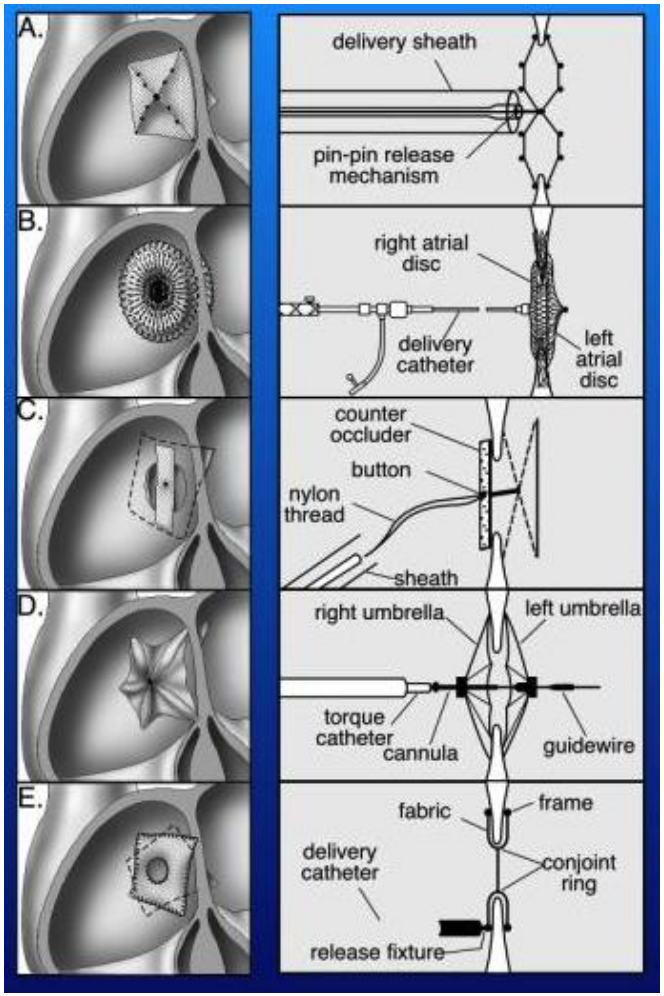
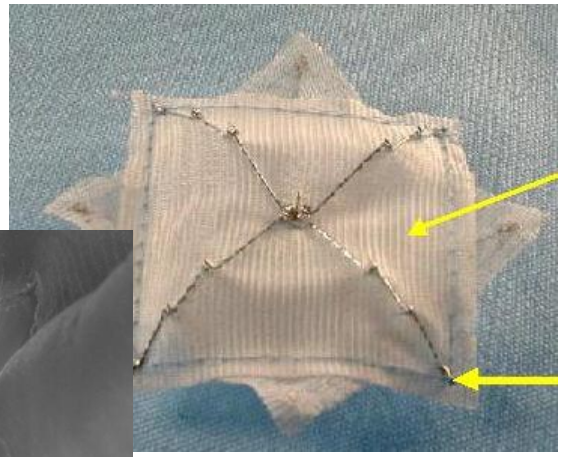
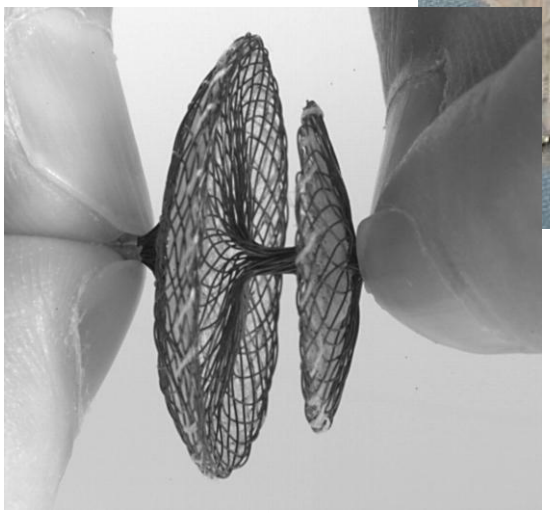
Katetrizační uzávěr PFO

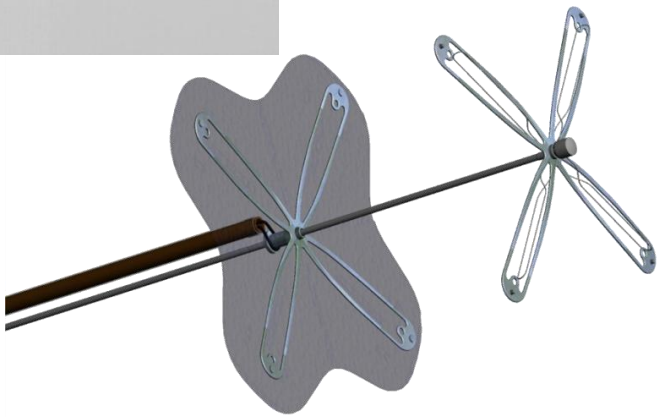
Martin Mates
Kardiologické oddělení
Nemocnice Na Homolce

