Pour ou contre : fermeture du foramen ovale perméable en haut de 60 ans

POUR

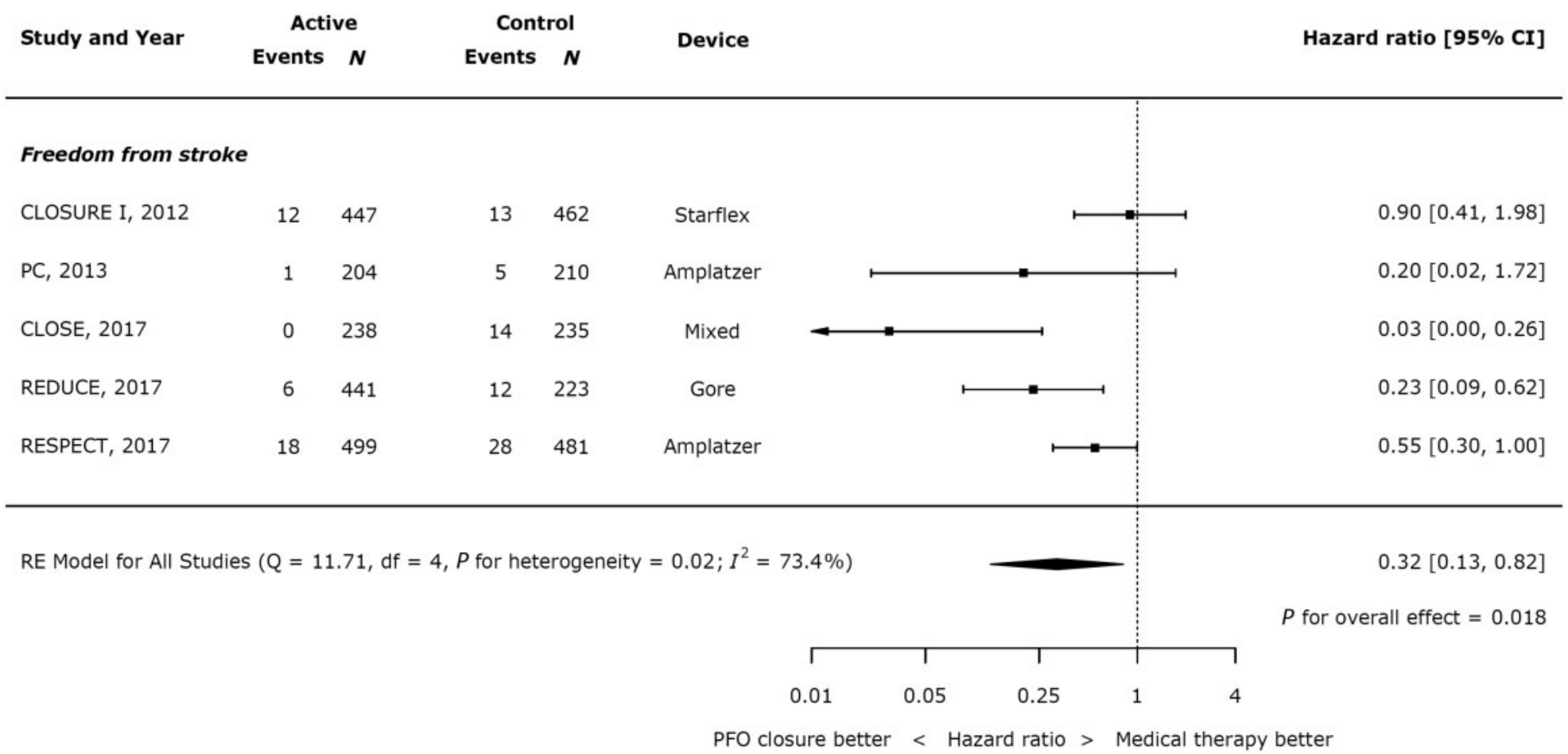
Josep Rodés-Cabau, MD, PhD

INSTITUT UNIVERSITAIRE
DE CARDIOLOGIE
ET DE PNEUMOLOGIE
DE QUÉBEC
UNIVERSITÉ LAVAL

Conflict of interest

- Institutional research grants and consultant/speaker fees from Edwards Lifesciences, Medtronic, Abbott

Randomized Trials on PFO closure



Ahmad et al. Eur Heart J 2018

Canadian Stroke Best Practice Recommendations: Secondary Prevention of Stroke Update 2020

*David J. Gladstone, M. Patrice Lindsay, James Douketis, Eric E. Smith, Dar Dowlatshahi, Theodore Wein, Aline Bourgoin, Jafna Cox, John B. Falconer, Brett R. Graham, Marilyn Labrie, Lena McDonald, Jennifer Mandzia, Daniel Ngui, Paul Pageau, Amanda Rodgerson, William Semchuk, Tammy Tebbutt, Carmen Tuchak, Stephen van Gaal, Karina Villaluna, Norine Foley, Shelagh Coutts, Anita Mountain, Gord Gubitz, Jacob A Udell, Rebecca McGuff, Manraj K.S. Heran, Pascale Lavoie, Alexandre Y. Poppe; on behalf of the Canadian Stroke Best Practice Recommendations Advisory Committee, in collaboration with the Canadian Stroke Consortium**

Section 10 Recommendations
10.1 Patent Foramen Ovale (PFO)

i. Patients with a recent ischemic stroke suspected to be related to a PFO should have an evaluation by healthcare professionals with stroke and cardiovascular expertise [Evidence Level C].

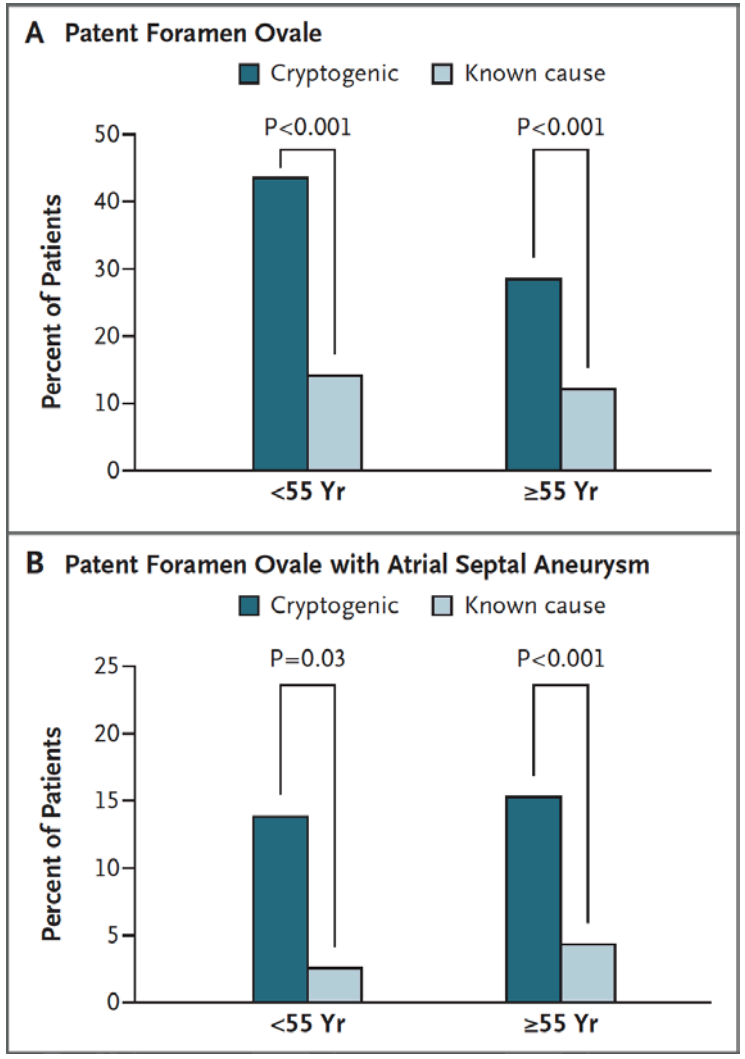
ii. For carefully selected patients with a recent ischemic stroke attributed to a PFO, PFO device closure plus long-term antiplatelet therapy is recommended over long-term antithrombotic therapy alone **provided all** the following criteria are met [Evidence Level A]:

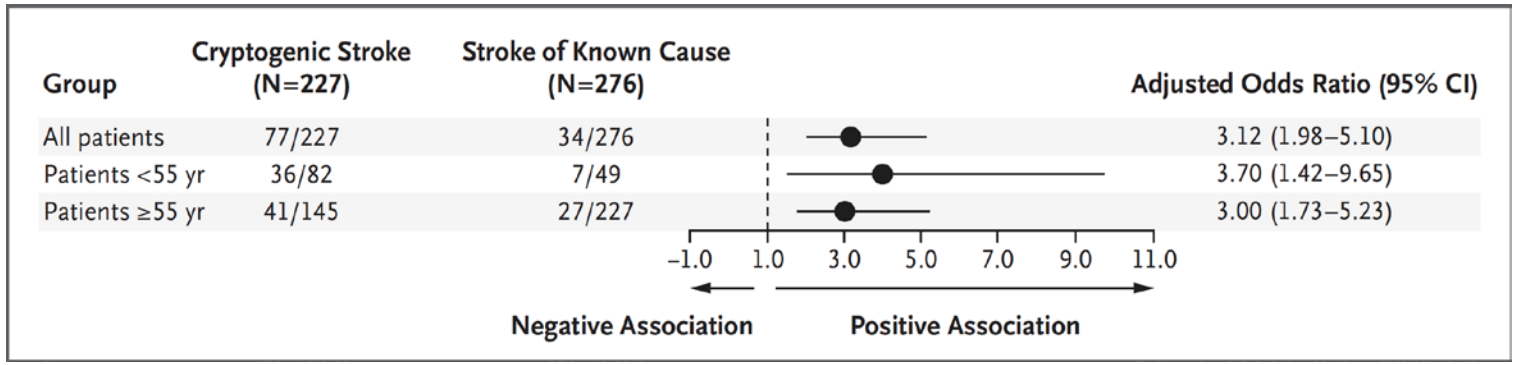
   a. Age 18–60 years.
   b. The diagnosis of the index stroke event is confirmed by imaging as a non-lacunar embolic ischemic stroke.
   c. The patient has been evaluated by a neurologist or healthcare professional with stroke expertise, and the PFO is felt to be the most likely cause for the index

Guideline	Young patients (18 to ≤60–65 years)	Older patients (>60–65 years)
American Heart Association/ American Stroke Association[8]	In patients 18 to 60 years of age with a non-lacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO with high-risk anatomic features, it is reasonable to choose closure with a transcatheter device and long-term antiplatelet therapy over anti-platelet therapy alone for preventing recurrent stroke.	None
American Academy of Neurology[6]	In patients younger than 60 years with a PFO and embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits (absolute recurrent stroke risk reduction of 3.4% at 5 years) and risks (periprocedural complication rate of 3.9% and increased absolute rate of non-periprocedural atrial fibrillation of 0.33% per year).	PFO closure may be offered in other populations, such as for a patient who is aged 60–65 years with a very limited degree of traditional vascular risk factors (i.e., hypertension, diabetes, hyperlipidemia, or smoking) and no other mechanism of stroke detected following a thorough evaluation, including prolonged monitoring for atrial fibrillation (level C).
European position paper on the management of patients with patent foramen ovale[7]	The position of our societies is to perform percutaneous closure of a PFO in carefully selected patients aged from 18 to 65 years with a confirmed cryptogenic stroke, TIA, or systemic embolism and an estimated high probability of a causal role of the PFO as assessed by clinical, anatomical, and imaging features.	With the same shared decision-making approach, PFO closure can also be considered in patients >65 or <18 years of age, taking into account on a case-by-case basis the lack of evidence, the age-related confounders and additional risks of interventional and drug therapies.
Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference[11]	In patients aged 18–60 years old with cryptogenic stroke/TIA and with high risk PFO features (moderate or severe shunt, ASA, atrial septal hypermobility) we recommend percutaneous closure plus medical therapy instead of antiplatelet therapy alone (Grade A).	- In patients between 60 and 65 years, percutaneous closure plus medical therapy instead of antiplatelet therapy alone can be offered (Grade B). - Percutaneous closure plus medical therapy can be considered in place of antiplatelet therapy alone also for patients aged <18 and >65 years old on an individual basis (Grade C).

Farjat-Pasos et al. J Stroke 2023

Association of PFO with cryptogenic stroke in older patients



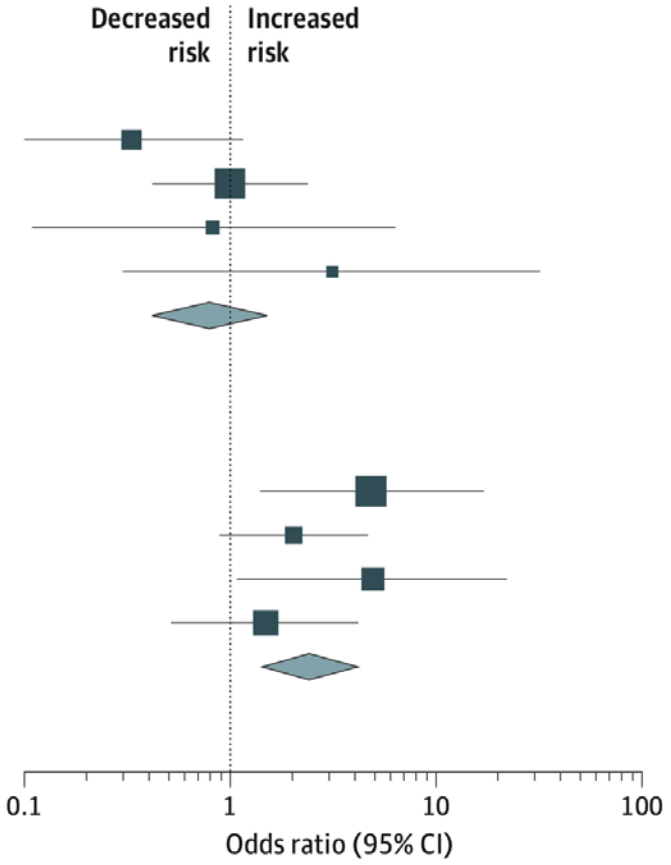


Handke et al. N Engl J Med 2007

PFO-related cryptogenic stroke with medical treatment alone in older patients

Figure 3. Risk of Ischemic Stroke Recurrence After Cryptogenic Transient Ischemic Attack/Stroke in Patients With Patent Foramen Ovale (PFO) vs Patients Without PFO

