Klinické studie CLOSE a REDUCE

Doc. MUDr. Josef Šťásek, Ph.D
Univerzita Karlova v Praze
Lékařská fakulta Hradec Králové
I. interní klinika a Kardiocentrum
Fakultní nemocnice Hradec Králové

Original Article

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

Jean-Louis Mas, M.D., Geneviève Derumeaux, M.D., Benoît Guillon, M.D., Evelyne Massardier, M.D., Hassan Hosseini, M.D., Ph.D., Laura Mechtouff, M.D., Caroline Arquizan, M.D., Yannick Béjot, M.D., Ph.D., Fabrice Vuillier, M.D., Olivier Detante, M.D., Ph.D., Céline Guidoux, M.D., Sandrine Canaple, M.D., Claudia Vaduva, M.D., Nelly Dequatre-Ponchelle, M.D., Igor Sibon, M.D., Ph.D., Pierre Garnier, M.D., Anna Ferrier, M.D., Serge Timsit, M.D., Ph.D., Emmanuelle Robinet-Borgomano, M.D., Denis Sablot, M.D., Jean-Christophe Lacour, M.D., Mathieu Zuber, M.D., Pascal Favrole, M.D., Jean-François Pinel, M.D., Marion Apoil, M.D., Peggy Reiner, M.D., Catherine Lefebvre, M.D., Patrice Guérin, M.D., Christophe Piot, M.D., Roland Rossi, M.D., Jean-Luc Dubois-Randé, M.D., Ph.D., Jean-Christophe Eicher, M.D., Nicolas Meneveau, M.D., Ph.D., Jean-René Lusson, M.D., Bernard Bertrand, M.D., Jean-Marc Schleich, M.D., Ph.D., François Godart, M.D., Ph.D., Jean-Benoit Thambo, M.D., Laurent Leborgne, M.D., Ph.D., Patrik Michel, M.D., Luc Pierard, M.D., Ph.D., Guillaume Turc, M.D., Ph.D., Martine Barthelet, M.D., Anaïs Charles-Nelson, M.Sc., Christian Weimar, M.D., Thierry Moulin, M.D., Ph.D., Jean-Michel Juliard, M.D., Gilles Chatellier, M.D., for the **CLOSE** Investigators

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Study Overview

- In patients with cryptogenic stroke and patent foramen ovale with atrial septal aneurysm or large interatrial shunt, closure of the PFO and administration of antiplatelet medications resulted in a lower rate of recurrent stroke than antiplatelet therapy alone.

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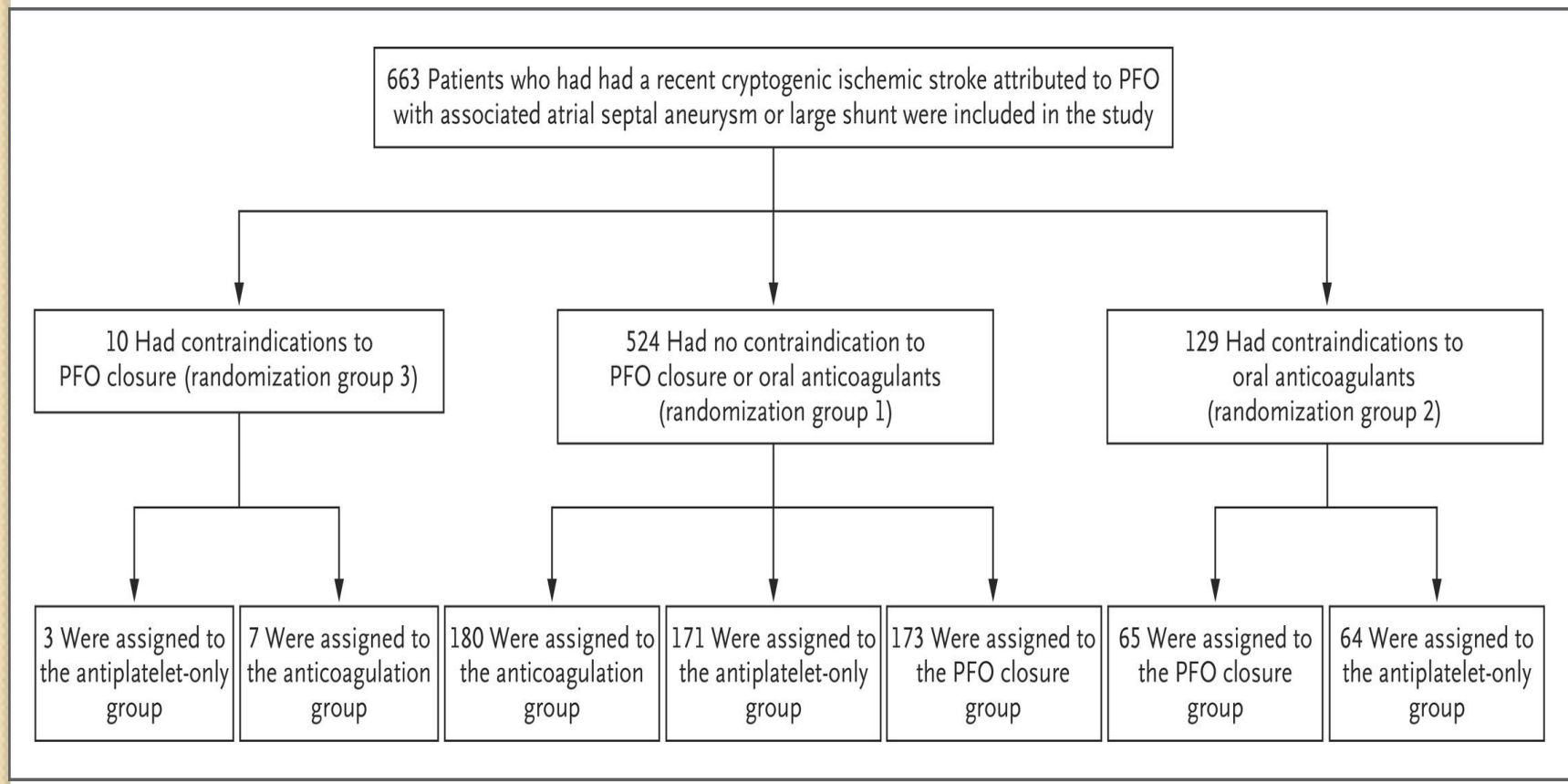
- 11 různých typů okluderů



