

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

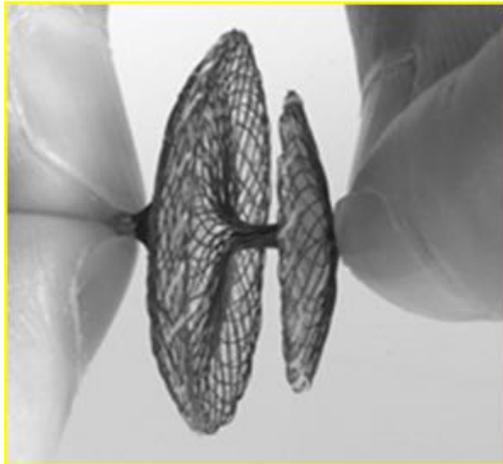
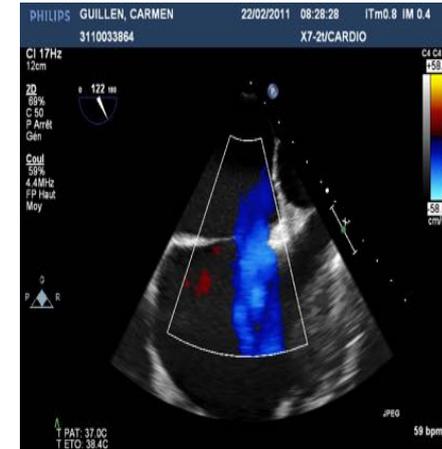
780 000 naissances / an en France

CIA

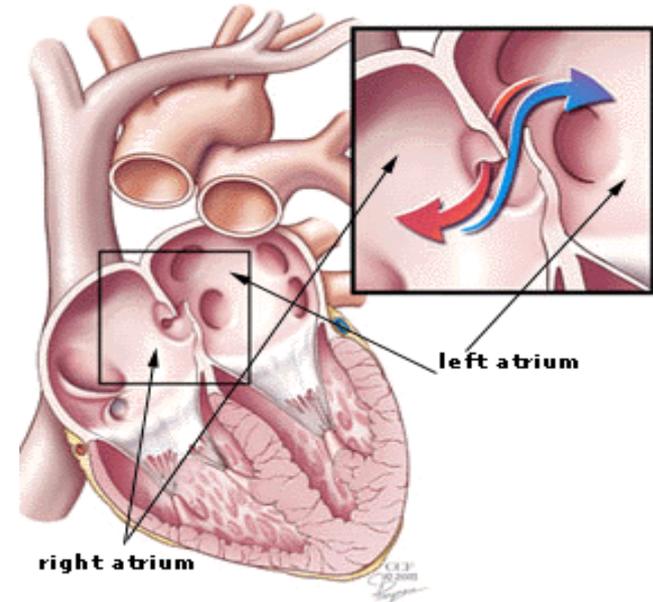
350 - 400 nouveau cas/an

FOP

~ 120 - 200 000 nouveau / an.



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



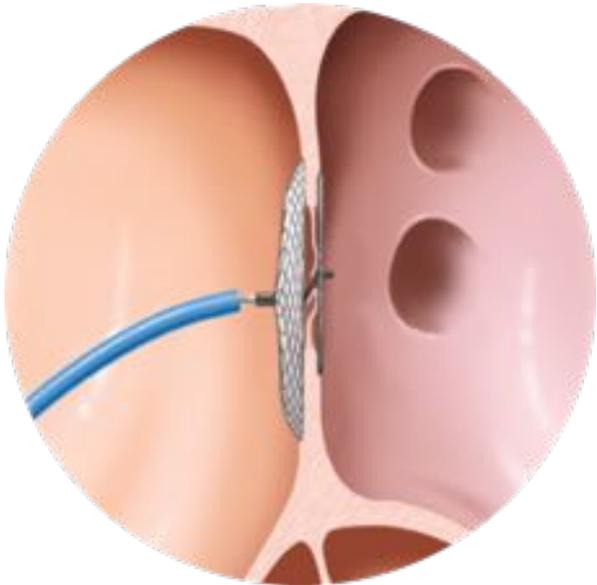
RESPECT : Résultats de la procédure

Succès d'implantation—
Pose de prothèse réussie

99.1%

Succès de la procédure—
Implantation sans évènement indésirable

96.1%



RESPECT : Taux de fermeture à 6 mois

FERMETURE COMPLETE :

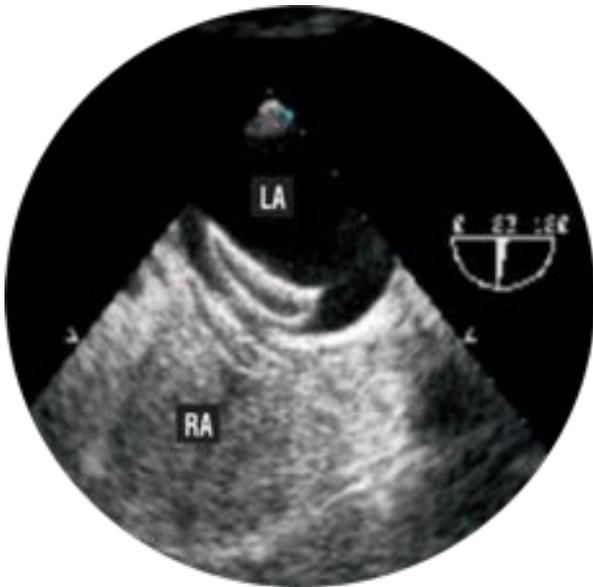
Absence de bulles au repos et en Valsalva

71.3%

FERMETURE EFFECTIVE—

Au plus, 9 Bulles au repos et en Valsalva

94.2%

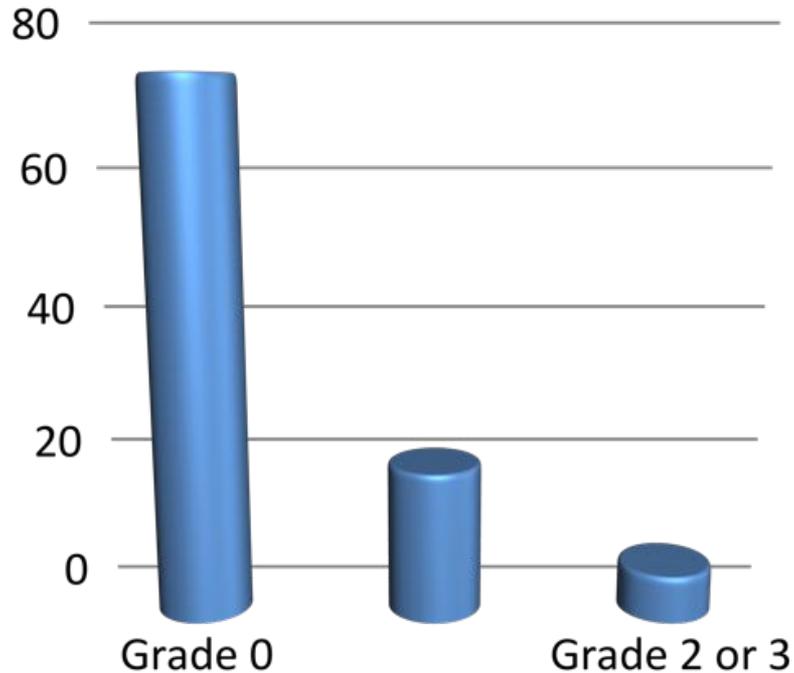


RESPECT : Evènements indésirables liés à la procédure et au dispositif

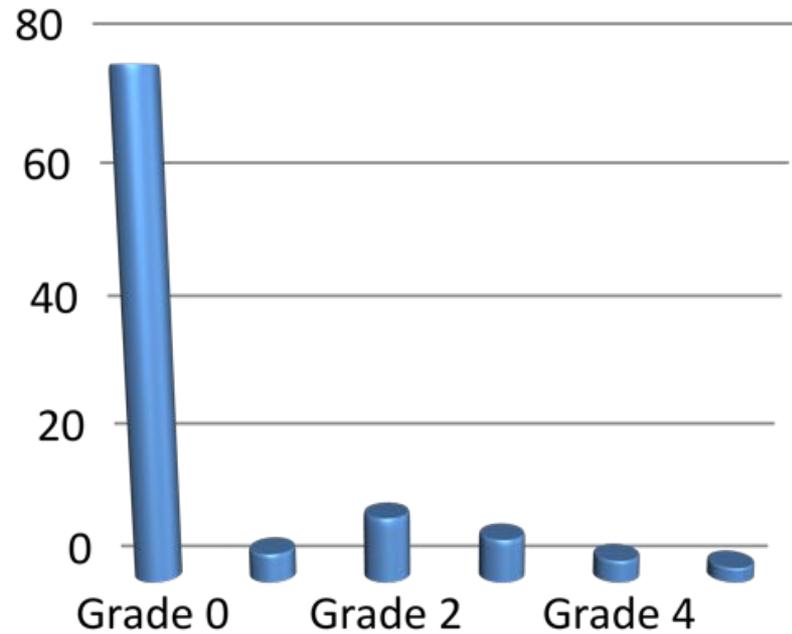
Evènement	Groupe fermeture du FOP (N=499; 3141 pt-yrs)
Nb total (par année-patient)	
Tout types d'évènement indésirable	201 (0.064)
Evènements indésirables liés au dispositif	13 (0.004)
Décès	7 (0.002)
Nb d'évènements (%)	
Evènements indésirables liés au dispositif	13 (2.6%)
– Embolisation de la prothèse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

