Fermeture de foramen ovale perméable

Les études

Sébastien Hascoet, Benoit Gerardin, Philippe Brenot, Jérôme Petit

Hôpital Marie Lannelongue

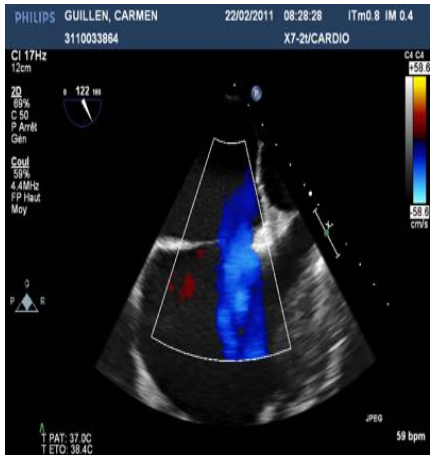
Biarritz, APPAC, Juin 2018


Et maintenant, bon appétit!...

COMMUNICATIONS DE LA CLOISON INTERAURICULAIRE

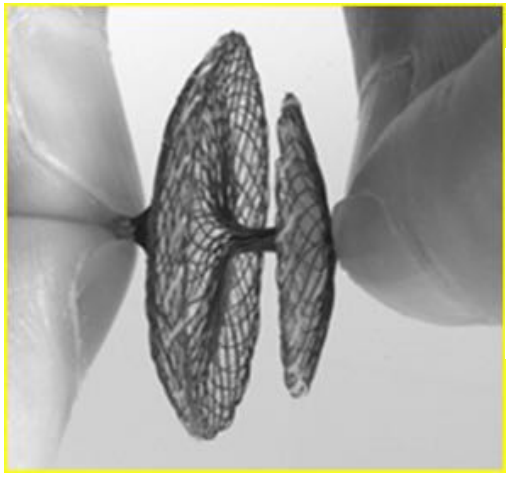
780 000 naissances / an en France

CIA
350 - 400 nouveau cas/an

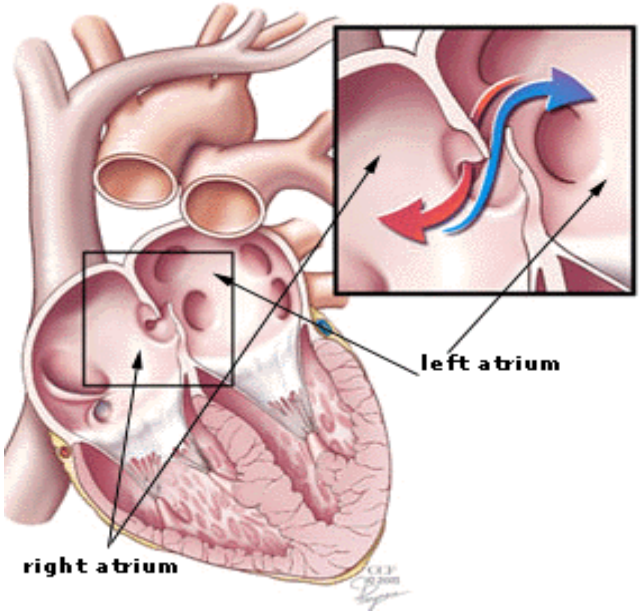


FOP

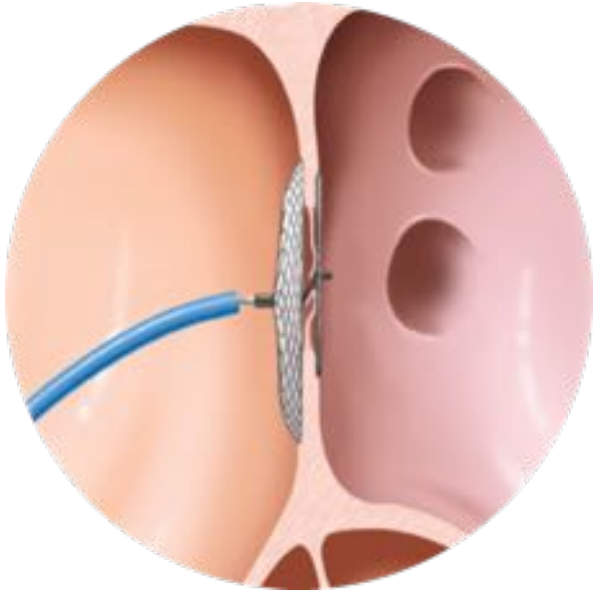
~ 120 - 200 000 nouveau / an.



GORE® HELEX® (left) and GORE® CARDIOFORM (right) Septal Occluders



RESPECT : Résultats de la procédure



Succès d'implantation—
Pose de prothèse réussie

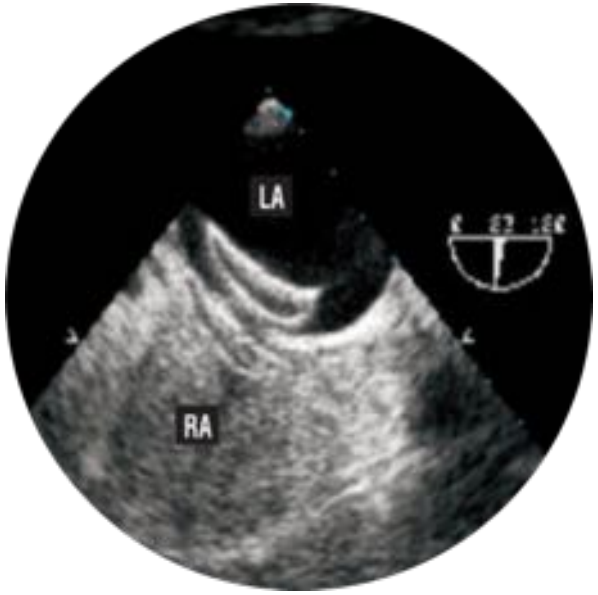
99.1%

Succès de la procédure—
Implantation sans évènement indésirable

96.1%

Carroll et al (2013). Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke. *N Engl J Med* 368;12 nejm.1092 org.

RESPECT : Taux de fermeture à 6 mois



FERMETURE COMPLETE :
Absence de bulles au repos et en Valsalva

71.3%

FERMETURE EFFECTIVE—
Au plus, 9 Bulles au repos et en Valsalva

94.2%

AMPLAZTER PFO Occluder Executive Summary Circulatory System Devices Panel, May 2015

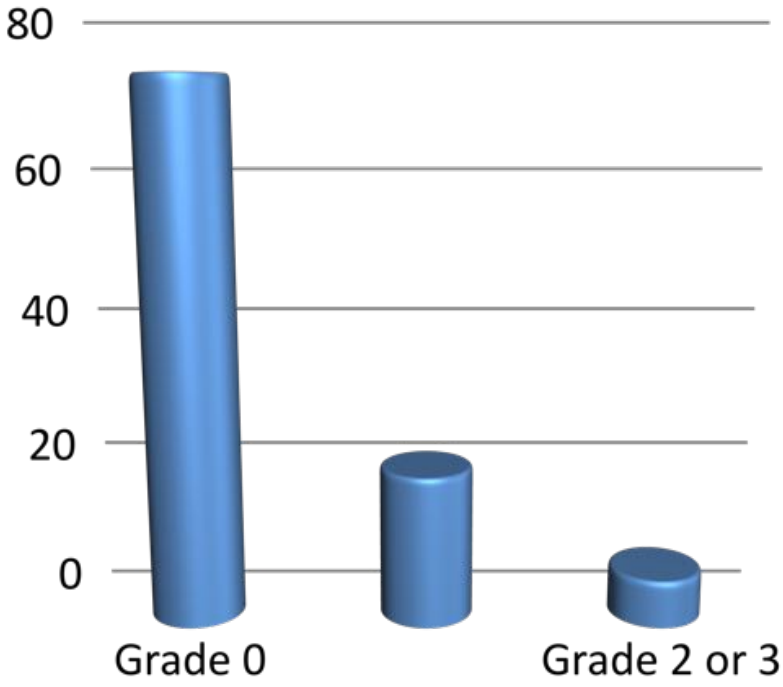
RESPECT : Evènements indésirables liés à la procédure et au dispositif

Evènement	Groupe fermeture du FOP (N=499; 3141 pt-yrs)
	Nb total (par année-patient)
Tout types d'évènement indésirable	201 (0.064)
Evènements indésirables liés au dispositif	13 (0.004)
Décès	7 (0.002)
	Nb d'évènements (%)
Evènements indésirables liés au dispositif	13 (2.6%)
– **Embolisation de la prothèse**	0 (0.0%)
– **Thrombus sur le dispositif**	0 (0.0%)
– **Dissection aortique**	0 (0.0%)
Evènements indésirables liés à la procédure	12 (2.4%)

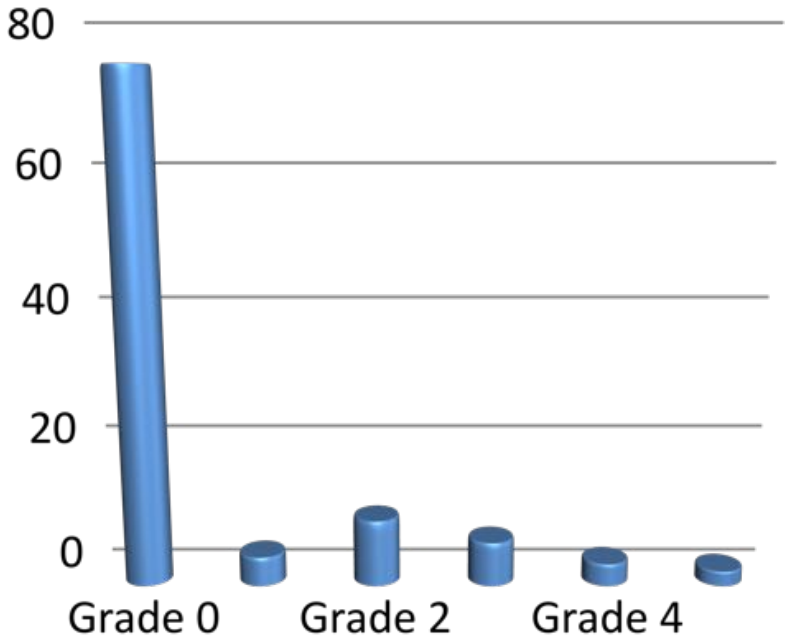
Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med 2017; 377: 1022-32.

