Complications séveres des fermetures de fop dans les études randomisées

Complications de la fermeture des FOP

- Aucun conflit d'intéret
- Mais beaucoup de conflits
- Et encore de l'intéret

Table 1. Main characteristics of included RCT.

	CLOSURE I	PC	RESPECT	CLOSE	Gore REDUCE	DEFENSE-PFO
Masking	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label
Design	Superiority[a,b]	Superiority[b]	Superiority[b]	Superiority[a]	Superiority[a,b]	Superiority[a,b]
Randomisation	1:1	1:1	1:1	1:1:1[c]	2:1	1:1
Centres	87	29	69	34	63	2
Region	USA and Canada	Switzerland, Germany, Austria, Belgium, Poland, Slovakia, United Kingdom, Australia, Canada, Brazil	USA and Canada	France and Germany	USA, Canada, Denmark, Finland, Sweden, United Kingdom	South Korea
Duration	June 2003-Oct 2008	Feb 2000-Feb 2009	Aug 2003-Dec 2011	Dec 2008-Dec 2016	Dec 2008-Feb 2015	June 2011-Oct 2017
Adjudication	Blinded	Blinded	Blinded	Blinded	Blinded	Not specified
Registration	NCT00201461	NCT00166257	NCT00465270	NCT00562289	NCT00738894	NCT01550588
Protocol	Published	Published	Published	Published	Published	Not available
Sponsor	NMT Medical	St. Jude Medical	St. Jude Medical	French Ministry of Health	W.L. Gore and Associates	Research Foundation
Qualifying event	TIA or ischaemic stroke <180 days	TIA with brain infarct at imaging or ischaemic stroke or extra-cranial embolism	Ischaemic stroke <270 days	Ischaemic stroke <180 days	TIA with new brain infarct at imaging and ischaemic stroke <180 days	Ischaemic stroke <180 days
Patients total (device/medical)	909 (447/462)	414 (204/210)	980 (499/481)	473 (238/235)	664 (441/223)	120 (60/60)
Device type	STARFlex septal occluder (100%)	AMPLATZER PFO Occluder (100%)	AMPLATZER PFO Occluder (100%)	– AMPLATZER PFO Occluder (51.5%) – Intrasept PFO occluder (13.2%) – Premere (9.4%) – STARFlex septal occluder (8.9%) – AMPLATZER Cribriform Occluder (6.4%) – Figulla Flex II PFO occluder (6.4%) – Other device (4.3%)	– HELEX septal occluder (38.7%) – Cardioform septal occluder (61.3%)	AMPLATZER PFO Occluder (100%)
Primary endpoint	Stroke or TIA, any-cause death within 30 days, or neurological death between 30 days and 2 years	Stroke, TIA, peripheral embolism, or death	Stroke, TIA, early any-cause death or neurological death	Stroke	Stroke or new lesion >3 mm[d]	Stroke, vascular death, TIMI major bleeding
Follow-up[e]	2.0 [1.5-2.0]	4.9 [3.5-5.0]	5.9 [4.2-8.0]	5.6 [3.8-7.1]	3.2 [2.2-4.8]	2.8 [0.9-4.1][f]
Person-years total (device/medical)	1,593 (798/795)	1,655 (841/814)	5,688 (3,080/2,608)	2,572 (1,338/1,234)	2,232 (1,529/703)	190 (97/93)[f]

[a] Original estimated sample size was not reached. [b] Lower than expected incidences. [c] Random assignment of treatments was based on patients' eligibility to PFO closure, antiplatelet therapy, and oral anticoagulation: no contraindications (Group 1); contraindication to anticoagulation (Group 2); contraindication to PFO closure (Group 3), but data were presented as 2×2-cohort study. [d] Brain imaging (97.7% MRI, 2.1% CT). [e] Unit is year and values are expressed as median [interquartile range]. [f] The median follow-up is reported as described in the paper. However, analyses were performed at 2-year follow-up and no information is disclosed after this time point, thus person-year estimates refer to time-to-event analysis. CT: computed tomography; MRI: magnetic resonance imaging

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.

among patients receiving medical treatment but 0% among patients who had undergone surgical closure of patent foramen ovale.[20,21] The patients in our study appeared to have been at lower risk for cardiovascular events than the cohorts of patients who underwent closure of patent foramen ovale in routine clinical settings[14] (Fig. S2 in the Supplementary Appendix), a factor that may have contributed to the considerably lower-than-expected event rate in our study.

