêntrico, aberto, centros da França e Alemanha | 2013<br>ECR, multicêntrico, Europa, Canadá, Br e Austrália | 2013<br>ECR, multicêntrico | 2017 | 2017<br>ECR, multicêntrico | 2018<br>ECR, multicêntrico Coreia do Sul |
| n=909 pts<br>18-60 anos | n=663 pts<br>16-60 anos | n=414 pts<br>< 60 anos | n=980 pts<br>18-60anos | Longo seguimento | n=664 pts<br>18-59 anos | 120 pts |
| PFO + AVE criptogênico ou AIT | PFO + AVE criptogênico recente + aneurisma (>10mm) e/ou shunt grande (>30 microbolhas/3 ciclos) | PFO + AVE ou AIT ou tromboembolismo periférico | PFO + AVE criptogênico | | PFO + AVE criptogênico com shunt D-E | PFO de alto risco: aneurisma (>15mm), hipermobilidade, (excursão ≥10mm), separação máxima ≥2mm + AVE |
| Starflex x OMT (retirado do mercado) | qualquer device x OMT (antiagregante plaquetário ou ACO) | Amplatzer x OMT | Amplatzer x OMT (antiagregante ou OAC) | | Cardioform x OMT | Amplatzer x OMT |
| Seguimento: 2 anos<br><br>AVC ou AIT 2a, morte em 30d, morte neurológica 30d-2a: 5,5% x 6,8% (HR 0,78; IC 95% 0,45-1,35; p=0,37)<br><br>AVC: 2,9% x 3,1%; p=0,79<br><br>AIT: 3,1% x 4,1%; p=0,44<br><br>Morte 30 dias: 0<br><br>Morte neurológica de 31 dias-2anos: 0<br><br>Qualquer evento adverso sério: 16,9% x 16,6%; p=0,9<br><br>Complicação vascular maior procedimento: 3,2%<br><br>FA: 5,7% x 0,7%; p<0,001 | Seguimento: 5,4 anos<br><br>Fechamento x antiagregante: AVC: 0 x 14 eventos (HR 0,03, IC 95% 0-0,26; p<0,001)<br><br>Probabilidade de AVC em 5 anos com antiagregante: 4,9%<br><br>Complicações do procedimento: 5,9%<br><br>Eventos adversos sérios: 35,7% x 33,2%; p=0,56<br><br>FA = 4,6% x 0,9%; p =0,02 | Seguimento: 4,1 anos<br><br>Morte, AVC, AIT ou embolia periférica: 3,4% x 5,2% (HR 0,63, IC 95% 0,24-1,62; p=0,34)<br><br>AVC: 0,5% x 2,4% (HR 0,2, IC 95% 0,02-1,72; p=0,14)<br><br>AIT: 2,5% x 3,3%<br><br>Qualquer evento adverso: 34,8% x 29,5%; p=0,25<br><br>Complicação maior procedimento 1,5%<br><br>FA: 2,9% x 1%; p=0,17 | Seguimento: 2,1 anos<br><br>AVC isquêmico ou morte precoce: 9 x 16 eventos (HR 0,49, IC 95% 0,22-1,11; p=0,08)<br><br>AVC: 1,6% x 3% em anos<br><br>AVC: 2,2% x 6,4% em 5 anos<br><br>AVC ou morte cardiovascular: HR 0,17, IC 95% 0,02-1,47; p=0,07<br><br>Eventos adversos sérios: 23% x 21,6%; p=0,65<br><br>Complicação adversa do procedimento/device: 4,2% | Seguimento: 5,9 anos<br><br>AVC: 18 x 28 eventos (HR 0,55, IC 95% 0,31-0,99; p=0,046)<br><br>AVC isquêmico recorrente de causa indeterminada: 10 x 23 eventos (HR 0,38, IC 95% 0,18-0,79; p=0,007)<br><br>Eventos adversos sérios: 40,3% x 36%; p=0,17<br><br>Embolismo pulmonar: 0,41/100 x 0,11/100; p=0,04<br><br>TVP: 0,16/100 x 0,04/100; p=0,14 | Seguimento: 3,2 anos<br><br>AVC: 1,4% x 5,4% (HR 0,23, IC95% 0,09-0,62; p=0,002)<br><br>Novo infarto cerebral (clínico ou silencioso): 4,7% x 10,7%; p=0,02<br><br>Eventos adversos sérios: 23,1% x 27,8%; p=0,22<br><br>Eventos adversos sérios relacionados ao device: 1,4%<br><br>FA: 6,6% x 0,4%; p<0,001 | Seguimento 2,8 anos<br><br>AVC, morte vascular, sangramento maior: 0 x 12,9%; p=0,013<br><br>AVC: 0 x 10,5%; p=0,023<br><br>Probabilidade de AVC em 2 anos em OMT: 10,5% (NNT 10) |