Katetrizační uzávěr

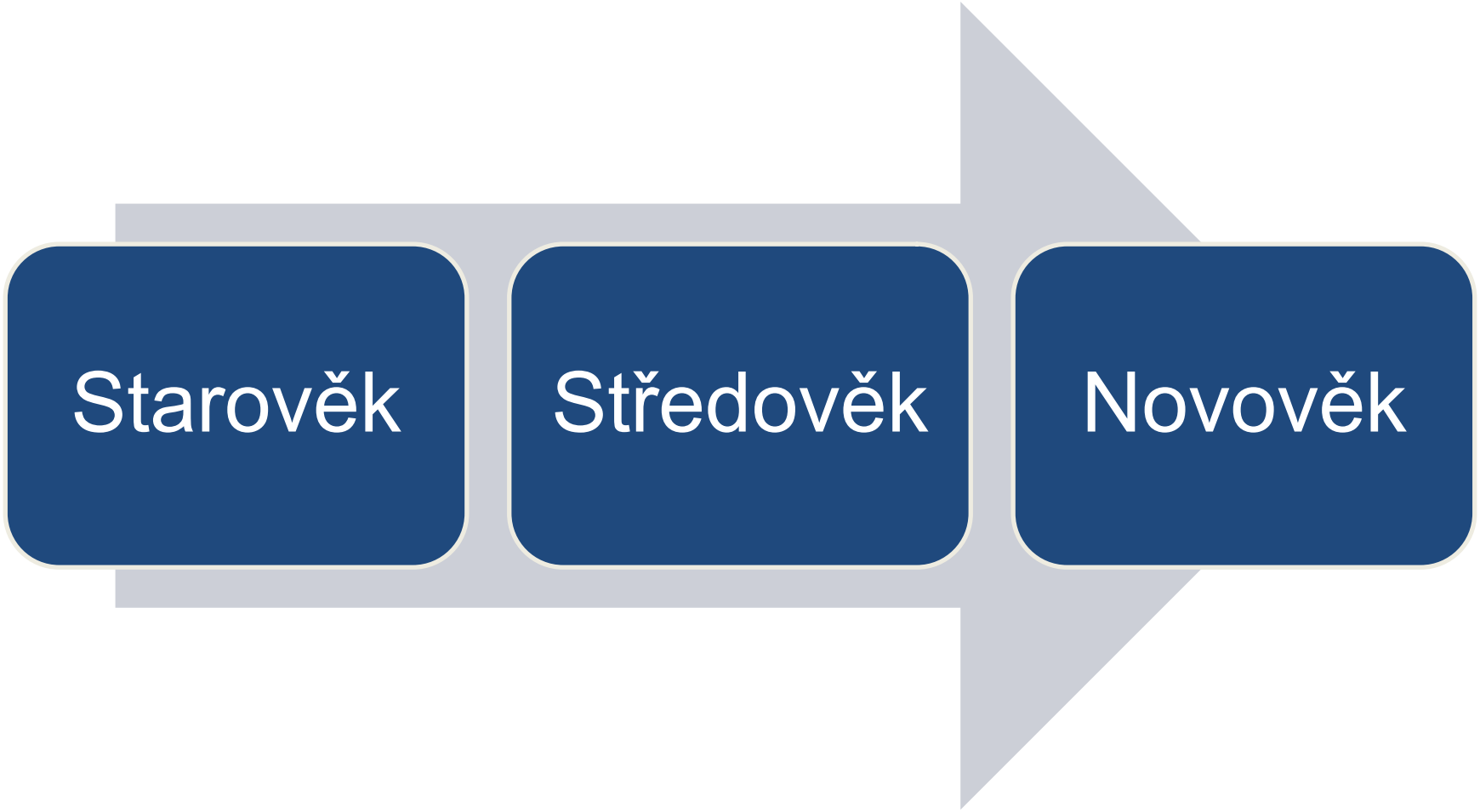






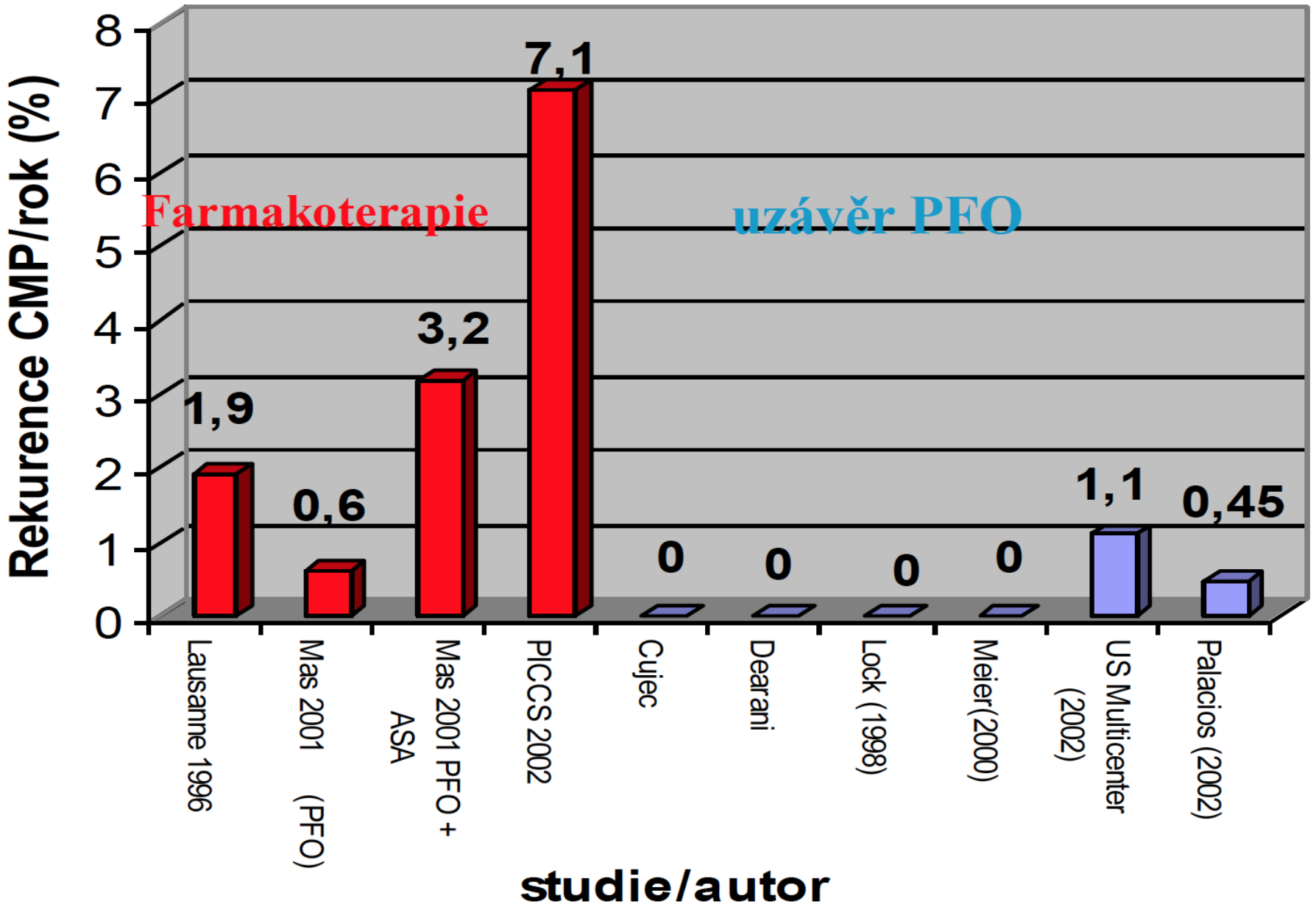


Vývoj katetrizačního uzávěru PFO



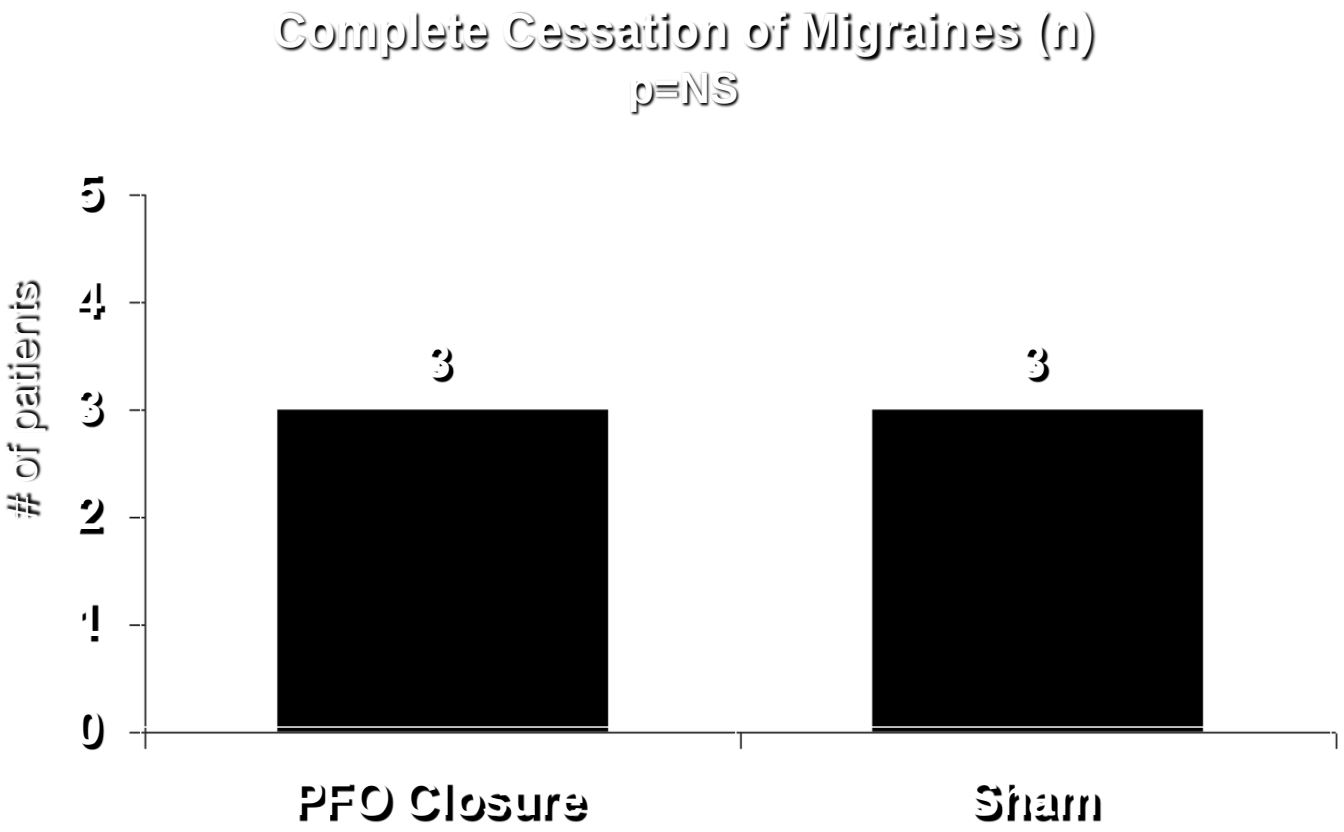
Starověk

- Registry
- Randomizována studie MIST (léčba migrény)