Study	Events/patients		Odds ratio (95% CI)
	PFO	No PFO	
Age <65 y			
Homma et al,[9] 2004	2/69	9/90	0.3 (0.1-1.2)
Weimar et al,[24] 2009	8/161	16/325	1.0 (0.4-2.4)
Nezu et al,[23] 2018	1/14	6/69	0.8 (0.1-6.4)
OxVasc 2020	2/55	1/83	3.1 (0.3-31.9)
Total	13/299	32/567	0.8 (0.4-1.5)
Significance: *P* =.49			
Heterogeneity: *P* =.32			
Age ≥65 y			
Homma et al,[9] 2004	8/29	5/62	4.8 (1.4-16.9)
Weimar et al,[24] 2009	12/73	21/223	2.0 (0.9-4.7)
Nezu et al,[23] 2018	5/48	4/135	4.9 (1.1-22.3)
OxVasc 2020	7/98	9/180	1.5 (0.5-4.3)
Total	32/248	39/600	2.5 (1.4-4.2)
Significance: *P* =.001			
Heterogeneity: *P* =.39			



Mazzucco et al. JAMA Neurol 2020

Circulation: Cardiovascular Interventions

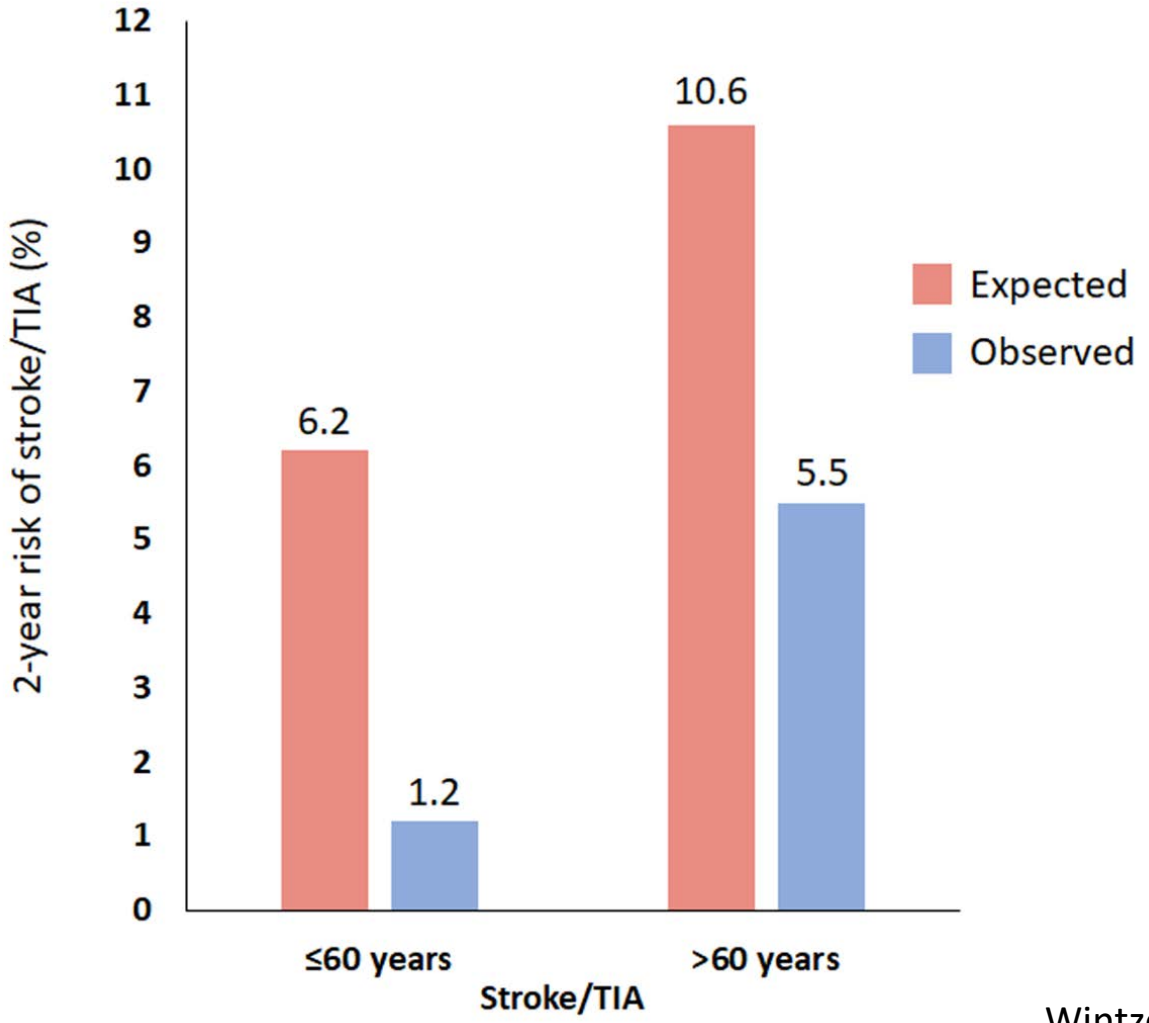
ORIGINAL ARTICLE

Transcatheter Closure of Patent Foramen Ovale in Older Patients With Cryptogenic Thromboembolic Events

Alberto Alperi, MD, PhD; Paul Guedeney, MD; Eric Horlick, MD; Luis Nombela-Franco, MD, PhD; Xavier Freixa, MD, PhD; Isaac Pascual, MD, PhD; Jules Mesnier, MD; Christine Houde, MD; Lusine Abrahamyan, MD, PhD; Gilles Montalescot, MD, PhD; Josep Rodés-Cabau, MD, PhD

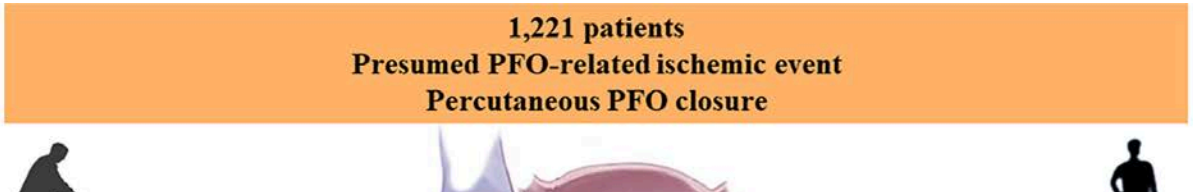
	Older cohort (>60 y; n=388)	Younger cohort (≤60 y; n=883)	*P* value
Successful device implantation	387 (99.9)	882 (99.9)	0.99
Device type			0.001
Amplatzer PFO	257 (66.2)	679 (76.9)	
Amplatzer ASD	11 (2.8)	47 (5.3)	
Amplatzer Cribiform	26 (6.7)	35 (3.9)	
Cardia atriasept	19 (4.9)	12 (1.4)	
Occlutech	28 (7.2)	92 (10.4)	
Starflex	36 (9.3)	0	
Gore cardioform	6 (1.5)	1 (0.1)	
Helex	1 (0.3)	0	
Noble stitch	1 (0.3)	0	
Premere	3 (0.8)	17 (1.9)	
Device size, mm			0.001
<25	13/354 (3.7)	39/778 (5)	
25	125/354 (35.3)	355/778 (45.6)	
>25	139/354 (61)	384/778 (49.4)	
In-hospital complications			
Device embolization*	2 (0.5)	1 (0.1)	0.22
Device thrombosis*	0	2 (0.2)	1
Cardiac perforation	0	0	-
Tamponade	0	0	-
Atrial fibrillation/flutter*	4 (1)	9 (1)	0.98
Myocardial infarction*	1 (0.3)	1 (0.1)	0.52
DVT/pulmonary embolism*	0	1 (0.1)	0.99
Aortic dissection	0	0	-
Atrioventricular block	0	0	-
Esophageal hematoma*	0	1 (0.1)	0.99
Minor vascular complication	2 (0.5)	7 (0.8)	0.73