# CLOSURE I:




**2 Years of Follow-up in the Closure and Medical-Therapy Groups.**

**Table 2. Kaplan–Meier Event Rates for Primary End Point at 2 Years.***

| End Point | Closure (N=447) | Medical Therapy (N=462) | Hazard Ratio (95% CI)†‡ | P Value† |
|---|---|---|---|---|
| **Intention-to-treat population** | | | | |
| Composite end point — no. (%) | 23 (5.5) | 29 (6.8) | 0.78 (0.45–1.35) | 0.37 |
| Stroke — no. (%) | 12 (2.9) | 13 (3.1) | 0.90 (0.41–1.98) | 0.79 |
| TIA — no. (%) | 13 (3.1) | 17 (4.1) | 0.75 (0.36–1.55) | 0.44 |
| **Modified intention-to-treat population** | | | | |
| Composite end point — no./total no. (%) | 22/400 (5.6) | 29/451 (6.9) | 0.78 (0.44–1.35) | 0.37 |
| Stroke — no./total no. (%) | 12/400 (3.1) | 13/451 (3.1) | 0.94 (0.43–2.07) | 0.88 |
| TIA — no./total no. (%) | 12/400 (3.0) | 17/451 (4.2) | 0.72 (0.34–1.51) | 0.38 |
| **Per-protocol population** | | | | |
| Composite end point — no./total no. (%) | 22/378 (5.8) | 29/375 (7.7) | 0.74 (0.42–1.29) | 0.28 |
| Stroke — no./total no. (%) | 12/378 (3.2) | 13/375 (3.5) | 0.91 (0.41–1.99) | 0.80 |
| TIA — no./total no. (%) | 12/378 (3.2) | 17/375 (4.6) | 0.68 (0.33–1.43) | 0.31 |

* Percentages in parentheses are Kaplan–Meier estimates of the event rates. Totals for the composite-end-point categories may be higher than the sum of the individual events in that category, since some patients may have had both types of events (i.e., stroke and transient ischemic attack [TIA]).
† Values were adjusted with the use of Cox proportional-hazards regression for age, presence or absence of atrial septal aneurysm, presence or absence of a history of TIA or cerebrovascular accident, and status with respect to smoking, hypertension, and hypercholesterolemia.
‡ The hazard ratio was calculated for the closure group as compared with the medical-therapy group.

**Table 3. Serious Adverse Events.***

| Event | Closure (N=402) | Medical Therapy (N=458) | P Value |
|---|---|---|---|
| Major vascular procedural complication — no. (%)† | 13 (3.2) | 0 | <0.001 |
| Atrial fibrillation — no. (%) | 23 (5.7)‡ | 3 (0.7) | <0.001 |
| Major bleeding episode — no./total no. (%)§ | 10/378 (2.6) | 4/374 (1.1) | 0.11 |
| Death other than end point — no. (%) | 2 (0.5)¶ | 4 (0.9)‖ | 0.51 |
| Nervous system disorder — no. (%)** | 6 (1.5) | 16 (3.5) | 0.15 |
| Convulsion | 1 | 3 | |
| Hypesthesia | 2 | 2 | |
| Migraine | 1 | 3 | |
| Headache | 0 | 2 | |
| Syncope | 0 | 2 | |
| Amyotrophic lateral sclerosis | 0 | 1 | |
| Brain abscess | 0 | 1 | |
| Facial palsy | 1 | 0 | |
| Loss of consciousness | 0 | 1 | |
| Paresthesia | 0 | 1 | |
| Parkinson's disease | 1 | 0 | |
| Any serious adverse event — no. (%) | 68 (16.9) | 76 (16.6) | 0.90 |

* The results shown include all treated patients.
† Major vascular events included hematoma larger than 5 cm in diameter at the access site (in 4 patients), procedure-related transfusion (3), retroperitoneal hemorrhage (3), perforation of the left atrium (1), vascular surgical repair (1), and peripheral-nerve injury (1).
‡ Of these 23 cases of atrial fibrillation, 14 were periprocedural.
§ Major bleeding status was not ascertained for all treated patients.
¶ The two deaths in the closure group were caused by cardiac arrest on day 232 and by cardiac arrhythmia on day 242.
‖ The four deaths in the medical-therapy group were caused by septic shock on day 269, suicide on day 489, amyotrophic lateral sclerosis on day 557, and metastatic cancer on day 569.
** This category excludes primary-end-point events.