Shunt residuel à 6 mois

RESPECT (Amplatzer)



OPPOSE (Occlutech)



CLOSE : répartition des types de prothèses

Device	n
Amplatzer PFO occluder (AGA Medical)	121
Intrasept PFO occluder (Cardia)	31
Premere (St. Jude Medical)	22
Starflex septal occluder system (NMT Medical)	21
Amplatzer cribriform occluder (AGA Medical)	15
Figulla Flex II PFO occluder (Occlutech, Inc)	15
Atriasept II occluder (Cardia)	3
Amplatzer ASD occluder (AGA Medical)	2
Figulla Flex II UNI occluder (Occlutech)	2
Gore septal occluder (Gore Medical)	2
Figulla Flex II ASD occluder (Occlutech)	1
Total	235

Pathologies potentiellement liées à un FOP

	Agent	Causalité
▪ AVC	thrombus veineux	
▪ Accident de décompression	bulles d'azote	
▪ Migraine	neuromédiateur	
▪ Syndrome carcinoïde	sérotonine	
▪ Hypoxémie	sang desaturé	

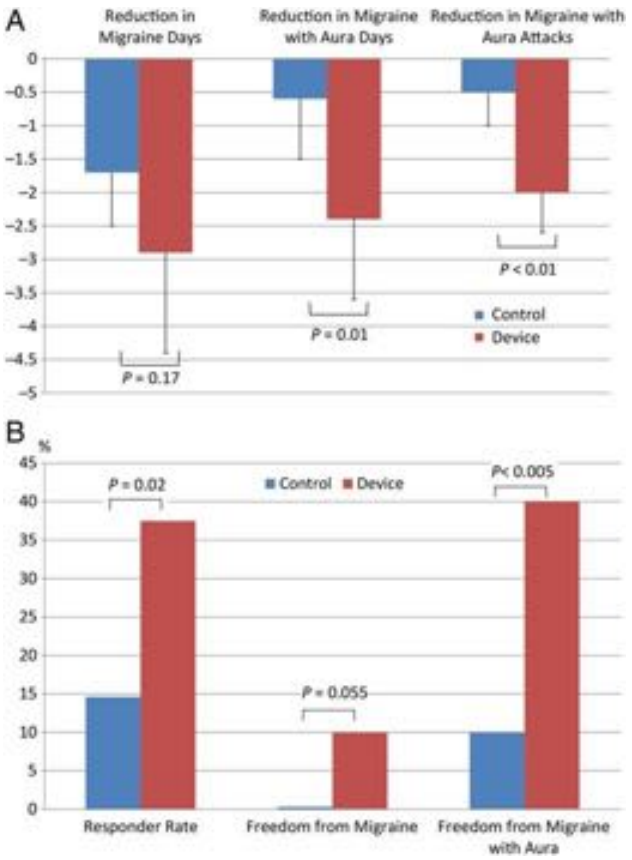
1/ Migraine
(#neuromédiateur)

Percutaneous Closure of PFO in Migraine with Aura - **PRIMA** (multicentrique, randomisé)
107 migraineux (avec aura) réfractaire au ttt

Fermeture FOP /med

Critère principal: comparaison du nombre de jours de migraine avant et 9-12 mois après randomisation: NS 22.9 av vs 21.7 jours ap

=> La fermeture du PFO n'est pas associée à une réduction sig du nombre de jours de migraine.



Mattle HP. Eur Heart J 2016

1/ Migraine **(# neuromédiateur)**

Percutaneous Closure of PFO in Patients with Migraine: the **PREMIUM trial**

(prospectif, multicentrique, randomisé, **double aveugle**)

230 migraineux (6-14 jours/mois) réfractaire au ttt

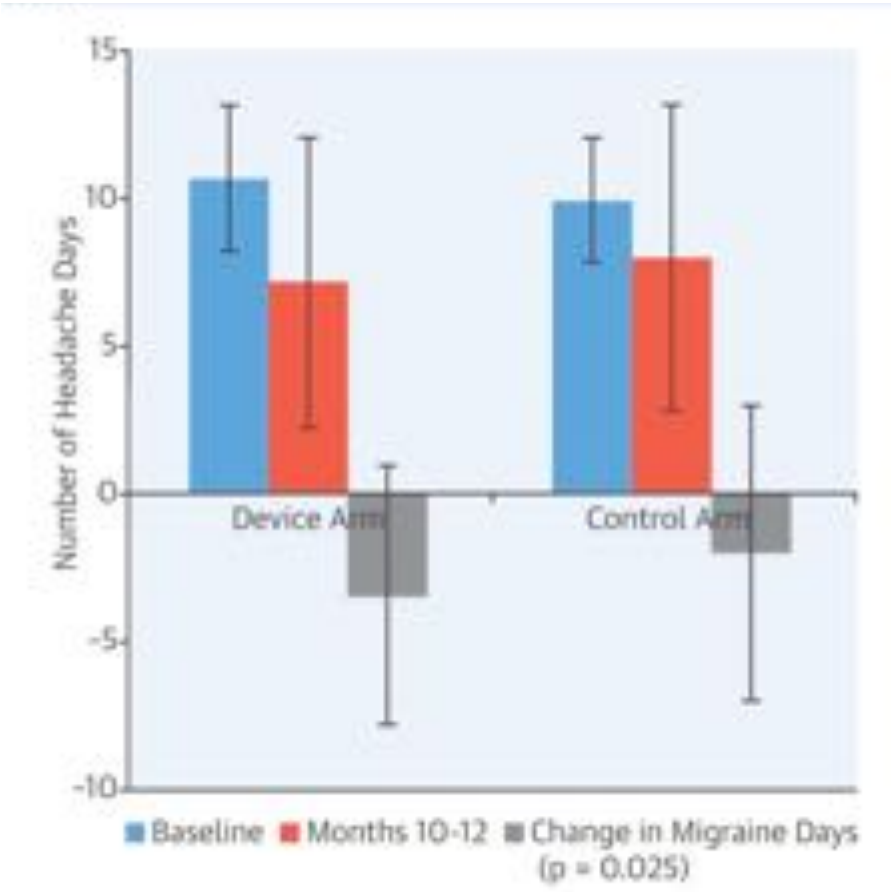
Critère principal: diminution 50 % de jours de migraines / mois. Suivi à 1 an.

Résultat : Echec sur critère principal fermeture =>

– 3,4 jours vs -2 jours/mois. (p=0.025)

disparition migraine :

10 (8.5%) vs 1 (1%) (p=0.01)



Tobis JM. J Am Coll Cardiol. 2017

2/platypnée - orthodéoxie

Fermeture FOP = indication formelle.

CardioVascular and Interventional Radiology

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Published Online: ■

Cardiovasc Intervent Radiol (2005) 28:1–5
DOI: 10.1007/s00270-004-0035-3

CLINICAL INVESTIGATION

Transcatheter Closure of Patent Foramen Ovale in Patients with Platypnea-Orthodeoxia: Results of a Multicentric French Registry

P. Guérin,[1] V. Lambert,[2] F. Godart,[3] A. Legendre,[2] J. Petit,[2] F. Bourlon,[4] B. De Geeter,[5] A. Petit,[6] B. Monrozier,[7] A.M. Rossignol,[8] M. Jimenez,[9] D. Crochet,[1] A. Choussat,[†] C. Rey,[3] J. Losay[2]

JESFC 2013
N=24

3/syndrome carcinoïde **(# sérotonine)**

Constatations:

-Fréquence PFO + importante (~ X 2 / pop générale)

-La fermeture du PFO réduit les symptômes.

Fermeture du FOP peut être intéressante en traitement complémentaire.

Mansécal & al. Am J Cardiol 2008 Apr 1;101(7):1035-8

4/ Fop et plongée : accidents de décompression

(# bulles d'azote)

Accidents de décompression et shunts droite-gauche. Faut-il fermer le foramen ovale perméable chez le plongeur ?

Decompression complications and right-to-left shunts. Should patent foramen ovale be closed in scuba divers?

J.-E. Blatteau

Service de médecine hyperbare et d'expertise plongée, hôpital d'instruction des armées Sainte-Anne, BP600, 83800 Toulon cedex 9, France

Arch Mal Coeur Vaiss Prat 2016;2016:8–11

4/ Fop et plongée : accidents de décompression

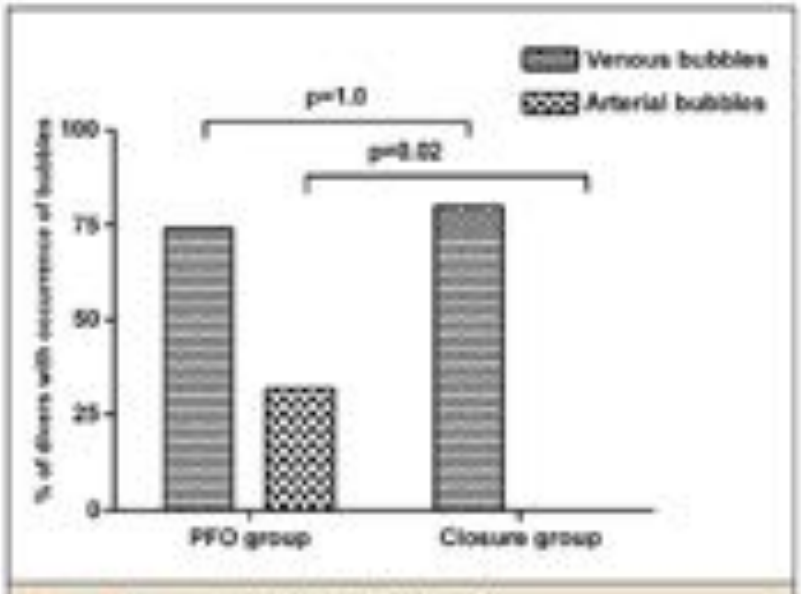
. ADD neuro : 2/10.000 plongées

. **Fréquentes transgressions de certaines règles.**

. ADD neuro : . séquelles dans 25% des cas.