Shunt résiduel 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)

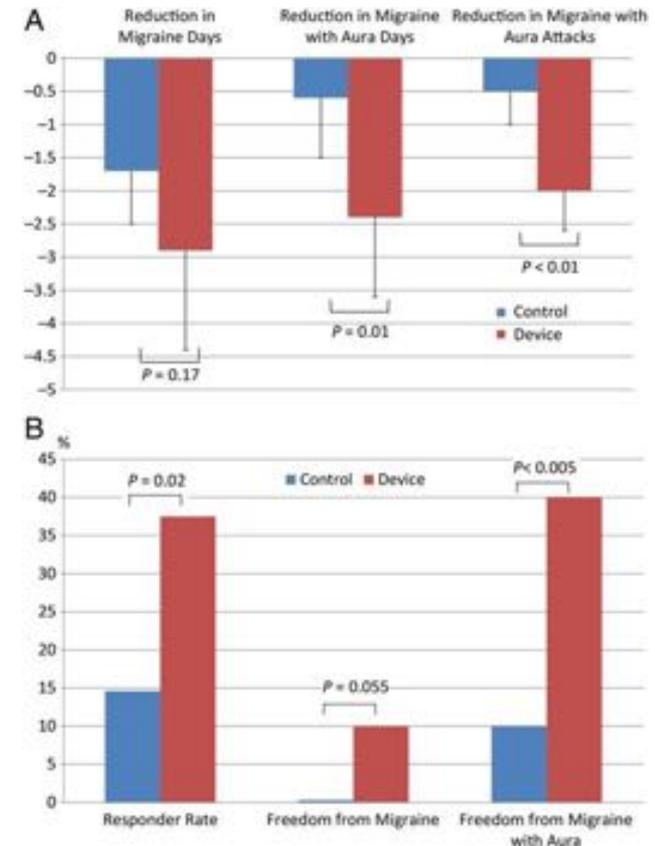
Percutaneous Closure of PFO in Migraine with Aura - **PRIMA** (multicentrique, randomisé)
107 migraineux (avec aura) réfractaire au ttt



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.*



1/ Migraine (# neuromédiateur)

Percutaneous Closure of PFO in Patients with Migraine: the **PREMIUM** trial
(prospectif, multicentrique, randomisé, **double aveugle**)

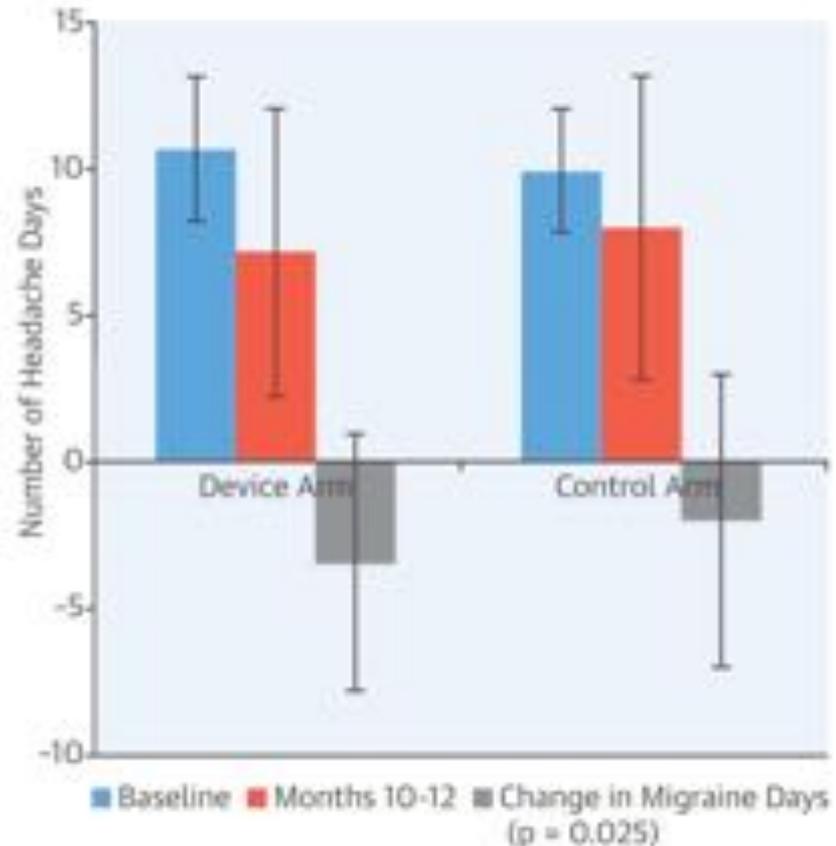
230 migraineux (6-14 jours/mois)
réfractaire au ttt

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)



2/platypnée - orthodéoxie

Fermeture FOP = indication formelle.

CardioVascular
and Interventional
Radiology

© Springer Science+Business Media, Inc. 2005
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. Losay²

Impact of patent foramen ovale closure in patients with platypnea-orthodeoxia syndrome.

MARCOET S.,¹ EBERT F.,² GALABRE M.,³ CARRIE O.,⁴ FREYCOQ D.,⁵ TRITU L.,⁶ VERNEJOUX J.M.,⁷ FRANCOIS M.,⁸ RONCALLI J.,⁹ BERRY M.,¹ MASSABEAU P.,¹ ROUSSET F.,¹ ANDREU T.,⁸ ROSSI R.,¹ ELBAZ M.,[†]

¹ Department of Pediatric Cardiology, Hôpital des enfants, Toulouse, France; ² Department of Cardiology, Rangueil Hospital, CHU Toulouse, France; ³ Department of Pneumology, Larrey Hospital, CHU Toulouse, France; ⁴ Department of Pneumology, Clinique du Pied de Cochon, Montauban, France; ⁵ Department of Radiology, Rangueil Hospital, CHU Toulouse, France; ⁶ Department of Cardiology, CHU Lyon, France

Introduction

Platypnea-orthodeoxia syndrome (POS) is a rare condition with right to left shunt through a Patent Foramen Ovale (PFO) at rest (PFO) that results in oxygen desaturation during postural changes. Few series are available on the functional status after PFO closure.[†]

The aim of our study was to describe the impact of long term of PFO closure in patients with POS.

Results

At baseline, all patients had dyspnea (56.3% NYHA I); Eight patients (33.3%) had a history of stroke attack. Suspected anatomic peculiarities leading to POS were: right pneumothorax in 3 patients (12.5%), ascending aortic ectasy in 11 patients (43.8%), right diaphragmatic crus elevation caused by hepatic renal polycystic disease in 2 patients (8.3%).

Analysis of the inter-atrial septum was observed in 12 patients (20%).

Pat22 measurements confirmed POS. Pat22 was lower in erect position compared to decubent position (30.4±8.8 mmHg vs 24.1±12.5 mmHg, p=0.005).

Closure of the PFO was performed percutaneously in 24 patients (100%); an additional surgical PFO closure was necessary in 1 patient because of significant residual shunting. Pat22 in erect position was significantly increased after closure (30.5±20%).

During follow-up 4 patients (16.7%, n=125) had a complete relief of their symptoms after closure. Dyspnea was significantly improved according to NYHA functional class (p=0.023). General status improved in 71% patients (p=0.025).

Eight patients died during follow up (33.3%). Four deaths (50%) were related to stroke attacks at respectively 18 days, 3, 11 and 39 months after PFO closure. Four deaths were not related to cardiac cause.

Discussion and conclusion

Patients with symptoms related to POS are relatively old and women at high risk of mortality, particularly from stroke attacks.

Pericardial PFO closure in this peculiar syndrome is associated with an improvement of the functional NYHA class and of the general status. Although PFO closure indicates remaining under anticoagulation for cryptogenic systemic thromboembolism[†] in POS our study provide further evidence that PFO closure is beneficial.

Our study also suggests that aortic ascending ectasy is a frequent anatomic condition associated to POS through a PFO.

These patients seem to remain at high risk of stroke after procedure. It could be interesting to find genetic or favoring stroke factor to adapt anticoagulant treatment embolism drug after procedure.

References

1. Guérin P. Cardiovasc Intervent Radiol 2005; 28:1-5. doi: 10.1007/s00270-004-0035-3.
2. Guérin P. et al. Heart failure with orthodeoxia: the case for right to left shunt. Chest 2002; 122:1010-1014.
3. Guérin P. et al. J Am Coll Cardiol 1997; 30:214-219.