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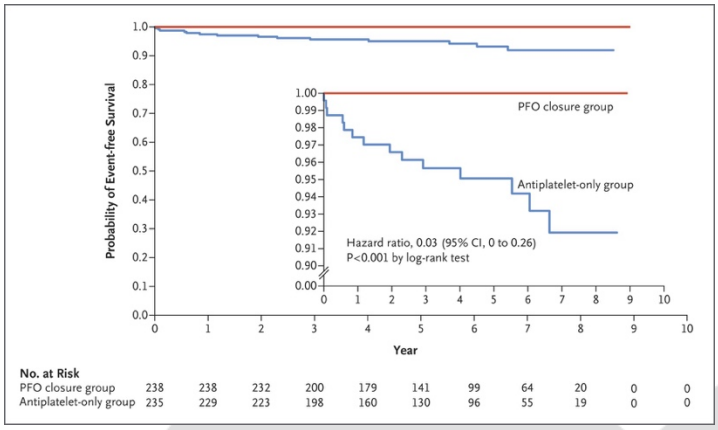
## CLOSE TRIAL:




**Stroke in the PFO Closure Group versus the Antiplatelet-Only Group.**

**Table 2. Efficacy Outcomes.***

| Outcome | Randomization Groups 1 and 2 | | | | Randomization Groups 1 and 3 | | |
|---|---|---|---|---|---|---|---|
| | PFO Closure Group (N=238) | Antiplatelet-Only Group (N=235) | Hazard Ratio (95% CI)† | P Value | Anticoagulant Group (N=187) | Antiplatelet-Only Group (N=174) | Hazard Ratio (95% CI)‡ |
| **Primary efficacy outcome** | | | | | | | |
| Stroke in the intention-to-treat population — no. of patients | 0 | 14§ | 0.03 (0.00–0.26) | <0.001 | 3¶ | 7§ | 0.44 (0.11–1.48) |
| Stroke in the per-protocol population — no./total no. of patients | 0/217 | 14/223§ | 0.04 (0.00–0.27) | <0.001 | 2/143¶ | 7/164§ | 0.37 (0.07–1.38) |
| **Secondary efficacy outcomes‖** | | | | | | | |
| Disabling stroke** | 0 | 1 | 0.33 (0.00–6.18) | 0.63 | 1 | 1 | 0.96 (0.08–11.85) |
| Cerebral hemorrhage | 0 | 0 | NA | NA | 0 | 0 | NA |
| Ischemic stroke, transient ischemic attack, or systemic embolism | 8 | 21 | 0.39 (0.16–0.82) | 0.01 | 8 | 12 | 0.64 (0.26–1.50) |
| Transient ischemic attack | 8 | 8 | 0.97 (0.37–2.56) | 0.96 | 5 | 6 | 0.80 (0.25–2.52) |
| Systemic embolism | 0 | 0 | NA | NA | 0 | 0 | NA |
| Death from any cause | 0 | 0 | NA | NA | 1†† | 0 | 2.84 (0.15–414.86) |
| Success of device implantation — no./total no. (%)‡‡ | 234/235 (99.6) | NA | NA | NA | NA | NA | NA |
| Success of PFO closure — no./total no. (%)§§ | 202/228 (88.6) | NA | NA | NA | NA | NA | NA |

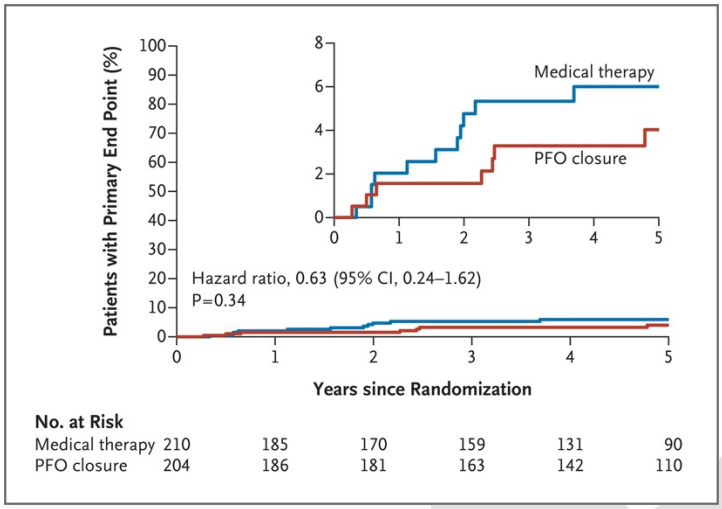
* NA denotes not applicable. The intention-to-treat cohort included all patients who were randomly assigned to a treatment. The per-protocol cohort included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment until the end of the trial, and did not have a major protocol violation.
† The hazard ratio was calculated for the PFO closure group as compared with the antiplatelet-only group.
‡ The hazard ratio was calculated for the anticoagulant group as compared with the antiplatelet-only group. Statistical significance was not analyzed because the study was not adequately powered to compare outcomes in these groups.
§ No patient had an alternative explanation for recurrent stroke.
¶ One patient had an alternative cause of stroke (aneurysmal subarachnoid hemorrhage complicated by vasospasm and ischemic strokes).
‖ Secondary efficacy outcomes were analyzed in the intention-to-treat cohort.
** Disabling stroke was defined as a modified Rankin scale score of 3 or higher.
†† The one death was due to pancreatic cancer.
‡‡ Success of device implantation was defined as deployment of the device in the appropriate place and removal of the placement system.
§§ Success of PFO closure was defined as successful implantation with no complication before the patient's discharge and no or minimal residual shunt.