. + fréquent quand FOP

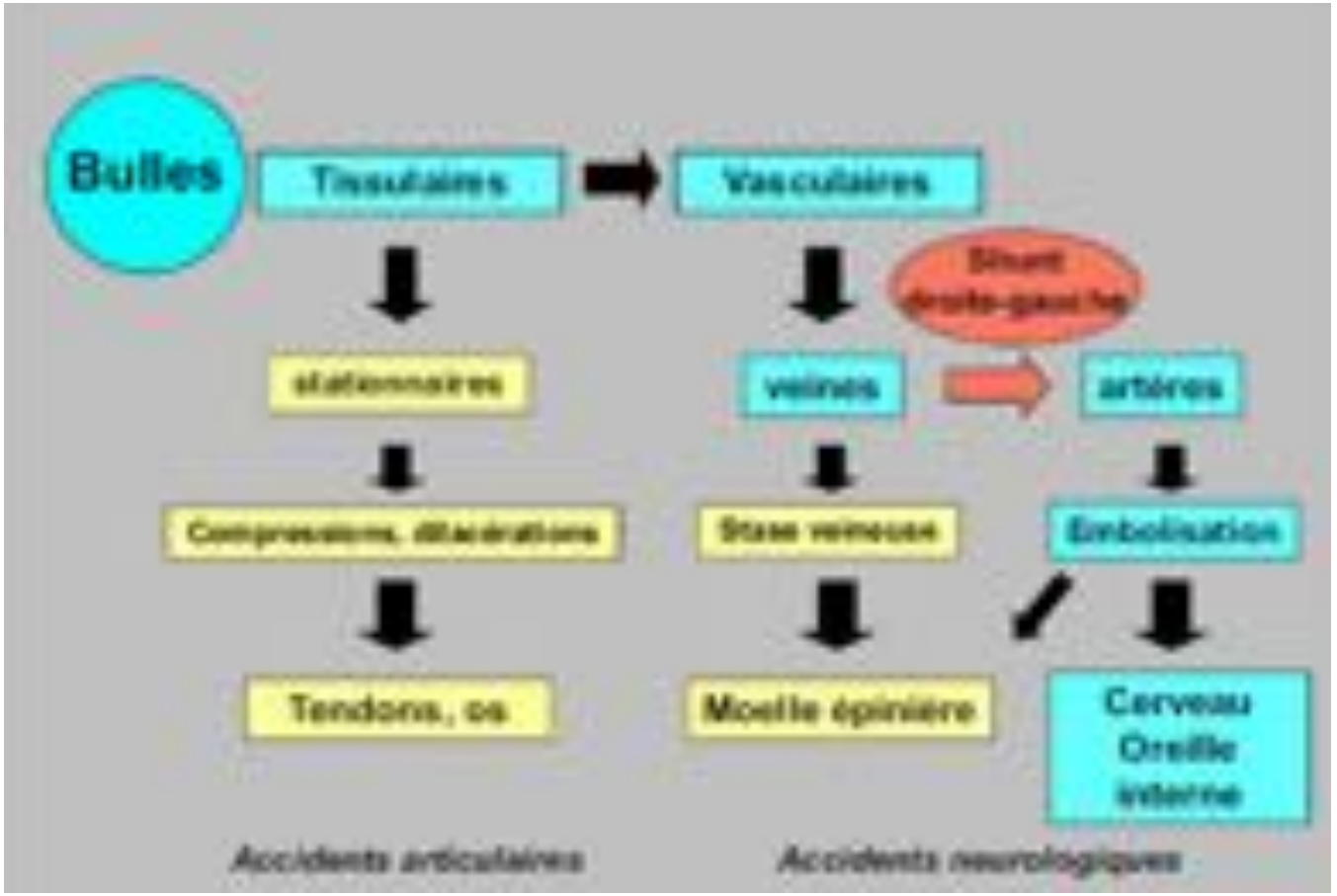
•Bulles artérielles absentes si Fermeture FOP versus FOP ouvert



JACC CI 2014

4/ Fop et plongée : accidents de décompression

Accidents de décompression (ADD)



Arch Mal Coeur Vaiss Prat 2016;2016:8–11

5/ FOP et AVC **(# thrombus)**

Accidents vasculaires cérébraux : 140 000/ an en France

. 80% ischémique ~ 110 000 / an

(FA (~ 20 000), valvulopathies mitrales, IDM, carotides,maladie des petites artères …)

. mais 20 - 25 % étiologie ??? = **cryptogénique** (~ 30 000)

Chez le moins de 55 ans : 20 000 / an

.AVC cryptogénique beaucoup + fréquent (# 50 %)

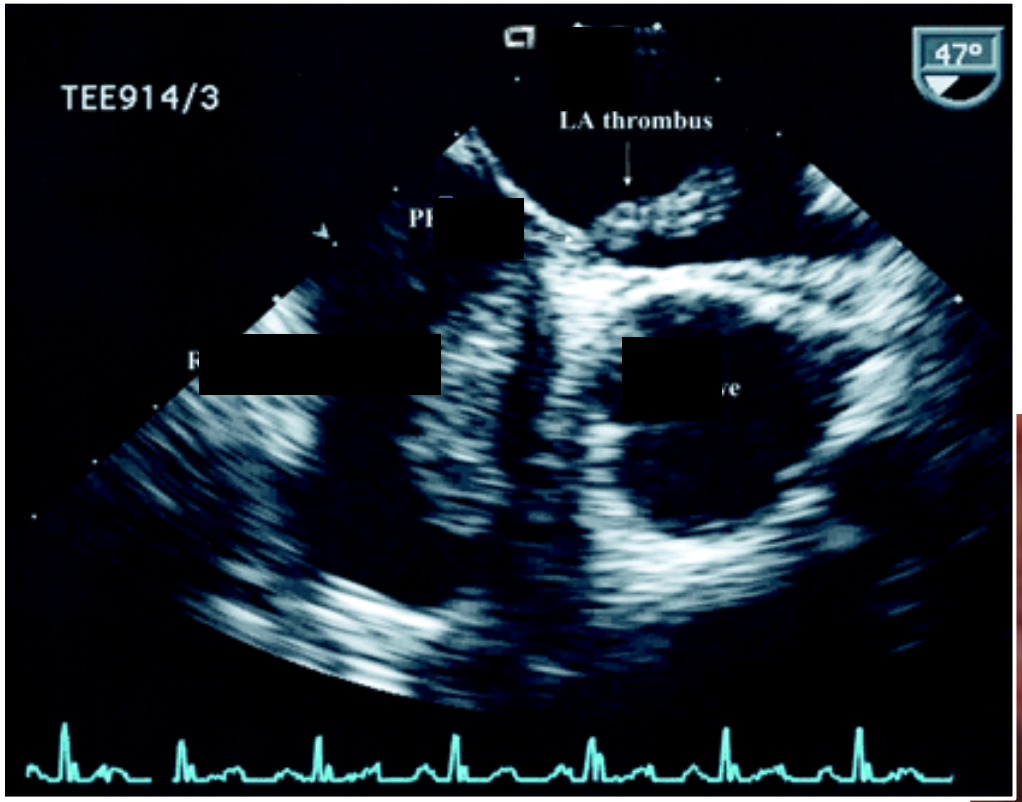
.Quand l'AVC est cryptogénique :

l'incidence du FOP (+/- ASIA) est beaucoup plus élevée (30-50%)

- NEJM 1998 : Lechat Ph et col.; 318: 1148-52

- Stroke 1993:24, 1665-73. L. Cabanes et col (Cochin)

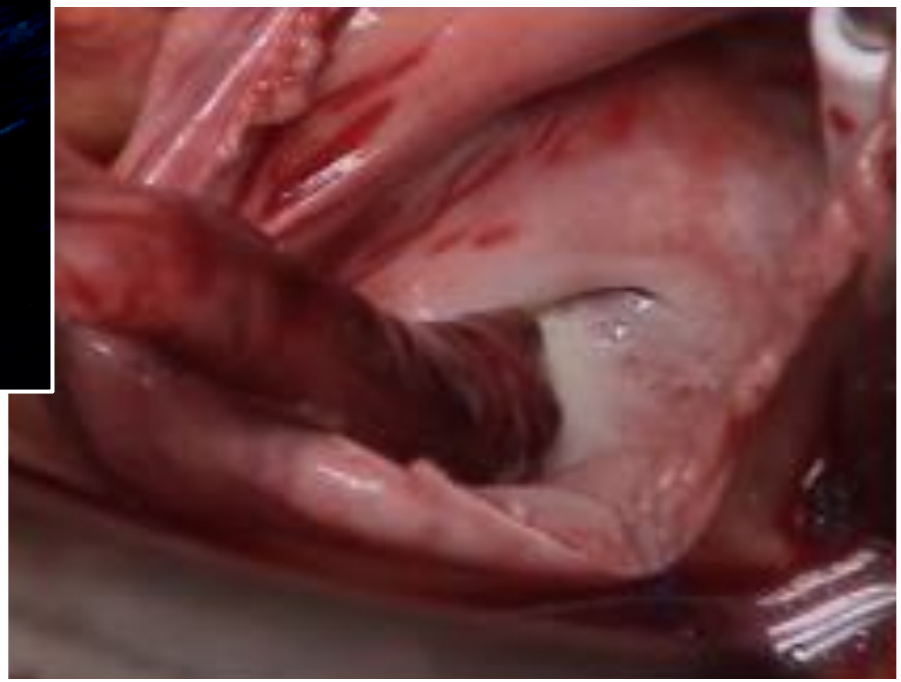
5/ Fop et AVC



mécanismes **possibles :**

. thrombus veineux profond

. thrombus siégeant dans l'ASIA



Koullias GJ et al *Circulation* 2004

5/ Fop et AVC : étude FOP – ASIA (2001)

étude européenne prospective multicentrique (30 services).

