CLOSE

Closure of Patent Foramen Ovale, Oral anticoagulants or Antiplatelet Therapy to Prevent Stroke Recurrence

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On behalf of Jean-Louis MAS and the CLOSE investigators

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Disclosure Statement of Financial Interest

I, Guillaume Turc DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

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Objectives and Methods

Objectives

To determine whether (1) **PFO closure plus antiplatelet therapy on one hand, and** (2) **oral anticoagulants on the other hand, are superior to antiplatelet therapy** to prevent stroke recurrence in patients with cryptogenic stroke and either PFO with large shunt or PFO associated with atrial septum aneurysm (ASA)

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 incidence 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

Methods

Key inclusion criteria

- Age 16 to 60 y.o
- Recent (≤ 6 months) ischemic stroke confirmed by neuroimaging, mRS ≤ 3
- Precisely 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
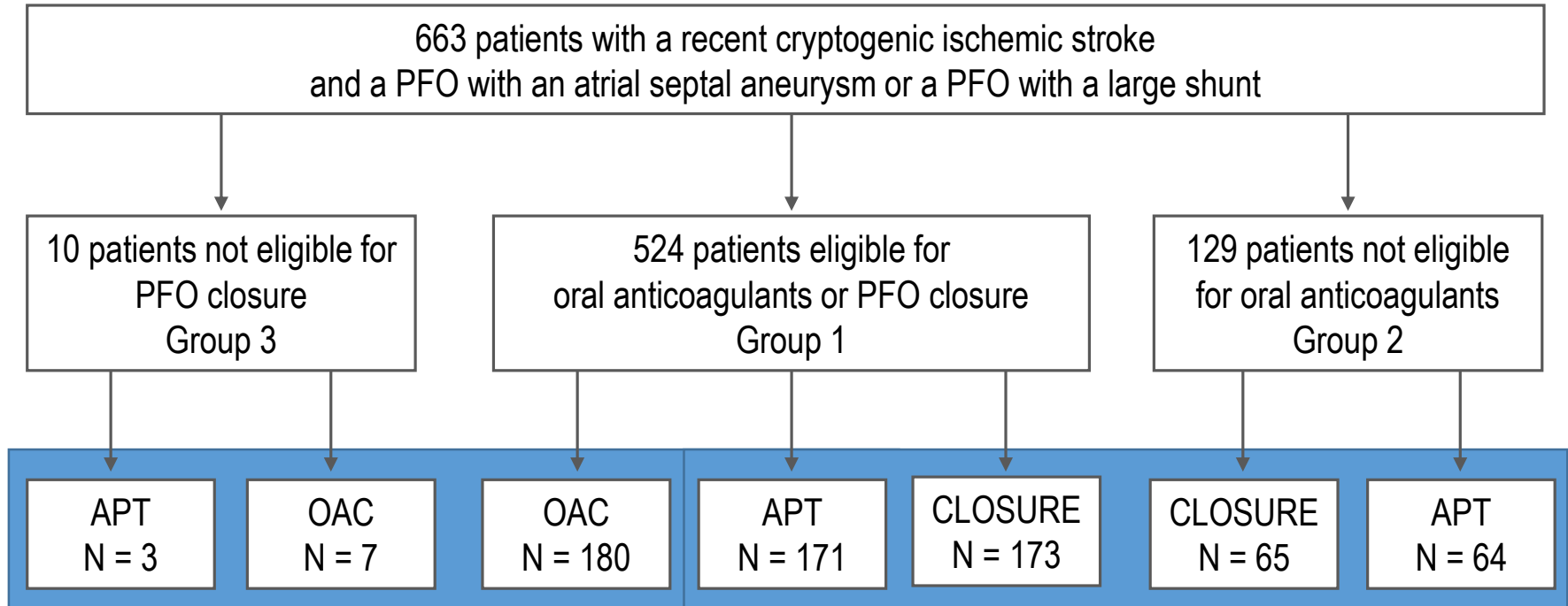
Key exclusion criteria

- 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; success of PFO closure
- Safety : major procedural complications and major hemorrhagic complications

