Evidenze e Nuove Prospettive nel Trattamento del Tromboembolismo Venoso

Varese 15-16 Marzo 2018

La gestione del PFO nella prevenzione secondaria dello stroke

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Stroke: epidemiology

- Stroke is **the fifth leading cause of death in the United States**, and the **second leading cause of death globally**
- In 2010, an estimated 16,9 million incident strokes occurred, which added to a pool of 33 million stroke survivors worldwide. There were **5,9 million deaths** and 102 million DALYs lost due to stroke[1]
- Stroke **is ischemic in the 85% pts** and more common in subjects > 65 ys with atherosclerotic disease
- 50% of patients in rehabilitation centers are < 65yrs of age and **12% are < 45 yrs[2]**

1 *Lancet* 2014; **383:** 245–54
2 Circulation 2016;133(4):e38–60

Stroke in young people

- The overall incidence of stroke in young is about **one episode per 10,000 patients per year**

- It's well documented that **mortality after ischemic stroke is low** in young but information on functional outcome is sparse

- These cases have a **profound social impact because of the indirect costs** due to the long period of lost productivity

- The main differences between ischemic strokes in young adults and those occurring later in life, are the breakdown of causes with a **prominence of "unknown" and "other determined" causes, and an overall good outcome**

- Cases with **no determined cause account for up to 50% of all strok**es depending on how exhaustive the diagnostic work-up was

Putaaala J.Stroke 2009;40:1195–2003

Cryptogenic Ischemic Stroke

Cryptogenic ischemic strokes are **symptomatic cerebral infarcts for which no probable cause is identified** after adequate diagnostic evaluation

- **“highly cryptogenic”** (with no probable and no possible cause discovered)

- **“possibly determined origin**” (with no probable, but one or more possible, causes identified).

As compared with strokes of determined origin, **cryptogenic ischemic strokes** typically result **in less severe presenting neurologic deficits, less final disability, and lower mortality**. In most though not all long-term follow-up studies, patients with cryptogenic ischemic stroke have a lower risk of recurrence than those with stroke of identified cause.

Top 5 most prevalent "rare" risk factors for stroke in young Western populations

Risk factor	TOAST classification‡	Prevalence in young patients with stroke§	Strength of association	Highest level of evidence‖
Migraine[99–103¶]	Unknown cause	20–24%	Pooled effect estimate ~2.0[104]	A1, association proven for migraine with aura only
Illicit drug use[105–109]	Other (rare) causes	9–20%	OR 2.0 for cocaine;[105] OR 2.3 for cannabis;[108#] no significant association for amphetamines[105]	A2 for cocaine; B for amphetamines, cannabis and heroin
Patent foramen ovale[110–113]	Possible cardiac embolism; low-risk source	24%, up to 50% in stroke, classified as cryptogenic	HR ~1.5 (nonsignificant)[111]	A2, contrasting with evidence from B-level studies
Oral contraceptives[102,114–119]	Other (rare) cause/unknown	10–40%	Summary OR 2.1[115]	B
Pregnancy/ puerperium[120–124]	Other (rare) cause/unknown	7.5% in women	Relative risk 8.7 during puerperium, not during pregnancy[122]	A2, conflicting results

Maijwee NAMM et al. *Nat Rev Neurosci* 2014;10(6):315-25

Patent Foramen Ovale

- It is an interatrial passage typically closes within 3 months after birth but may persist throughout life
- The prevalence decreases gradually with increasing age, from 34% during the first three decades to 20% during the ninth decade.
- It is the most common cause of a right to-left shunt.
- It potentially allows venous thromboemboli to avoid filtration in the pulmonary vasculature and enter the systemic arterial circulation: Paradoxical Embolism
- The mean diameter of a patent foramen ovale is 4.9 mm, which is more than sufficient to permit the passage of emboli that are large enough to occlude the trunk of the middle cerebral artery (3 mm) and major cortical branches (1 mm).

N Engl J Med 2001; 345: 1740-6.

Patent Foramen Ovale

- PFO is present in approximately **one quarter of the general patient population** but in one **half of patients with cryptogenic stroke.**

- A Bayesian attributable risk analysis of pooled data from 12 studies suggested that among patients with cryptogenic stroke who had a patent foramen ovale, it is probably causally related to the stroke in approximately half of cases

- **Factors increasing this risk of stroke :**

➢ younger age;
➢ Valsalva maneuver at the onset of stroke;
➢ extended airplane or car travel preceding the stroke or documented concomitant venous thrombosis;
➢ coexisting venous hypercoagulable state;
➢ history of migraine with aura
➢ cortical location, multiplicity, and large size of cerebral infarcts;
➢ absence of hypertension, diabetes, and smoking.

Saver et al Curr Atheroscler Rep 2007; 9: 319-25
Alsheikh-Ali AA et al Stroke 2009; 40: 2349-55

ORIGINAL ARTICLE

Interaction between proatherosclerotic factors and right-to-left shunt on the risk of cryptogenic stroke: the Italian Project on Stroke in Young Adults

Alessandro Pezzini,[1] Mario Grassi,[2] Corrado Lodigiani,[3] Rosalba Patella,[4] Carlo Gandolfo,[5] Andrea Zini,[6] Rossella Musolino,[7] Rocco Salvatore Calabrò,[8] Paolo Bovi,[9] Alessandro Adami,[10] Maria Luisa DeLodovici,[11] Elisabetta Del Zotto,[1] Lidia Luciana Rota,[3] Maurizia Rasura,[4] Massimo Del Sette,[12] Alessandra Spalloni,[4] Alessia Giossi,[1] Irene Volonghi,[1] Federica Casoni,[6] Paolo Cerrato,[13] Paolo Costa,[1] Mauro Magoni,[14] Antonella Toriello,[15] Maurizio Paciaroni,[16] Giorgio Dalla Volta,[17] Licia Iacoviello,[18] Alessandro Padovani,[1] on behalf of the Italian Project on Stroke in Young Adults (IPSYS) Investigators

Table 2 Right-to-left shunt and proatherosclerotic score interaction effect on the risk of cryptogenic stroke

Right-to-left shunt	Proatherosclerotic score	Cases*	Controls	OR (95% CI)	RD (95% CI)†
Absent	0	114 (19.8)	303 (51.8)	1	0
	1 or more	181 (31.5)	163 (27.9)	2.73 (1.98 to 3.76)	+0.246 (+0.17 to +0.32)
Present	0	125 (21.8)	62 (10.6)	5.14 (3.49 to 7.58)	+0.388 (+0.31 to +0.47)
	1 or more	154 (26.9)	57 (9.7)	7.38 (4.97 to 11.0)	+0.462 (+0.38 to +0.54)

Conclusions **The influence of RLS on the risk of CS decreases with increasing number of atherosclerotic factors, and is highest when such factors are absent.**

Individual pro-atherosclerotic profiles may help to identify patients with CS whose patent foramen ovale is probably pathogenic.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Patent Foramen Ovale and Cryptogenic Stroke in Older Patients

Michael Handke, M.D., Andreas Harloff, M.D., Manfred Olschewski, M.Sc., Andreas Hetzel, M.D., and Annette Geibel, M.D.

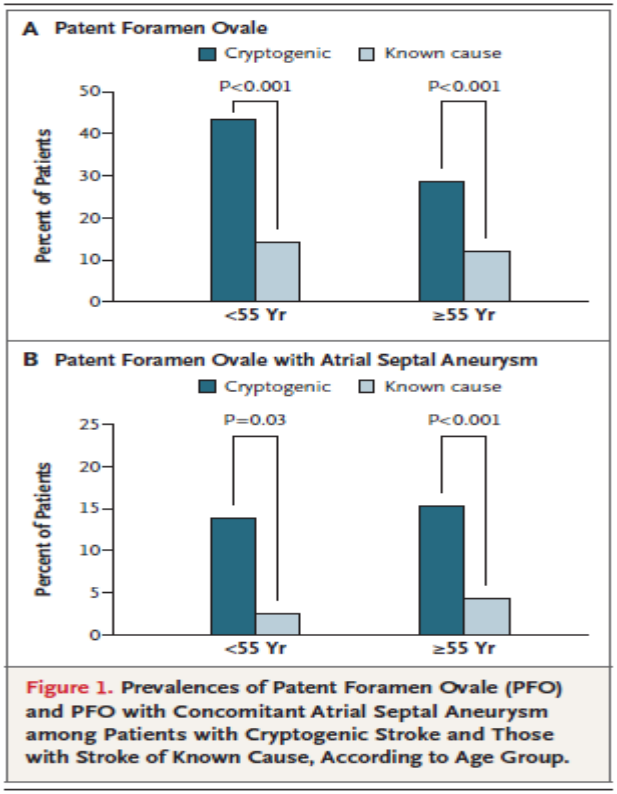


Figure 1. Prevalences of Patent Foramen Ovale (PFO) and PFO with Concomitant Atrial Septal Aneurysm among Patients with Cryptogenic Stroke and Those with Stroke of Known Cause, According to Age Group.