**Table 3. Procedural Complications and Serious Adverse Events.***

| Complication or Event | Randomization Groups 1 and 2 | | | Randomization Groups 1 and 3 | | |
|---|---|---|---|---|---|---|
| | PFO Closure Group (N=238) | Antiplatelet-Only Group (N=235) | P Value | Anticoagulant Group (N=187) | Antiplatelet-Only Group (N=174) | P Value |
| | *no. of patients (%)* | | | *no. of patients (%)* | | |
| Major or fatal device-related or procedure-related complication† | 14 (5.9) | NA | NA | NA | NA | NA |
| Major or fatal bleeding complication | 2 (0.8) | 5 (2.1) | 0.28 | 10 (5.3) | 4 (2.3) | 0.18 |
| Atrial fibrillation or flutter‡ | 11 (4.6)§ | 2 (0.9) | 0.02 | 0 | 2 (1.1) | 0.23 |
| Death | 0 | 0 | NA | 1 (0.5)¶ | 0 | 0.65 |
| At least one serious adverse event | 85 (35.7) | 78 (33.2) | 0.56 | 62 (33.2) | 59 (33.9) | 0.88 |

* Definitions of major or fatal device-related or procedure-related complications, definitions of major or fatal bleeding complications, and a full list of serious adverse events are provided in the Supplementary Appendix.
† Major or fatal device-related or procedure-related complications in the PFO closure group are listed for those that occurred within 30 days after the procedure and included atrial fibrillation (9 patients), atrial flutter (1 patient), supraventricular tachycardia (2 patients), air embolism (1 patient), and hyperthermia resulting in prolongation of hospitalization (1 patient).
‡ Atrial fibrillation or flutter was classified as cases that required treatment for more than 1 month.
§ In 10 patients, atrial fibrillation or flutter occurred within 30 days after the procedure.
¶ The one death was due to pancreatic cancer.

## PC trial




**Rate of the Primary End Point.**

**Table 2. Clinical Outcomes.***

| Outcome | PFO Closure (N=204) | Medical Therapy (N=210) | Hazard Ratio or Relative Risk (95% CI)† | P Value |
|---|---|---|---|---|
| | *no. of patients (%)* | | | |
| Primary composite outcome of death, stroke, TIA, or peripheral embolism | 7 (3.4) | 11 (5.2) | 0.63 (0.24–1.62) | 0.34 |
| Death‡ | 2 (1.0) | 0 | 5.20 (0.25–107.61) | 0.24 |
| Cardiovascular | 0 | 0 | NA | |
| Noncardiovascular | 2 (1.0) | 0 | 5.20 (0.25–107.61) | 0.24 |
| Thromboembolic event | | | | |
| Stroke§ | 1 (0.5) | 5 (2.4) | 0.20 (0.02–1.72) | 0.14 |
| TIA | 5 (2.5) | 7 (3.3) | 0.71 (0.23–2.24) | 0.56 |
| Peripheral embolism | 0 | 0 | NA | |
| Secondary composite outcome of stroke, TIA, or peripheral embolism | 5 (2.5) | 11 (5.2) | 0.45 (0.16–1.29) | 0.14 |

* NA denotes not applicable, PFO patent foramen ovale, and TIA transient ischemic attack.
† Hazard ratios were calculated by means of the Cox proportional-hazards model. For the comparison of deaths (for which one group had no events), the relative risk was calculated instead of the hazard ratio with the use of continuity correction, and the corresponding P value was obtained by means of a two-sided Fisher's exact test.
‡ One patient died of respiratory failure because of chronic obstructive pulmonary disease; the other died from a glioma.
§ All listed strokes were major strokes.