- Récurrences d'AIC (hors AIT) à 4 ans sous aspirine.
  - PFO seul : 2.3 %
  - ASIA seul : 0
  - aucune anomalie cardiaque : 4.2 %
  - FOP + ASIA : 15.2 %

- Conclusion : AVC avec FOP + ASIA = sous groupe à risque de récurrence d'AVC => *D'autres stratégies que l'aspirine devraient être envisagées.*

NEJM 2001. JL Mas. 345 ; 24, 1740-46

5/ Fop et AVC : Etudes prospectives contrôlées 1ère partie

CLOSURE I
Investigating the PFO Stroke Connection

N Engl J Med 2012

- 900 patients (<60 ans)
- Suivi 2 ans
- Starflex® NMT Medical

négative

RESPECT
CLINICAL TRIAL

N Engl J Med 2013

- 980 patients (< 60 ans)
- Suivi moyen 2 ans
- Amplatzer

négative

PC Trial

N Engl J Med 2013

- 414 patients (< 60 ans)
- Suivi moyen 4 ans
- Amplatzer

négative

RESPECT
CLINICAL TRIAL

Suivi moyen : 2.6±2.0 ans (0 to 8.1 ans)

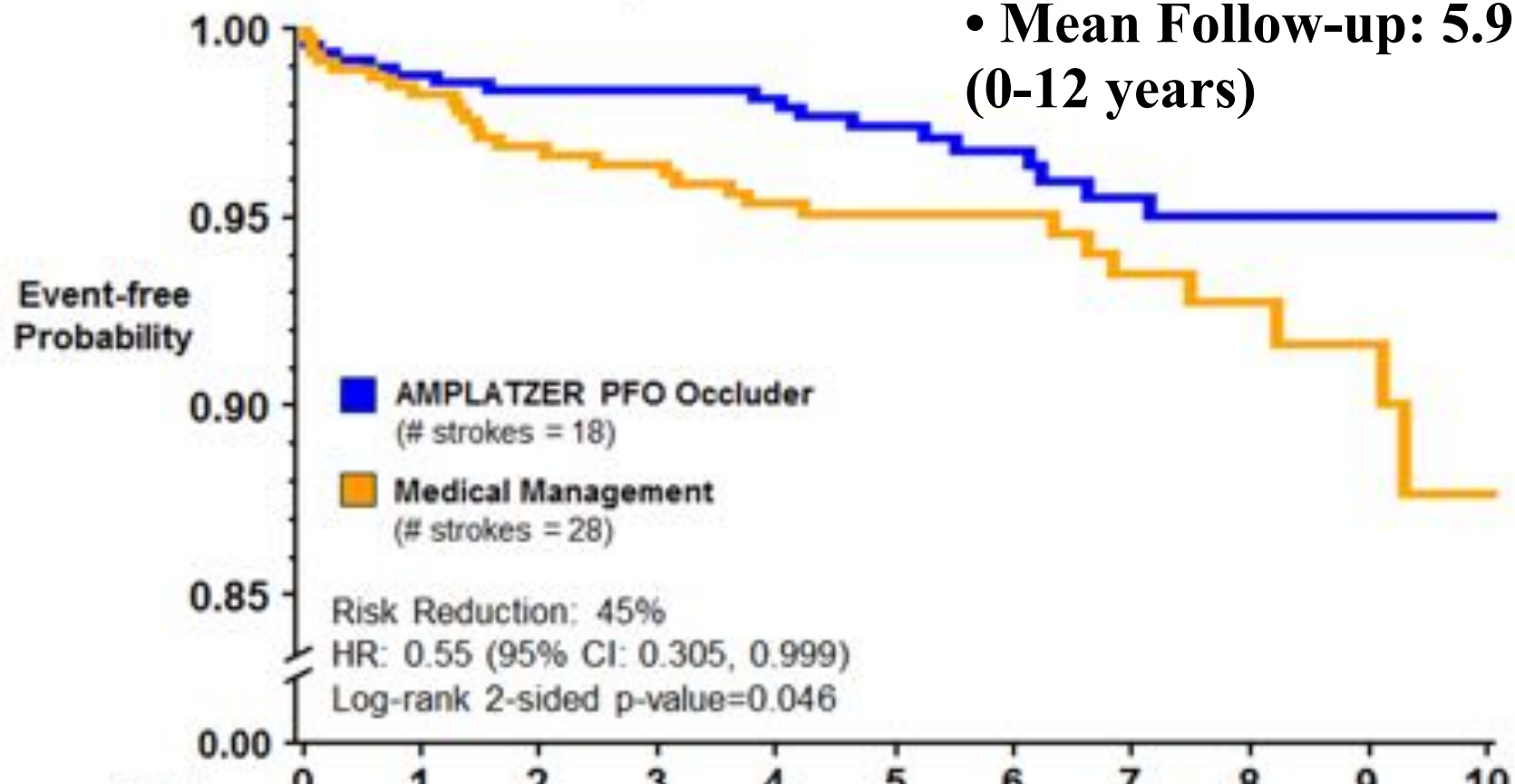
Récidive d'AVC	Fermeture	Médical
A 1 an	1.3%	1.7%
A 2 ans	1.6%	3.0%
A 5 ans	2.2%	6.4%

N Engl J Med 2013

RESPECT Final Results

Freedom from Recurrent Ischemic Stroke (Intention to Treat)

- **Mean Follow-up: 5.9 years (0-12 years)**



# at Risk (KM Estimates)											
AMPLATZER	499 (0%)	476 (1.4%)	464 (1.6%)	447 (1.6%)	421 (1.9%)	352 (2.6%)	262 (3.3%)	197 (4.5%)	128 (5.0%)	77 (5.0%)	41 (5.0%)
MM	481 (0%)	433 (1.8%)	394 (3.2%)	380 (3.7%)	354 (4.7%)	282 (5.0%)	218 (5.0%)	150 (6.6%)	104 (7.3%)	59 (8.5%)	31 (12.5%)

NEJM du 14 septembre 2017 : 3 études randomisées sur la fermeture de FOP par voie percutanée

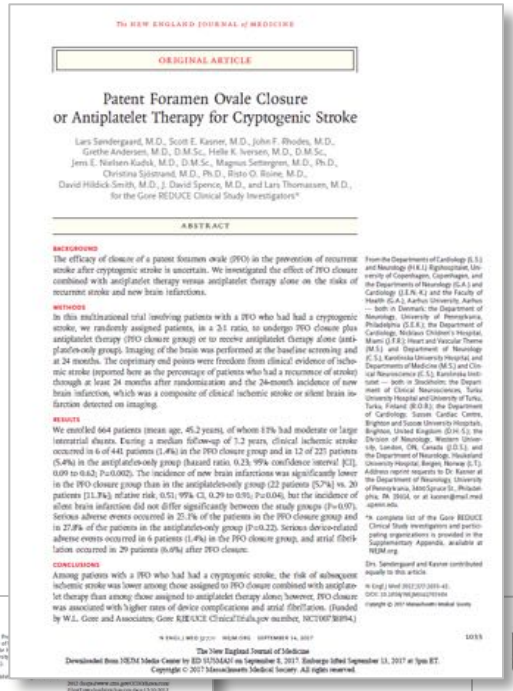
RESPECT

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Commentaire

Patent Foramen Ovale after Cryptogenic Stroke — Assessing the Evidence for Closure

REDUCE

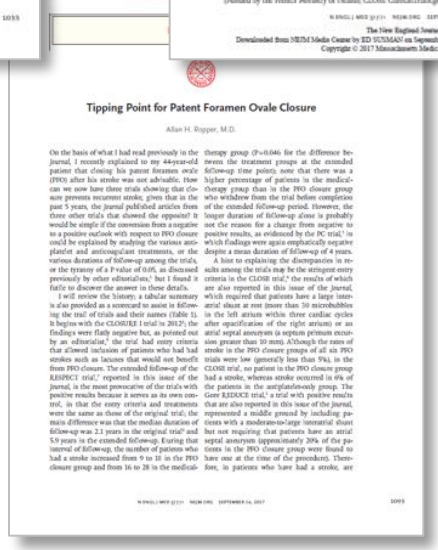


Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

CLOSE

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

Editorial



Tipping Point for Patent Foramen Ovale Closure

*Foramen Ovale Perméable

5/ Fop et AVC : Etudes prospectives contrôlées
2ème partie : NEJM 14 septembre 2017

CLOSE

France – Allemagne
11 prothèses / aag
FOP large ou FOP-ASIA

- 633 patients <60 ans. Age moyen: 43 ans
- Suivi moyen 5.3 ans
- Aag seul (235) : 14 récidives
  Fermeture (238): 0 récidive
  FA transitoires précoces (11)

Positive

RESPECT CLINICAL TRIAL

USA – Canada
Amplatzer/ aag / anticoag
FOP

- 980 patients 18- 60 ans ; m = 46 ans
- Suivi moyen 5.9 ans (jusqu'à 13 ans)
- Diminution 45% récidive AVC

Positive

REDUCE

7 pays
Tous FOP
 / aag

- 414 patients 18 - 60 ans ; m = 45 ans
- Evaluation à 2 ans.
- RR : - 77% mais 6 pb # prothèses
  FA transitoires post op

Positive

RESPECT : points clés

La plus grande étude randomisée

-980 patients dans 69 centres (US et Canada)

-Comparaison au ttt méd de référence (antiagrégants ou anticolagulants)

–Le plus long suivi des patients

- 5 810 années-patient
- Suivi moyen de 5.9 ans

–Excellent profil de sécurité (seulement 2.6% d'évènements indésirables liés au dispositif)

–45% de réduction du risque d'AVC ischémique (p<0.05)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

ABSTRACT

BACKGROUND

Whether closure of a patent foramen ovale reduces the risk of recurrence of ischemic stroke in patients who have had a cryptogenic ischemic stroke is unknown.