Our trial has several limitations. First, our primary composite end point may be considered problematic. Overall death accounts for all potential benefits and harms of the experimental intervention but is not specific to the studied condition. TIA is a less clear-cut end point than stroke. Including TIA as a component resulted in an increased event rate but also may have resulted in a dilution of effects, as suggested by the difference in the estimated hazard ratios for stroke (0.20) and TIA (0.71). Second, we had difficulty recruiting patients, which led to an unusually long recruitment period and a selected patient population, which may in turn limit the generalizability of our findings.[24] Third, patient retention was lower than expected, which might have resulted in attrition bias that could distort the results in either direction.[24] Fourth, the clinical-events committee discounted potential primary-end-point events more often in the medical-therapy group than in the closure group. Even though the numbers of discounted events were small, this difference could constitute indirect evidence of selective reporting of potential events, owing to the open nature of the trial:

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

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.

7 patients in antiplatelet-only group. Outcomes of subgroup analyses are shown in Figure S8 in the Supplementary Appendix.

DISCUSSION

ratios in favor of PFO closure of 0.20 (95% CI, 0.02 to 1.72)[9] and 0.49 (95% CI, 0.22 to 1.11).[10] Furthermore, in a pooled analysis of individual participant data from the three trials, rates of recurrent stroke were significantly lower with

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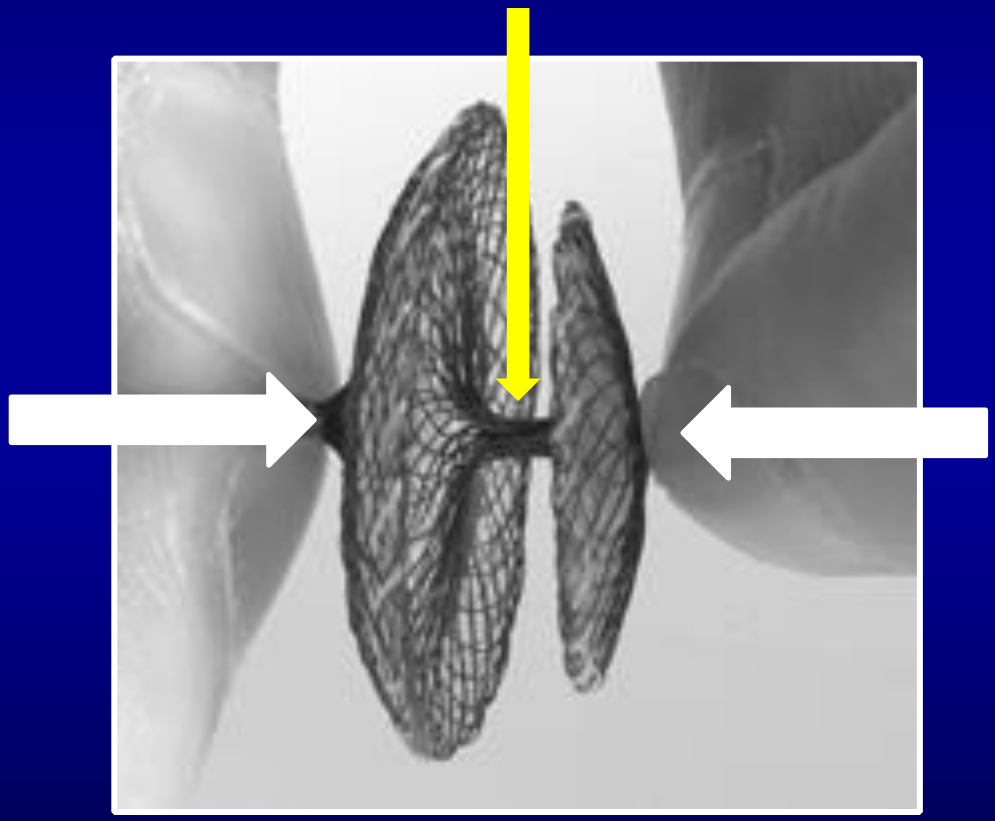
Table 3. Adverse Events.

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.