Podle M- Polozcek 2018

MIST Trial: Primary Endpoint

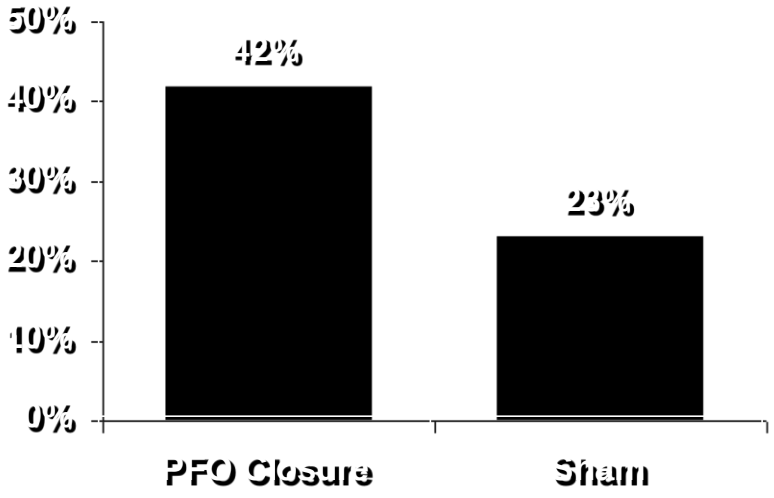


- There was no difference between groups in the primary endpoint of complete cessation of migraines with 3 patients in each group.