PFO closure in older patients



Wintzer-Wehekind et al. Rev Esp Cardiol 2020

PFO closure in older patients



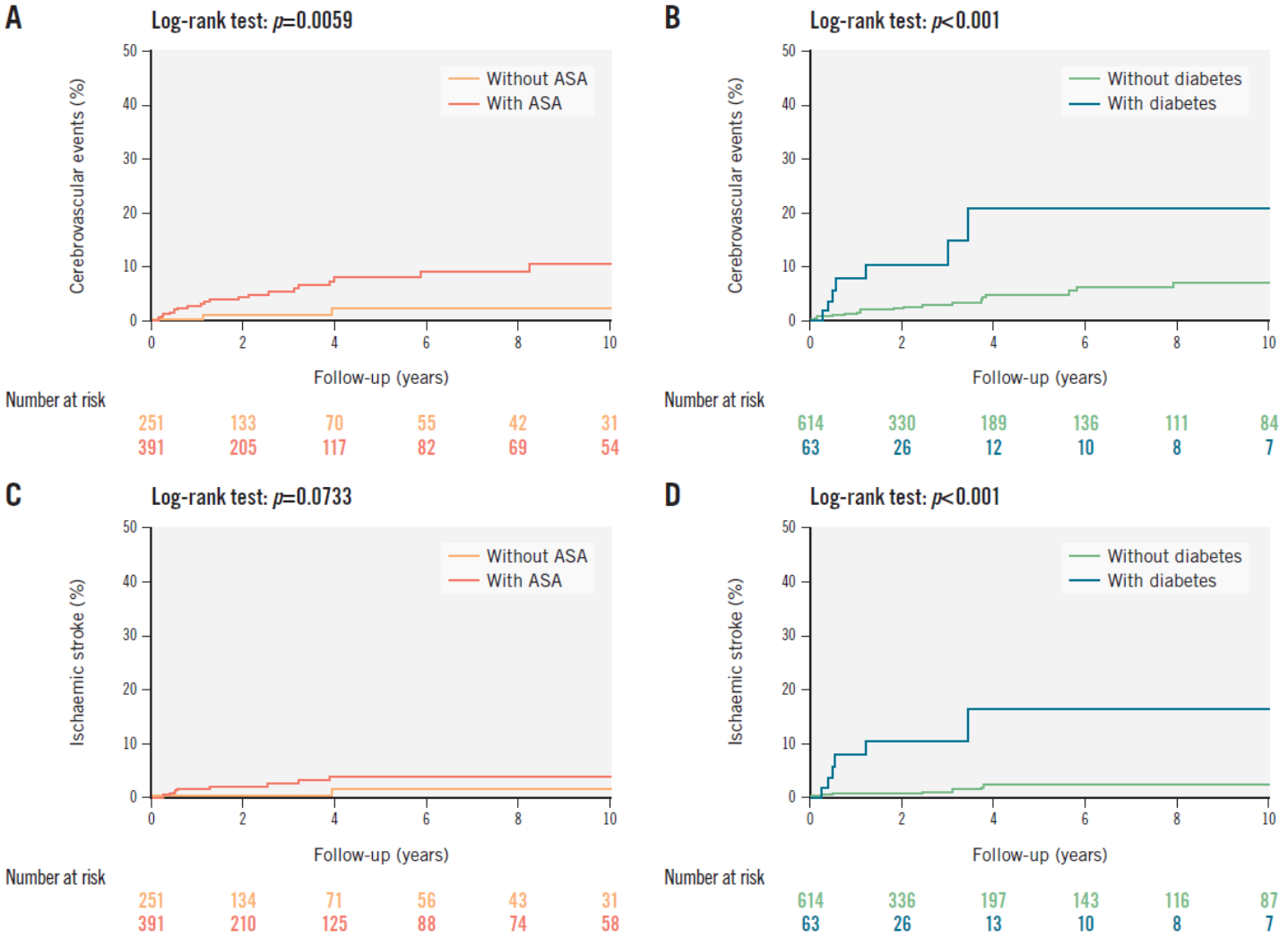
Observed-to-Expected Rates of TIA/Stroke

The observed 2-year rate of TIA/stroke among patients with available RoPE score in the older group (n=271) was 3.3%, whereas the estimated 2-year recurrence according to the RoPE score was 10.6%, yielding an observed-to-expected ratio of 0.31 (95% CI, 0.11–0.91).

0.59 events per 100 patient-years	IRR: 6.1 (95%CI 1.7-27.3)	0.09 events per 100 patient-years
	TIA	
1.05 events per 100 patient-years	IRR: 4.6 (95%CI 1.96-12.1)	0.22 events per 100 patient-years
	STROKE/TIA	
1.64 events per 100 patient-years	IRR: 4.7 (95%CI 2.36-9.80)	0.34 events per 100 patient-years

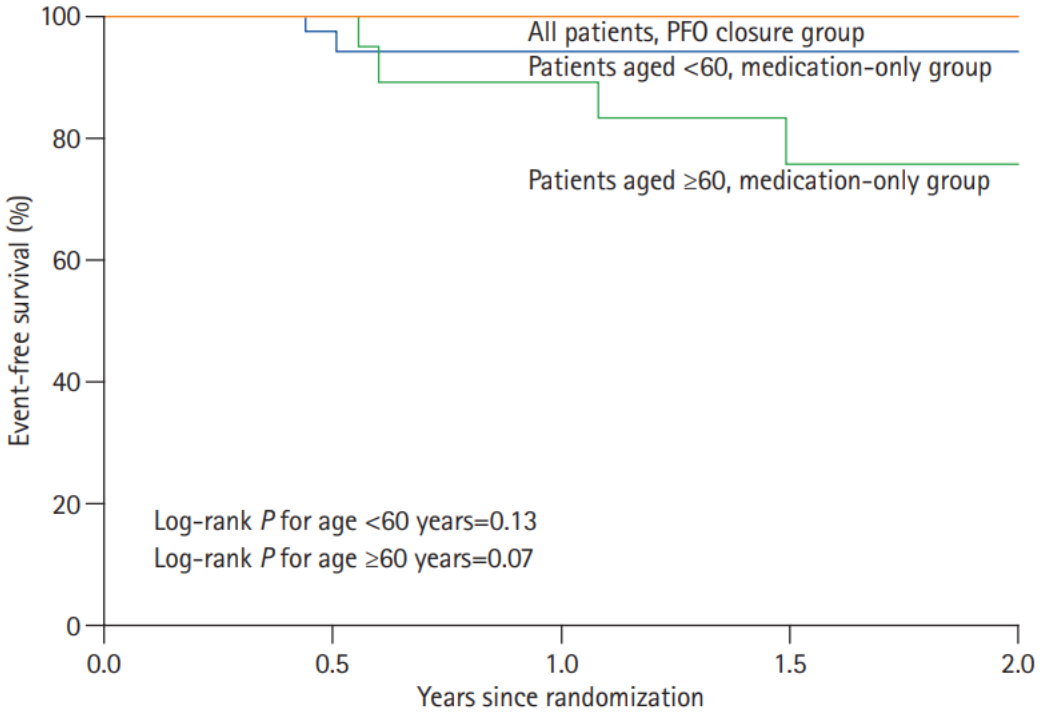
Alperi et al.
Circ Cardiovasc Interv 2022