FERMETURE PERCUTANÉE DU FORAMEN OVALE PERMÉABLE

tunnel FOP



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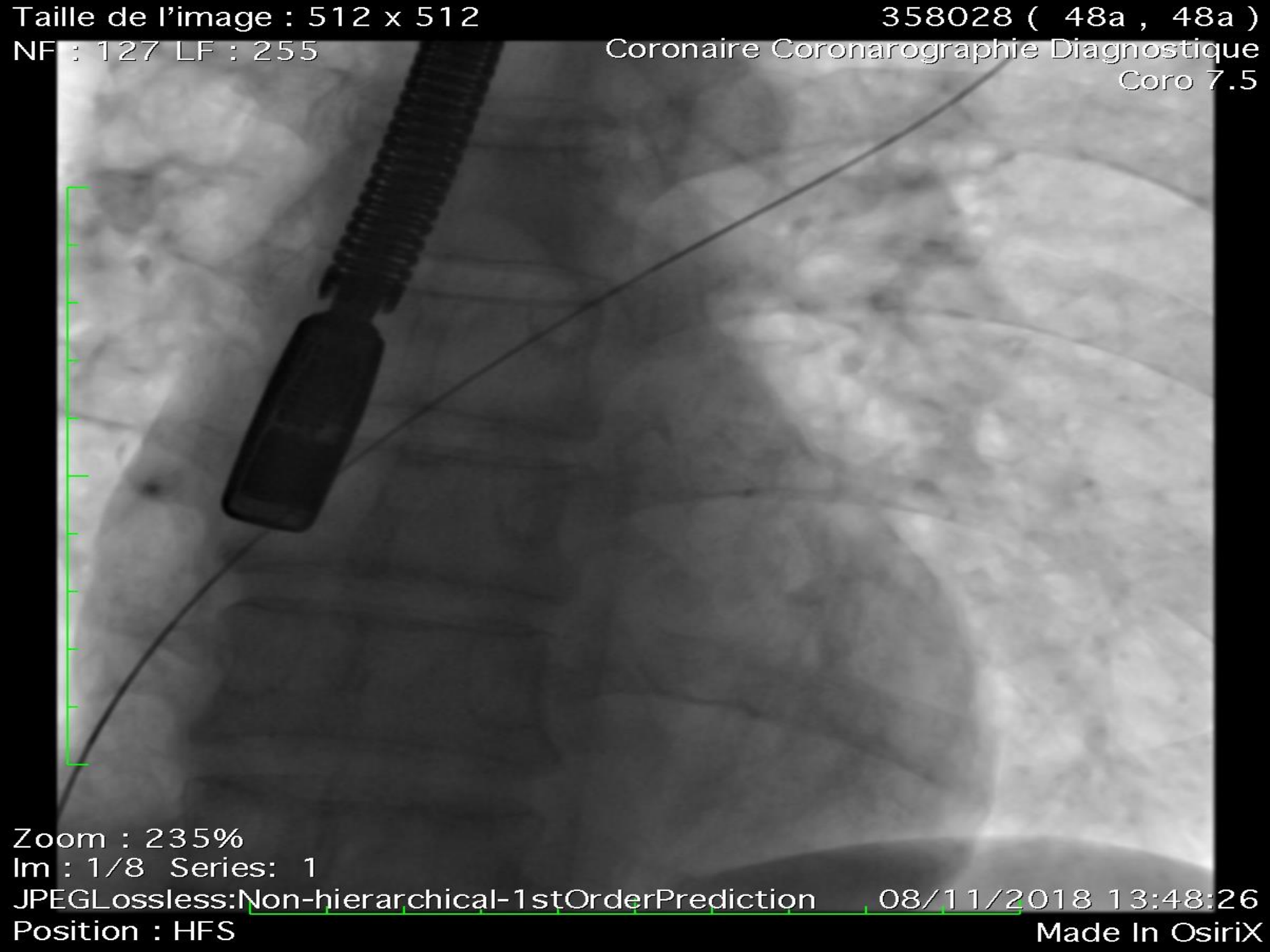