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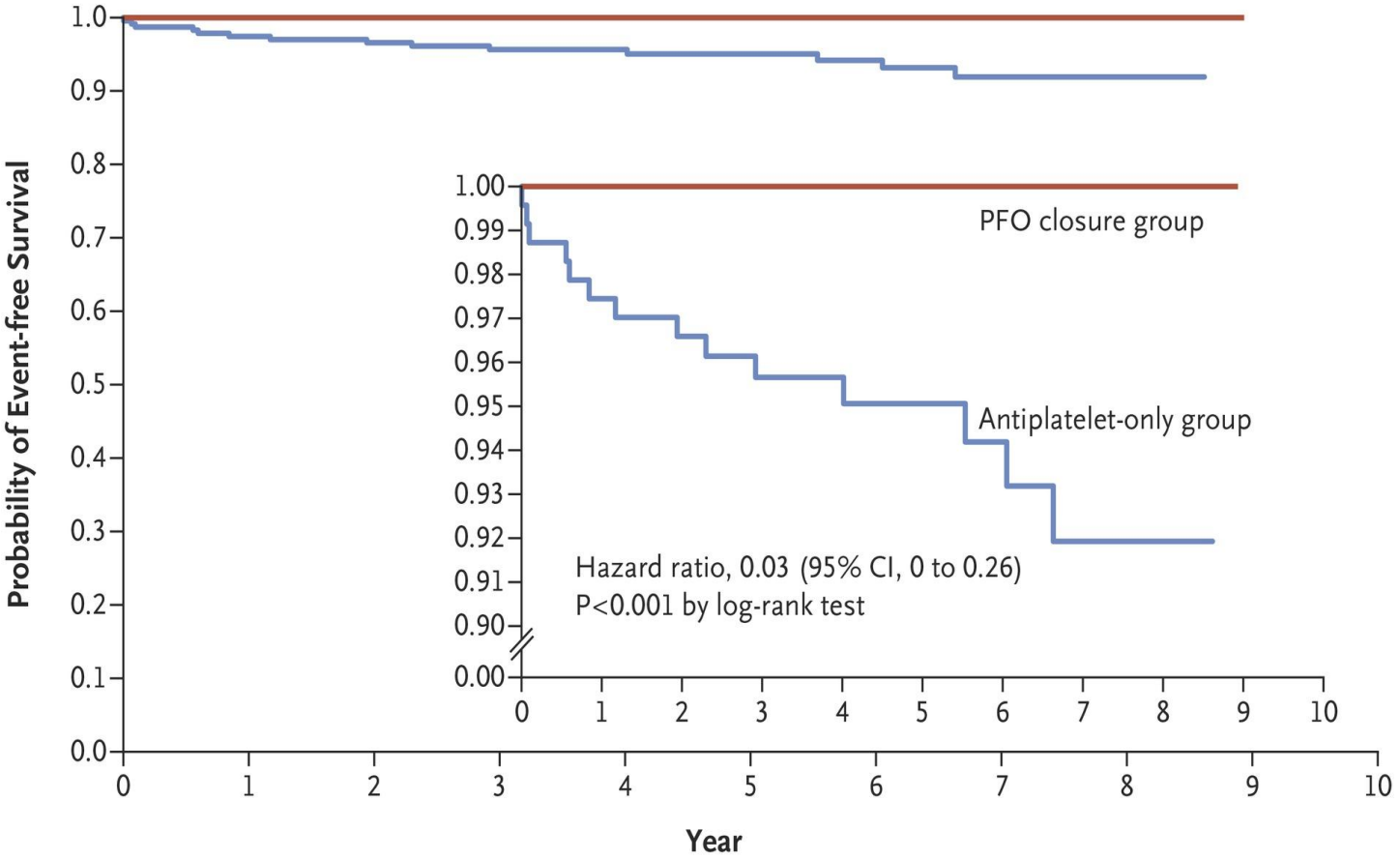