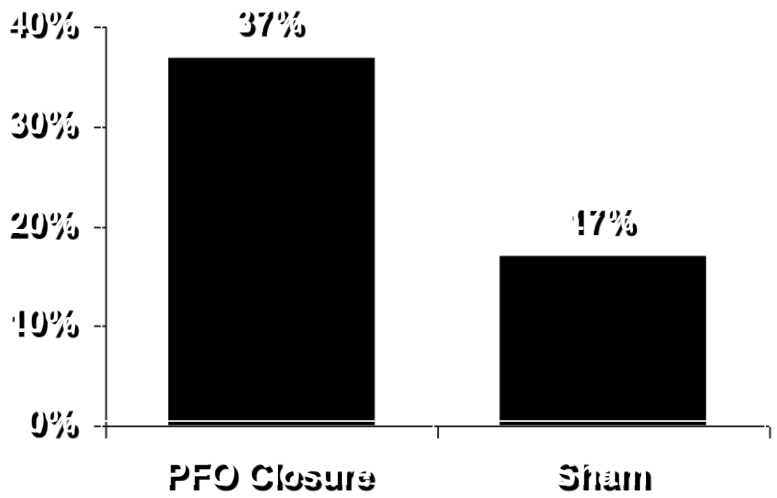
www.Clinical trial results.org

Presented at ACC 2005

MIST Trial: PCI



p=0.033



- Reduction in headache days by 50% was significantly greater in the PFO closure group than in the sham procedure group (42% vs. 23%, p=0.038).
- Reduction in headache burden, defined as the frequency of headaches times the duration, was significantly greater in the PFO closure group than in the sham procedure group (37% vs. 17%, p=0.033).

www.Clinical trial results.org

Presented at ACC 2005

Souhrn case-control studií (2009):

„… u pacientů s kryptogenní CMP je u přibližně třetiny náhodný nález PFO, bez benefitu uzávěru.“

Patent Foramen Ovale in Cryptogenic Stroke

Incidental or Pathogenic?

Alawi A. Alsheikh-Ali, MD; David E. Thaler, MD, PhD; David M. Kent, MD, MS

Background and Purpose—Patent foramen ovale (PFO) is significantly associated with cryptogenic stroke (CS). However, even in patients with CS, a PFO can be an incidental finding. We sought to estimate the probability that a PFO in a patient with CS is incidental.

Methods—A systematic search identified 23 case–control studies examining the prevalence of PFO in patients with CS versus control subjects with stroke of known cause. Using simple assumptions and Bayes' theorem, we calculated the probability a PFO is incidental in patients with CS. Random effects meta-analyses estimated the odds ratio (OR) of a PFO in CS versus control subjects in different age populations, with or without atrial septal aneurysms, and were used to summarize across studies the probability that a PFO in CS is incidental.

Results—The summary OR (95% CIs) for PFO in CS versus control subjects was 2.9 (CI, 2.1 to 4.0). The corresponding ORs for young and old patients (< or ≥55 years) were 5.1 (3.3 to 7.8) and 2.0 (>1.0 to 3.7), respectively. The corresponding probabilities that a PFO in patients with CS is incidental were 33% (28% to 39%) in age-inclusive studies, 20% (16% to 25%) in younger patients, and 48% (34% to 66%) in older patients. These probabilities were much lower when an atrial septal aneurysm was present.

Conclusions—In patients with otherwise CS, approximately one third of discovered PFOs are likely to be incidental and hence not benefit from closure. This probability is sensitive to patient characteristics such as age and the presence of an atrial septal aneurysm, suggesting the importance of patient selection in therapeutic decision-making. **(*Stroke*. 2009; 40:2349-2355.)**

Středověk: od 2012

- Výsledky prvních randomizovaných studií CLOSURE trial, PC Trial a Respect

ORIGINAL ARTICLE FREE PREVIEW

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D. for the CLOSURE I Investigators*

March 15, 2012
N Engl J Med 2012; 366:991-999
DOI: 10.1056/NEJMoa1009639

Abstract

CONCLUSIONS In patients with cryptogenic stroke or TIA who had a patent foramen ovale, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA. (Funded by NMT Medical; ClinicalTrials.gov number, NCT00201461.)