JESFC 2013
N=24

3/syndrome carcinoïde (# sérotonine)

Constatations:

- Fréquence PFO + importante ($\sim X 2$ / pop générale)
- La fermeture du PFO réduit les symptômes.

Fermeture du FOP peut être intéressante en traitement complémentaire.

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?

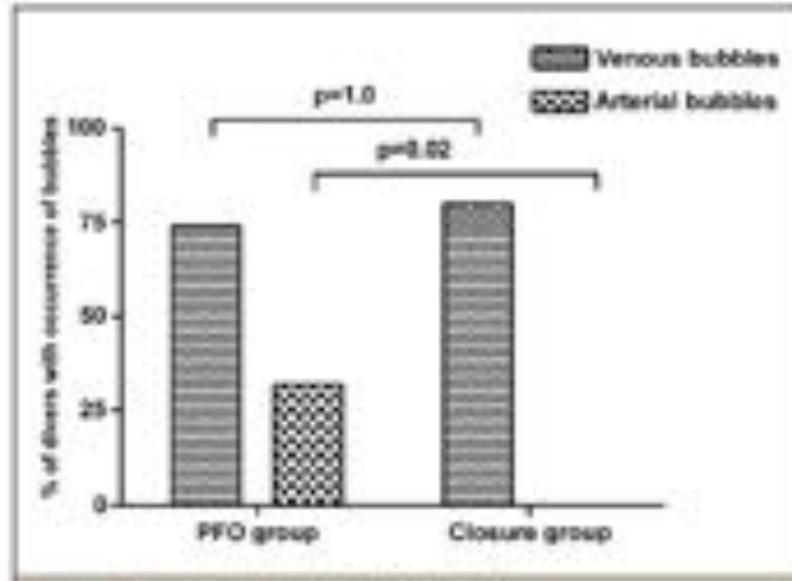
J.-E. Blatteau

Service de médecine hyperbare et d'expertise plongée, Hôpital d'Instruction des armées Sainte-Anne, BP600, 83800 Toulon cedex 3, France

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

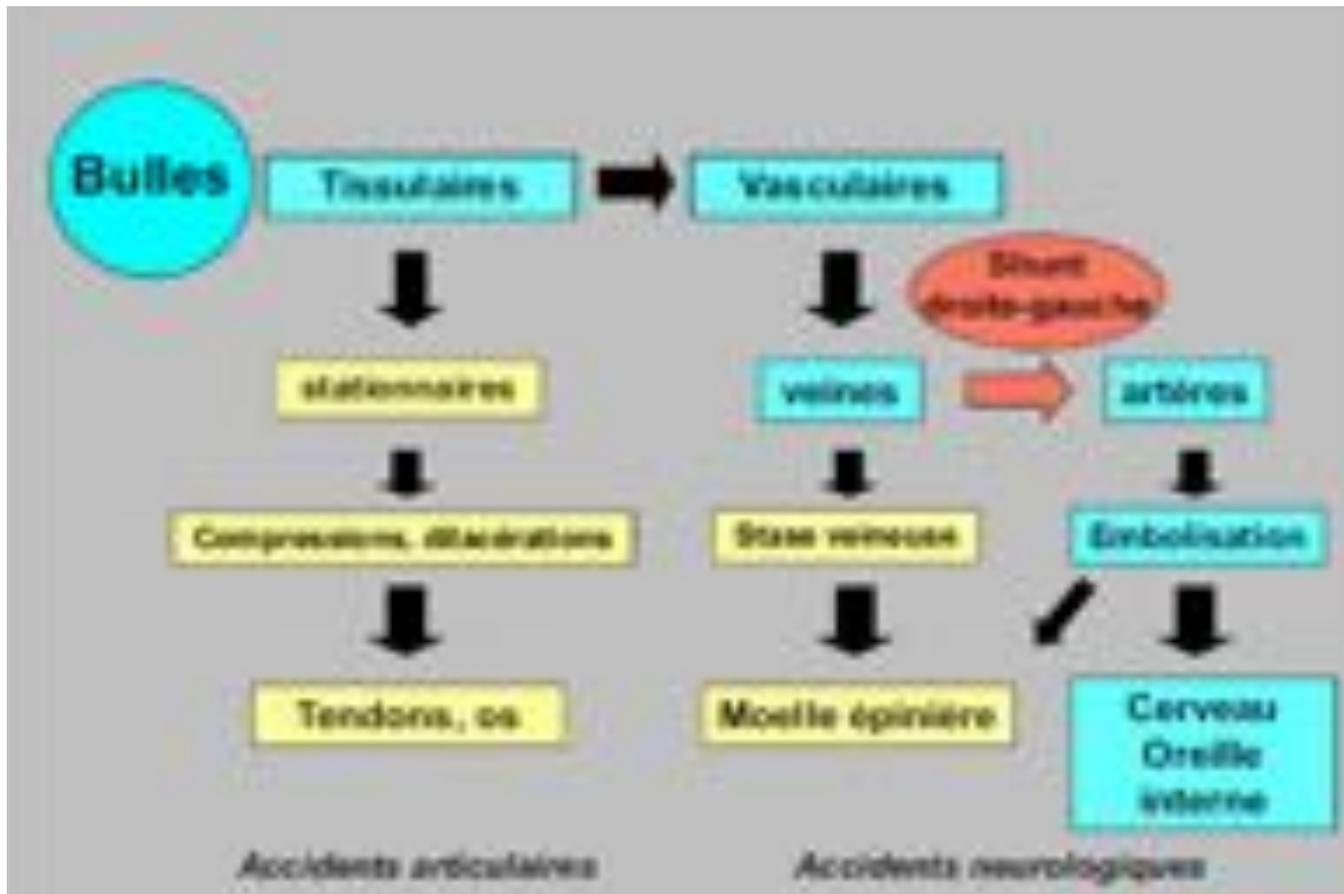
- Bulles artérielles absentes si Fermeture FOP versus FOP ouvert



JACC CI 2014

4/ Fop et plongée : accidents de décompression

Accidents de décompression (ADD)



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 %)

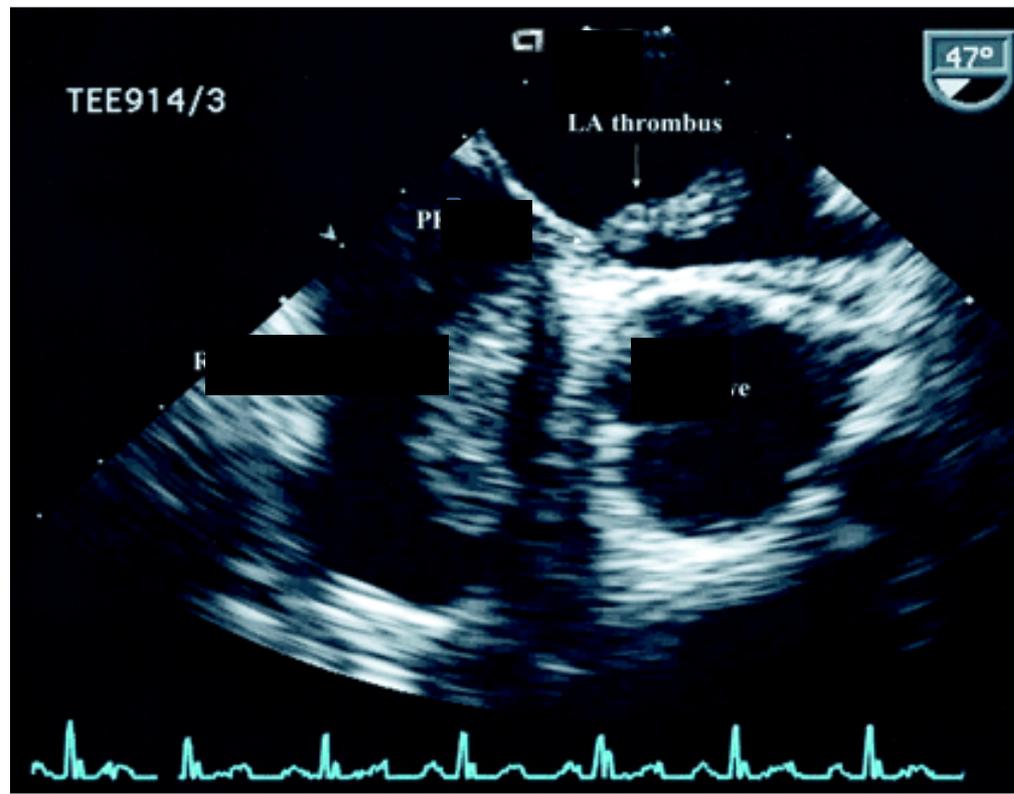
.Quand l'AVC est cryptogénique :

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



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

étude européenne prospective multicentrique (30 services).