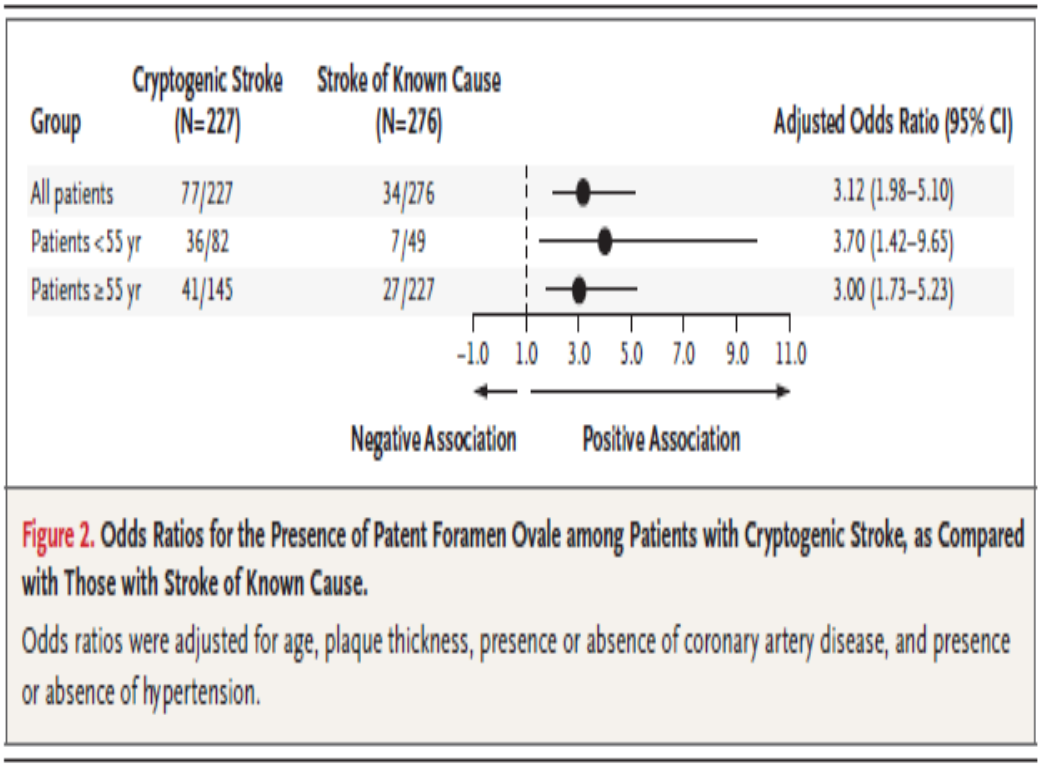


Figure 2. Odds Ratios for the Presence of Patent Foramen Ovale among Patients with Cryptogenic Stroke, as Compared with Those with Stroke of Known Cause.

Odds ratios were adjusted for age, plaque thickness, presence or absence of coronary artery disease, and presence or absence of hypertension.

N Engl J Med 2007;357:2262-8.

ASA and PFO

Meta-analysis of 4 studies:

A hypermobile septum primum, referred to as an **atrial septal aneurysm (ASA**), associated **with a PFO** has been found to increase

-the risk of an initial stroke (OR: 4.96; 95% CI: 2.37 to 10.39)

-and recurrent stroke (OR: 23.93; 95% CI:3.09 to 185.42)

JACC. 2018, Vol 71

Medical Prophylaxis in PFO pts with stroke

- **Aspirin** at a dose of 300 mg daily is associated with low rates of recurrent stroke[1]
- Meta-analyses of data from observational and randomized trials suggest that **warfarin has efficacy that is similar to or greater than aspirin**, particularly among patients with superficial territory infarcts[2,3].
- Newer, **direct oral anticoagulants** have not been formally tested

1. Mas J-L. N Engl J Med 2001; 345: 1740-6.
2. Kent D.M. Eur Heart J 2015; 36: 2381-9
3. Kitsios GDStroke 2012; 43: 422-31.

Closure vs Medical Therapy: Observational Studies

A meta-analysis of 48 observational comparative studies (n: 10,327)

patients with cryptogenic stroke or transient ischemic attack (TIA) who received medical therapy had a 6.3-fold increased rate of recurrent neurological events compared with patients who underwent percutaneous PFO closure

Agarwal S, J Am Coll Cardiol Intv 2012;5:577

2012: CLOSURE I

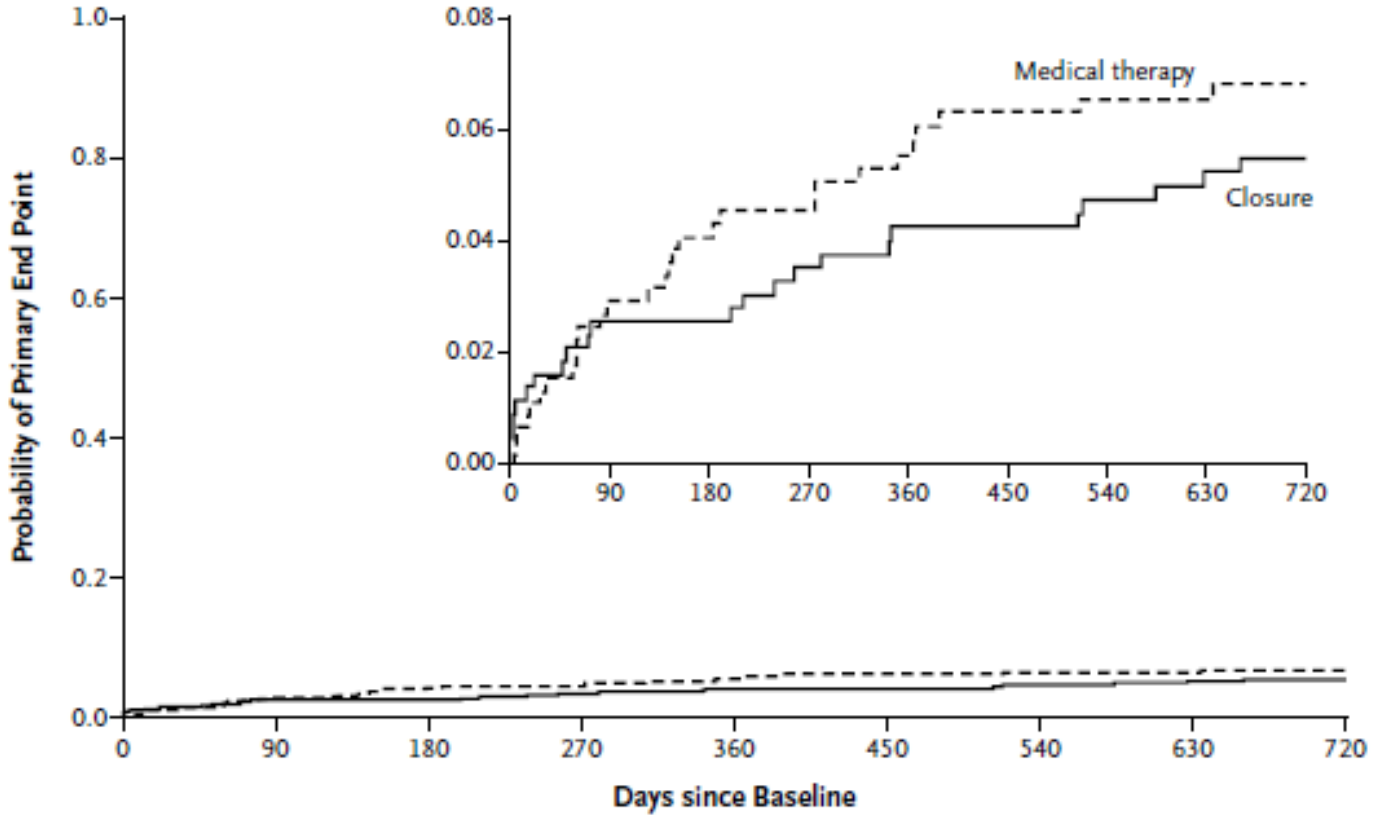
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

- 909 Pts
- AntiPLT vs AntiPLT + PFO closure
- Primary endpoint: stroke or TIA in 2 ys f-up, death for any cause in the first 30dd, death for neurologic causes between 31 days and 2 years

CLOSURE I



No. at Risk									
Closure	447	411	406	399	392	389	384	380	254
Medical therapy	462	421	405	388	378	365	359	356	242

Figure 1. Kaplan–Meier Curve of Time to Primary End Point through 2 Years of Follow-up in the Closure and Medical-Therapy Groups.