No. at Risk											
PFO closure group	238	238	232	200	179	141	99	64	20	0	0
Antiplatelet-only group	235	229	223	198	160	130	96	55	19	0	0

Mas J-L et al. N Engl J Med 2017;377:1011-1021

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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.

Mas J-L et al. N Engl J Med 2017;377:1011-1021

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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.

Mas J-L et al. N Engl J Med 2017;377:1011-1021

Conclusions

- Among patients who had had a recent cryptogenic stroke attributed to ***PFO with an associated atrial septal aneurysm or large interatrial shunt,*** the rate of stroke recurrence was lower among those assigned to PFO closure combined with ***antiplatelet therapy*** than among those assigned to antiplatelet therapy alone.
- PFO closure was associated with an increased risk of atrial fibrillation.

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Original Article

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., Lars Thomassen, M.D., for the Gore **REDUCE Clinical Study** Investigators

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- **In a randomized trial involving 664 patients who had had a cryptogenic stroke, closure of a PFO combined with antiplatelet therapy resulted in significantly lower rates of subsequent stroke than antiplatelet therapy alone over a median follow-up of 3.2 years.**
- **Gore device – Helax, GSO**

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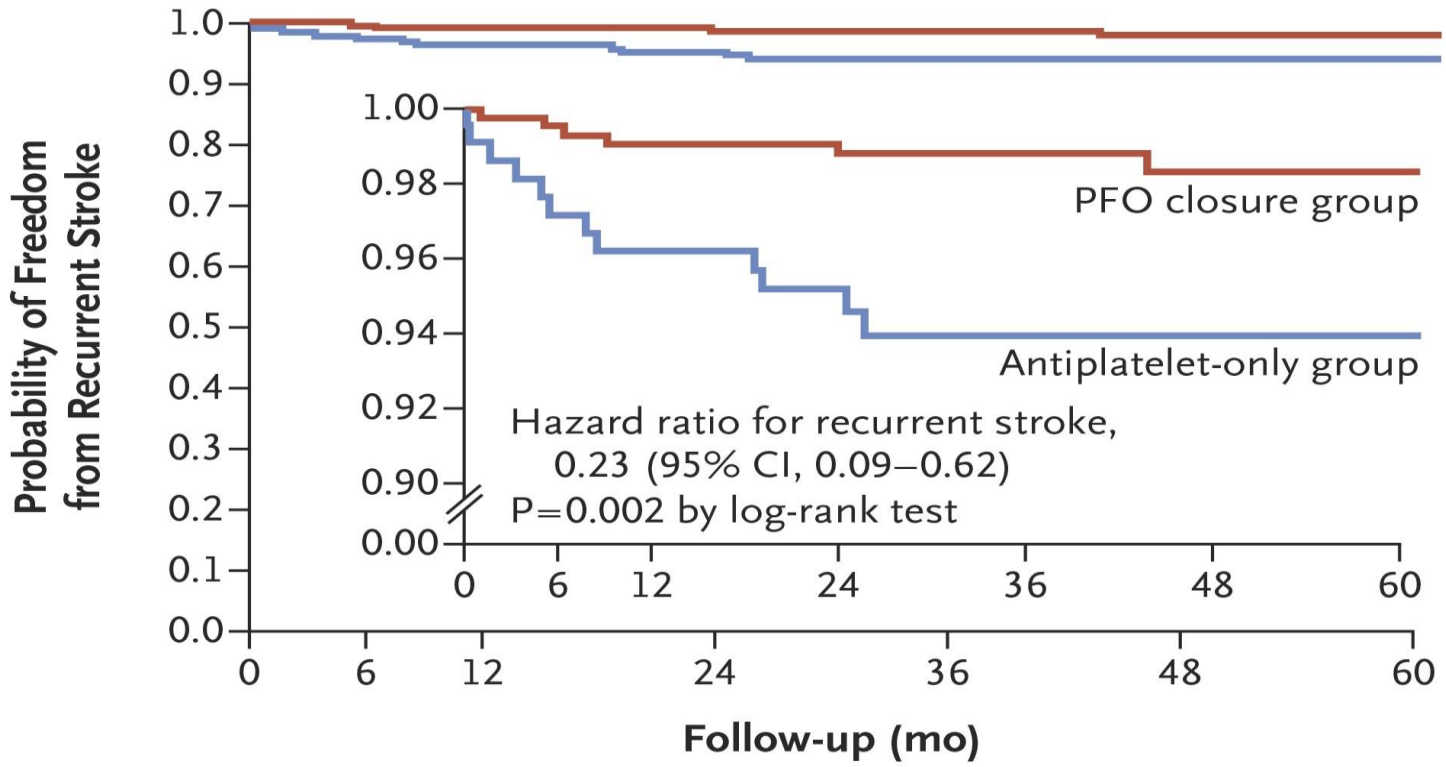