PFO closure in older patients



Farjat-Pasos et al.
Eurointervention 2024

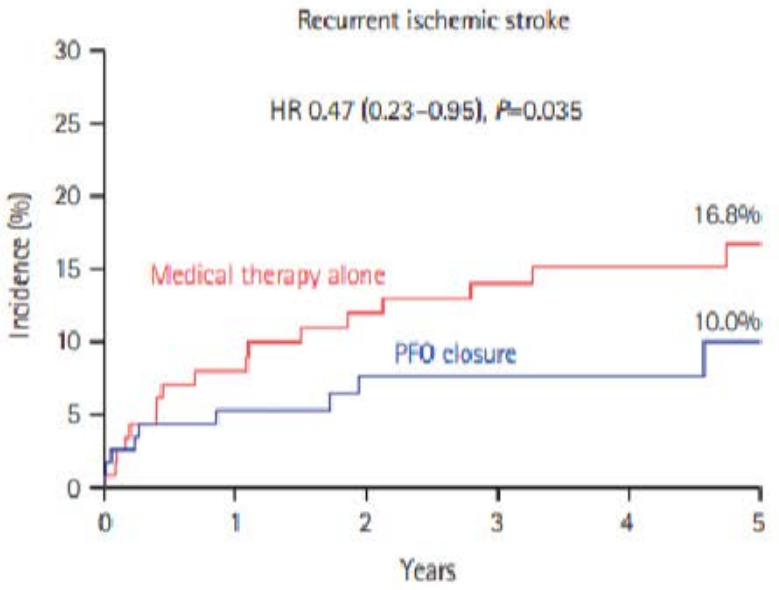
PFO closure vs. Medical treatment in older patients



Number at risk					
Age <60 years					
PFO closure	47	39	35	31	29
Medication-only	39	32	28	26	25
Age ≥60 years					
PFO closure	13	13	12	12	12
Medication-only	21	19	15	10	10

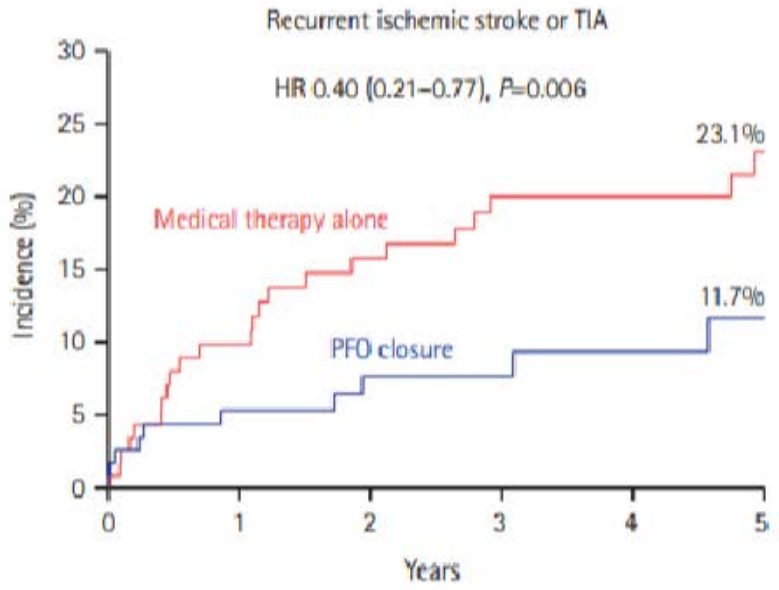
Kwon et al. J Stroke 2021

PFO closure vs. Medical treatment in older patients



Number at risk

Medical therapy alone	116	95	89	80	63	51
PFO closure	116	97	80	57	44	37



Number at risk

Medical therapy alone	116	93	85	74	60	48
PFO closure	116	97	80	57	44	37

Lee et al. J Stroke 2024

DEVICE CLOSURE OF PATENT FORAMEN OVALE IN PATIENTS >60 YEARS WITH ISCHEMIC STROKE: RESULTS FROM U.S. MEDICARE BENEFICIARIES

Jeffrey L Saver, MD

David Geffen School of Medicine, University of California-Los Angeles, Los Angeles

Ruby Satpathy, Josep Rodés-Cabau, David Thaler, David Kent, Samuel Turner, Srini Potluri,

Kranthi Kolli, Nils Peter Borgstrom, Julie B Prillinger, Jeffrey L Saver

ESOC 2024

Background and Objective

- Randomized clinical trials have demonstrated reduction of recurrent ischemic stroke events following transcatheter PFO closure in patients with age 18 – 60 years

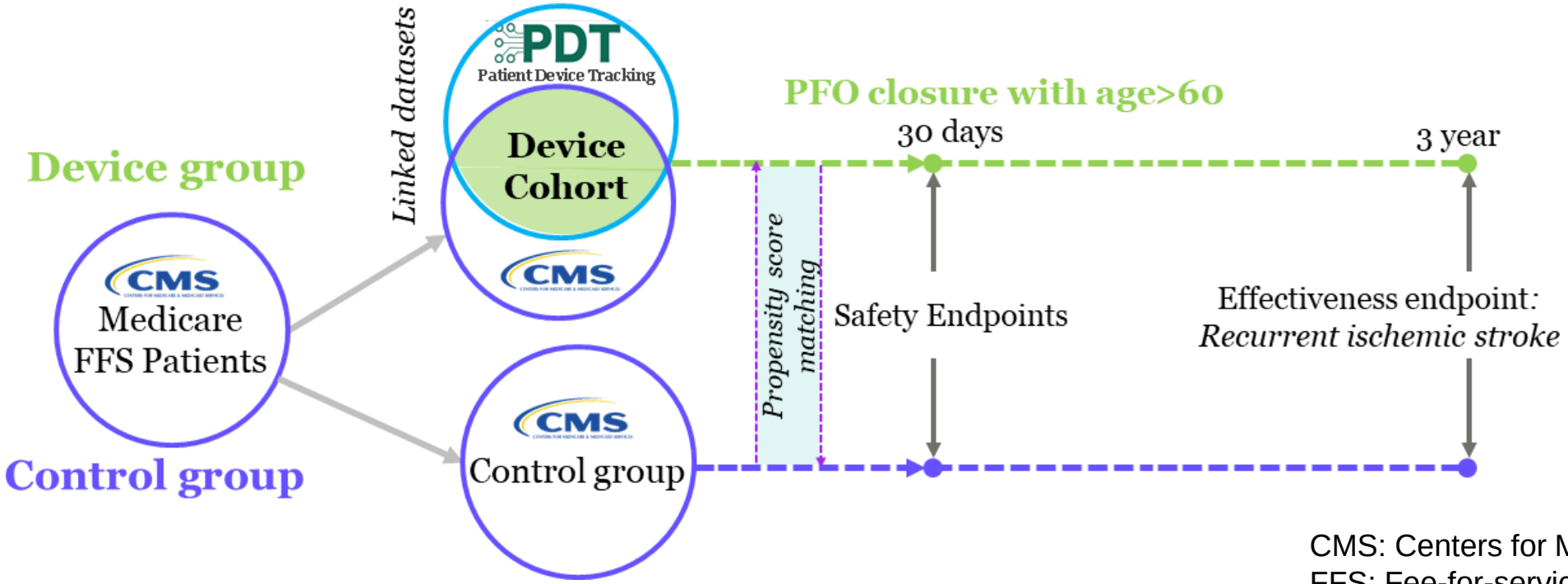
- Data in patients with age>60 is currently lacking
  - Studies reporting device related outcomes in patients with age>60 are currently limited by cohort size