CLOSURE I

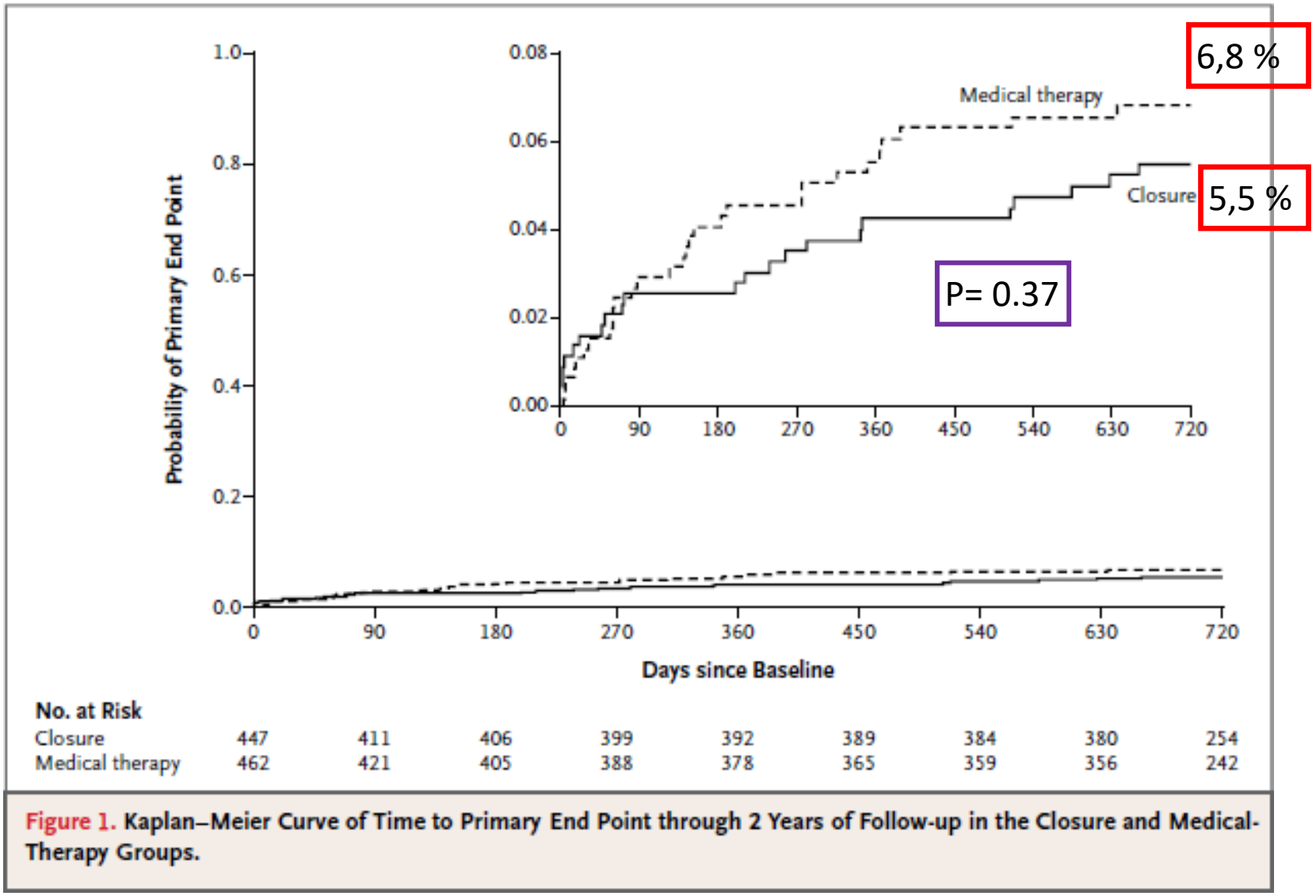


Figure 1. Kaplan–Meier Curve of Time to Primary End Point through 2 Years of Follow-up in the Closure and Medical-Therapy Groups.

2013: RESPECT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

- 980 Pts
- AntiPLT vs AntiPLT + PFO closure
- Primary endpoint:

  recurrent nonfatal ischemic stroke, fatal ischemic stroke, early death after randomization

RESPECT

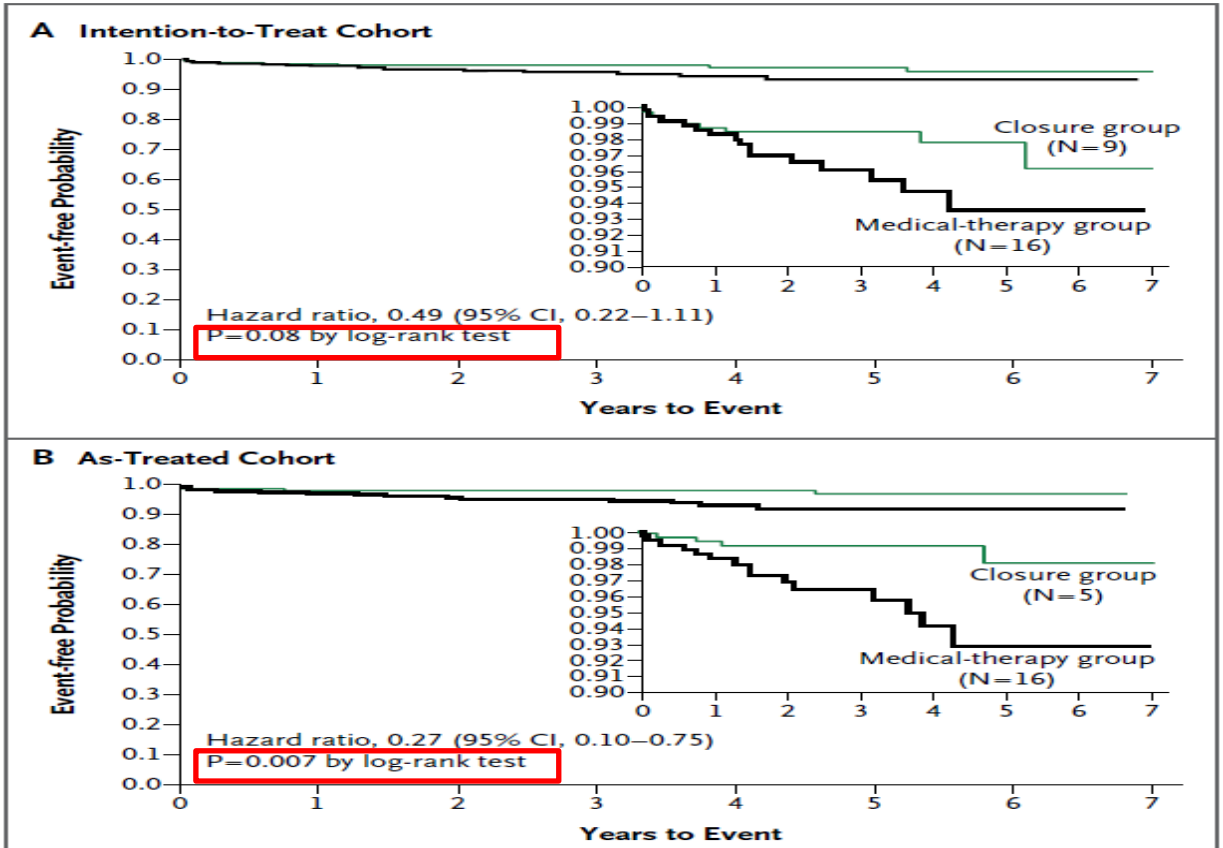


Figure 1. Primary End-Point Events in the Intention-to-Treat and As-Treated Cohorts.