METHODS

In a multicenter, randomized, open-label trial, with blinded adjudication of endpoint events, we randomly assigned patients 18 to 60 years of age who had a patent foramen ovale (PFO) and had had a cryptogenic ischemic stroke to undergo closure of the PFO (PFO closure group) or to receive medical therapy alone (aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole; medical-therapy group). The primary efficacy end point was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization. The results of the analysis of the primary outcome from the original trial period have been reported previously; the current analysis of data from the extended follow-up period was considered to be exploratory.

RESULTS

We enrolled 980 patients (mean age, 45.9 years) at 69 sites. Patients were followed for a median of 5.9 years. Treatment exposure in the two groups was unequal (3141 patient-years in the PFO closure group vs. 2669 patient-years in the medical-therapy group), owing to a higher dropout rate in the medical-therapy group. In the intention-to-treat population, recurrent ischemic stroke occurred in 18 patients in the PFO closure group and in 28 patients in the medical-therapy group, resulting in rates of 0.58 events per 100 patient-years and 1.07 events per 100 patient-years, respectively (hazard ratio with PFO closure vs. medical therapy, 0.55; 95% confidence interval [CI], 0.31 to 0.99; P=0.046 by the log-rank test). Recurrent ischemic stroke of undetermined cause occurred in 10 patients in the PFO closure group and in 23 patients in the medical-therapy group (hazard ratio, 0.38; 95% CI, 0.18 to 0.79; P=0.007). Venous thromboembolism (which comprised events of pulmonary embolism and deep-vein thrombosis) was more common in the PFO closure group than in the medical-therapy group.

CONCLUSIONS

Among adults who had had a cryptogenic ischemic stroke, closure of a PFO was associated with a lower rate of recurrent ischemic strokes than medical therapy alone during extended follow-up. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)

From the University of California, Los Angeles (UCLA), Ronald Reagan UCLA Medical Center, Los Angeles (J.L.S.); University of Colorado, Denver, and University of Colorado Hospital, Aurora (J.D.C.), and South Denver Cardiology, Swedish Medical Center, Littleton (R.W.S.) — all in Colorado; Tufts University, Tufts Medical Center, Boston (D.E.T.); University of Texas, Memorial Hermann Heart and Vascular Institute, Houston (R.W.S.); Medical College of Wisconsin, Milwaukee (D.S.M.); and University of Washington, Seattle (D.L.T.). Address reprint requests to Dr. Saver at UCLA Neurology Department, 710 Westwood Plaza, Los Angeles, CA 90095, or at jsaver@mednet.ucla.edu.

*A complete list of investigators in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2017;377:1022-32.
DOI: 10.1056/NEJMoa1610057

Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med 2017; 377: 1022-32.

RESPECT : Historique de l'étude

RESPECT 2012[1]
Critère primaire

- L'analyse en intention de traiter a montré une **réduction relative de 51%** du risque d'AVC ischémique en faveur de la fermeture de FOP
- L'analyse par protocole a montré une **réduction relative de 63%** du risque d'AVC ischémique en faveur de la fermeture de FOP
- Résultats sur le critère primaire non statistiquement significatifs
- L'analyse sur le critère primaire portait sur tous les types d'AVC ischémiques
- Les AVC cryptogéniques n'étaient pas définis comme critère primaire

RESPECT 2015[2]
Analyse additionnelle

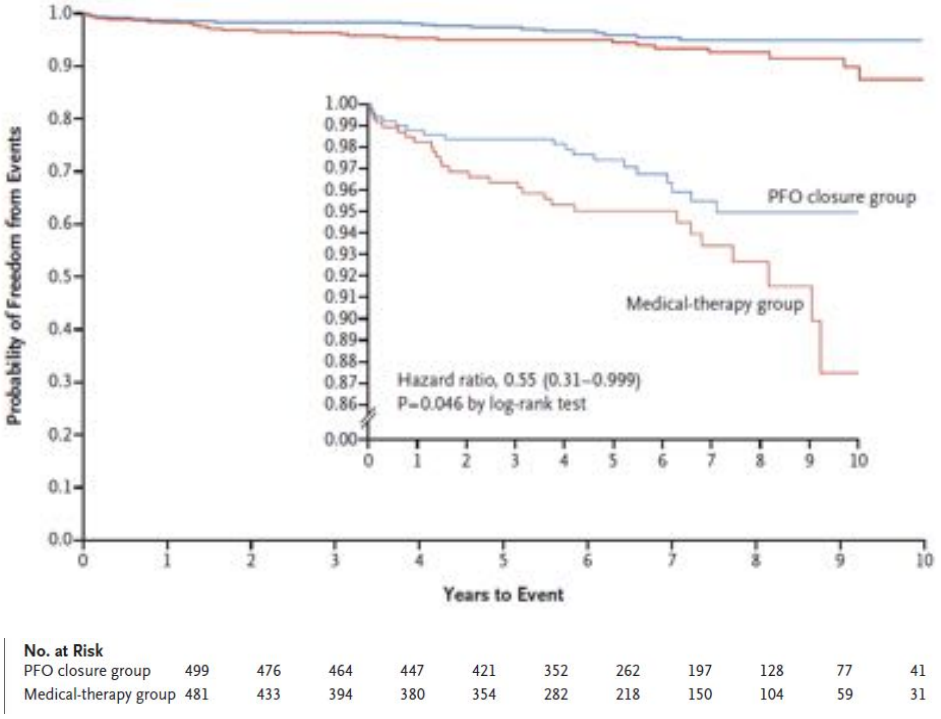
- Données sur le suivi étendu (5 ans en moyenne)
- L'analyse additionnelle en intention de traiter a montré une **réduction relative de 54%** du risque d'AVC cryptogénique en faveur de la fermeture de FOP

RESPECT 2016[3]
Analyse finale

- Analyse demandée par la FDA
- Données de suivi à long terme (5.9 ans en moyenne)
- L'analyse en intention de traiter sur le critère primaire (tous types d'AVC) a montré une **réduction relative statistiquement significative de 45%** du risque d'AVC ischémique en faveur de la fermeture de FOP ($p < 0.05$)
- L'analyse en intention de traiter sur AVC cryptogéniques a montré une **réduction relative statistiquement significative de 62%** du risque d'AVC ischémique en faveur de la fermeture de FOP (p=0,007)

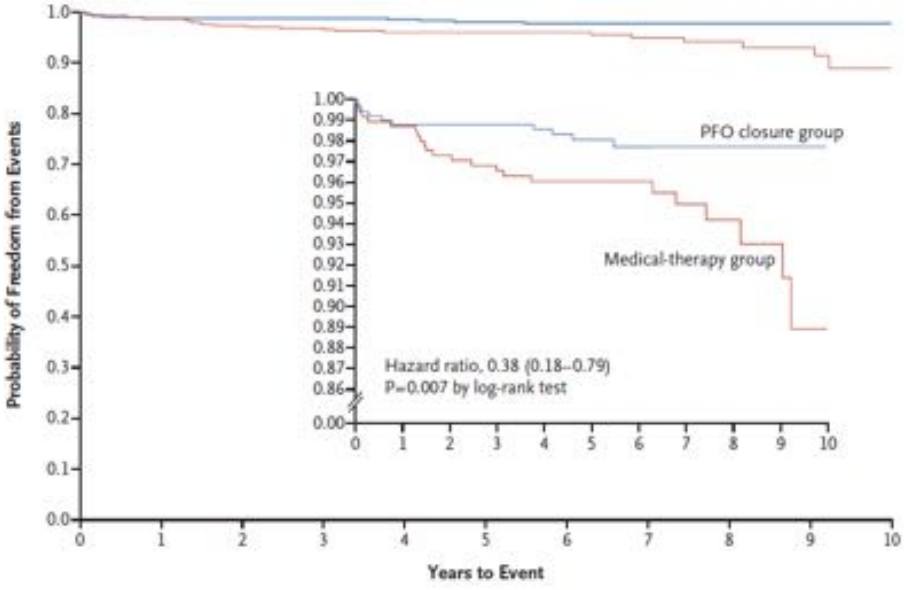
[1]Carroll et al (2013). Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke. *N Engl J Med* 368;12 nejm.1092 org.
[2] Carroll, J. On Behalf of RESPECT Investigators. "RESPECT Extended Follow-up Results", presented at TCT 2015.
[3] Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med 2017; 377: 1022-32

RESPECT : Efficacité sur le critère primaire récidive d'AVC



No. at Risk											
PFO closure group	499	476	464	447	421	352	262	197	128	77	41
Medical-therapy group	481	433	394	380	354	282	218	150	104	59	31

Réduction de 45% du risque de récidive d'AVC ischémique sur 5,9 années de suivi (p<0.05)