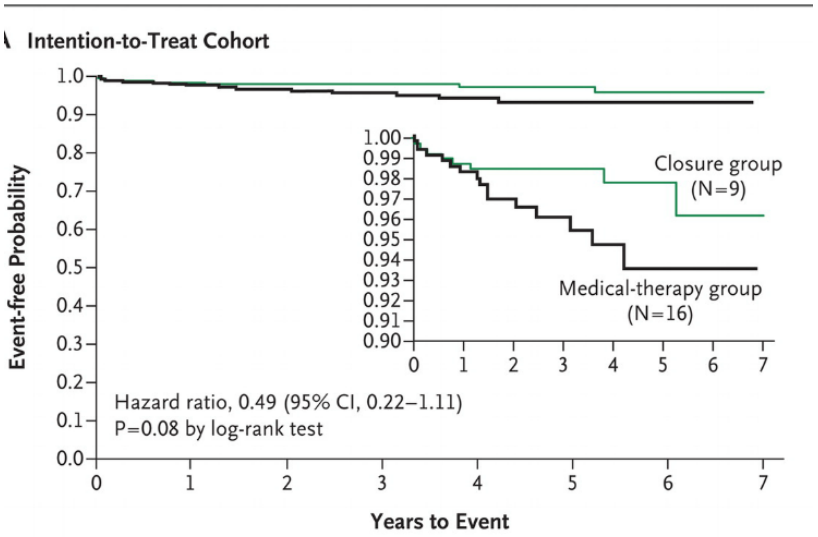
RESPECT Trial

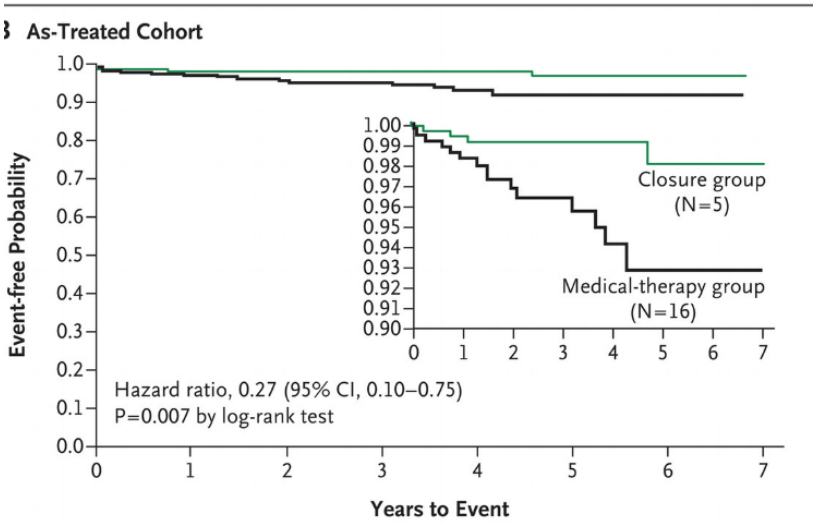
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

John D. Carroll, M.D., Jeffrey L. Saver, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Scott Berry, Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*





25 příhod během sledování
Nefatální CMP

Středně velká, velká nebo masivní CMP:

69% pacientů (9 of 13 pac.) v konzervativní větvi

14% pacientů (1 of 7) ve větvi uzávěr(P = 0.06).

3 pacienti ve větvi Okluderu neměli v době příhody implantovaný okluder

N Engl J Med 2013;368:1092-100.

NEMOCNICE NA HOMOLCE

RESPECT Primary Endpoint Results

- **Enrollment ended when 25 ischemic stroke events occurred - results were reported in NEJM**

Analysis Population	Relative Risk Reduction	P-Value
Intention-to-Treat	50%	0.089
Per-Protocol	58%	0.048
As Treated	67%	0.013

Carroll et al. *NEJM* 2012;368:1092-100.
Note: Per Protocol and As Treated analysis modified from NEJM analysis in response to FDA questions.

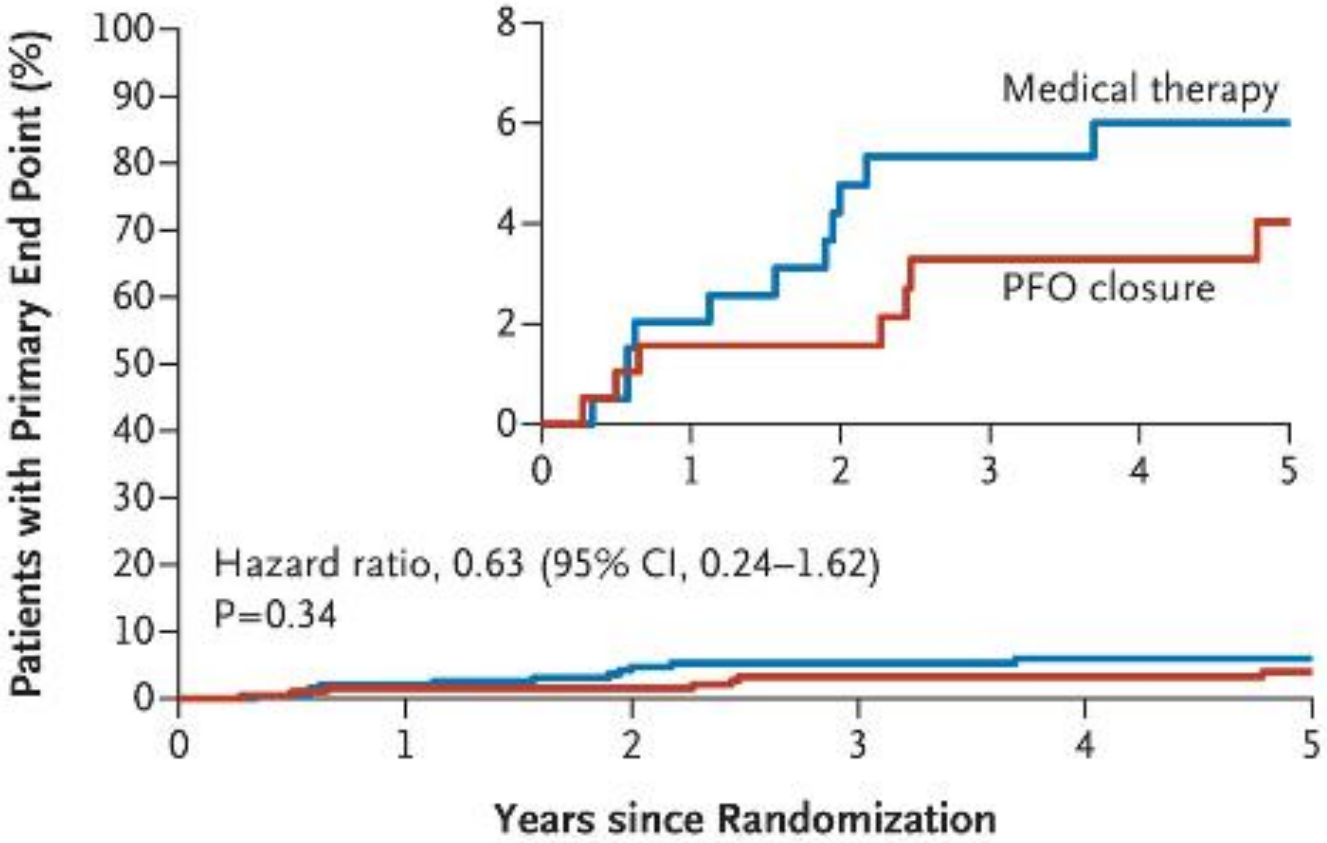
PC Trial

N Engl J Med 2013;368:1083-91

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MARCH 21, 2013 VOL. 368 NO. 12

Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

Bernhard Meier, M.D., Bindu Kalesan, Ph.D., Heinrich P. Mattle, M.D., Ahmed A. Khattab, M.D., David Hildick-Smith, M.D., Dariusz Dudek, M.D., Grethe Andersen, M.D., Reda Ibrahim, M.D., Gerhard Schuler, M.D., Antony S. Walton, M.D., Andreas Wahl, M.D., Stephan Windecker, M.D., and Peter Jüni, M.D., for the PC Trial Investigators*



No. at Risk

Medical therapy	210	185	170	159	131	90
PFO closure	204	186	181	163	142	110

NEMOCNICE NA HOMOLCE

Metaanalýza (2013)

„… does not support PFO closure for secondary prevention….“

Int J Cardiol. 2013 Oct 30;169(2):101-5. doi: 10.1016/j.ijcard.2013.08.058. Epub 2013 Aug 28.

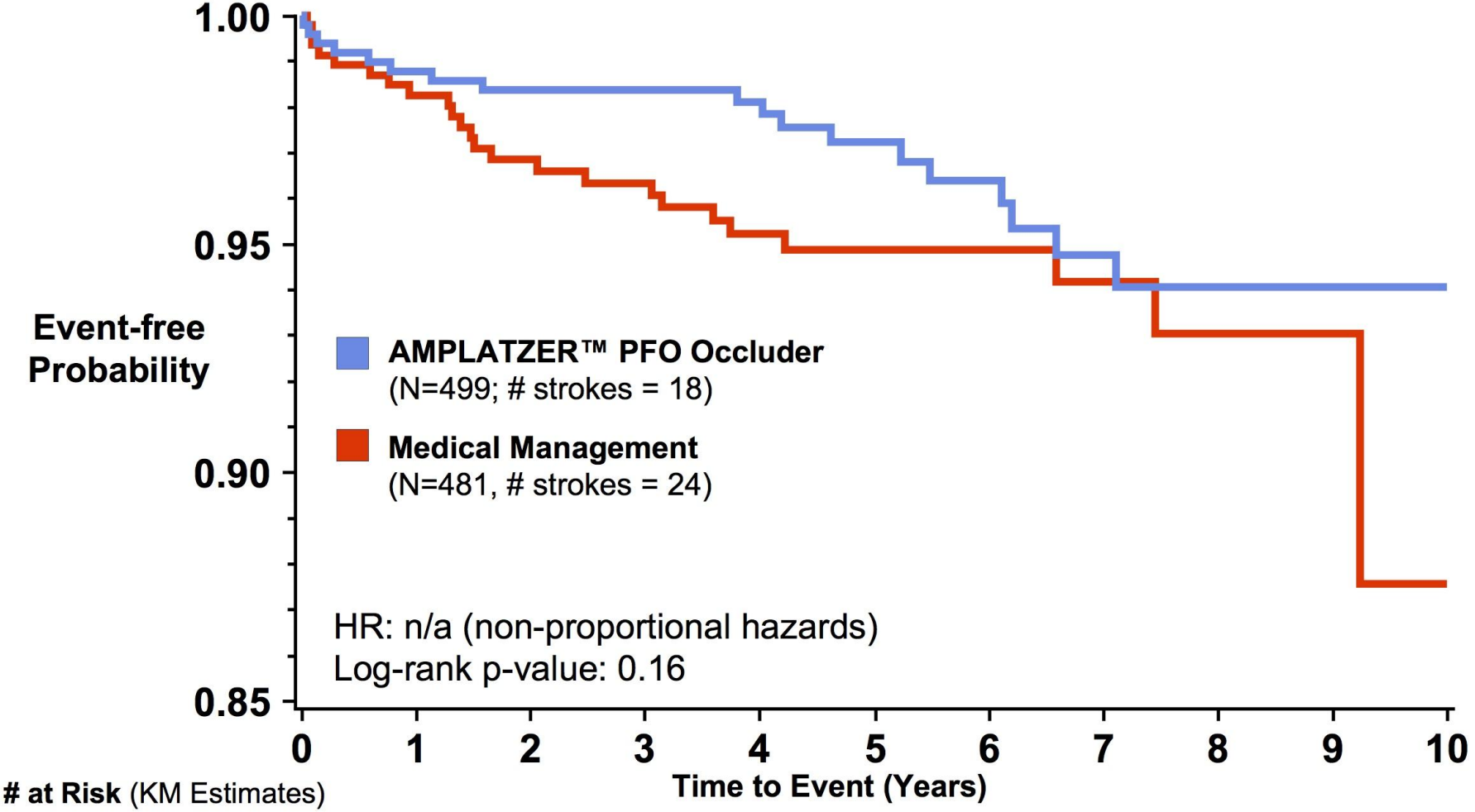
PFO closure vs. medical therapy in cryptogenic stroke or transient ischemic attack: a systematic review and meta-analysis.

Ntaios G[1], Papavasileiou V, Makaritsis K, Michel P.

CONCLUSIONS: This meta-analysis does not support PFO closure for secondary prevention with unselected devices in cryptogenic stroke/TIA. In subgroup analysis, selected closure devices may be superior to medical therapy without increasing the risk of new-onset AF, however. This observation should be confirmed in further trials using inclusion criteria for patients with high likelihood of PFO-related stroke recurrence.