In the intention-to-treat cohort (Panel A), there were 25 primary end-point events, all of which were recurrent nonfatal ischemic strokes; 9 occurred in patients who were assigned to the closure group and 16 in patients assigned to the medical-therapy group. Three patients with recurrent ischemic stroke who had been randomly assigned to the closure group did not have a device in place at the time of the recurrent stroke. The as-treated cohort (Panel B) included all patients who received a protocol-approved treatment and adhered to the protocol-mandated medical treatment; in this cohort, patients were classified according to the treatment they actually received, regardless of the randomization assignment. The insets show the same data on an enlarged y axis.

RESPECT

CONCLUSIONS

In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ischemic stroke. However, closure was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks.

Raccomandazione 11.2.a **Forte a favore** **Grado A**

Nei pazienti con ictus ischemico o TIA criptogenetico associati a forame ovale pervio (FOP) che non abbiano altre indicazioni a terapia anticoagulante è raccomandato il trattamento con ASA 100- 325 mg/die.

Raccomandazione 11.2.b **Forte a favore** **Grado A**

Nei pazienti con ictus ischemico o TIA criptogenetico associati a FOP che abbiano altre indicazioni alla TAO, quali evidenza di TVP o embolia polmonare, è raccomandato il trattamento con terapia anticoagulante.

Raccomandazione 11.2.c **Debole a favore** **Grado D**

Nei pazienti con recidiva di ictus ischemico o TIA associati a FOP pur in trattamento con antiaggreganti o con TAO, dopo una rivalutazione multidisciplinare del caso ed in accordo con il paziente, è indicata la chiusura del FOP.

Practice advisory: Recurrent stroke with patent foramen ovale (update of practice parameter)

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

ABSTRACT

Objective: To update the 2004 American Academy of Neurology guideline for patients with stroke and patent foramen ovale (PFO) by addressing whether (1) percutaneous closure of PFO is superior to medical therapy alone and (2) anticoagulation is superior to antiplatelet therapy for the prevention of recurrent stroke.

Methods: Systematic review of the literature and structured formulation of recommendations.

Conclusions: Percutaneous PFO closure with the STARFlex device possibly does not provide a benefit in preventing stroke vs medical therapy alone (risk difference [RD] 0.13%, 95% confidence interval [CI] −2.2% to 2.0%). Percutaneous PFO closure with the AMPLATZER PFO Occluder possibly decreases the risk of recurrent stroke (RD −1.68%, 95% CI −3.18% to −0.19%), possibly increases the risk of new-onset atrial fibrillation (AF) (RD 1.64%, 95% CI 0.07%–3.2%), and is highly likely to be associated with a procedural complication risk of 3.4% (95% CI 2.3%–5%). There is insufficient evidence to determine the efficacy of anticoagulation compared with antiplatelet therapy in preventing recurrent stroke (RD 2%, 95% CI −21% to 25%).

Recommendations: Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting (Level R). In rare circumstances, such as recurrent strokes despite adequate medical therapy with no other mechanism identified, clinicians may offer the AMPLATZER PFO Occluder if it is available (Level C). In the absence of another indication for anticoagulation, clinicians may routinely offer antiplatelet medications instead of anticoagulation to patients with cryptogenic stroke and PFO (Level C). **Neurology® 2016;87:815–821**

2017: REDUCE

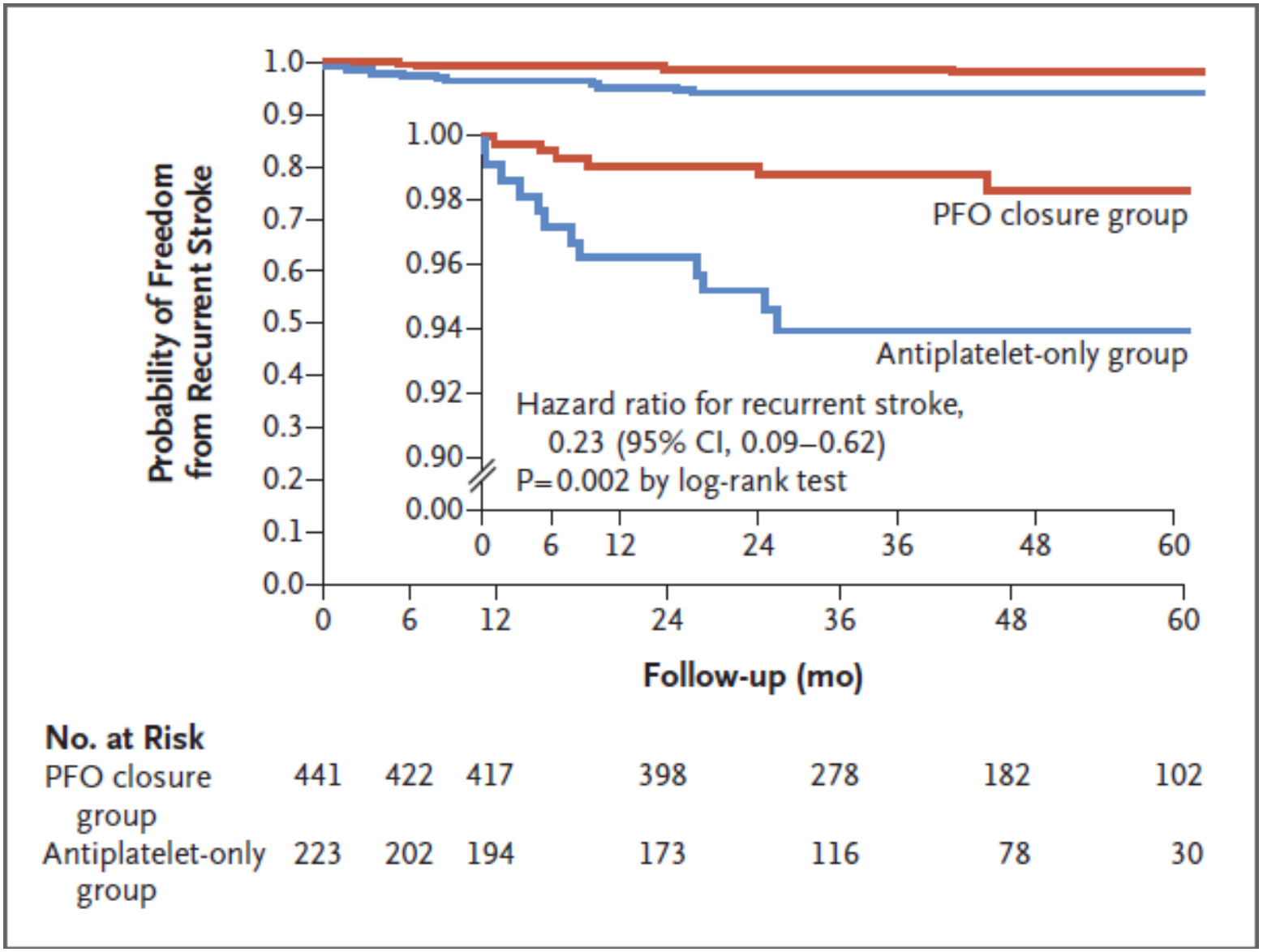
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

- 664 Pts
- Closure + antiPLT vs antiPLT alone
- Coprimary end point: clinical ischemic stroke or silent brain infarction on imaging