- Récurrences d'AVC (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.*

5/ Fop et AVC : Etudes prospectives contrôlées

1ère partie



N Engl J Med 2012

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

négative



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



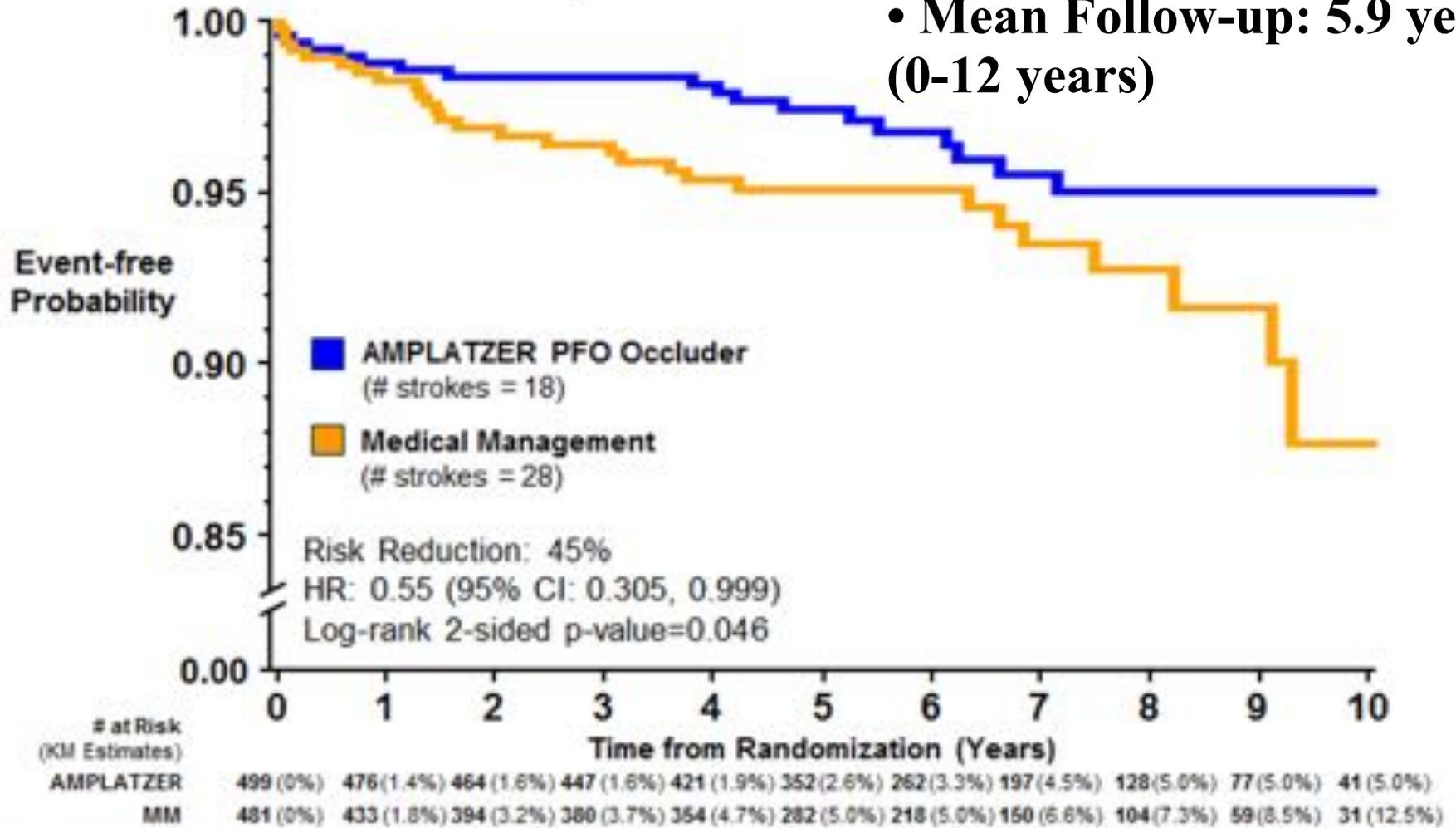
Suivi moyen : 2.6 ± 2.0 ans (0 to 8.1 ans)

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%

RESPECT Final Results

*Freedom from Recurrent Ischemic Stroke
(Intention to Treat)*

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



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

RESPECT

REDUCE

CLOSE

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. Carmel, M.D., David S. Bruck, D.D., Ph.D., Richard W. Souders, M.D., Ph.D., Jane A. MacDermott, M.D., David S. Mittleman, M.D., and David J. Fairhead, M.D., for the RESPECT Investigators*

ABSTRACT

BACKGROUND

Patent closure of a patent foramen ovale reduces the risk of recurrence of ischemic stroke in patients who have had a cryptogenic ischemic stroke, a substudy.

DESIGN

In a multicenter, randomized, open-label trial, with blinded adjudication of end-point 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 (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 primary outcome from the original trial 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, 45.0 years) at 30 sites. Patients were followed for a median of 5.0 years. Treatment exposure in the two groups was equal (340 patient-years in the PFO closure group vs. 350 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 0.77 events per 100 patient-years, respectively (hazard ratio with PFO closure vs. medical therapy, 0.75; 95% confidence interval [CI], 0.31 to 1.83; *P* = 0.59). For the by-lesion rate, recurrent ischemic stroke of undetermined cause occurred in 20 patients in the PFO closure group and in 23 patients in the medical-therapy group (hazard ratio, 0.36; 95% CI, 0.18 to 0.70; *P* = 0.003). Worse thromboembolic events comprised more of poststroke morbidity and mortality 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 stroke than medical therapy alone during extended follow-up. (Funded by the French Ministry of Health.)

RESPECT ClinicalTrials.gov number, NCT01040237.

Dr. Saver will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Carmel will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Bruck will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Souders will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. MacDermott will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Mittleman will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Fairhead will have full access to all of the data and will have final approval of all versions of the manuscript.

Dr. Saver will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Carmel will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Bruck will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Souders will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. MacDermott will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Mittleman will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Fairhead will have full access to all of the data and will have final approval of all versions of the manuscript.

Commentaire

Il est apparu que la fermeture de l'orifice ovale patent (FOP) par voie percutanée (PVP) est associée à une réduction du risque de récurrence d'un AVC ischémique cryptogène chez les patients atteints d'un FOP. Cette réduction a été observée dans une étude randomisée contrôlée à court terme (1). Cependant, les données à long terme sont limitées. L'étude RESPECT (2) a évalué les résultats à long terme de la PVP par rapport à une thérapie médicale chez les patients atteints d'un FOP et d'un AVC ischémique cryptogène. Les résultats de cette étude ont été présentés à la conférence de consensus de la Société américaine d'angiologie et de médecine vasculaire (SAHA) en octobre 2016. Les données de cette étude ont été présentées à la conférence de consensus de la SAHA en octobre 2016. Les données de cette étude ont été présentées à la conférence de consensus de la SAHA en octobre 2016.

*Foramen Ovale Perméable

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Sandberg, M.D., Scott E. Kanner, M.D., John F. Rhodes, M.D., Gertre Anderson, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens I. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Serrhini, M.D., Ph.D., Christina Kyriakou, M.D., Ph.D., Risto O. Sillanpaa, M.D., David Hildick-Smith, M.D., D. David Spencer, M.D., and Lars Thomassen, M.D., for the GORE REDUCE Clinical Study Investigators*

ABSTRACT

BACKGROUND

The efficacy of closure of a patent foramen ovale (PFO) in the prevention of recurrent stroke after cryptogenic stroke is uncertain. We investigated the effect of PFO closure combined with aspirin/platelet therapy versus aspirin/platelet therapy alone on the risks of recurrent stroke and new brain infarctions.

DESIGN

In this multicenter trial involving patients with a PFO who had had a cryptogenic stroke, we randomly assigned patients to a 2:1 ratio, to undergo PFO closure plus aspirin/platelet therapy (PFO closure group) or to receive aspirin/platelet therapy alone (antiplatelet group). Imaging of the brain was performed at the baseline screening and at 24 months. The primary end point was freedom from clinical evidence of ischemic stroke (reported here as the percentage of patients who had a recurrence of stroke) through at least 24 months after randomization and the 24-month incidence of new brain infarction, which was a composite of clinical ischemic stroke or silent brain infarction detected on imaging.

RESULTS

We enrolled 664 patients (mean age, 45.2 years), of whom 17% had moderate or large interatrial shunts. During a median follow-up of 3.2 years, clinical ischemic stroke occurred in 6 of 441 patients (1.4%) in the PFO closure group and in 12 of 223 patients (5.4%) in the antiplatelet group (hazard ratio, 0.28; 95% confidence interval [CI], 0.09 to 0.82; *P* = 0.002). The incidence of new brain infarction was significantly lower in the PFO closure group than in the antiplatelet group (23 patients [5.2%] vs. 20 patients [9.1%]; hazard ratio, 0.55; 95% CI, 0.29 to 1.00; *P* = 0.048), but the incidence of silent brain infarction did not differ significantly between the study groups (*P* = 0.97). Serious adverse events occurred in 25.1% of the patients in the PFO closure group and in 27.4% of the patients in the antiplatelet group (FISH-22). Serious discontinuation adverse events occurred in 6 patients (1.4%) in the PFO closure group, and atrial fibrillation occurred in 29 patients (6.6%) after PFO closure.