Flow diagram

663 patients with a recent cryptogenic ischemic stroke
and a PFO with an atrial septal aneurysm or a PFO with a large shunt

| 10 patients not eligible for PFO closure Group 3 | 524 patients eligible for oral anticoagulants or PFO closure Group 1 | 129 patients not eligible for oral anticoagulants Group 2 |

| APT N = 3 | OAC N = 7 | OAC N = 180 | APT N = 171 | CLOSURE N = 173 | CLOSURE N = 65 | APT N = 64 |

APT = antiplatelet therapy   OAC = oral anticoagulants   CLOSURE = closure + antiplatelet therapy
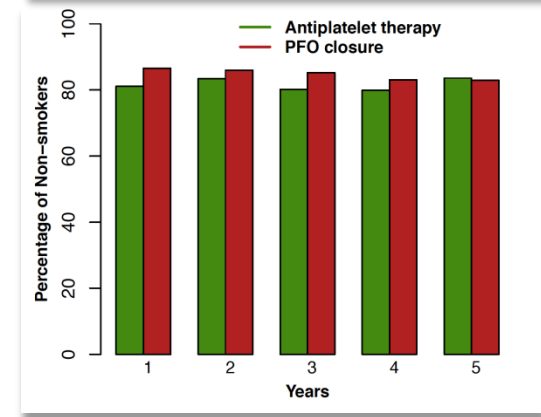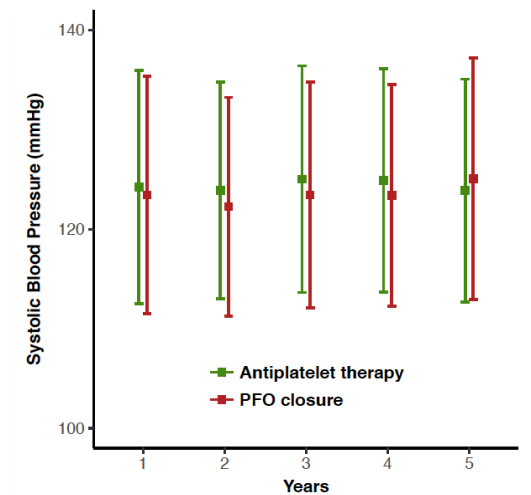
CLOSURE versus ANTIPLATELET THERAPY

Selected baseline characteristics

	CLOSURE (n = 238)	APT (n = 235)
Age – yr	42.9 +/- 10.1	43.8 +/- 10.5
Male gender	137 (57.6%)	142 (60.4%)
Hypertension	27 (11.3%)	24 (10.2%)
Smoking	68 (28.6%)	69 (29.4%)
BMI >= 30	32 (13.4%)	27 (11.5%)
Contraceptive pill	42 (41.6%)	37 (39.8%)
Prior stroke	10 (4.2%)	7 (3.0%)
PFO with ASA	81 (34.0%)	74 (31.5%)
PFO with large shunt and no ASA	157 (66.0%)	161 (68.5%)
Time from qualifying event to rand. (wks)	12.4 +/- 7.7	11.7 +/- 7.6

APT = antiplatelet therapy   CLOSURE = closure + antiplatelet therapy

Control of risk factors

CLOSURE versus ANTIPLATELET THERAPY

	CLOSURE (n = 238)	APT (n = 235)
Lost to follow-up	0	2
No PFO, atrial septal defect	2	
Refused PFO closure	2	
Discontinued antiplatelet therapy	17	10*
Mean follow-up, yr.	5.4 +/-1.9	5.2 +/-2.1

* 3 had PFO closure

APT = antiplatelet therapy   CLOSURE = closure + antiplatelet therapy

CLOSURE versus ANTIPLATELET THERAPY

Mean follow-up (years) = 5.4 +/-1.9 (CLOSURE) vs. 5.2 +/-2.1 (APT)