**Table 3. Adverse Events.***

| Adverse Event | PFO Closure (N=204) | Medical Therapy (N=210) | P Value |
|---|---|---|---|
| | *no. of patients (%)* | | |
| Procedural complication† | 3 (1.5) | 0 | 0.12 |
| PFO-related hospital admission‡ | 13 (6.4) | 13 (6.2) | 0.95 |
| Myocardial infarction‡ | 2 (1.0) | 1 (0.5) | 0.62 |
| Atrial fibrillation§ | 6 (2.9) | 2 (1.0) | 0.17 |
| Serious | 2 (1.0) | 2 (1.0) | 1.00 |
| Minor | 4 (2.0) | 0 | 0.058 |
| Bleeding | 8 (3.9) | 12 (5.7) | 0.40 |
| Serious | 1 (0.5) | 3 (1.4) | 0.62 |
| Minor | 7 (3.4) | 9 (4.3) | 0.65 |
| Any adverse event | 71 (34.8) | 62 (29.5) | 0.25 |
| Serious | 43 (21.1) | 37 (17.6) | 0.37 |
| Minor | 40 (19.6) | 42 (20.0) | 0.92 |
| Other adverse event, occurring in ≥3 patients | | | |
| Headache | 3 (1.5) | 1 (0.5) | 0.37 |
| Migraine | 5 (2.5) | 5 (2.4) | 1.00 |
| Syncope | 2 (1.0) | 1 (0.5) | 0.62 |
| Dizziness | 1 (0.5) | 4 (1.9) | 0.37 |
| Paresthesia | 0 | 3 (1.4) | 0.25 |
| Seizure | 1 (0.5) | 3 (1.4) | 0.62 |
| Dyspnea | 0 | 4 (1.9) | 0.12 |
| Chest pain | 3 (1.5) | 4 (1.9) | 1.00 |
| Anxiety | 1 (0.5) | 4 (1.9) | 0.37 |
| Depression | 1 (0.5) | 2 (1.0) | 1.00 |
| Diverticulitis | 1 (0.5) | 2 (1.0) | 1.00 |
| Inguinal hernia | 1 (0.5) | 2 (1.0) | 1.00 |
| Bariatric surgery | 4 (2.0) | 1 (0.5) | 0.21 |
| Viral infection | 1 (0.5) | 2 (1.0) | 1.00 |
| Allergic drug reaction | 1 (0.5) | 2 (1.0) | 1.00 |
| Traumatic injury | 6 (2.9) | 3 (1.4) | 0.33 |
| Vaginal childbirth¶ | 2 (1.0) | 3 (1.4) | 1.00 |

* Not listed are primary composite end point events (see Table 2) and PFO closures in the medical-therapy group (see Fig. S3 in the Supplementary Appendix). P values were obtained from a chi-square test (or Fisher's exact test if the expected number of events was less than 5).
† Procedural complications included two episodes of minor bleeding at the access site and one periprocedural episode of atrial fibrillation that resolved within 6 hours; all were classified as minor.
‡ All admissions and myocardial infarctions were classified as serious adverse events.
§ One atrial fibrillation was periprocedural and resolved within 6 hours. In the PFO-closure group, one patient had atrial ectopy, one had sick sinus syndrome, and one had atrioventricular block. In the medical-therapy group, one patient had atrial ectopy.
¶ Vaginal childbirth was subsumed under adverse events for the purpose of analysis.