- **Objective of this study is to assess the clinical outcomes of U.S. Medicare beneficiaries >60 years old implanted with Abbott Amplatzer™ and Amplatzer™ Talisman™ PFO Occluder compared with those without the device**

Methods

Retrospective observational study using Medicare administrative claims data

- Key Inclusion criteria: 6 months of prior enrollment, history of ischemic stroke diagnosis
- Key Exclusion criteria: history of atrial fibrillation or flutter



CMS: Centers for Medicare & Medicaid Services
FFS: Fee-for-service
PDT: Patient device tracking

Methods: Consort diagram

Device Group

Patients >60 years with IS and Amplatzer PFO Occluder in Abbott PDT (N=5,520)

Linked to Medicare fee-for-service claims data (N=2,154)

Meeting study eligibility criteria (N=1,132)

Matched treatment arm (**N=1,132**)

Control Group

Patients >60 years with IS and PFO/ASD diagnosis (N=49,311)

Patients without a PFO/ASD intervention during study period (N=45,568)

Meeting study eligibility criteria (N=19,867)

Matched control arm (**N=4,376**)

1:4 Propensity score (PS) Matching

IS: Ischemic stroke
ASD: Atrial septal defect
PFO: Patent foramen ovale
PDT: Patient device tracking

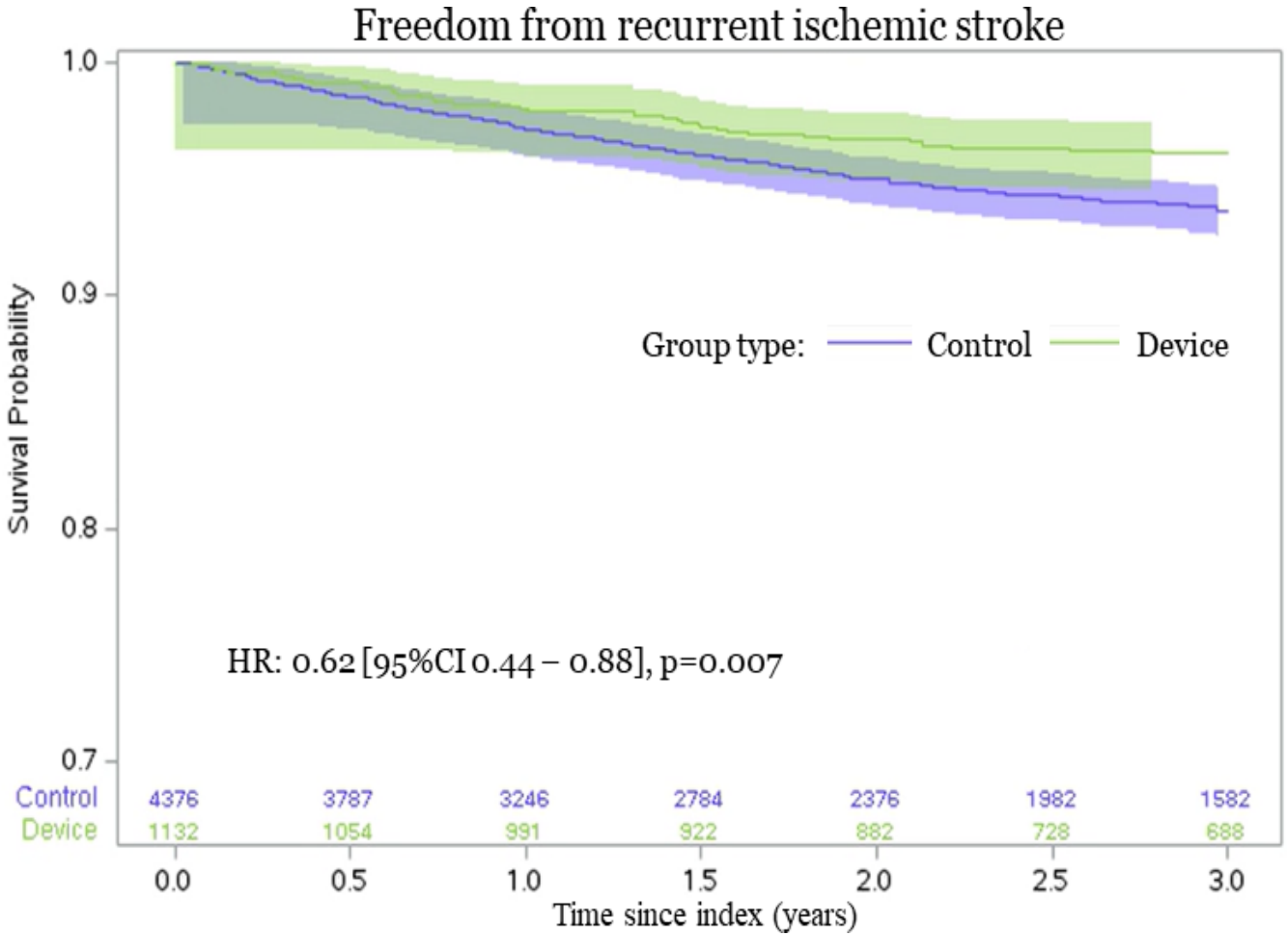
Results: Patient demographics

	Before matching			After matching		
	Device group (N=1,132)	Control group (N=19,867)	SMD	Device group (N=1,132)	Control group (N=4,376)	SMD
Age (years)	71.6±5.39	76.3±7.97	-0.691	71.6±5.39	71.8±6.11	-0.041
Female gender	510 (45.1%)	10,099 (50.8%)	-0.116	510 (45.1%)	1,938 (44.3%)	-0.015
Race						
White	983 (86.8%)	15,844 (79.8%)	0.191	983 (86.8%)	3,785 (86.5%)	0.010
Black	58 (5.1%)	2,113 (10.6%)	-0.206	58 (5.1%)	243 (5.6%)	-0.019
Other	91 (8.0%)	1,910 (9.6%)	-0.070	91 (8.0%)	348 (7.9%)	-0.010
Comorbidity						
Smoking	521 (46.0%)	10,528 (51.6%)	-0.112	521 (46.0%)	2,053 (46.9%)	-0.018
Hyperlipidemia	987 (87.2%)	17,784 (89.5%)	-0.073	987 (87.2%)	3,836 (87.7%)	-0.014
Systemic emboli	72 (6.4%)	1,191 (6.0%)	0.015	72 (6.4%)	291 (6.6%)	-0.012
Migraine	163 (14.4%)	1,339 (6.7%)	0.251	163 (14.4%)	577 (13.2%)	0.035
Peripheral vascular disease	394 (34.8%)	9,072 (45.7%)	-0.228	394 (34.8%)	1,533 (35.0%)	-0.005
Thrombophilia	99 (8.7%)	1,363 (6.9%)	0.070	99 (8.7%)	358 (8.2%)	0.02
Johns Hopkins claims-based frailty index (JH-CFI) category*						
Low-risk (<0.12)	644 (56.9%)	5,055 (25.4%)	0.674	644 (56.9%)	2,379 (54.4%)	0.051
Intermediate-risk (0.12-0.20)	275 (24.3%)	4,376 (22.0%)	0.054	275 (24.3%)	1,149 (26.3%)	-0.045
High-risk (>0.20)	213 (18.8%)	10,436 (52.5%)	-0.752	213 (18.8%)	848 (19.4%)	-0.014