Intention-To-Treat

HR = 0.03 (95% CI, 0 to 0.25); P < 0.001

	0	1	2	3	4	5	6	7	8	9	10
Antiplatelet therapy	235	229	223	198	160	130	96	55	19	0	0
PFO closure	238	238	232	200	179	141	99	64	20	0	0
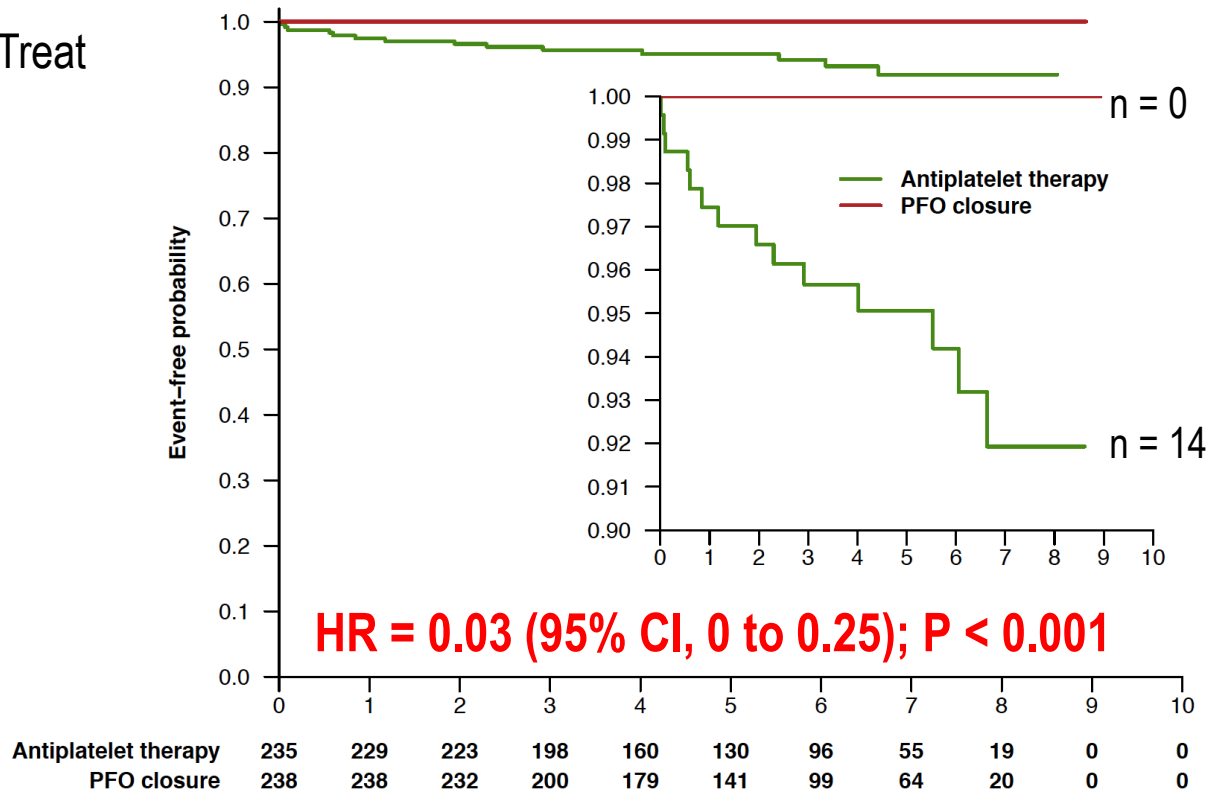
5-yr absolute risk reduction = 4.9%

1 avoided stroke at 5 years for every 20 (17 to 25) patients treated with closure

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CLOSURE versus ANTIPLATELET THERAPY

Secondary outcomes	CLOSURE (n = 238)	APT (n = 235)	HR (95%CI)
Ischemic stroke, TIA, or systemic embolism – no.	8	21	0.38 (0.16-0.81) P = 0.01
TIA – no.	8	8	0.98 (0.37-2.59)
Systemic embolism – no.	0	0	NA
Death – no.	0	0	NA
Effective PFO closure - no./total no. (%)	212/228 (93.0%)	-	NA

Safety outcomes	CLOSURE (n = 238)	APT (n = 235)	P value
Major procedural complications – no. (%)*	14 (5.9)	-	NA
Atrial fibrillation/flutter – no. (%)	11 (4.6)	2 (0.9)	0.02
Major bleeding complications – no. (%)	2 (0.89)	5 (2.1)	0.28

* atrial fibrillation (9), atrial flutter (1), supraventricular tachycardia (2), air embolism (1), and hyperthermia (1)

APT = antiplatelet therapy   CLOSURE = closure + antiplatelet therapy

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CLOSURE versus ANTIPLATELET THERAPY

Subgroup	PFO Closure	Antiplatelet therapy	Hazard Ratio (95% CI)	P for interaction
	No. of strokes (%)			
Primary endpoint	(0)	14 (6)	0.03 (0.00-0.26)	
Age at randomisation				0.83
< 44.6	(0)	5 (4)	0.09 (0.00-0.80)	
≥ 44.6	(0)	9 (7)	0.06 (0.00-0.44)	
Gender				0.37
Female	(0)	1 (1)	0.37 (0.00-6.87)	
Male	(0)	13 (9)	0.04 (0.00-0.29)	
Rope score				0.62
< 7	(0)	4 (5)	0.15 (0.00-1.39)	
≥ 7	(0)	10 (6)	0.05 (0.00-0.36	
History of CV disease				0.46
No	(0)	12 (6)	0.04 (0.00-0.30)	
Yes	(0)	2 (9)	0.17 (0.00-2.14)	
Patent foramen ovale				0.73
Large shunt	(0)	5 (3)	0.10 (0.00-0.91)	
PFO + ASA	(0)	9 (12)	0.05 (0.00-0.36)	