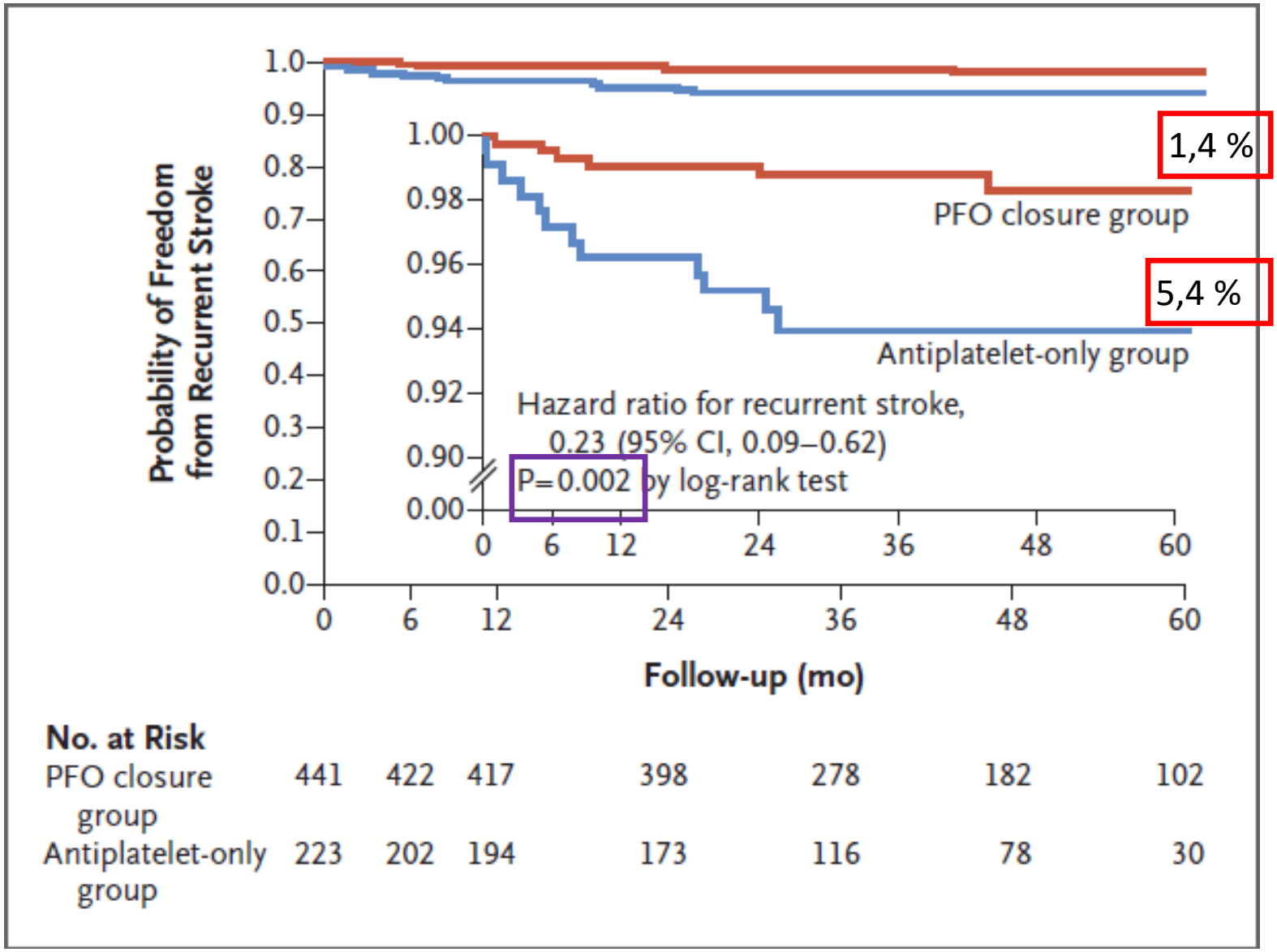
REDUCE



No. at Risk

PFO closure group	441	422	417	398	278	182	102
Antiplatelet-only group	223	202	194	173	116	78	30

REDUCE

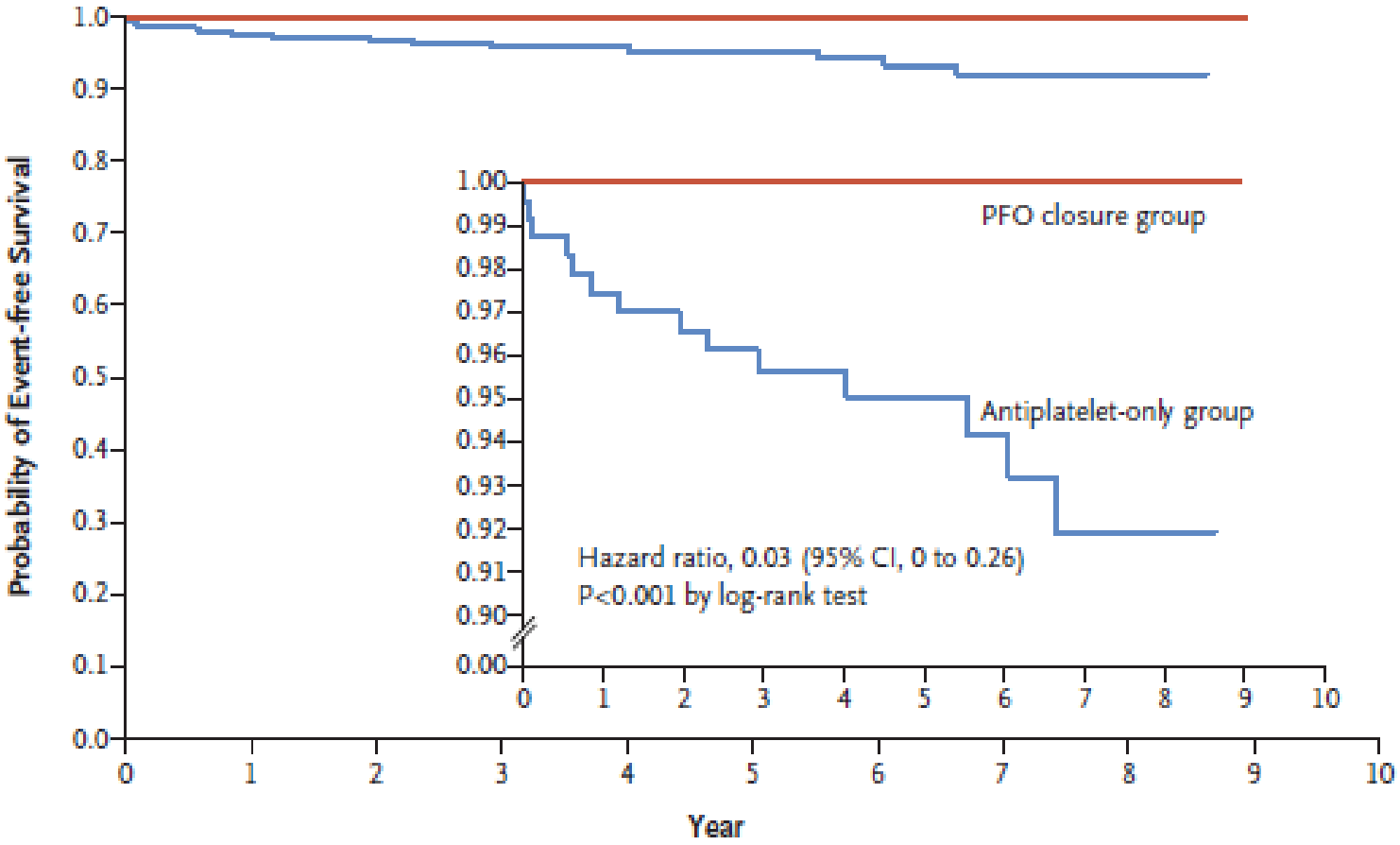


No. at Risk							
PFO closure group	441	422	417	398	278	182	102
Antiplatelet-only group	223	202	194	173	116	78	30

2017: CLOSE

- 663 Pts
- PFO closure + long-term antiPLT vs antiPLT only vs OAC
- Primary end point: fatal or nonfatal stroke