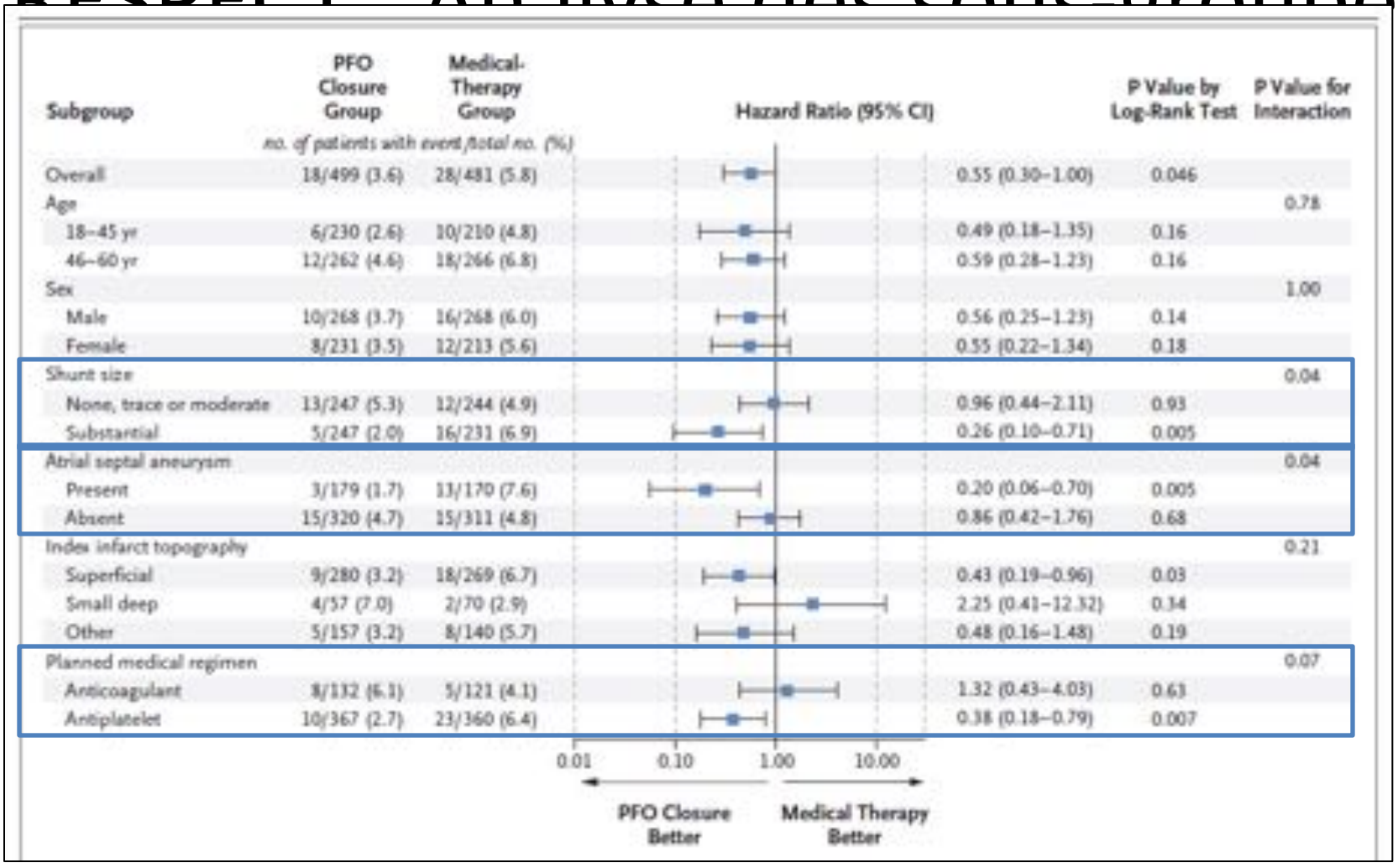


No. at Risk											
PFO closure group	499	476	464	447	421	352	262	197	128	77	41
Medical-therapy group	481	433	394	380	354	282	218	150	104	59	31

Réduction de 62% du risque de récidive d'AVC cryptogénique (p=0.007)

Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med 2017; 377: 1022-32.

RESPECT : Analyse des sous-groupes



Subgroup	PFO Closure Group	Medical-Therapy Group	Hazard Ratio (95% CI)	P Value by Log-Rank Test	P Value for Interaction
	no. of patients with event/total no. (%)				
Overall	18/499 (3.6)	28/481 (5.8)	0.55 (0.30–1.00)	0.046	
Age					0.78
18–45 yr	6/230 (2.6)	10/210 (4.8)	0.49 (0.18–1.35)	0.16	
46–60 yr	12/262 (4.6)	18/266 (6.8)	0.59 (0.28–1.23)	0.16	
Sex					1.00
Male	10/268 (3.7)	16/268 (6.0)	0.56 (0.25–1.23)	0.14	
Female	8/231 (3.5)	12/213 (5.6)	0.55 (0.22–1.34)	0.18	
Shunt size					0.04
None, trace or moderate	13/247 (5.3)	12/244 (4.9)	0.96 (0.44–2.11)	0.93	
Substantial	5/247 (2.0)	16/231 (6.9)	0.26 (0.10–0.71)	0.005	
Atrial septal aneurysm					0.04
Present	3/179 (1.7)	13/170 (7.6)	0.20 (0.06–0.70)	0.005	
Absent	15/320 (4.7)	15/311 (4.8)	0.86 (0.42–1.76)	0.68	
Index infarct topography					0.21
Superficial	9/280 (3.2)	18/269 (6.7)	0.43 (0.19–0.96)	0.03	
Small deep	4/57 (7.0)	2/70 (2.9)	2.25 (0.41–12.32)	0.34	
Other	5/157 (3.2)	8/140 (5.7)	0.48 (0.16–1.48)	0.19	
Planned medical regimen					0.07
Anticoagulant	8/132 (6.1)	5/121 (4.1)	1.32 (0.43–4.03)	0.63	
Antiplatelet	10/367 (2.7)	23/360 (6.4)	0.38 (0.18–0.79)	0.007	

Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med 2017; 377: 1022-32.

REDUCE 664 patients 2/1 (63 centres)

Critère primaire 1 :

77% de réduction relative du risque d'AVC par fermeture de FOP vs AAP

Critère primaire 2:

Incidence des nouveaux infarctus cérébraux significativement plus faible dans le groupe fermeture

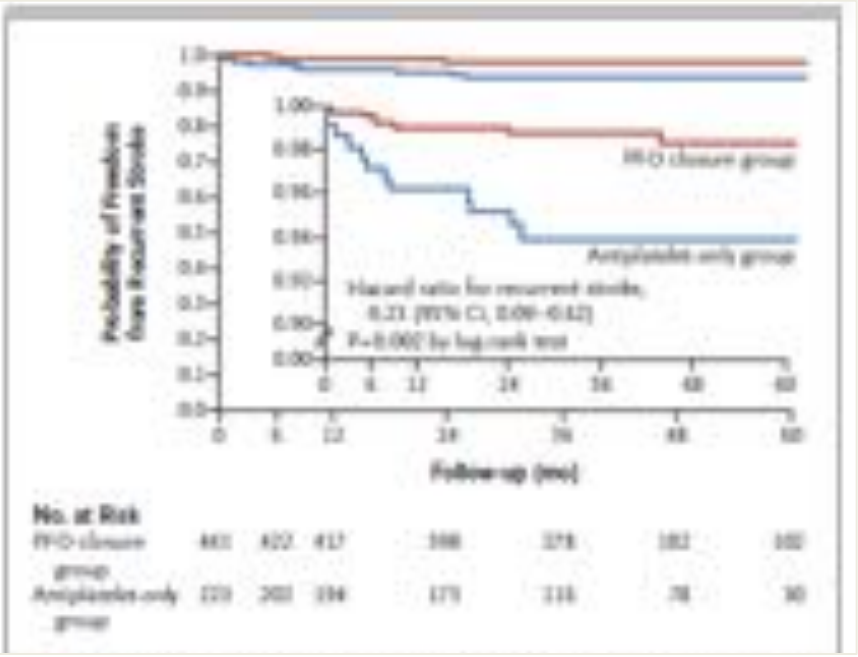


Table 2. Coprimary End Points at Freedom from Clinical Ischemic Stroke and Incidence of New Brain Infarction.*

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¶	22/183 (5.7)	20/177 (11.3)	0.51 (0.29–0.91)‡	0.04**
Recurrent clinical ischemic stroke	5/183 (2.3)	12/177 (6.8)	0.19 (0.07–0.54)‡	0.005**
Silent brain infarction only	17/183 (9.4)	8/177 (4.5)	0.98 (0.43–2.21)‡	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.

- Le nombre de patients à traiter pour éviter un AVC sur 24 mois était d'environ 28 patients

Søndergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med 2017; 377: 1033-42.

REDUCE : Evènements indésirables

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, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med 2017; 377: 1033-42.

CLOSE
Methods

Objective

To assess whether (1) PFO closure with device plus (chronic) antiplatelet therapy on one hand, and (2) oral anticoagulants on the other hand, are superior to antiplatelet therapy, to prevent stroke recurrence in patients 16 to 60 years old with cryptogenic stroke and PFO with atrial septal aneurysm or PFO with large shunt.

Trial design

- Academic-driven, multicenter (32 sites in France and 2 sites in Germany), randomized, open-label, three-arm superiority trial with blinded adjudication of outcome events.
- Funded by the French Ministry of Health.
- 900 patients. 80% power to detect a 50% reduction in the rate of the primary outcome (3.5%/yr in the reference arm) in at least one experimental arm, 5-year study, α=5%.
- 663 patients included from Dec. 2008 to Dec. 2014. Follow-up until Dec. 2015. Mean follow-up 5.3 years (3544 patient-years).