No. at Risk							
PFO closure group	441	422	417	398	278	182	102
Antiplatelet-only group	223	202	194	173	116	78	30

Søndergaard L et al. N Engl J Med 2017;377:1033-1042

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Subgroup	PFO Closure Group	Antiplatelet-Only Group	Hazard Ratio (95% CI)	P Value	P Value for Interaction
	no. of patients who had recurrent stroke/total no. (%)				
All patients	6/441 (1.4)	12/223 (5.4)	0.23 (0.09–0.62)	0.002	
Age					0.85
18–45 yr	3/204 (1.5)	6/114 (5.3)	0.26 (0.07–1.04)	0.04	
46–59 yr	3/237 (1.3)	6/109 (5.5)	0.21 (0.05–0.84)	0.02	
Sex					0.62
Male	3/261 (1.1)	8/138 (5.8)	0.19 (0.05–0.71)	0.01	
Female	3/180 (1.7)	4/85 (4.7)	0.31 (0.07–1.40)	0.11	
Region					1.00
Europe and Canada	3/225 (1.3)	6/108 (5.6)	0.23 (0.06–0.93)	0.03	
United States	3/215 (1.4)	6/115 (5.2)	0.24 (0.06–0.94)	0.03	
Shunt size					0.77
Small	1/77 (1.3)	2/43 (4.7)	0.27 (0.03–3.03)	0.26	
Moderate-to-large	4/348 (1.1)	10/173 (5.8)	0.18 (0.06–0.58)	0.001	

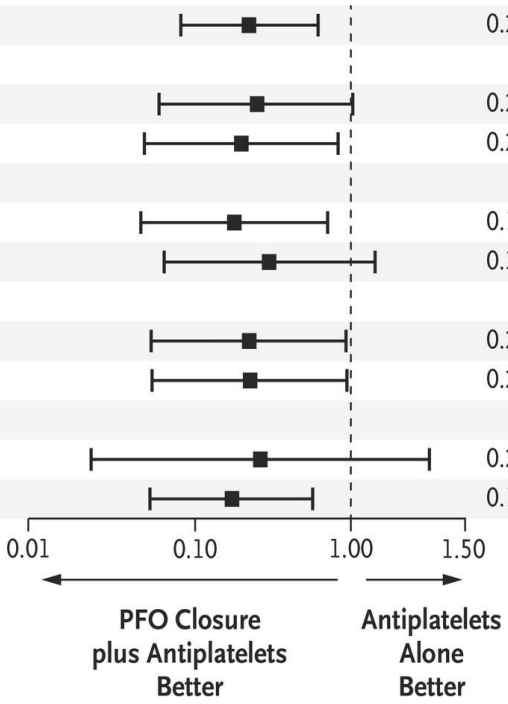

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Table 2. Coprimary End Points of Freedom from Clinical Ischemic Stroke and Incidence of New Brain Infarction.*

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	17/383 (4.4)	8/177 (4.5)	0.98 (0.43–2.23)‖	0.97**

* 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.