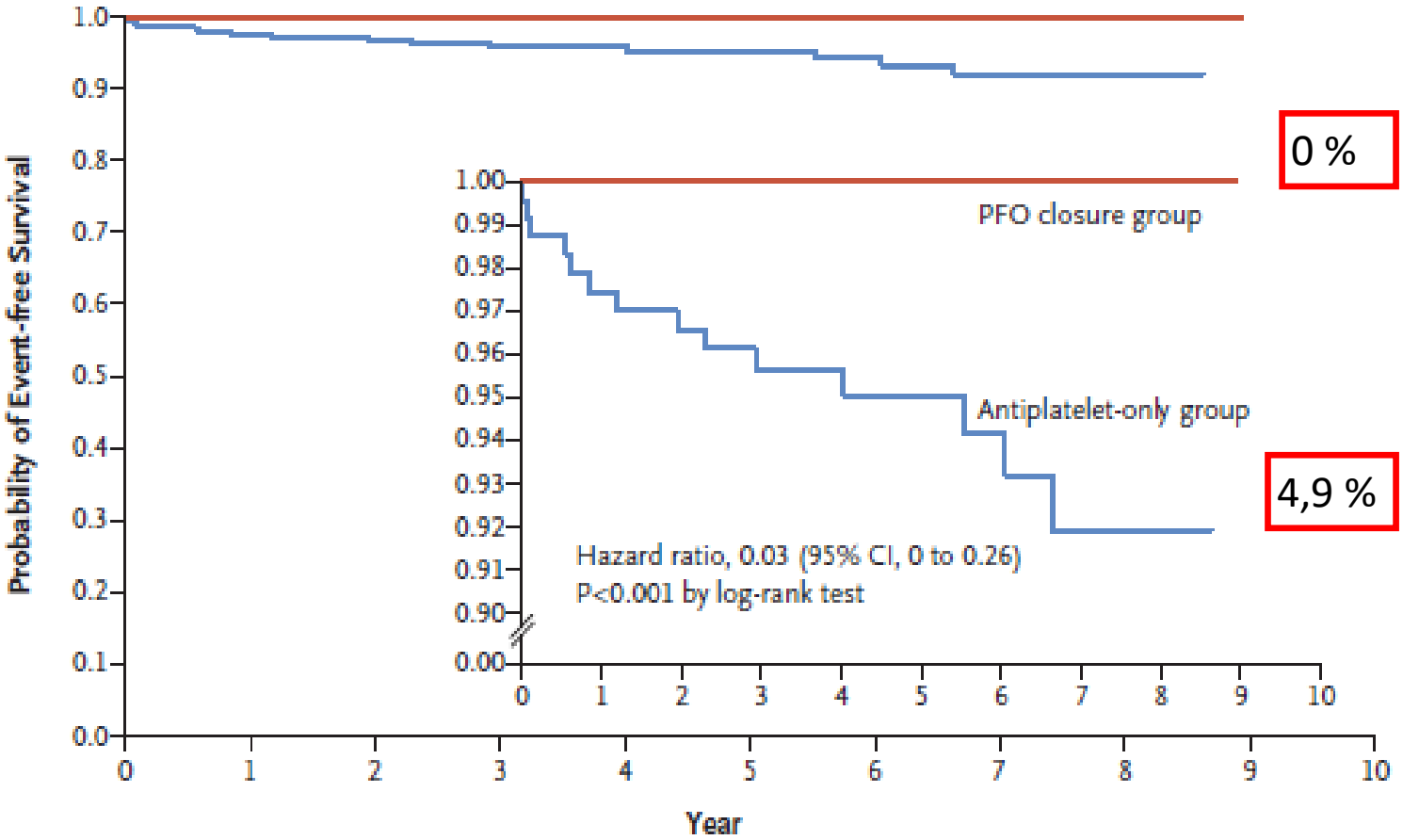
CLOSE



No. at Risk

PFO closure group	238	238	232	200	179	141	99	64	20	0	0
Antiplatelet-only group	235	229	223	198	160	130	96	55	19	0	0

CLOSE



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PFO closure group	238	238	232	200	179	141	99	64	20	0	0
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2017: long term from RESPECT

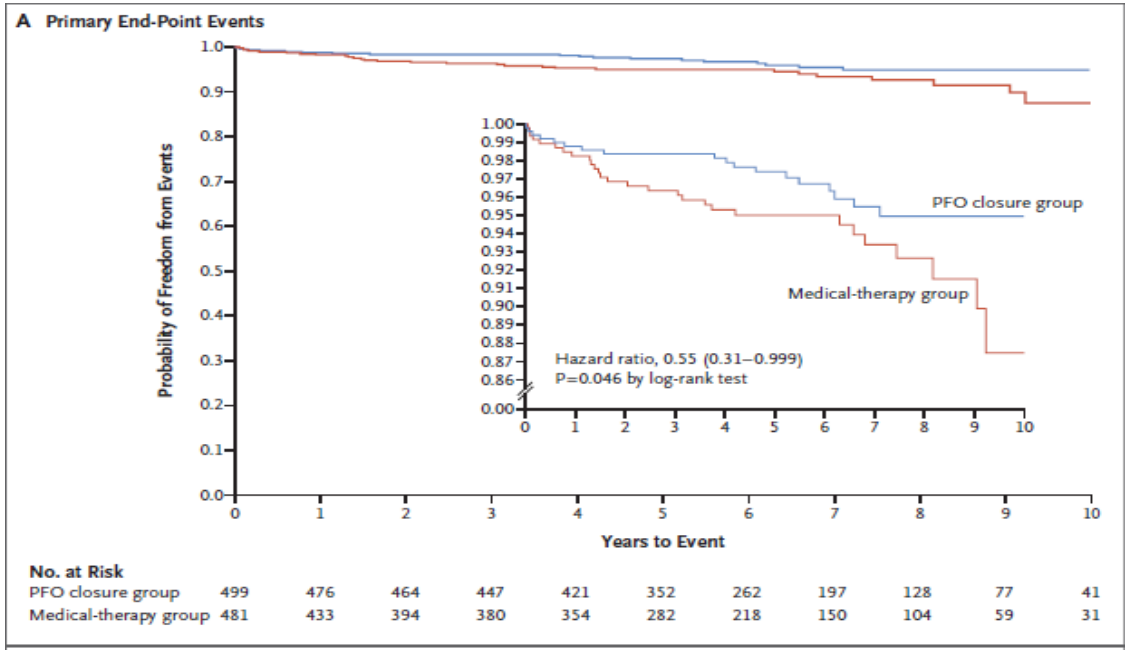
The NEW ENGLAND JOURNAL of MEDICINE

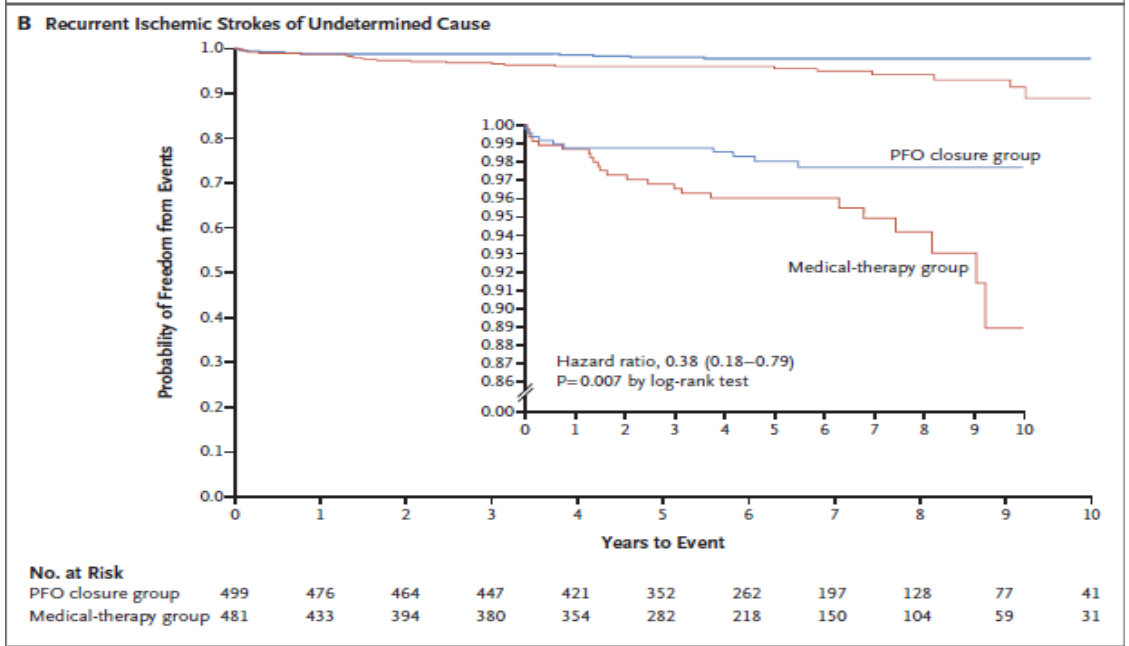
ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

- 980 Pts
- AntiPLT vs AntiPLT + PFO closure
- Primary endpoint: recurrent nonfatal ischemic stroke, fatal ischemic stroke, early death after randomization
- MEDIAN 5.9 Yrs f-up