0.01 0.05 0.1 0.2 0.5 1 2 5

PFO Closure better   Antiplatelets better
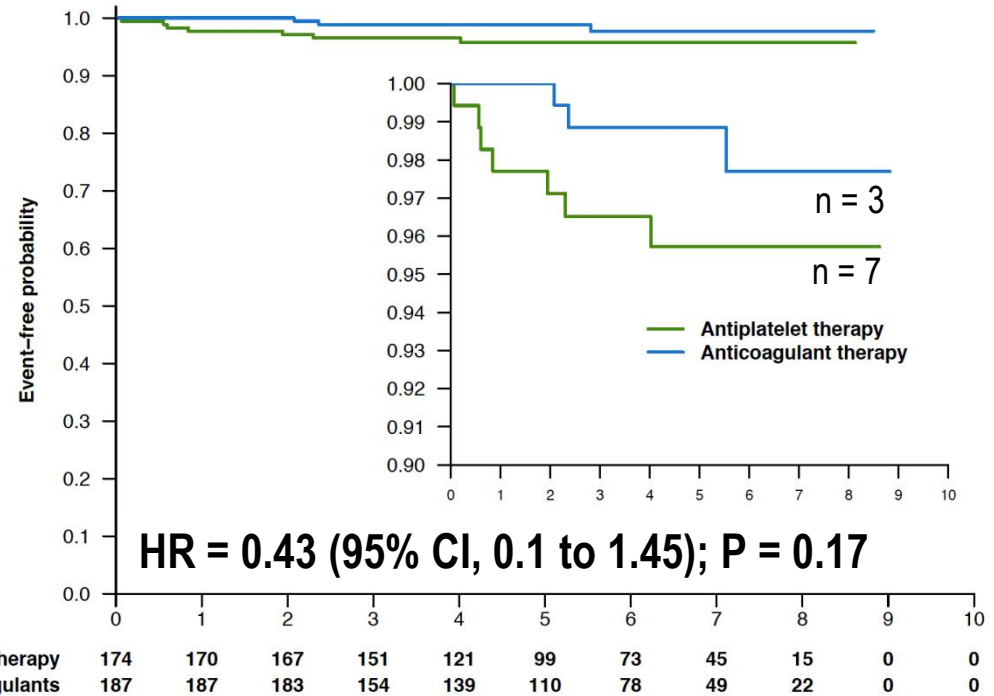
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ORAL ANTICOAGULANTS vs. ANTIPLATELET THERAPY

No between-group difference with regard
to baseline characteristics
and control of risk factors during follow-up

	OAC (n = 187)	APT (n = 174)
Lost to follow-up	5 (2.7%)	1 (0.6%)
Did not receive allocated treatment	1	0
Discontinued OAC or APT	38*	9*
Mean follow-up, yr.	5.4 +/-2.0	5.2 +/-2.0

* 3 had PFO closure

Intention-To-Treat cohort

n = 3

n = 7

— Antiplatelet therapy
— Anticoagulant therapy

Event–free probability

$HR = 0.43$ (95% CI, 0.1 to 1.45); $P = 0.17$

	0	1	2	3	4	5	6	7	8	9	10
Antiplatelet therapy	174	170	167	151	121	99	73	45	15	0	0
Oral anticoagulants	187	187	183	154	139	110	78	49	22	0	0

APT = antiplatelet therapy   OAC = oral anticoagulants

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ORAL ANTICOAGULANTS vs. ANTIPLATELET THERAPY

Secondary outcomes	OAC (n = 187)	APT (n = 174)	HR (95%CI)
Ischemic stroke, TIA, or systemic embolism – no.	8	12	0.62 (0.25-1.47); P = 0.28
TIA – no.	5	6	0.78 (0.24-2.47); P = 0.67
Systemic embolism – no.	0	0	NA
Death – no.	1	0	NA

Safety outcomes	OAC (n = 187)	APT (n = 174)	P value
Major bleeding complications – no. (%)	10 (5.4)	4 (2.3)	0.18

APT = antiplatelet therapy   OAC = oral anticoagulants

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Conclusions

- PFO closure plus long-term antiplatelet therapy reduced the risk of stroke recurrence in patients 16 to 60 years old with cryptogenic stroke and PFO with ASA or PFO with large shunt, compared with antiplatelet therapy alone.

- PFO closure was associated with an increased risk of new onset atrial fibrillation.

- Oral anticoagulants did not significantly reduce the risk of stroke recurrence compared with antiplatelet therapy. However, there was a trend in favor of oral anticoagulants.

- The risk of cryptogenic stroke recurrence on antiplatelet therapy was significantly higher in patients with PFO + ASA than in those with PFO with large shunt.

Mas et al, NEJM 2017;377:1011-21.