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 aspirin/platelet therapy than among those assigned to aspirin/platelet therapy alone. However, PFO closure was associated with higher rates of device complications and atrial fibrillation. (Funded by W.L. Gore and Associates; Gene Research Clinical Study Center; NCT01071004.)

REDUCE ClinicalTrials.gov number, NCT01071004.

Downloaded from NEJM Media Center by ED USTADIA on September 1, 2017. Evidence listed September 13, 2017 at IP: 87.107.107.107.

Copyright © 2017 Massachusetts Medical Society. All rights reserved.

Dr. Sandberg will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Kanner will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Rhodes will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Anderson will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Iversen will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Nielsen-Kudsk will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Serrhini will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Kyriakou will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Sillanpaa will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Hildick-Smith will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Spencer will have full access to all of the data and will have final approval of all versions of the manuscript. Dr. Thomassen will have full access to all of the data and will have final approval of all versions of the manuscript.

Editorial

On the basis of what I had read previously in the Journal, I recently realized that we do have a patient foramen ovale (PFO) who has had a cryptogenic stroke and who has had a PFO closure. This patient was enrolled in the REDUCE trial, a multicenter, randomized, open-label trial comparing PFO closure with aspirin/platelet therapy versus aspirin/platelet therapy alone in patients with a PFO and a cryptogenic stroke. The results of this trial were reported in the Journal in August 2017. The results of this trial were reported in the Journal in August 2017. The results of this trial were reported in the Journal in August 2017.

Downloaded from NEJM Media Center by ED USTADIA on September 1, 2017. Evidence listed September 13, 2017 at IP: 87.107.107.107.

THE NEW ENGLAND JOURNAL OF MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 14, 2017 VOL. 377, NO. 37

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

J.-L. Mas, G. Durieux, B. Gullon, E. Maseras, H. Hossain, L. Mechtouff, C. Arizgon, Y. Béjot, F. Veillet, O. Cantan, C. Guisou, S. Canale, P. Valosa, N. Douque-Pouchelle, I. Sloan, P. Gerner, A. Ferrer, S. Trillat, E. Rivolin-Borghomani, D. Saba, J.-C. Lacomme, M. Zuber, P. Fauriol, J.-P. Poin, M. Aguil, P. Bremer, C. Lefebvre, P. Godec, C. Pisk, B. Riou, J.-L. Dubois-Randé, J.-C. Fisher, N. Monneron, J.-B. Lussier, B. Borhani, J.-M. Schriock, F. Godart, J.-B. Thambou, L. Laroque, P. Michel, L. Plazard, G. Turc, M. Barthelot, A. Charles-Nelson, C. Weimar, T. Mounin, J.-M. Juhan, and G. Chabrier, for the CLOSE Investigators*

ABSTRACT

BACKGROUND

Stroke patients with patent foramen ovale (PFO) closure to prevent recurrent stroke have been inconclusive. We investigated whether patients with cryptogenic stroke and echocardiographic features suggesting a high risk of stroke would benefit from PFO closure or anticoagulation, as compared with antiplatelet therapy.

DESIGN

In a multicenter, randomized, open-label trial, we assigned, in a 1:1:1 ratio, patients to 60 years of age who had had a recent stroke attributed to PFO, with an associated atrial septal aneurysm or large interatrial shunt, to transcatheter PFO closure plus aspirin/platelet therapy (PFO closure group), antiplatelet therapy alone (antiplatelet group), or aspirin/platelet therapy plus anticoagulation (anticoagulation group). Patients with contraindications to anticoagulation or to PFO closure were randomly assigned to the alternative nonconcomitant treatment or to aspirin/platelet therapy (randomization groups 2 and 3). The primary end point was occurrence of stroke. The comparison of PFO closure plus aspirin/platelet therapy with aspirin/platelet therapy alone was performed with combined data from randomization groups 1 and 2, and the comparison of oral anticoagulation with aspirin/platelet therapy alone was performed with combined data from randomization groups 1 and 3.

RESULTS

A total of 967 patients underwent randomization and were followed for a mean (SD) of 3.1 (2.6) years. In the analysis of randomization groups 1 and 2, no stroke occurred among the 238 patients in the PFO closure group, whereas stroke occurred in 34 of the 238 patients in the antiplatelet group (hazard ratio, 0.05; 95% confidence interval [CI], 0.01 to 0.26; *P* = 0.001). Poststroke complications from PFO closure occurred in 34 patients (9.6%). The rate of atrial fibrillation was higher in the PFO closure group than in the antiplatelet group (4.6% vs. 10.9%, *P* = 0.002). The number of serious adverse events did not differ significantly between the treatment groups. In the analysis of randomization groups 1 and 2, stroke occurred in 17 of 234 patients assigned to oral anticoagulation and in 7 of 234 patients assigned to aspirin/platelet therapy.

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 aspirin/platelet therapy than among those assigned to aspirin/platelet therapy alone. PFO closure was associated with increased risk of atrial fibrillation. (Funded by the French Ministry of Health; CLOSE ClinicalTrials.gov number, NCT01092203.)

REDUCE ClinicalTrials.gov number, NCT01092203.

Downloaded from NEJM Media Center by ED USTADIA on September 1, 2017. Evidence listed September 13, 2017 at IP: 87.107.107.107.

Copyright © 2017 Massachusetts Medical Society. All rights reserved.

Tiping Point for Patent Foramen Ovale Closure

Alan H. Roger, M.D.

On the basis of what I had read previously in the Journal, I recently realized that we do have a patient foramen ovale (PFO) who has had a cryptogenic stroke and who has had a PFO closure. This patient was enrolled in the REDUCE trial, a multicenter, randomized, open-label trial comparing PFO closure with aspirin/platelet therapy versus aspirin/platelet therapy alone in patients with a PFO and a cryptogenic stroke. The results of this trial were reported in the Journal in August 2017. The results of this trial were reported in the Journal in August 2017. The results of this trial were reported in the Journal in August 2017.

On the basis of what I had read previously in the Journal, I recently realized that we do have a patient foramen ovale (PFO) who has had a cryptogenic stroke and who has had a PFO closure. This patient was enrolled in the REDUCE trial, a multicenter, randomized, open-label trial comparing PFO closure with aspirin/platelet therapy versus aspirin/platelet therapy alone in patients with a PFO and a cryptogenic stroke. The results of this trial were reported in the Journal in August 2017. The results of this trial were reported in the Journal in August 2017. The results of this trial were reported in the Journal in August 2017.

Downloaded from NEJM Media Center by ED USTADIA on September 1, 2017. Evidence listed September 13, 2017 at IP: 87.107.107.107.

5/ Fop et AVC : Etudes prospectives contrôlées

2^{ème} 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 récurrences
- Fermeture (238): 0 récurrence
- 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% récurrence 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 ($p < 0.05$)



RESPECT : Historique de l'étude



RESPECT 2012¹ *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 2015² *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 2016³ *Analyse finale*

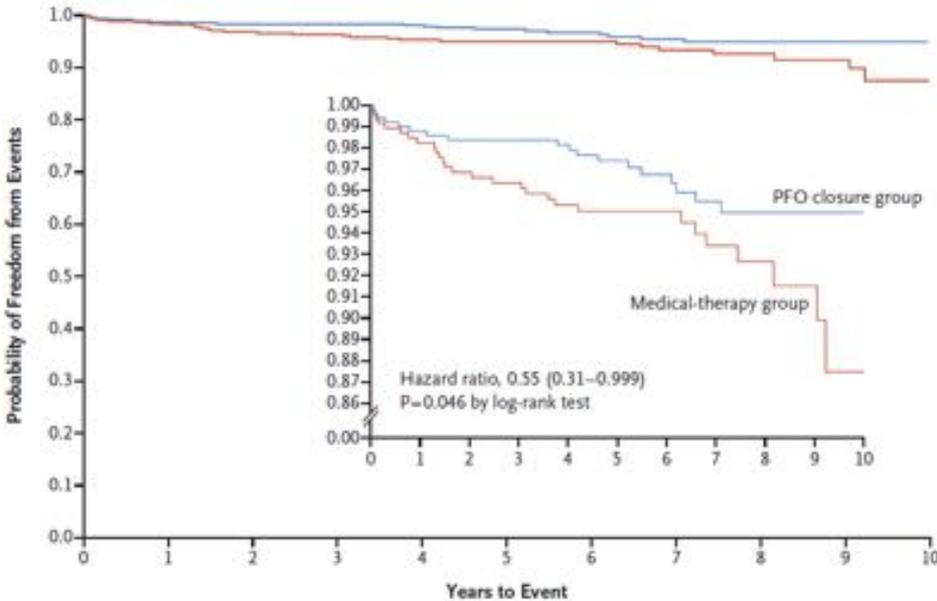
- Analyse demandée par la FDA
-
- Données de suivi à long terme (5.9 ans en moyenne)
-
- L'analyse en intention de traiter sur le critère primaire (tous types d'AVC) a montré une **réduction relative statistiquement significative de 45%** du risque d'AVC ischémique en faveur de la fermeture de FOP ($p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

¹Carroll 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.