RESPECT long term follow-up





RESPECT long term follow-up

Table 2. Long-Term Efficacy End Points.*

End Point	PFO Closure Group (N=499)		Medical-Therapy Group (N=481)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate per 100 Patient-Yr	Patients with Event	Event Rate per 100 Patient-Yr		
	no. (%)		*no. (%)*			
Recurrent ischemic stroke	18 (3.6)	0.58	28 (5.8)	1.07	0.55 (0.31–0.999)	0.046
Recurrent ischemic stroke of undetermined cause as adjudicated with the use of ASCOD	10 (2.0)	0.32	23 (4.8)	0.86	0.38 (0.18–0.79)	0.007
Recurrent cryptogenic ischemic stroke as adjudicated with the use of TOAST	1 (0.2)	0.03	11 (2.3)	0.41	0.08 (0.01–0.58)	0.01
Transient ischemic attack	17 (3.4)	0.54	23 (4.8)	0.86	0.64 (0.34–1.20)	0.16

RESPECT long term follow-up

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Recurrent cryptogenic ischemic stroke as adjudicated with the use of TOAST	1 (0.2)	0.03	11 (2.3)	0.41	0.08 (0.01–0.58)	0.01
Transient ischemic attack	17 (3.4)	0.54	23 (4.8)	0.86	0.64 (0.34–1.20)	0.16

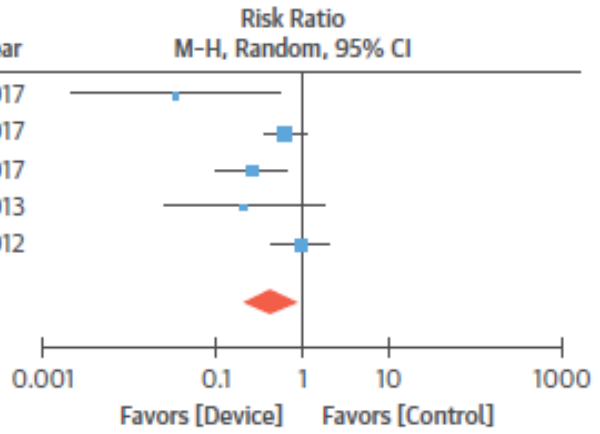
FIGURE 2 Recurrent Stroke and Atrial Fibrillation/Flutter Outcomes in Cryptogenic Stroke Patients Randomized to PFO Closure or Medical Therapy

A Recurrent Stroke

Study or Subgroup	Device Events	Device Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
CLOSE (40)	0	238	14	235	6.1%	0.03 [0.00-0.57]	2017
RESPECT (27)	18	499	28	481	32.2%	0.62 [0.35-1.11]	2017
REDUCE (41)	6	441	12	223	24.1%	0.25 [0.10-0.66]	2017
PC (23)	1	204	5	210	9.5%	0.21 [0.02-1.75]	2013
CLOSURE I (20)	12	447	13	462	28.0%	0.95 [0.44-2.07]	2012
Total (95% CI)		1829		1611	100.0%	0.42 [0.20-0.91]	
Total events	37		72				

Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 9.72$, df = 4 (P = 0.05); $I^2 = 59\%$

Test for overall effect: Z = 2.22 (P = 0.03)



B Atrial Fibrillation/Flutter

Study or Subgroup	Device Events	Device Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
CLOSE (40)	11	238	2	235	19.0%	5.43 [1.22-24.24]	2017
RESPECT (27)	7	499	4	481	25.5%	1.69 [0.50-5.73]	2017
REDUCE (41)	29	441	1	223	12.0%	14.66 [2.01-106.95]	2017
PC (23)	6	204	2	210	17.3%	3.09 [0.63-15.12]	2013
CLOSURE I (20)	23	447	3	462	26.2%	7.92 [2.40-26.21]	2012
Total (95% CI)		1829		1611	100.0%	4.55 [2.16-9.60]	
Total events	76		12				

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 5.33$, df = 4 (P = 0.26); $I^2 = 25\%$

Test for overall effect: Z = 3.98 (P < 0.0001)

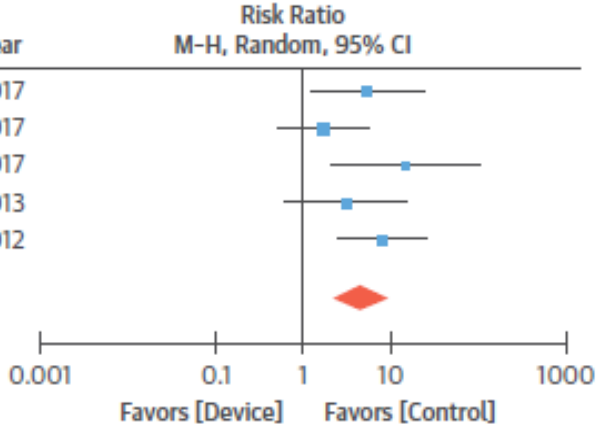
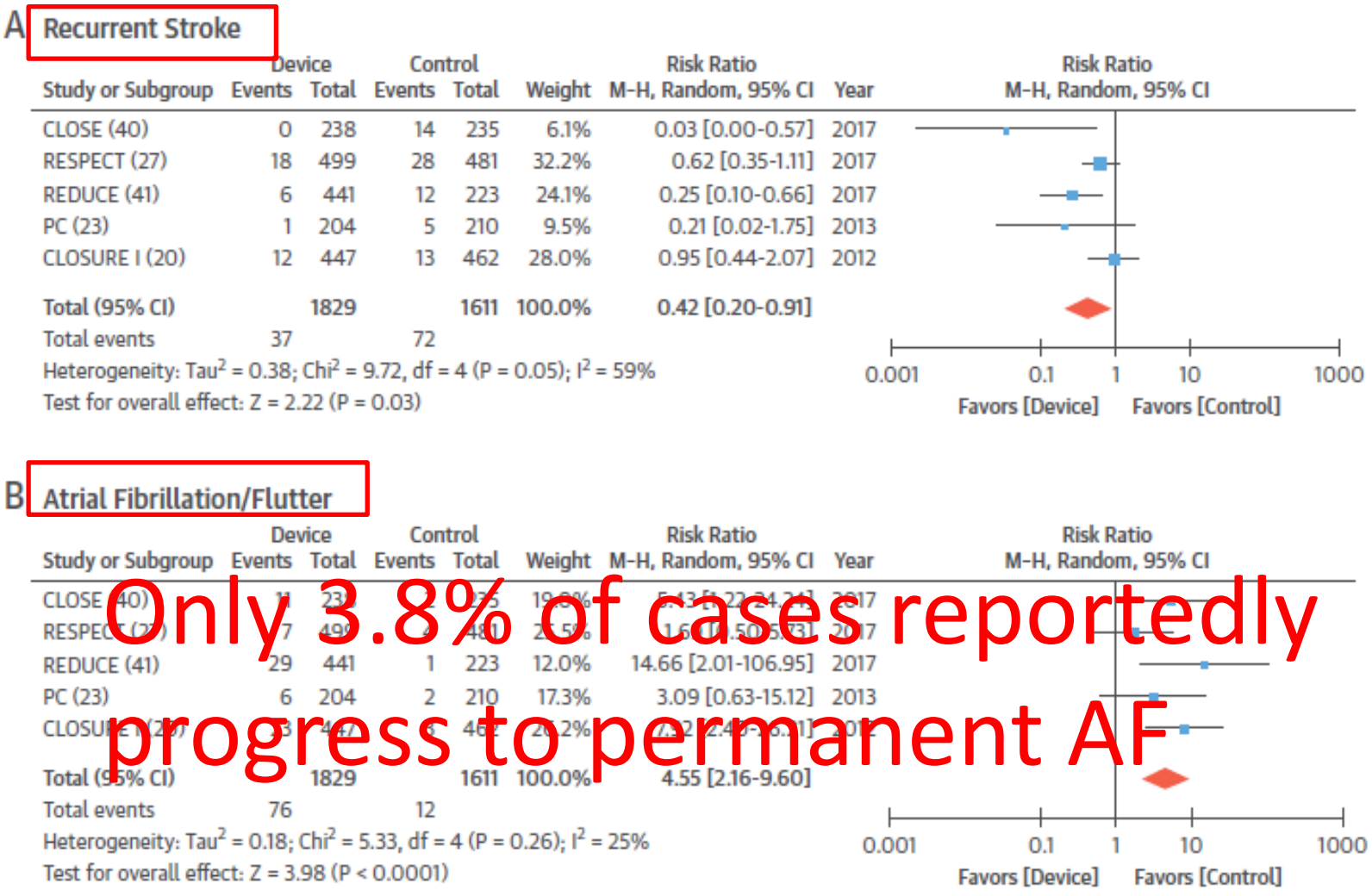