disque auriculaire gauche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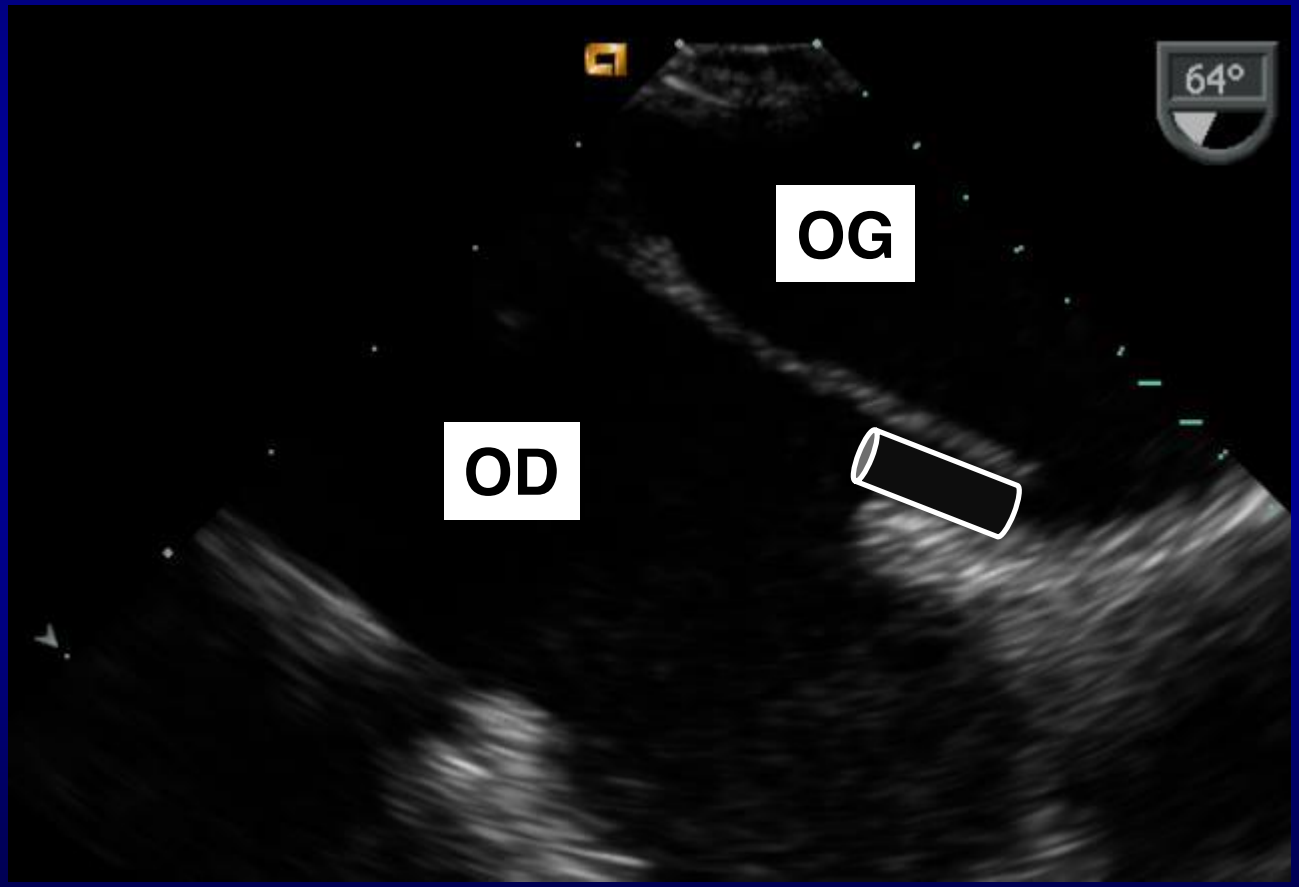
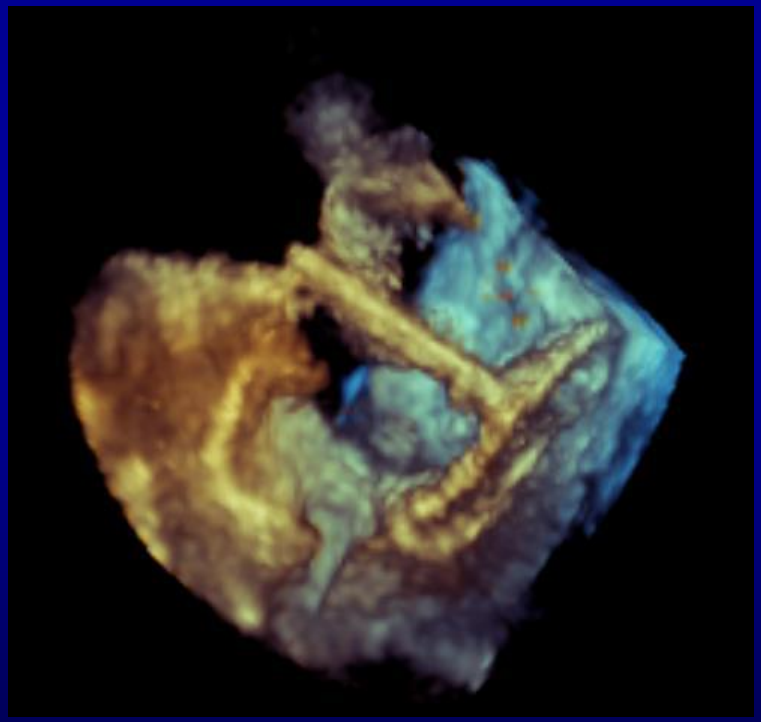
COMMUNICATIONS DE LA CLOISON INTERAURICULAIRE