Freedom from All-cause Stroke

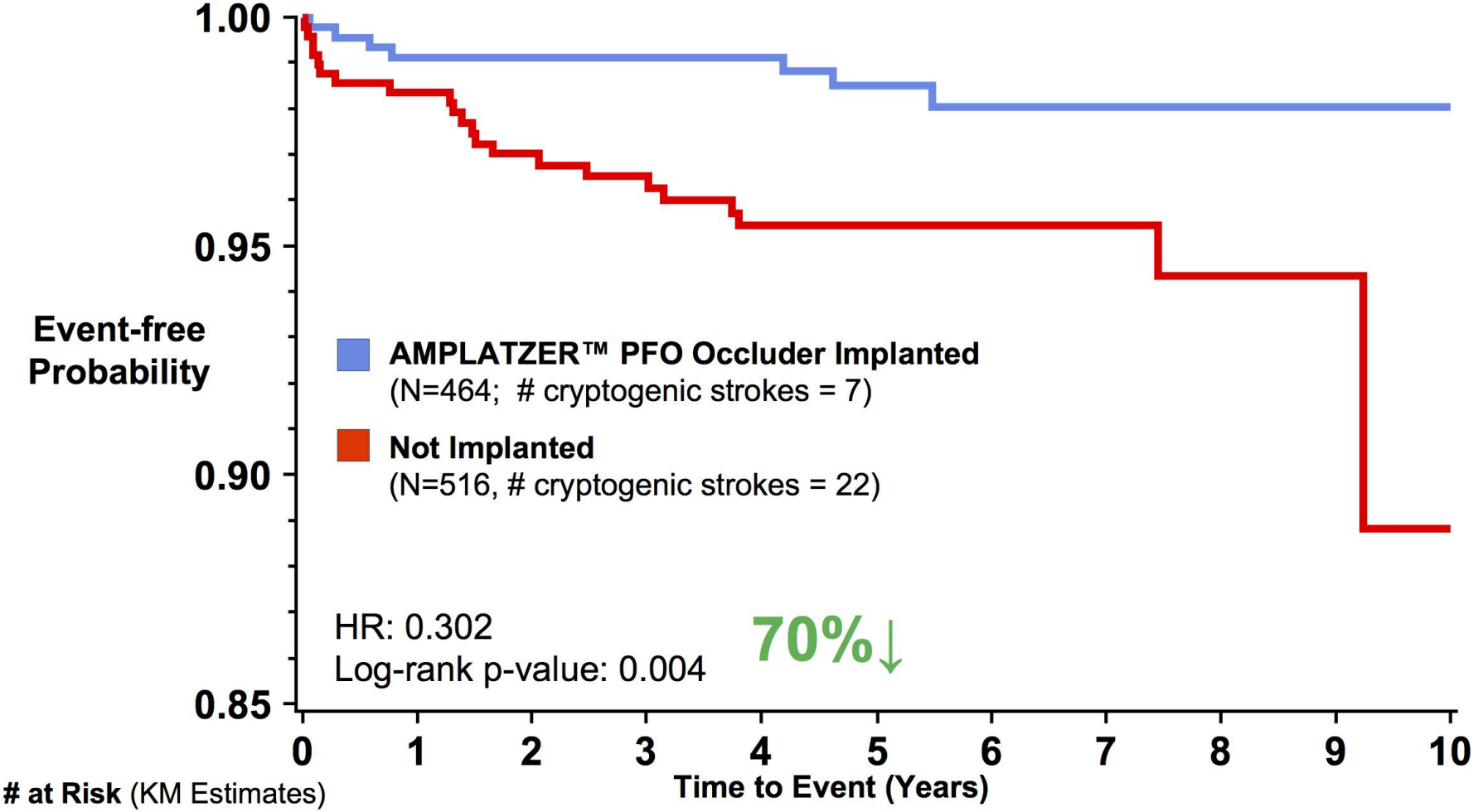
Extended Follow-up in ITT Population



 # at Risk (KM Estimates)

AMPLATZER	**499** (0%)	**463** (1.6%)	**369** (1.9%)	**212** (3.6%)	**86** (6.0%)	**20** (6.0%)
MM	**481** (0%)	**394** (3.2%)	**307** (4.8%)	**168** (5.1%)	**71** (7.0%)	**10** (12.4%)

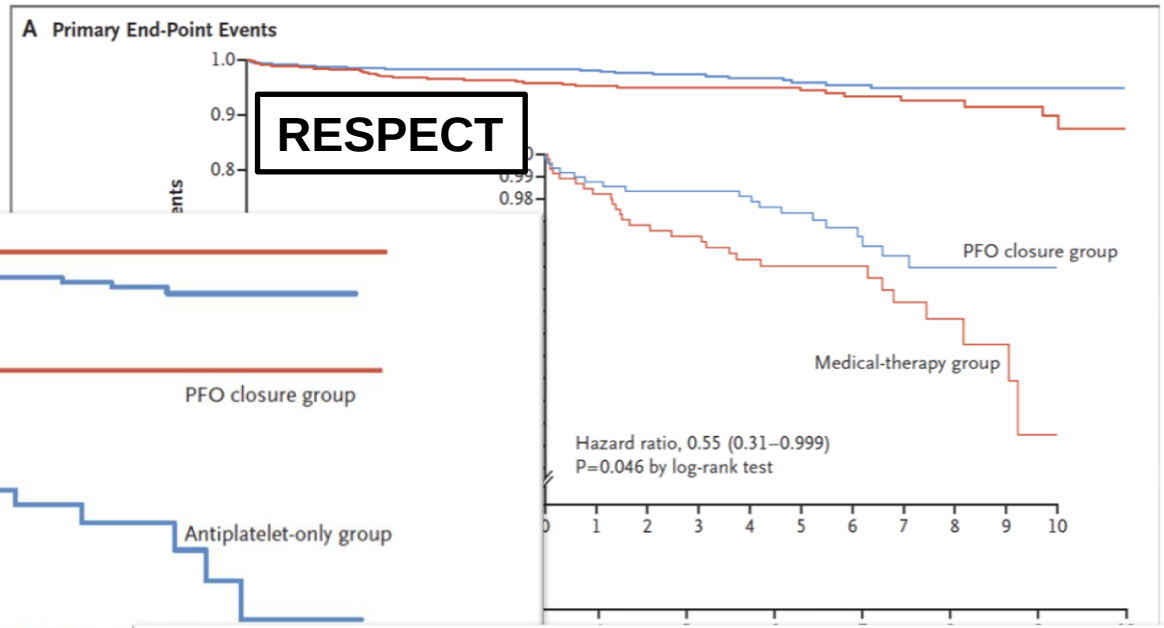
Freedom from Recurrent Cryptogenic Stroke With Device In Place