FIGURE 2 Recurrent Stroke and Atrial Fibrillation/Flutter Outcomes in Cryptogenic Stroke Patients Randomized to PFO Closure or Medical Therapy



Only 3.8% of cases reportedly progress to permanent AF

Other Safety Results

- No significant difference in all-cause serious adverse events including major bleeding
- 0% significant device thrombosis

TABLE 1 Clinical Trials Randomizing Cryptogenic Stroke Patients to Percutaneous PFO Closure or Medical Therapy

Randomized Clinical Trial (Ref. #)	Cohort (Number of Patients)	Device Arm	Medical Arm	Follow-Up	Primary Outcome	Results
CLOSURE I (20)	Cryptogenic stroke or TIA + PFO; age 18-60 yrs (909)	PFO closure + aspirin and warfarin for 1 month, then aspirin for 2 yrs	Aspirin, warfarin or both	2 yrs	Composite of stroke, TIA, early death from any etiology and late neurological death	PFO closure did not significantly reduce recurrent stroke or TIA compared with medical therapy
PC (23)	Cryptogenic stroke, TIA or peripheral embolism + PFO; age <60 yrs (414)	PFO closure + aspirin for 5-6 months + clopidogrel or ticlopidine for 1-6 months	Antiplatelet or antithrombotic therapy	Mean 4 yrs	Composite of death, nonfatal stroke, TIA, or peripheral embolism	PFO closure did not significantly reduce recurrent embolic events or death compared with medical therapy
RESPECT (27) (extended follow-up)	Cryptogenic stroke + PFO; age 18-60 yrs (980)	PFO closure + aspirin and clopidogrel for 1 month, then aspirin for 5 months	Aspirin, warfarin, clopidogrel or aspirin + extended release dipyridamole	Median 5.9 yrs	Composite of recurrent nonfatal and fatal stroke and early death	PFO closure reduced recurrent stroke events compared with medical therapy
CLOSE (40)	Cryptogenic stroke + PFO with large shunt or atrial septal aneurysm; age 16-60 yrs (663)	PFO closure + aspirin and clopidogrel for 3 months, then single antiplatelet therapy	Aspirin, clopidogrel, or aspirin + extended-release dipyridamole or vitamin K antagonist or direct oral anticoagulant	Mean 5.3 ± 2.0 yrs	Fatal or nonfatal stroke	PFO closure reduced recurrent stroke events compared with medical therapy
Gore REDUCE (41)	Cryptogenic stroke + PFO; age 18-59 yrs (664)	PFO closure + aspirin, aspirin and dipyridamole, or clopidogrel	Aspirin, aspirin and dipyridamole, or clopidogrel	Median 3.2 yrs	Freedom from stroke; incidence of new brain infarct on MRI	PFO closure reduced recurrent stroke events and new brain infarcts on MRI compared with medical therapy

MRI = magnetic resonance imaging; PFO = patent foramen ovale; TIA = transient ischemic attack.

Reasons for the discrepancy?

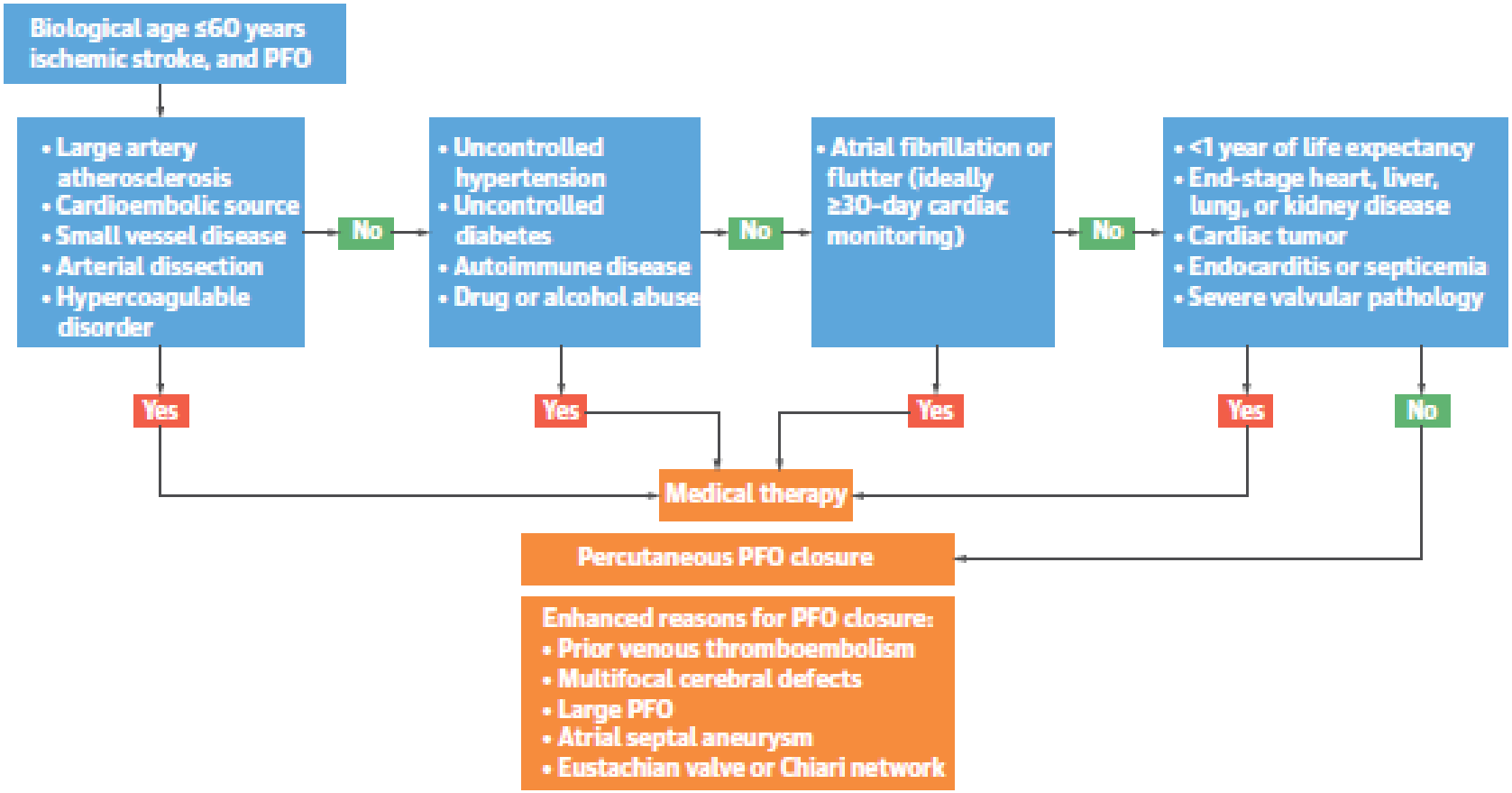
- **Newer studies included pts with index strokes more likely secondary to paradoxical embolism or higher-risk PFOs :**

REDUCE had very strict exclusion criteria to omit pts with other causes of stroke as large-artery atherosclerotic disease and small vessel disease, based on extensive cerebrovascular imaging
It also excluded pts with uncontrolled risk factors

CLOSE only included pts with atrial septum aneurysm or large shunt

- Longer folow-up period

CENTRAL ILLUSTRATION Evidence-Based Algorithm for PFO Closure in Ischemic Stroke Patients for Highest Clinical Yield, Based on Randomized Trials



Mojadidi, M.K. et al. J Am Coll Cardiol. 2018;71(9):1035-43.

Patients can expect the greatest benefit from percutaneous PFO closure if they have no other cardiovascular stroke causes on imaging/laboratory analyses, no uncontrolled risk factors, no atrial fibrillation or flutter, and no poor prognostic markers. PFO = patent foramen ovale.

JACC. 2018, Vol 71

Grazie per l’attenzione