CLOSE
Methods

Key inclusion criteria

- Recent (<= 6 months) ischemic stroke, confirmed by neuroimaging, mRS <= 3
- Strictly defined causes of stroke other than PFO ruled out by appropriate investigations
- PFO with ASA > 10 mm (TTE), PFO with large shunt > 30 microbubbles (TTE,TEE) confirmed by echo core lab before randomization

Key exclusion criteria

- Contraindication to oral anticoagulants and PFO closure
- Contraindication to antiplatelet therapy
- Increased bleeding risk
- Expected poor compliance or inability to attend follow-up visits
- Anatomical to device placement

Outcomes

- **Primary** : fatal or nonfatal stroke
- **Secondary** : composite of ischemic stroke, TIA, or systemic embolism, all-cause mortality, vascular death, success of device implantation and success of PFO closure
- **Safety** : major procedural complications and major hemorrhagic complications

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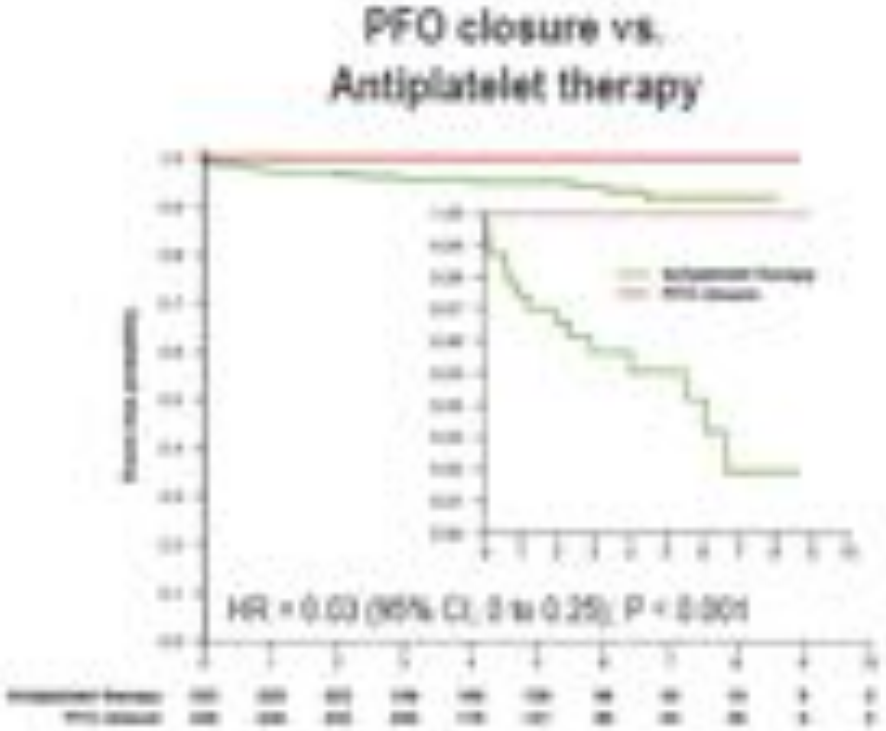
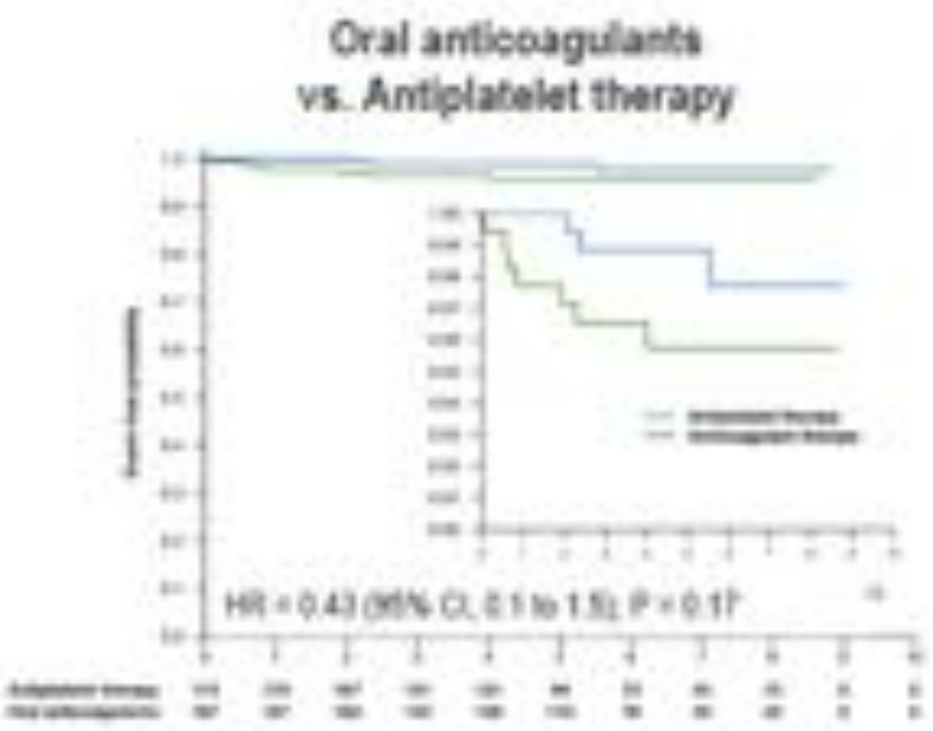




- 1 AVC évité à 5 ans pour 20 patients traités
- **Aucun AVC dans le groupe fermeture** vs 14 dans le groupe AAP

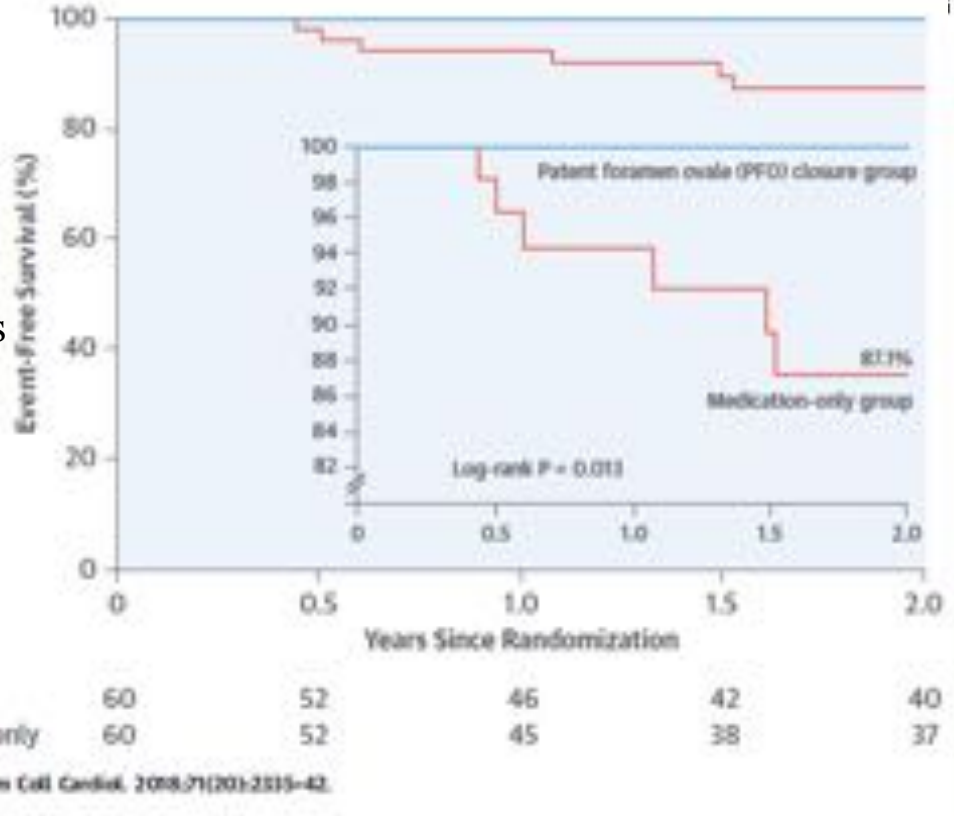
Cryptogenic Stroke and High-Risk Patent Foramen Ovale

The DEFENSE-PFO Trial

Pil Hyung Lee, MD,[a] Jae-Kwan Song, MD, PhD,[a] Jong S. Kim, MD, PhD,[b] Ran Heo, MD,[a] Sahmin Lee, MD,[a] Dae-Hee Kim, MD, PhD,[a] Jong-Min Song, MD, PhD,[a] Duk-Hyun Kang, MD, PhD,[a] Sun U. Kwon, MD, PhD,[b] Dong-Wha Kang, MD, PhD,[b] Dongwhane Lee, MD,[b] Hyuk Sung Kwon, MD,[b] Sung-Cheol Yun, PhD,[c] Byung Joo Sun, MD, PhD,[d] Jae-Hyeong Park, MD, PhD,[d] Jae-Hwan Lee, MD, PhD,[d] Hye Seon Jeong, MD, PhD, Hee-Jung Song, MD, PhD,[e] Jei Kim, MD, PhD,[e] Seung-Jung Park, MD, PhD[a]

JACC mai 2018

AVC
Deces CV
TIMI saignements majeurs



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

ASIA ≥ 15mm
Hypermob ≥10mm
Diam ≥ 2mm

Cryptogenic Stroke and High-Risk Patent Foramen Ovale

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Cryptogenic Stroke and
High-Risk Patent Foramen Ovale
The DEFENSE-PFO Trial

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.

ASIA ≥ 15mm
Hypermob ≥10mm
Diam ≥ 2mm

5/ Fop et AVC : 4 Etudes prospectives contrôlées
BILAN

POSITIVE :

Suivi prolongé

Bonne sélection des patients : **. Âge**

. Cryptogénique

. FOP large shunt ou FOP-ASIA

QUESTIONS EN SUSPENS :

. Petit FOP ?

. Pronostic des FA transitoires post fermetures ?

. Patients > 60 ans ?

. strategie traitement AAP après fermeture ?

