Does the presence of atrial septal aneurysm and/or a large degree of shunting identify patients most likely to benefit ?

Yes !

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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.

Does the presence of ASA and/or a large shunt identify patients most likely to benefit from PFO closure ?

- Are patients with ASA and/or large shunt at higher risk of recurrent stroke ?
- Is presence of ASA and/or large shunt a modifier of the effect of PFO closure on recurrent stroke prevention?

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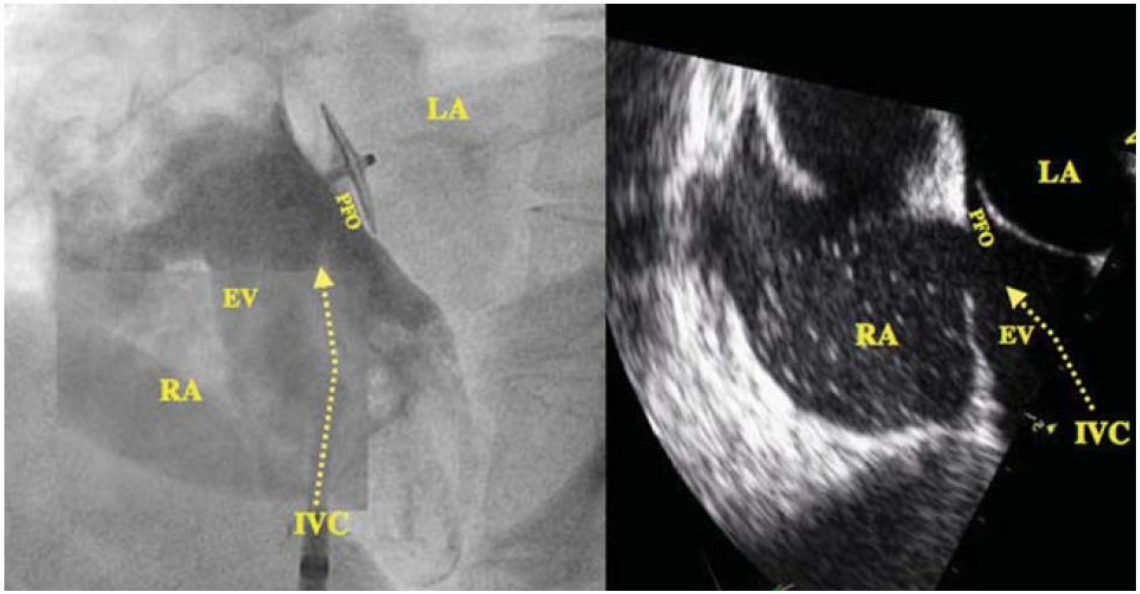
Higher risk of stroke recurrence in patients with ASA or large shunt

- **Pathophysiological plausibility**
  - ASA associated with larger PFO size and prominent Eustachian valve
  - Increased septal mobility may enhance the probability of paradoxical embolism by mechanically directing blood flow from the inferior vena cava into the PFO



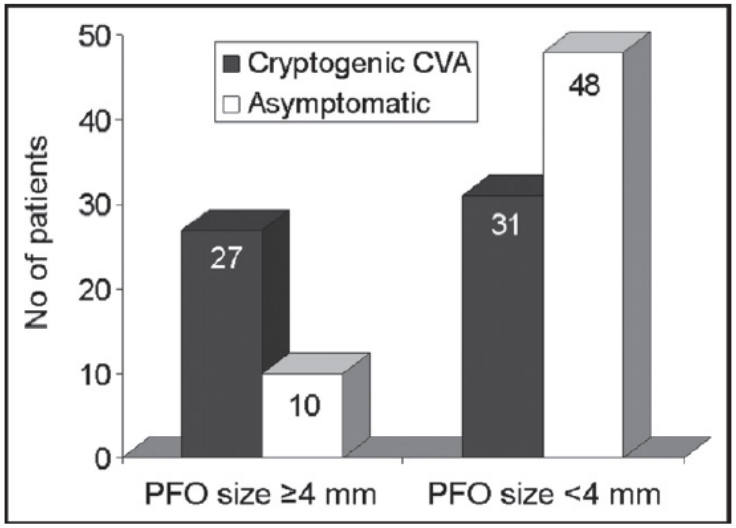
De Castro et al, Stroke 2000 *Meier et al, Eur Heart J 2012*

Higher risk of stroke recurrence in patients with ASA or large shunt

- **Indirect evidence**: case-control studies
  - Cryptogenic strokes vs. strokes of determined cause (*Overell et al, Neurology 2000*)

(n studies)	Random-effects meta-analysis OR (95% CI)
PFO (22)	3.2 (2.3–4.4)
ASA (4)	3.7 (1.3–10.0)
PFO + ASA (2)	**23.3 (5.2–103.2)**

  - Cryptogenic strokes vs. no stroke among patients with PFO (*Goel et al, Am J Cardiol 2009*)