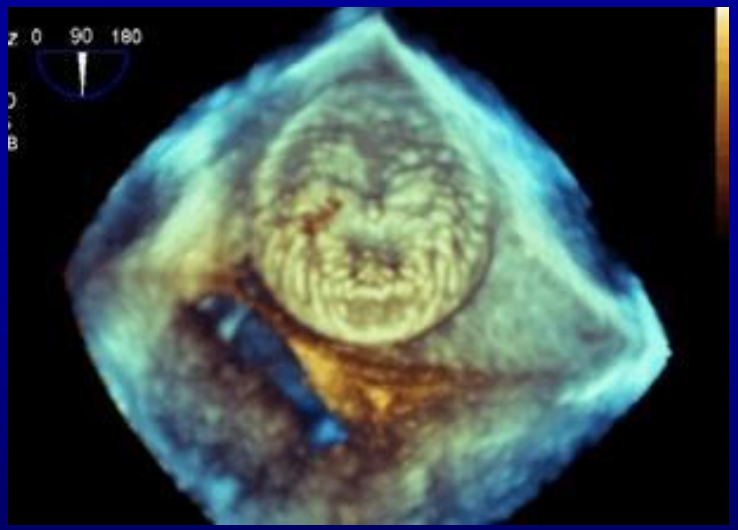
FORAMEN OVALE PERMÉABLE = TUNNEL



FERMETURE PERCUTANÉE DU FORAMEN OVALE PERMÉABLE

guidage échographique





Complications procedurales

- MIGRATION
- THROMBUS IN SITU:ACT>250
- PERFORATION/EPANCHEMENT PERICARDIQUE
- EMBOLIE GAZEUSE

COMPLICATIONS VASCULAIRES

* ACCIDENTS THROMBOEMBOLIQUES
* ACCIDENTS HEMORRAGIQUES
* COMPLICATIONS LIEES A L ETO

FERMETURE FOP ET COMPLICATIONS RYTHMIQUES

- AC/FA ET FLUTTER:2 à 6%
- SOUVENT PRECOCES ET TEMPORAIRES
- RECHERCHE PREALABLE A LA FERMETURE.HOLTER LONGUE DUREE
- ATTITUDE PREVENTIVE.TAILLE DE LA PROTHESE

ATRIAL FIBRILLATION AND MAJOR BLEEDING

Compared with ATA, tPFOc was associated with a more than fourfold increase in the risk of atrial fibrillation **(Figure 9A)**. Heterogeneity was moderate (I=44.8%; p=0.124). The risk of major bleeding was overall low and comparable between treatments **(Figure 9B)**. Heterogeneity was not significant (I=34.5%; p=0.191). Rates of other major cardiovascular adverse events are summarised in **Supplementary Table 9.**