SMD: Standardized mean difference

**Segal et al., Development of a Claims-based Frailty Indicator Anchored to a Well-established Frailty Phenotype. Med. Care. 2017.*

Results: Effectiveness endpoint through 3 years



Event rate (per 100 PY)		Incidence rate ratio (IRR) (control as reference)
Device	1.65 [1.18-2.13]	**0.62** [0.46-0.85]
Control	2.66 [2.33-3.00]	

Relative risk reduction (RRR)=**38%**

Conclusions

- **Largest** comparative study in patients over 60 years
- *Effectiveness endpoint*
  - Recurrent Ischemic stroke (IS) event rate post PFO implant is comparable to that reported in literature[1]
  - RRR in age>60 was about **38%** compared to 59% in age<60[2] as seen in RCTs

Study	Sample size: Device	Recurrent IS event rate (device)	IRR / Hazard ratio
Current study (Incidence of Ischemic stroke in pts >60)	1,132	1.65 [1.18 – 2.13] per 100 PY	IRR: 0.62 [0.46-0.85] => RRR=38%
Alperi et al[1] (Incidence of Stroke/TIA/peripheral embolism in pts >60 yrs)	388	1.61 [1.06 – 2.40] per 100 PY	NR
SCOPE consortium: Meta analysis[2] of 6 PFO RCT's (Incidence of Ischemic stroke in from 6 PFO RCT's in age≤60)	1,889	0.47 [0.35 – 0.65] per 100 PY	HR: 0.41 [0.28 -0.60]] => RRR=59%

- *Safety endpoints*
  - Rate of patients with safety endpoint related outcomes is low
- In properly selected patients >60 years of age PFO closure may be beneficial in reducing recurrent ischemic stroke with a low incidence of adverse events.

1. *Alperi et al., Transcatheter Closure of Patent Foramen Ovale in Older Patients With Cryptogenic Thromboembolic Events. Cicr. Card. Interv. 2022.*
2. *Kent et al, Heterogeneity of Treatment Effects in an Analysis of Pooled Individual Patient Data From Randomized Trials of Device Closure of Patent Foramen Ovale After Stroke. JAMA 2021*

Guideline

EUROPEAN STROKE JOURNAL

European Stroke Journal
1–35

DOI: 10.1177/23969873241247978
journals.sagepub.com/home/eso
Sage

European Stroke Organisation (ESO) Guidelines on the diagnosis and management of patent foramen ovale (PFO) after stroke

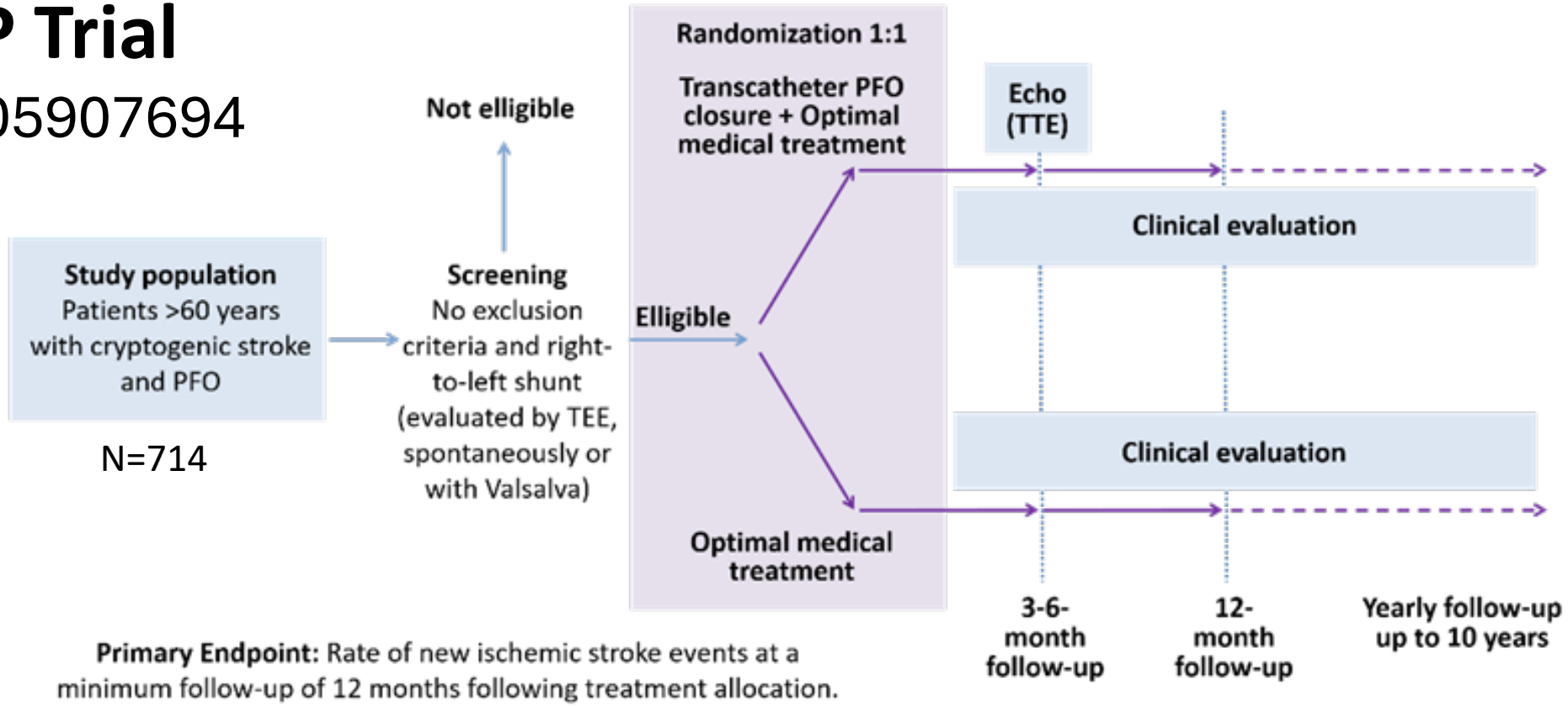
Valeria Caso[1], Guillaume Turc[2], Azmil H Abdul-Rahim[3,4,5], Pedro Castro[6], Salman Hussain[7], Avtar Lal[7], Heinrich Mattle[8], Eleni Korompoki[9], Lars Søndergaard[10], Danilo Toni[11], Silke Walter[12] and Christian Pristipino[13]