Søndergaard L et al. N Engl J Med 2017;377:1033-1042

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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.

Søndergaard L et al. N Engl J Med 2017;377:1033-1042

Conclusions

- Among patients with a PFO who had had a cryptogenic stroke, the risk of subsequent ischemic stroke was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone; however, PFO closure was associated with higher rates of device complications and atrial fibrillation.

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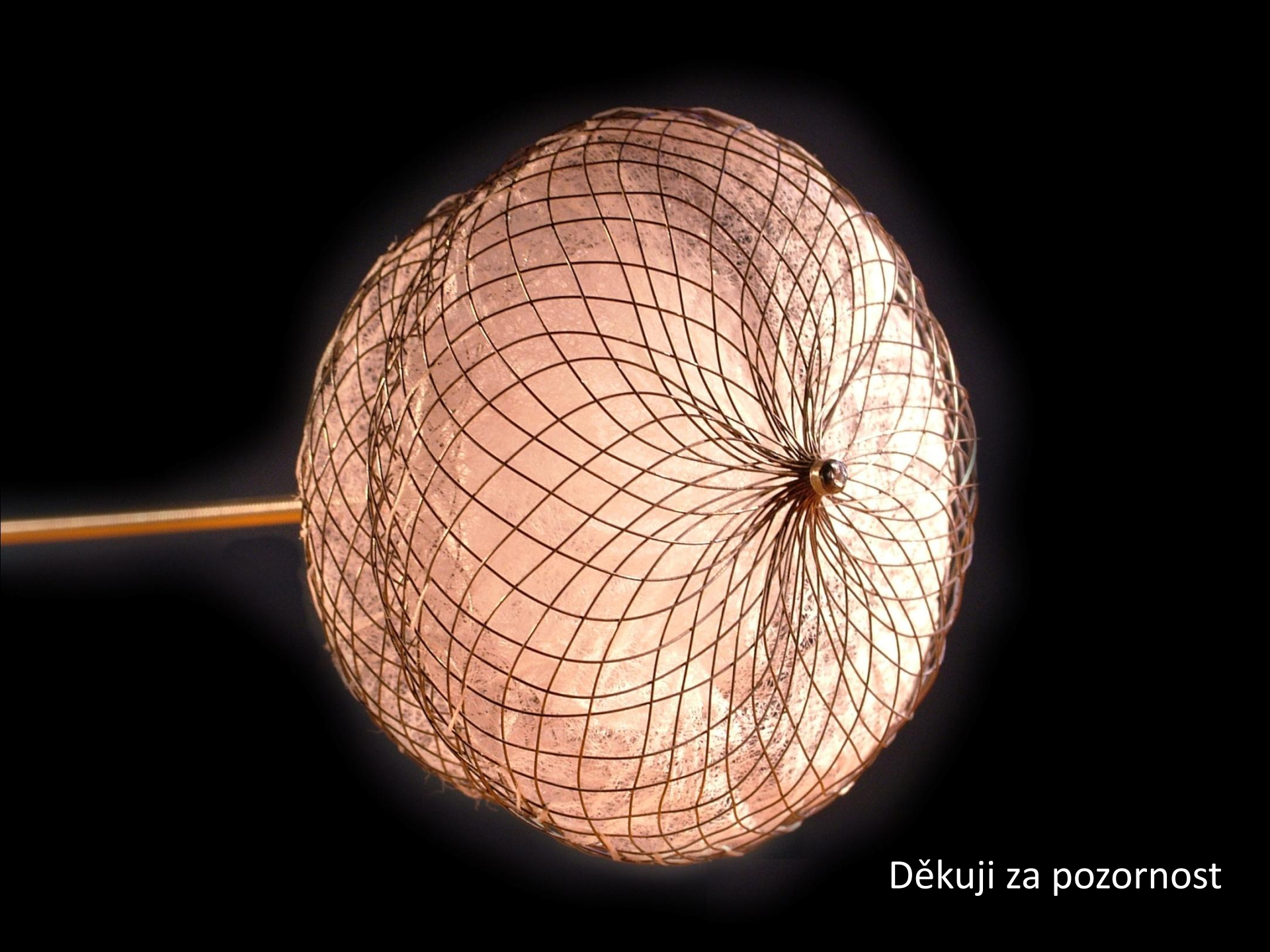
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