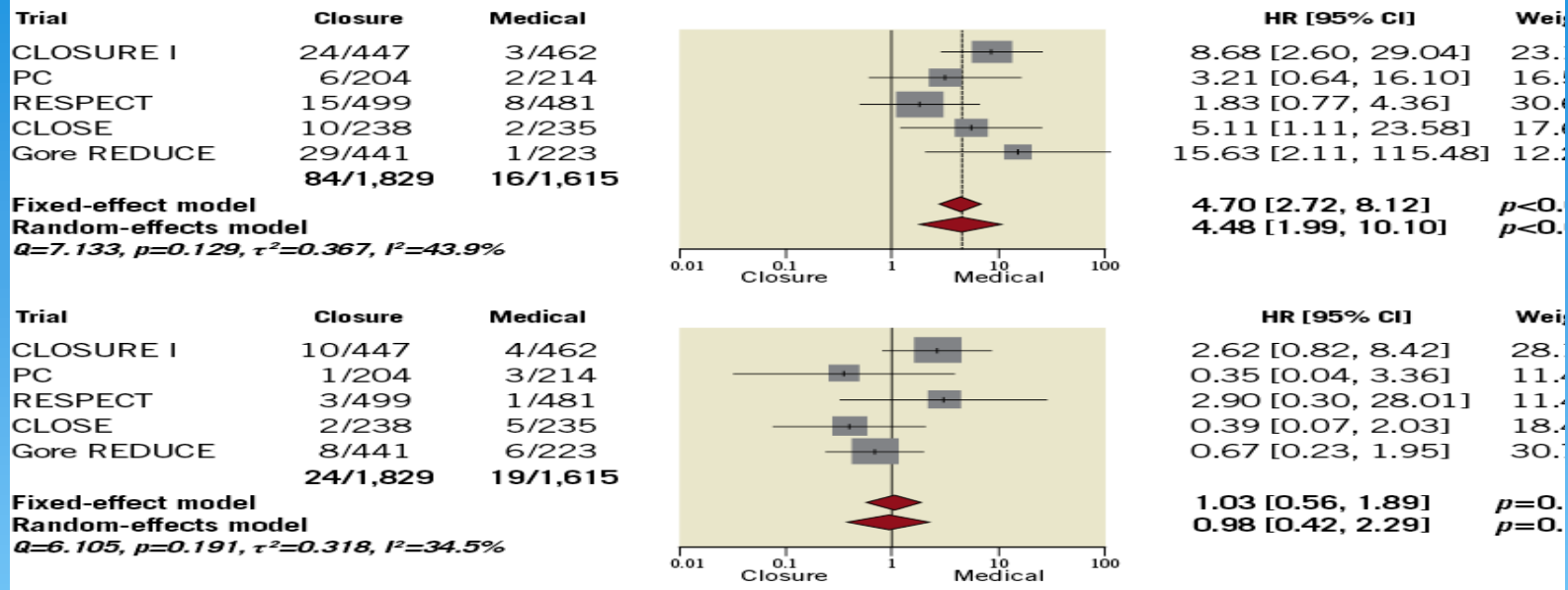


Figure 9. Atrial fibrillation and major bleeding. A) Atrial fibrillation. B) Major bleeding.

MIGRAINE

Compared with ATA, tPFOc did not seem to produce any benefit in terms of migraine **(Supplementary Figure 4)**.

BIAS ASSESSMENT AND STUDY RELIABILITY

Overall, the quality of the included trials was moderate-to-high, but some possible sources of bias need to be taken into account, as illustrated in **Supplementary Figure 5.** According to GRADE, the reliability of our conclusions is acceptable **(Supplementary Table 10)**.

Discussion

The findings of this meta-analysis can be summarised as follows: 1) compared with ATA, tPFOc reduces the risk of stroke at very long-term follow-up; 2) the results are robust, do not depend on individual trials and do not change across analyses accounting for multiple testing and clinical subgroups; 3) although substantial heterogeneity was observed, this depended on differences in magnitude rather than direction of treatment effects; 4) although pathophysiologically correlated with stroke, tPFOc does not protect from TIA; 5) tPFOc imposes a higher post-procedural risk of atrial fibrillation, while no difference in major bleeding was observed; 6) no benefit of tPFOc against migraine is observed.

A major finding of our study was that the relative risk reduction of stroke was detectable after approximately one

FERMETURE FOP:SHUNT RESIDUEL

* ANNONCEE AUTOUR DE 15%
* F FAVORISANTS:EXPERIENCE.CONTROLE ECHOGRAPHIQUE.QUALITES DES PROTHESES
* SELECTION DES PATIENTS:ASIA. QUALITE DU SEPTUM.SCORE ROPE

SYNTHESE

- COMPLICATIONS PROCEDURALES:1.5 %
- COMPLICATIONS VASCULAIRES:2.5 à 3.5%
- COMPLICATIONS RYTHMIQUES:2 à 6%
- SHUNT RESIDUEL? 2 à ……15% ?