# RESPECT 2013

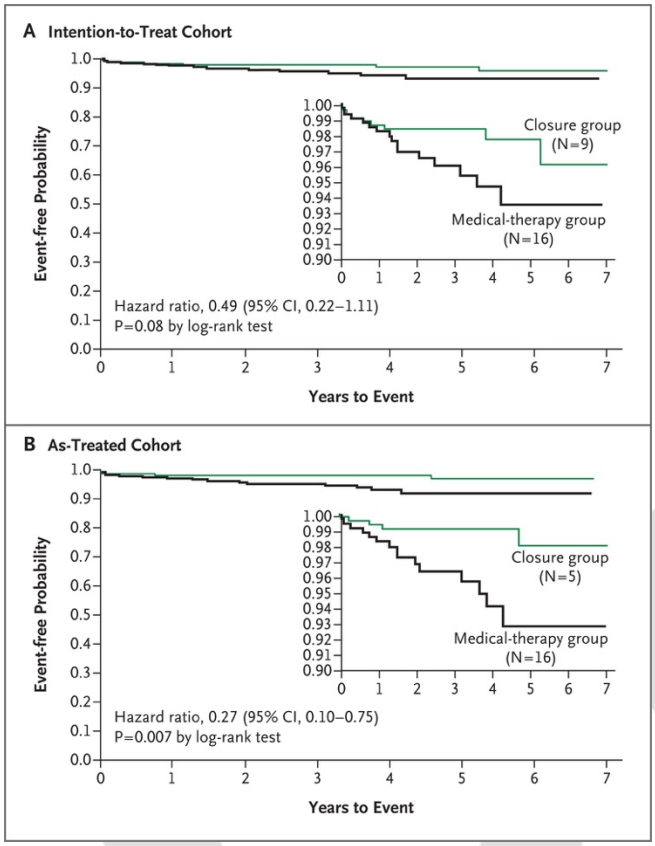



**Table 2. Serious Adverse Events Related to the Procedure or Device among the 499 Patients in the Closure Group.***

| Serious Adverse Event | Patients with Event | Total No. of Events | Procedure-Related Events | Device-Related Events |
|---|---|---|---|---|
| | *no. (%)* | | *no. (%)* | |
| Allergic drug reaction | 1 (0.2) | 1 | 1 (0.2) | — |
| Atrial fibrillation | 1 (0.2) | 1 | 1 (0.2) | — |
| Atrial flutter | 1 (0.2) | 1 | — | 1 (0.2) |
| Cardiac perforation | 1 (0.2) | 1 | 1 (0.2) | — |
| Cardiac thrombus | 2 (0.4) | 2 | 1 (0.2) | 1 (0.2) |
| Chest tightness | 1 (0.2) | 1 | — | 1 (0.2) |
| Deep-vein thrombosis | 1 (0.2) | 1 | 1 (0.2) | — |
| Infective or bacterial endocarditis | 1 (0.2) | 1 | — | 1 (0.2) |
| Ischemic stroke | 2 (0.4) | 2 | — | 2 (0.4) |
| Pericardial effusion | 1 (0.2) | 1 | 1 (0.2) | — |
| Pericardial tamponade | 2 (0.4) | 2 | 2 (0.4) | — |
| Pulmonary embolism | 1 (0.2) | 1 | — | 1 (0.2) |
| Residual shunt requiring closure | 1 (0.2) | 1 | — | 1 (0.2) |
| Sepsis | 1 (0.2) | 1 | — | 1 (0.2) |
| Nonsustained ventricular tachycardia | 1 (0.2) | 1 | — | 1 (0.2) |
| Major vascular complications | | | | |
| Bleeding | 2 (0.4) | 2 | 2 (0.4) | — |
| Hematoma | 1 (0.2) | 1 | 1 (0.2) | — |
| Vasovagal reaction | 1 (0.2) | 1 | 1 (0.2) | — |
| Total | 21 (4.2) | 22 | 12 (2.4) | 10 (2.0) |

* The serious adverse events listed here were adjudicated by the data and safety monitoring committee as having been related to the device or procedure. All the adjudicated serious adverse events that occurred in the two groups are listed in Table S5 in the Supplementary Appendix.

# RESPECT 2017:

**Table 2. Long-Term Efficacy End Points.***

| End Point | PFO Closure Group (N = 499) | | Medical-Therapy Group (N = 481) | | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|---|---|
| | Patients with Event | Event Rate per 100 Patient-Yr | Patients with Event | Event Rate per 100 Patient-Yr | | |
| | *no. (%)* | | *no. (%)* | | | |
| Recurrent ischemic stroke | 18 (3.6) | 0.58 | 28 (5.8) | 1.07 | 0.55 (0.31–0.999) | 0.046 |
| Recurrent ischemic stroke of undetermined cause as adjudicated with the use of ASCOD | 10 (2.0) | 0.32 | 23 (4.8) | 0.86 | 0.38 (0.18–0.79) | 0.007 |
| Recurrent cryptogenic ischemic stroke as adjudicated with the use of TOAST | 1 (0.2) | 0.03 | 11 (2.3) | 0.41 | 0.08 (0.01–0.58) | 0.01 |
| Transient ischemic attack | 17 (3.4) | 0.54 | 23 (4.8) | 0.86 | 0.64 (0.34–1.20) | 0.16 |

* The end points shown are the first such event that occurred in a patient, not second or later recurrences. ASCOD denotes atherosclerosis (A), small-vessel disease (S), cardiac pathology (C), other causes (O), dissection (D),[12] and TOAST Trial of ORG 10172 in Acute Stroke Treatment.[13]