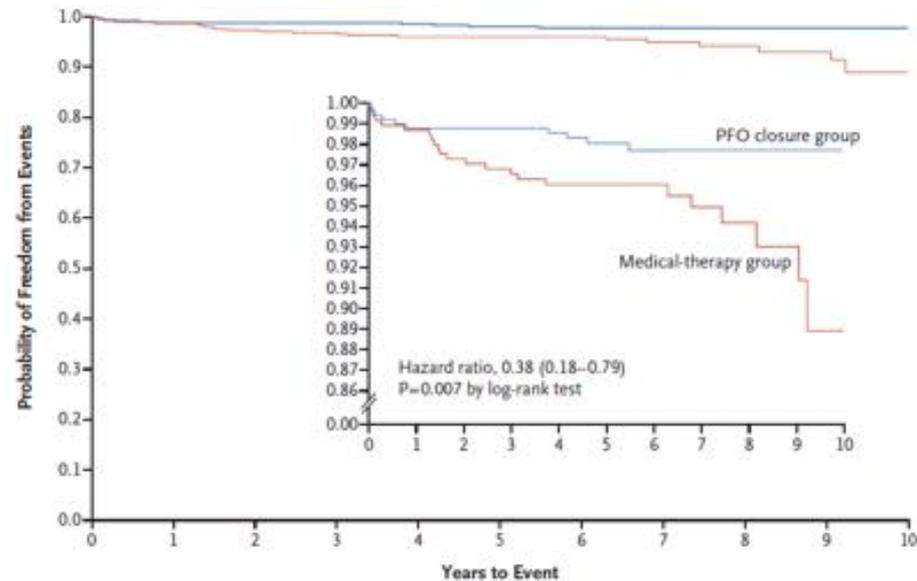
³ Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017; 377: 1022-32

RESPECT : Efficacité sur le critère primaire récidive d'AVC



No. at Risk	0	1	2	3	4	5	6	7	8	9	10
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

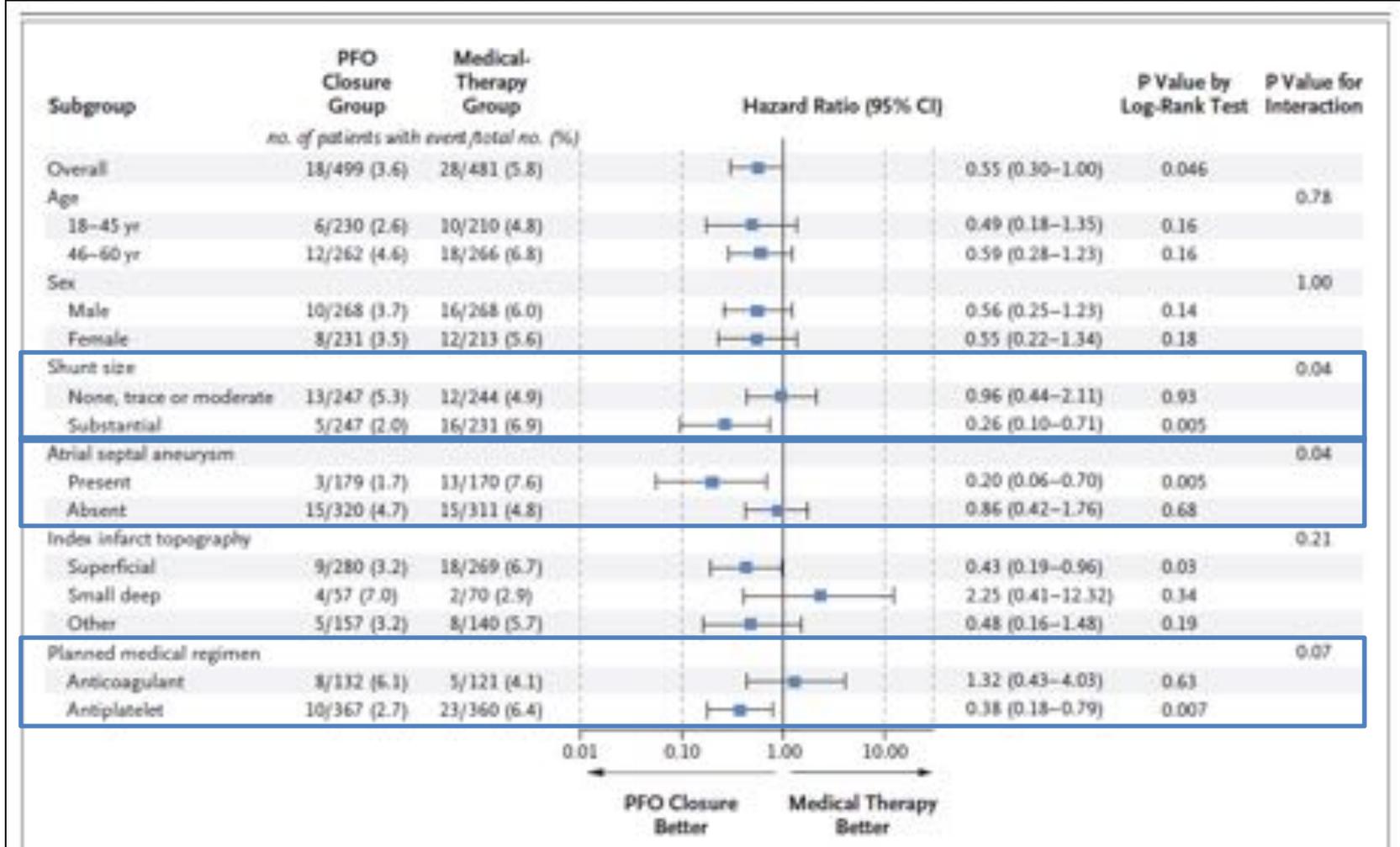
Réduction de 45% du risque de récidive d'AVC ischémique sur 5,9 années de suivi ($p < 0.05$)



No. at Risk	0	1	2	3	4	5	6	7	8	9	10
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 ($p = 0.007$)

RESPECT • Analyse des sous-groupes



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

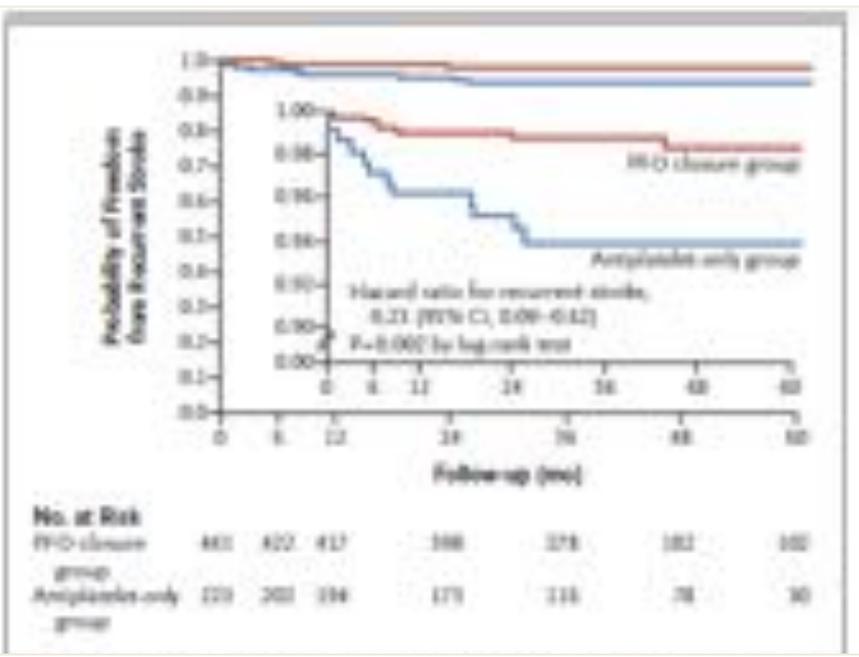


Table 2. Coprimary End Points of Freedom from Clinical Ischemic Stroke and Incidence of New Brain Infarction.*

End Point	PFO Closure Group no. of patients/total no. (%)	Antiplatelet-Only Group no. of patients/total no. (%)	Relative Risk (95% CI)	P Value
Clinical ischemic stroke†	6/441 (1.4)	12/423 (2.8)	0.21 (0.09-0.42)‡	0.002‡
New brain infarction¶	22/383 (5.7)	20/377 (5.3)	0.50 (0.29-0.81)‡	0.04**
Recurrent clinical ischemic stroke	5/383 (1.3)	12/377 (3.2)	0.18 (0.07-0.54)‡	0.002**
Silent brain infarction only	17/383 (4.4)	8/377 (2.1)	0.98 (0.43-2.21)‡	0.97**

* Freedom from clinical ischemic stroke is reported here as the number of recurrent strokes through or just 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

REDUCE : Evènements indésirables

Table 3. Adverse Events.