…

5/ Fop et AVC : lien de causalité FOP - AVC

RoPE (Risk of Paradoxical Embolism) score

TABLE 1. RoPE SCORE CALCULATOR		
Characteristic	**Points**	**Score**
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age (y)		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥ 70	0	
Total score (sum of individual points)		

Kent DM et al. Neurology 2013

5/ FOP – AVC : score ROPE

Lien de causalité entre FOP et AVC cryptogénique

Total score (sum of individual points)	
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)	10
Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)	0

Kent DM et al. Neurology 2013

5/ FOP – AVC : score ROPE

Score RoPE (Risk of Paradoxical Embolism)

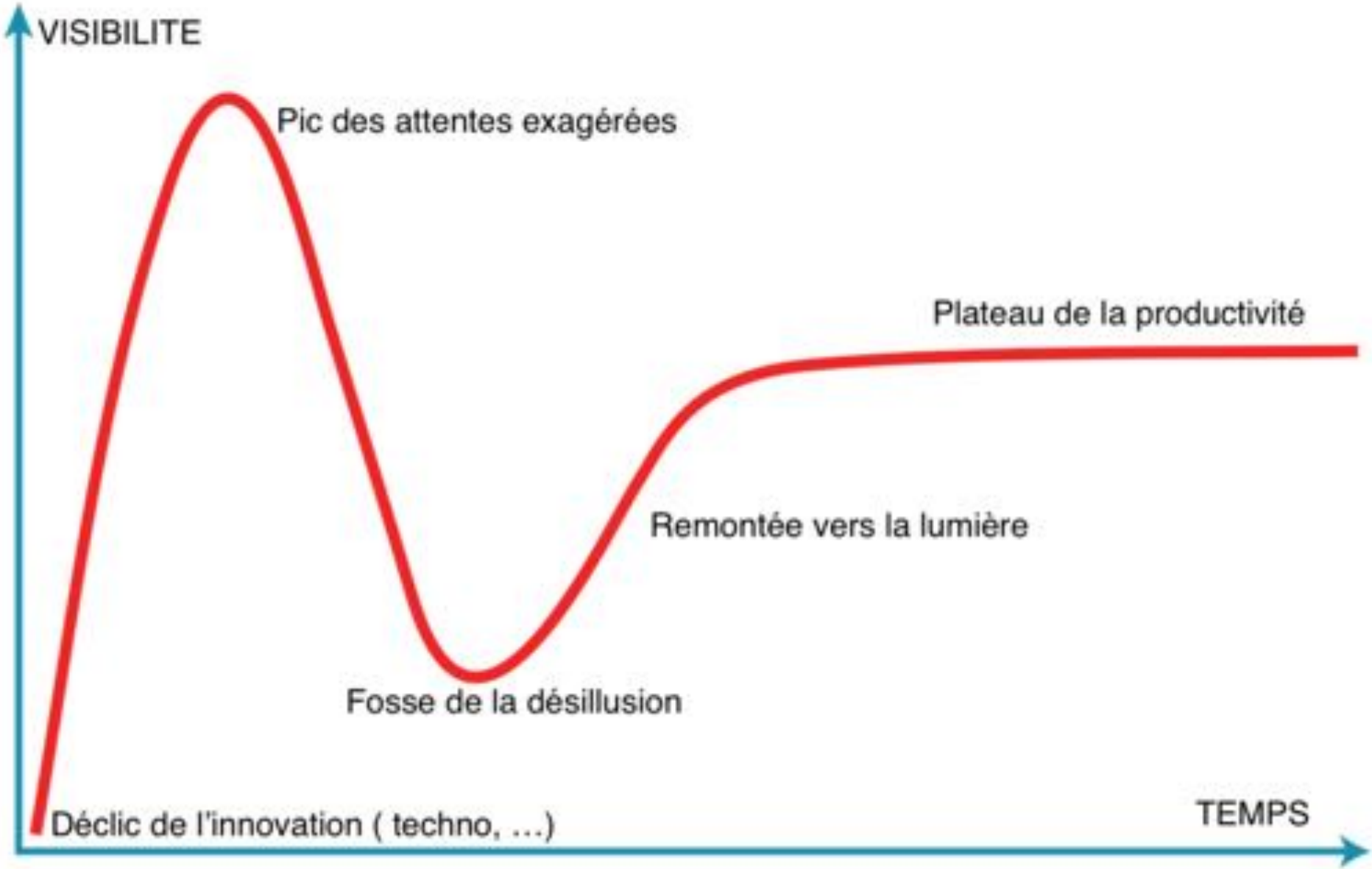
	Cryptogenic stroke (n = 3,023)		
RoPE score	No. of patients	Prevalence of patients with a PFO, % (95% CI)[a]	PFO-attributable fraction, % (95% CI)[a]
0-3	613	23 (19-26)	0 (0-4)
4	511	35 (31-39)	38 (25-48)
5	516	34 (30-38)	34 (21-45)
6	482	47 (42-51)	62 (54-68)
7	434	54 (49-59)	72 (66-76)
8	287	67 (62-73)	84 (79-87)
9-10	180	73 (66-79)	88 (83-91)

Kent DM et al. Neurology 2013

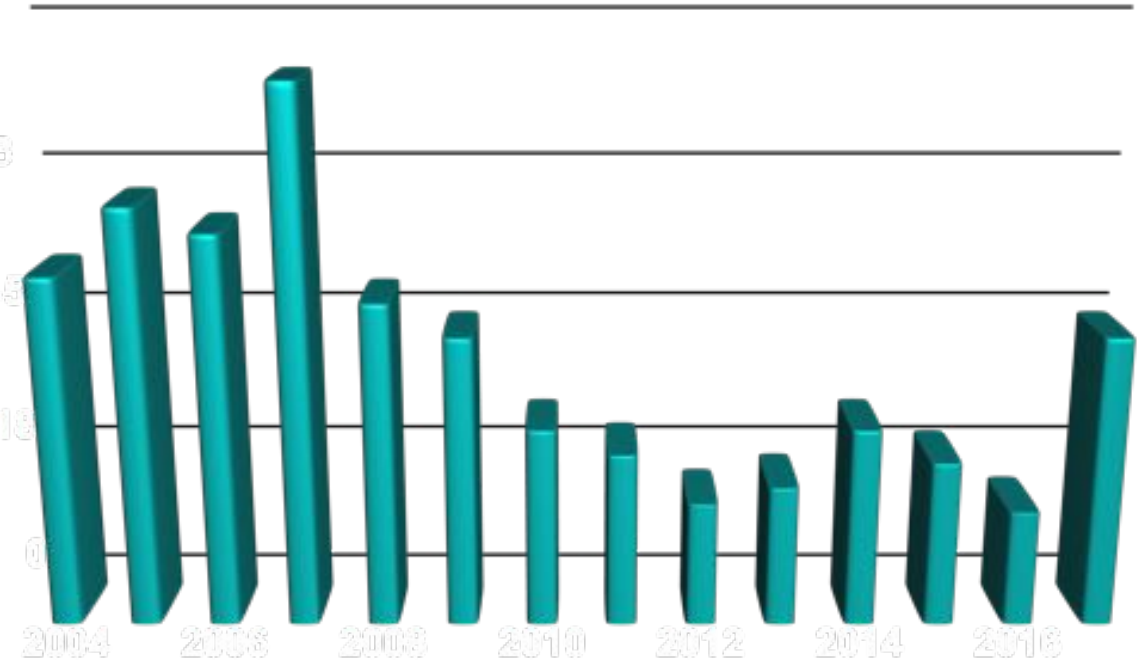
Fermeture FOP
Limites médicales

	Agent	Causalité
▪ AVC	thrombus veineux	Probable(Rope>5)
▪ Accident de décompression	bulles d'azote	probable
▪ Migraine	neuromédiateur	aucune
▪ Syndrome carcinoïde	sérotonine	probable
▪ Hypoxémie	sang veineux	certaine

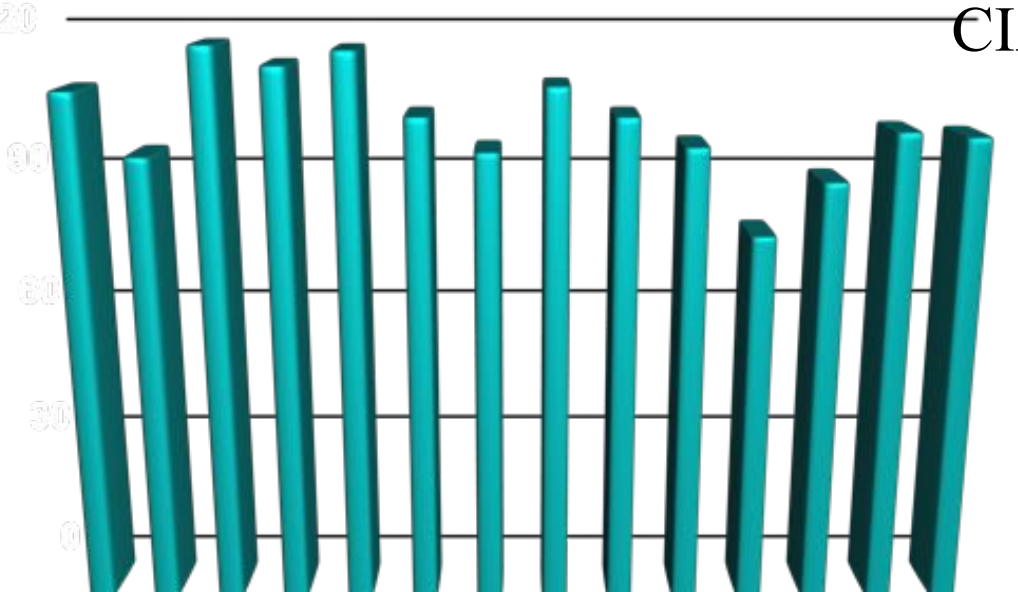
Courbe de Gartner



En pratique => Hôpital Marie Lannelongue



CIA



Fermeture de foramen ovale perméable

Les études

Merci de votre attention

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Philippe Brenot, Jérôme Petit

Hôpital Marie Lannelongue

Biarritz, APPAC, Juin 2018