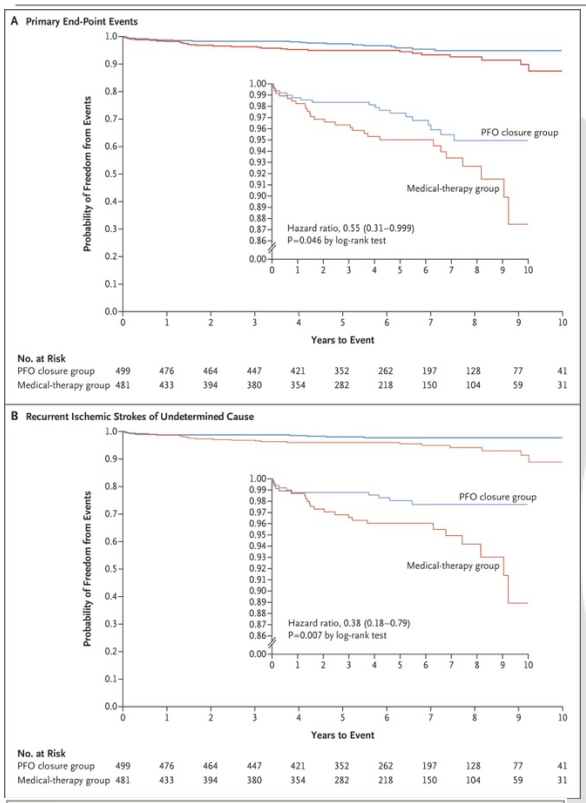



**Table 3. Serious Adverse Events Related to the Procedure or Device among the 499 Patients in the PFO Closure Group.***

| Serious Adverse Event | Patients with Event | Total No. of Events | Procedure-Related Events | Device-Related Events |
|---|---|---|---|---|
| | *no. (%)* | | *no. (%)* | |
| Allergic drug reaction | 1 (0.2) | 1 | 1 (0.2) | 0 |
| Atrial fibrillation | 2 (0.4) | 2 | 1 (0.2) | 1 (0.2) |
| Atrial flutter | 1 (0.2) | 1 | 0 | 1 (0.2) |
| Cardiac perforation | 1 (0.2) | 1 | 1 (0.2) | 0 |
| Cardiac thrombus | 2 (0.4) | 2 | 1 (0.2) | 1 (0.2) |
| Chest tightness | 1 (0.2) | 1 | 0 | 1 (0.2) |
| Deep-vein thrombosis | 1 (0.2) | 1 | 1 (0.2) | 0 |
| Infective endocarditis | 1 (0.2) | 1 | 0 | 1 (0.2) |
| Ischemic stroke | 2 (0.4) | 2 | 0 | 2 (0.4) |
| Pericardial effusion | 1 (0.2) | 1 | 1 (0.2) | 0 |
| Pericardial tamponade | 2 (0.4) | 2 | 2 (0.4) | 0 |
| Pulmonary embolism | 2 (0.4) | 2 | 0 | 2 (0.4) |
| Residual shunt requiring closure | 2 (0.4) | 2 | 0 | 2 (0.4) |
| Sepsis | 1 (0.2) | 1 | 0 | 1 (0.2) |
| Nonsustained ventricular tachycardia | 1 (0.2) | 1 | 0 | 1 (0.2) |
| Major vascular complications | | | | |
| Bleeding | 2 (0.4) | 2 | 2 (0.4) | 0 |
| Hematoma | 1 (0.2) | 1 | 1 (0.2) | 0 |
| Vasovagal reaction | 1 (0.2) | 1 | 1 (0.2) | 0 |
| Total | 21 (4.2) | 25 | 12 (2.4) | 13 (2.6) |

* The serious adverse events listed here were adjudicated by the data and safety monitoring committee as having been related to the device or procedure. All the adjudicated serious adverse events that occurred in the two groups are listed in Table S9 in the Supplementary Appendix.

# REDUCE

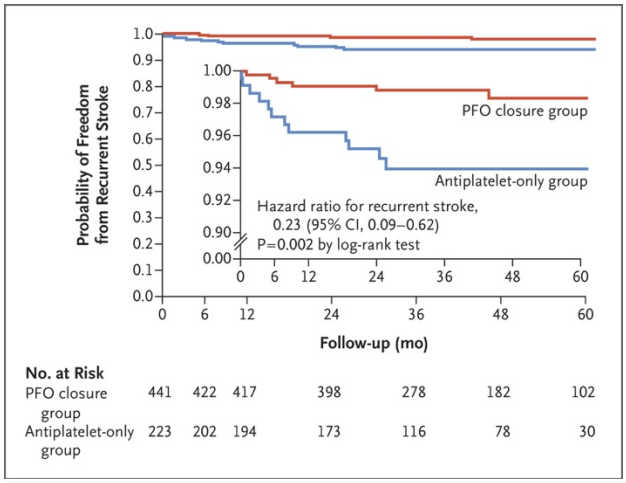



**Table 2. Coprimary End Points of Freedom from Clinical Ischemic Stroke and Incidence of New Brain Infarction.***

| End Point | PFO Closure Group | Antiplatelet-Only Group | Effect Size | P Value |
|---|---|---|---|---|
| | *no. of patients/total no. (%)* | | | |
| Clinical ischemic stroke† | 6/441 (1.4) | 12/223 (5.4) | 0.23 (0.09–0.62)‡ | 0.002§ |
| New brain infarction¶ | 22/383 (5.7) | 20/177 (11.3) | 0.51 (0.29–0.91)‖ | 0.04** |
| Recurrent clinical ischemic stroke | 5/383 (1.3) | 12/177 (6.8) | 0.19 (0.07–0.54)‖ | 0.005** |
| Silent brain infarction only | 13/383 (3.4) | 7/177 (4.0) | 0.86 (0.35–2.11)‖ | 0.75** |

* Freedom from clinical ischemic stroke is reported here as the number of recurrent strokes through at least 24 months. New brain infarction was a composite of clinical ischemic stroke or silent brain infarction detected on imaging at 24 months.
† Clinical evidence of ischemic stroke was reported through the time of available follow-up, with a minimum of 2 years, maximum of 5 years, and median of 3.2 years.
‡ Data are presented as a hazard ratio with a 95% confidence interval in the PFO closure group as compared with the antiplatelet-alone group.
§ The P value was calculated with the use of a log-rank test.
¶ One additional clinical stroke occurred in the PFO closure group after 2 years and therefore was not included in the composite new brain infarction end point at 24 months. Recurrent clinical ischemic stroke and silent brain infarction are the two components of the second coprimary end point.
‖ Data are presented as a relative risk with a 95% confidence interval in the PFO closure group as compared with the antiplatelet-alone group.
** The P value was calculated with the use of a binomial proportions test.