Adverse Event	WFO Closure Group (N=441)	Aspirin-Only Group (N=223)	P Value*
	no. of patients (%)		
Any serious adverse event	102 (23.1)	62 (27.8)	0.23
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
New 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	1 (0.2)		
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.

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, $\alpha=5\%$.
- 663 patients included from Dec. 2008 to Dec. 2014. Follow-up until Dec. 2016. Mean follow-up 5.3 years (3644 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

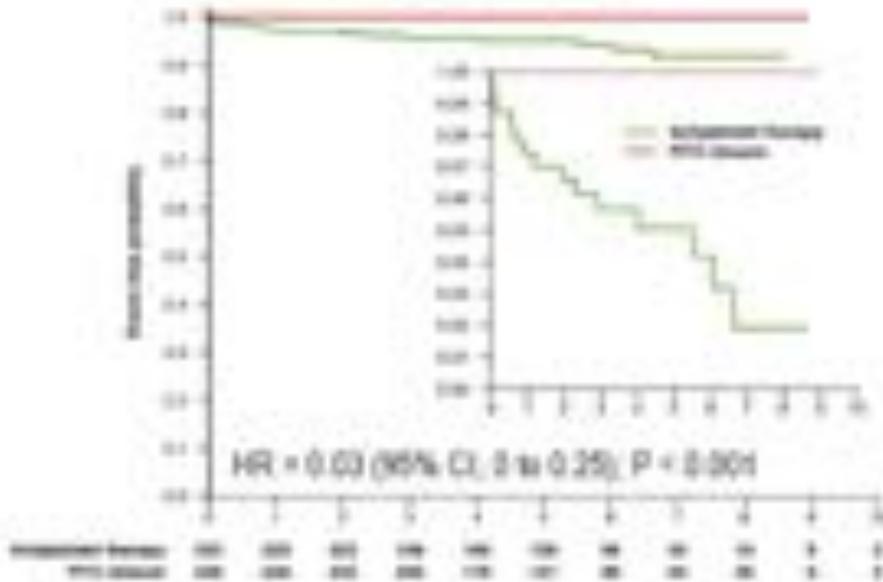
- Contraindication to oral anticoagulants and PFO closure
- Contraindication to antiplatelet therapy
- Increased bleeding risk
- Expected poor compliance or inability to attend follow-up visits
- Anatomical to device placement

Outcomes

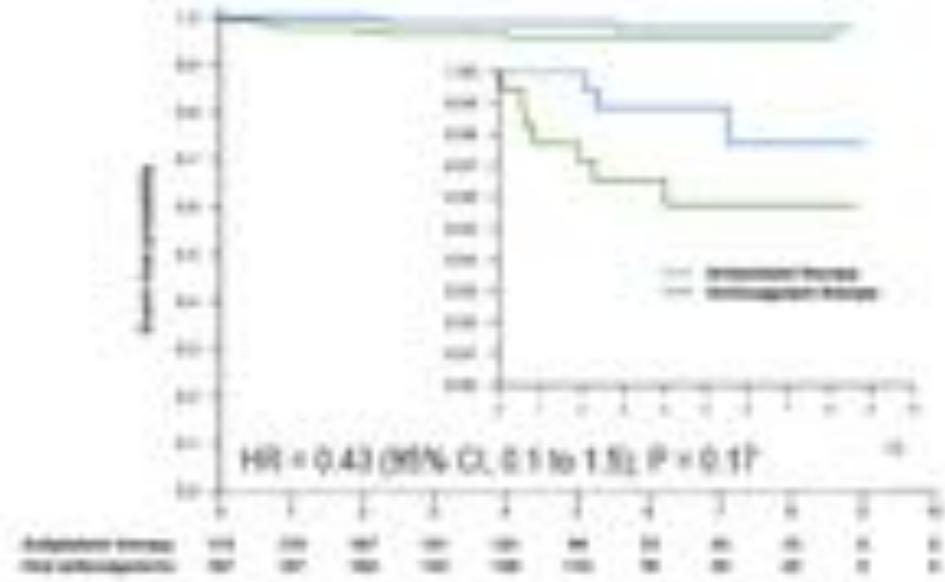
- **Primary** : fatal or nonfatal stroke
- **Secondary** : composite of ischemic stroke, TIA, or systemic embolism, all-cause mortality, vascular death, success of device implantation and success of PFO closure
- **Safety** : major procedural complications and major hemorrhagic complications

CLOSE

PFO closure vs.
Antiplatelet therapy



Oral anticoagulants
vs. Antiplatelet therapy



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

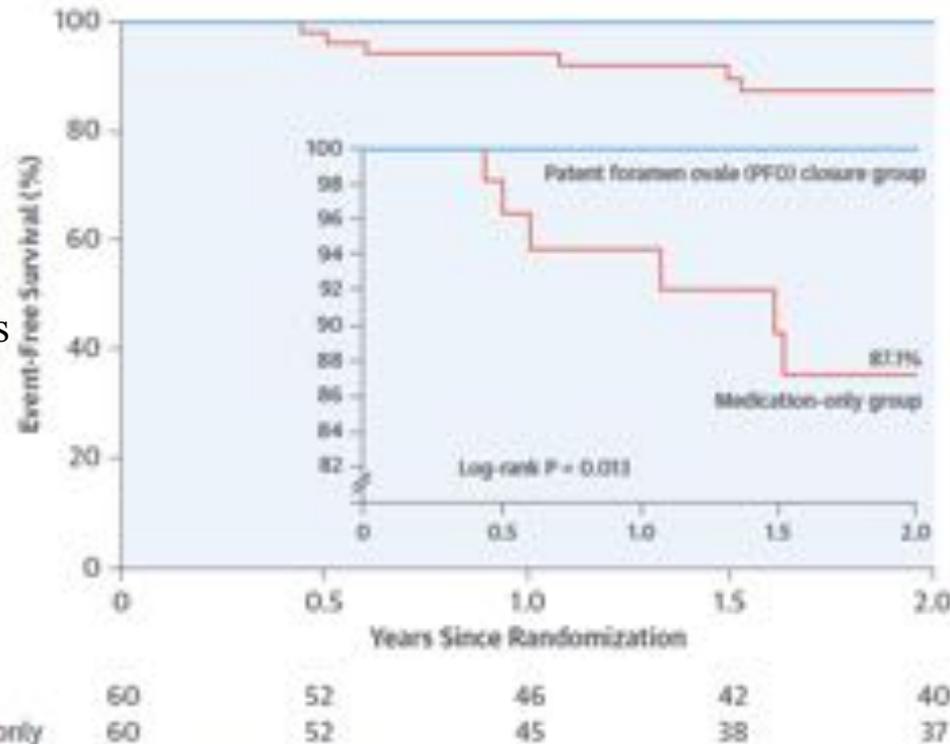
Cryptogenic Stroke and High-Risk Patent Foramen Ovale

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,^e Hee-Jung Song, MD, PhD,^c Jei Kim, MD, PhD,^c Seung-Jung Park, MD, PhD^f

JACC mai 2018

AVC
Deces CV
TIMI saignements
majeurs



Lee, P.H. et al. / Am Coll Cardiol. 2018;71(20):2515-42.



ASIA ≥ 15mm
Hypermob ≥10mm
Diam ≥ 2mm

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,^e Hee-Jung Song, MD, PhD,^e Jei Kim, MD, PhD,^e Seung-Jung Park, MD, PhD^f

JACC mai 2018

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)		

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

5/ FOP – AVC : score ROPE

Score RoPE (Risk of Paradoxical Embolism)