Expert consensus statement

This panel encourages the inclusion of patients **older than 60 years old** with stroke and PFO in randomised trials whenever possible, or at least in a registry. If this is not possible, the majority of the module working group members suggest using the PASCAL Classification System and clinical judgement to guide therapy.
Vote: 8/9 experts agree
This panel suggests PFO closure in selected patients aged between 13 and 17 with PFO-related stroke according to PFO anatomy.
Vote:9/9 experts agree

STOP Trial

(NCT05907694)



Supported by the ***Canadian Institutes of Health Research***

Study design

STOP TRIAL: PARTICIPATING SITES

Activated

- IUCPQ, Quebec (PI: Josep Rodés Cabau; Steve Verreault)
- CHUM, Montreal (PIs:Jean-Bernard Masson, Alexandre Poppe)

REB/contract pending

- MHI, Montreal (PIs: Sylvain Lanthier, Reda Ibrahim)
- OHI, Ottawa (PIs: Omar Abdel-Razek, Dylan Blacquiere)
- TGH, Toronto (PIs: Eric Horlich, Kanjana Perera)
- St-Boniface, Winnipeg (PIs: A. Shah, E. Ghrooda)
- Sunnybrook, Toronto (PI: David J. Gladstone)
- Southlake Regional Center, Ontario (PI: Asim Cheema)

Activated

- Hospital Clínic Barcelona(PIs: Xavier Freixa, A Chamorro)

REB/contract pending

- Hospital Clínico San Carlos (PI: Luis Nombela, Patricia Simal)
- Hospital de la Santa Creu i Sant Pau (PI: Dabit Arzamendi, Pol Camps-Renom)
- Hospital Central de Asturias (PI: Alberto Alperi, María Rico)
- Hospital Universitari Son Espases (PI: Tania Rodríguez Gabella, Rosa Díaz)
- University Hospital Donostia (PI: Miren Telleria)
- Hospital Alvaro Conquerio (PI: Rodrigo Estevez, Jose Maciñeiras)
- Hospital Universitario de Salamanca (PI: Ignacio Cruz Gonzalez)
- Hospital La Paz (PI: Raul Moreno, Blanca Fuentes)
- Hospital Josep Trueta (PI: Sergi Moral Torres, Yolanda Silva)
- Hospital Arnau de Vilanova de Lleida (PI: Francesc Purroy)
- Hospital Universitario Fundación Jiménez Díaz (PI:Felipe Navarro del Amo, Inmaculada Navas Vinagre)
- Hospital Universitario 12 de Octubre (PI: Jorge Nuche, Patricia Calleja Castano)
- Hospital Universitario Miguel Servet (PI: Marta López Ramón, Herbert Tejada Meza)
- Hospital Clinico Universitario Virgen de la Arrixaca(PI: Eduardo Pinar Bermudez, Laura Albert Lacal)
- A Coruña (PI: Fernando Rueda, M Castellanos)

STOP TRIAL PARTICIPATING QUÉBEC CENTRES

IUCPQ-ULaval
Hôpital de l'Enfant-Jésus
Hôtel-Dieu de Lévis
Hôpital de Chicoutimi
Centre hospitalier régional du Grand-Portage (Rivière-du-Loup)

- **Principal investigators**
  - Neurologist: Steve Verreault
  - Cardiologist: Josep Rodés-Cabau
- **Global Study Coordinator**
  - Mélanie Côté (melanie.cote@criucpq.ulaval.ca)

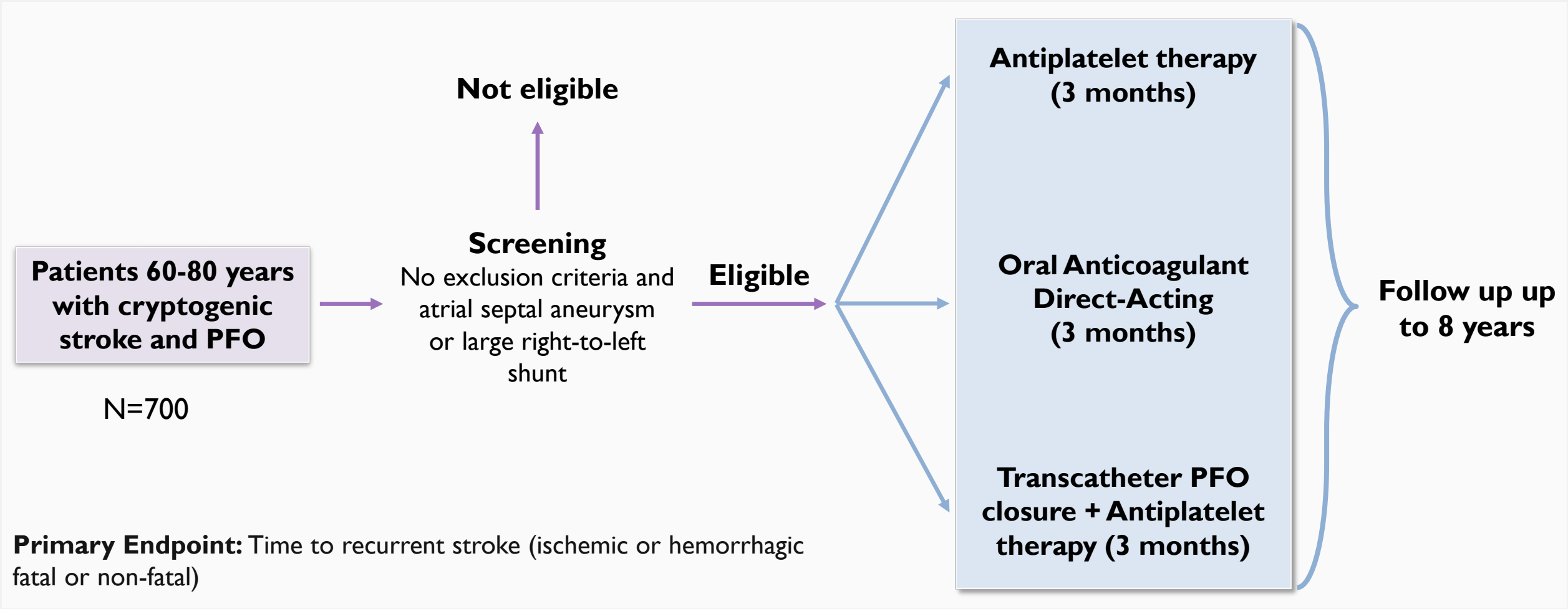
Montreal Heart Institute
Hôpital du Sacré-Cœur de Montréal

- **Principal investigators**
  - Neurologist: Sylvain Lanthier
  - Cardiologist: Reda Ibrahim
- **Study Coordinator**
  - Sophie Robichaud

Centre hospitalier de l'Université de Montréal (CHUM)

- **Principal investigators**
  - Neurologist: Alexandre Y. Poppe
  - Cardiologist: Jean-Bernard Masson
- **Study Coordinators**
  - Émilie Sau and Adriana Carbonaro

CLOSE 2 TRIAL: STUDY DESIGN



Primary Endpoint: Time to recurrent stroke (ischemic or hemorrhagic fatal or non-fatal)

NCT05387954

Fermeture du foramen ovale perméable en haut de 60 ans: POUR

- FOP et patients âgés avec AVC cryptogénique: ↑ Prevalence; ↑ Risk
- Fermeture FOP: sécuritaire
- Études préliminaires: Diminution risque d'AVC (38% a 53%)
- Études randomisés: STOP, CLOSE 2