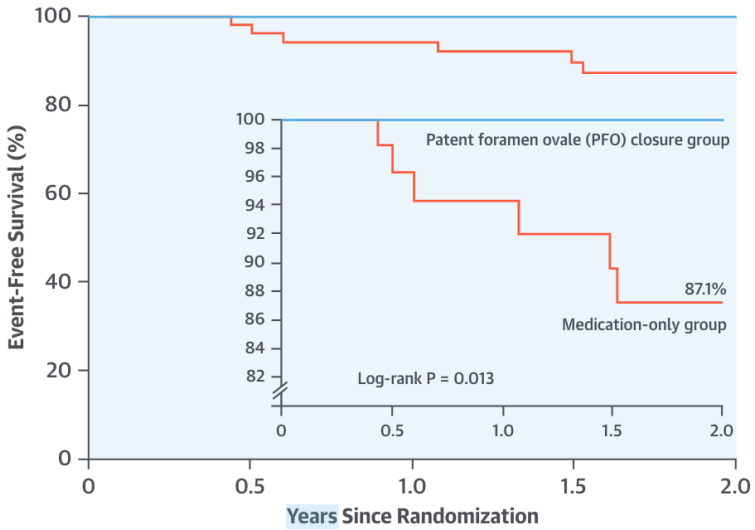
**Table 3. Adverse Events.**

| Adverse Event | PFO Closure Group (N=441) | Antiplatelet-Only Group (N=223) | P Value* |
|---|---|---|---|
| | *no. of patients (%)* | | |
| Any serious adverse event | 102 (23.1) | 62 (27.8) | 0.22 |
| Device related | 6 (1.4) | NA | NA |
| Procedure related | 11 (2.5) | NA | NA |
| Death† | 2 (0.5) | 0 | 0.55 |
| Serious bleeding adverse event | 8 (1.8) | 6 (2.7) | 0.57 |
| Procedure associated‡ | 4 (0.9) | NA | NA |
| Other§ | 4 (0.9) | 6 (2.7) | 0.09 |
| Any atrial fibrillation or flutter | 29 (6.6) | 1 (0.4) | <0.001 |
| Serious atrial fibrillation or flutter¶ | 10 (2.3) | 1 (0.4) | 0.11 |
| Serious device-related adverse event‖ | 6 (1.4) | NA | NA |
| Device dislocation | 3 (0.7) | | |
| Device-related thrombosis | 2 (0.5) | | |
| Aortic dissection | 1 (0.2) | | |
| Any deep-vein thrombosis or pulmonary embolism | 3 (0.7) | 2 (0.9) | 1.00 |

* P values were calculated with the use of Fisher's exact test.
† One suicide related to depression occurred 131 days after randomization, and one fatal myocardial infarction occurred 1045 days after randomization.
‡ Procedure-associated serious bleeding adverse events were events of bleeding within 30 days after the procedure at the vascular access site (three patients) or cardiac tamponade (one patient).
§ Other serious bleeding adverse events were events of bleeding in the reproductive, visual, gastrointestinal, and musculoskeletal systems.
¶ Atrial fibrillation or flutter was classified as a serious adverse event by the local investigator.
‖ A serious device-related adverse event was any adverse event that involved or was related to the device, with the exclusion of arrhythmia.

**DEFENSE**

**CENTRAL ILLUSTRATION** Device Closure for High-Risk PFO: Kaplan-Meier Cumulative Estimates




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| PFO closure | 60 | 52 | 46 | 42 | 40 |
| Medication-only | 60 | 52 | 45 | 38 | 37 |

Lee, P.H. et al. J Am Coll Cardiol. 2018;71(20):2335-42.

Kaplan-Meier cumulative estimates of the primary endpoint in the patent foramen ovale (PFO) closure group versus the medication-only group.

**TABLE 3** Clinical Outcomes

| 2-Yr Outcome | PFO Closure Group (n = 60) | Medication-Only Group (n = 60) | p Value |
|---|---|---|---|
| Primary endpoint | 0 (0.0) | 6 (12.9) | 0.013 |
| Secondary endpoint | | | |
| Ischemic stroke | 0 (0.0) | 5 (10.5) | 0.023 |
| Vascular death | 0 (0.0) | 0 (0.0) | NA |
| TIMI-defined major bleeding | 0 (0.0) | 2 (4.9) | 0.15 |
| Hemorrhagic stroke | 0 (0.0) | 1 (2.5) | 0.30 |
| Transient ischemic attack | 0 (0.0) | 1 (2.0) | 0.32 |
| Systemic embolism | 0 (0.0) | 0 (0.0) | NA |
| New ischemic lesion on MRI | 3/34 (8.8) | 7/38 (18.4) | 0.24 |

Values are n (%) (Kaplan-Meier estimates) or n/N (%).

MRI = magnetic resonance imaging; NA = not applicable; PFO = patent foramen ovale; TIMI = Thrombolysis In Myocardial Infarction.