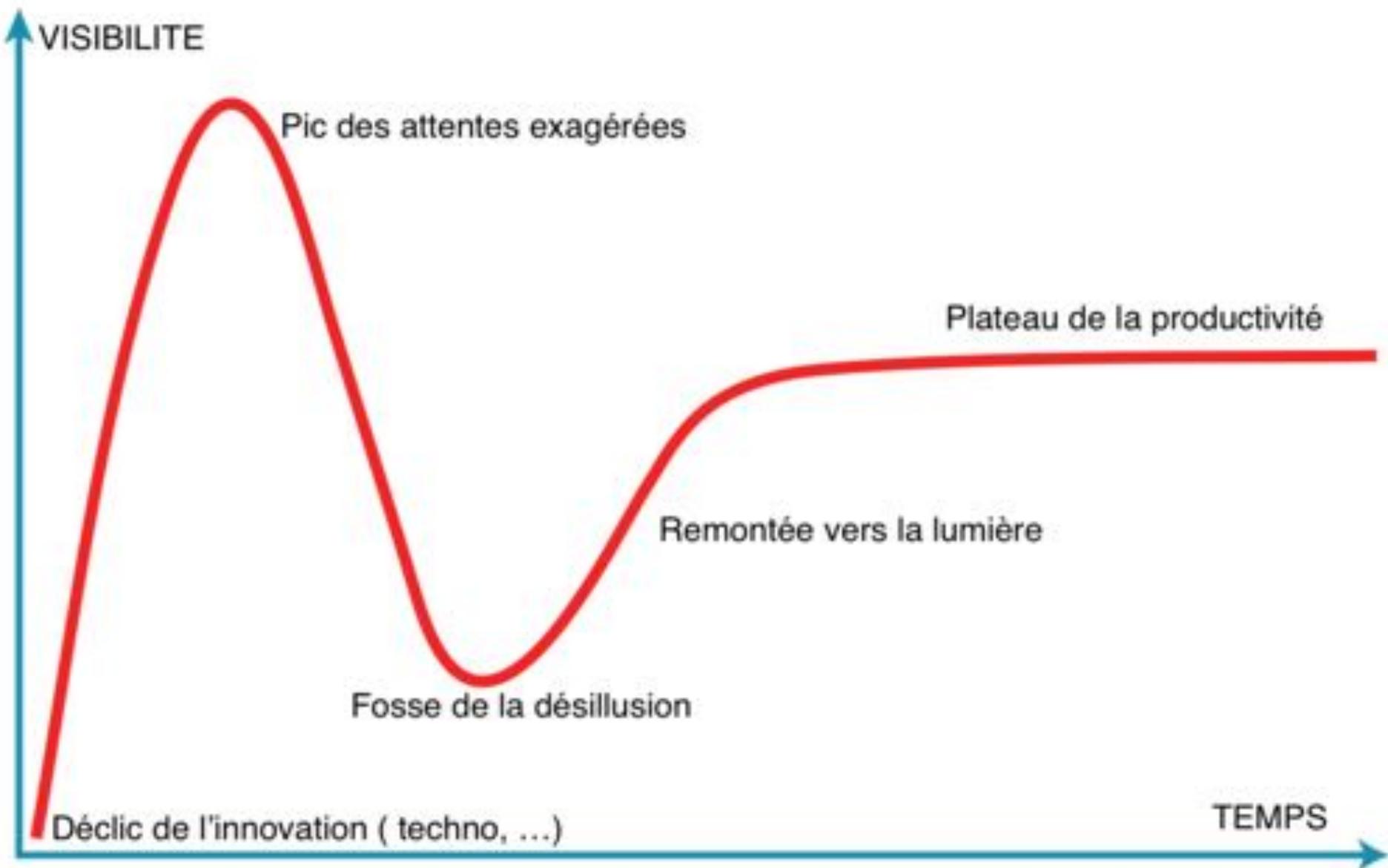
Cryptogenic stroke (n = 3,023)			
RoPE score	No. of patients	Prevalence of patients with a PFO, % (95% CI) ^a	PFO-attributable fraction, % (95% CI) ^a
0-3	613	23 (19-26)	0 (0-4)
4	511	35 (31-39)	38 (25-48)
5	516	34 (30-38)	34 (21-45)
6	482	47 (42-51)	62 (54-68)
7	434	54 (49-59)	72 (66-76)
8	287	67 (62-73)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

Fermeture FOP

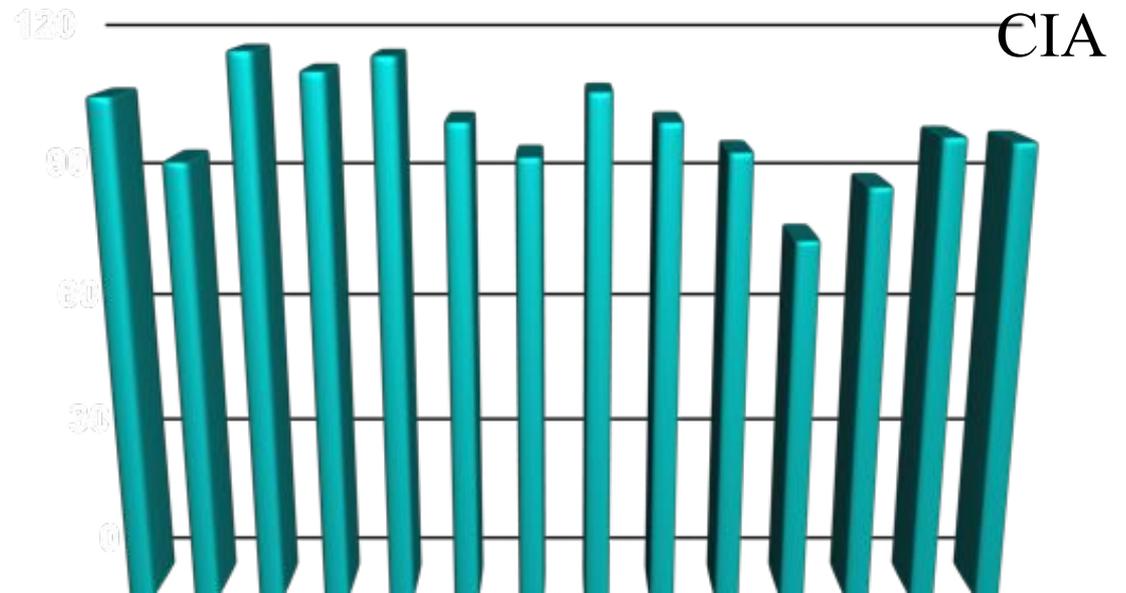
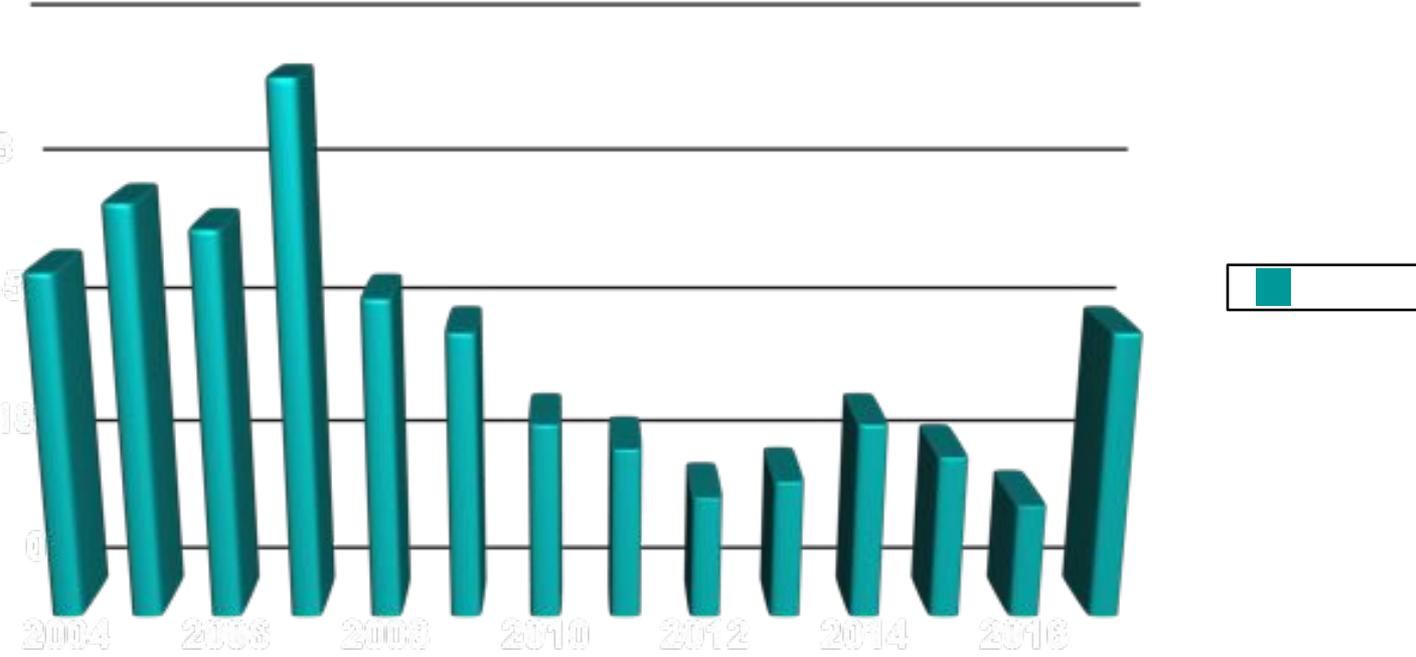
Limites médicales

	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



Fermeture de foramen ovale perméable

Les études

Merci de votre attention



Sébastien Hascoet, Benoit Gerardin,
Philippe Brenot, Jérôme Petit

Hôpital Marie Lannelongue

Biarritz, APPAC, Juin 2018