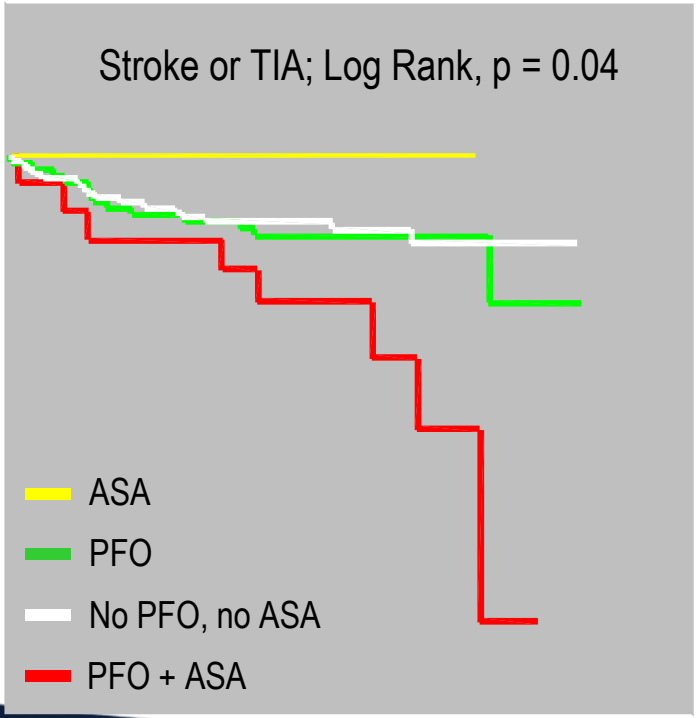


Patent foramen ovale morphology

Morphologic Characteristic	Symptomatic PFO (Stroke or TIA) (n = 58)	Asymptomatic PFO (n = 58)	p Value
Size (mm)	3.9 ± 1.6	2.9 ± 1.4	0.001
Large PFO (size ≥4 mm)	27 (46%)	10 (17%)	0.001
Presence of ASA	26 (45%)	12 (21%)	0.005
Length of the tunnel (mm)	14 ± 6	12 ± 6	0.05
Long tunnel (≥1 cm)	45 (78%)	32 (55%)	0.01
Degree of shunting			
Mild	30 (52%)	35 (60%)	0.34
Moderate	12 (21%)	12 (21%)	1.0
Severe	9 (16%)	3 (5%)	0.06
Prominent Eustachian valve	12 (21%)	9 (16%)	0.4
Prominent Chiari's network	1 (2%)	1 (2%)	1.0

Higher risk of stroke recurrence in patients with ASA or large shunt

- **Direct evidence**: prospective cohort study (*Mas et al, NEJM 2001*)
- 581 patients ≤55 y.o. with recent cryptogenic stroke undergoing TEE (central reading)
- Standardized treatment: aspirin
- Mean F-U: 37.7 +/- 9.8 months
- 24 Strokes, 13 TIAs (blinded adjudication)



Stroke recurrence	4 year-risk (95% CI)	Annual risk	Adjusted HR (95% CI)
No PFO, no ASA (n = 304)	4.2 (1.8-6.6)	1.1	1
PFO, no ASA (n = 216)	2.3 (0.3-4.3)	0.6	**0.9 (0.3-2.4)**
ASA, no PFO (n=10)	-	-	-
PFO and ASA (n = 51)	**15.2 (1.8-28.6)**	**4.0**	**4.2 (1.5-11.8)**

	Small shunt	Large shunt
HR (95%CI) versus no PFO	1.01 (0.23 – 4.52)	1.10 (0.39 – 3.11)

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ASA and/or large shunt: an effect modifier ?

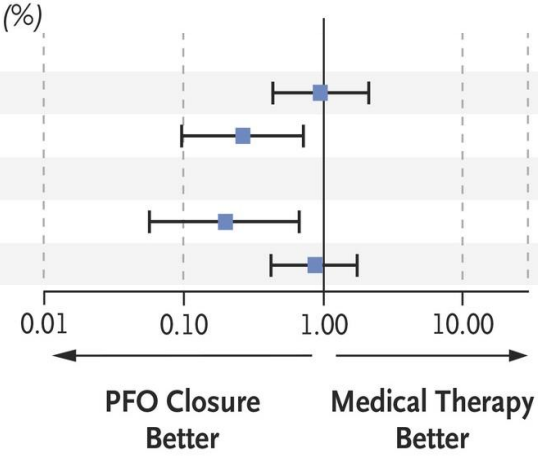
- Subgroup analyses of RCTs of PFO closure vs. medical therapy

Study	CLOSURE I (2012)	PC Trial (2013)	RESPECT (2013; 2017)	CLOSE (2017)	REDUCE (2017)
Sample size	N=909	N=414	N=980	N=663	N=664
Definition of large shunt	≥25 bubbles	> 20 bubbles	> 20 bubbles	>30 bubbles	>25 bubbles
Definition of ASA	≥10mm	≥15mm	≥10mm	>10mm	?
Large shunt (%)	20.8%	21.7%	48.8%	94.2% (with or without ASA)	40.7%
ASA (%)	36.6%	23.7%	35.7%	34.7%	20.4% (closure arm)
Comments	-	-	-	Patients included only if large shunt or PFO + ASA	Information on ASA only available for closure arm

ASA and/or large shunt: an effect modifier ?

- Subgroup analyses of RCTs of PFO closure vs. medical therapy
  - RESPECT extended follow-up (Saver et al, NEJM 2017)

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. (%)				
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	



- Such an interaction was not observed in CLOSURE I or PC Trial

Does the presence of ASA and/or a large shunt identify patients most likely to benefit from PFO closure ?

- Several clues in favor of this hypothesis
- But an updated individual patient data meta-analysis is required to (hopefully) provide definitive answers, by:
  - Standardizing definition of outcome (recurrent stroke) +/- definition of ASA/large shunt
  - Adjusting for potential confounders
  - Addressing missing data by multiple imputation
- Will we have sufficient statistical power ?