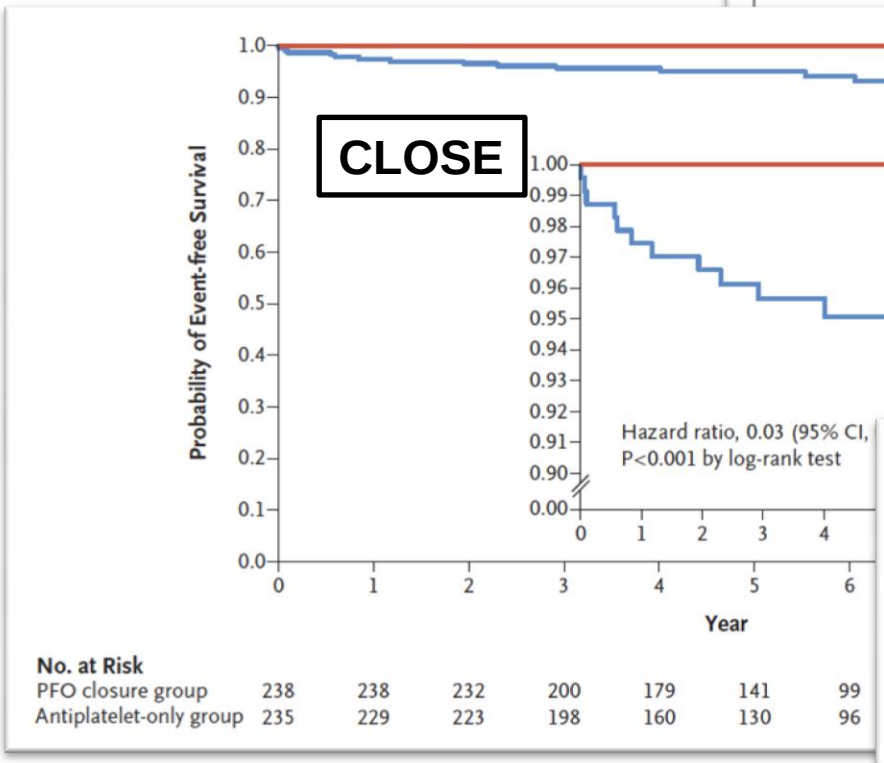


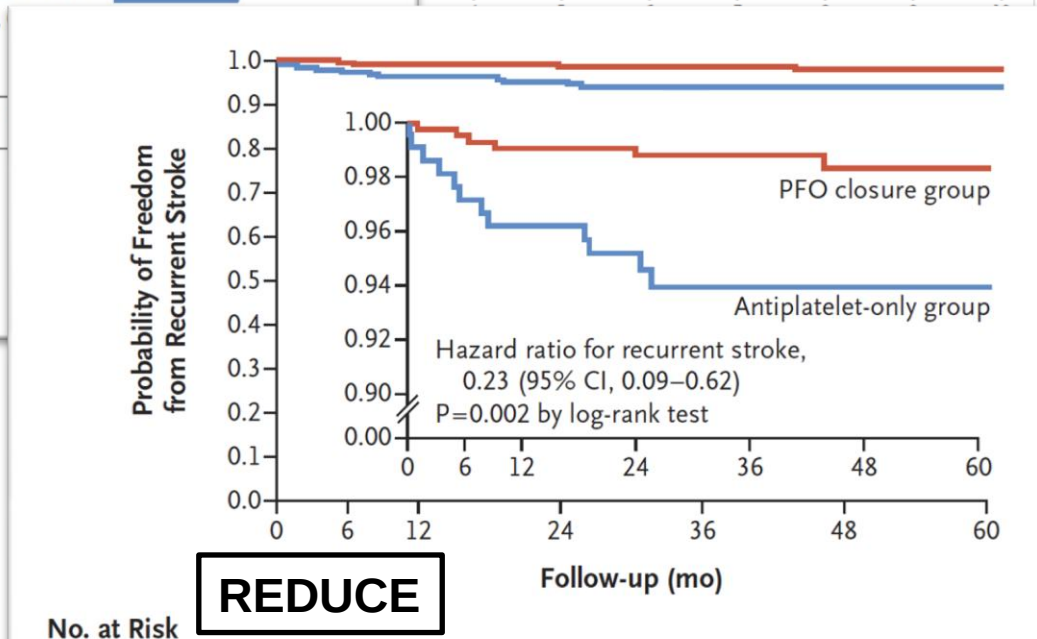
 # at Risk (KM Estimates)

AMPLATZER	**464** (0%)	**445** (0.9%)	**357** (0.9%)	**206** (1.9%)	**82** (1.9%)	**20** (1.9%)
Not Implanted	**516** (0%)	**412** (3.0%)	**319** (4.6%)	**174** (4.6%)	**75** (5.7%)	**10** (11.2%)

Novověk – 14.září 2017







The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 377;11 September 14, 2017

Randomizované studie
Uzávěr PFO vs. Konzervativní

	CLOSURE 1	PC TRIAL	RESPECT	REDUCE	CLOSE
Počet pac.	909	414	980	664	663
Random.	1:1	1:1	1:1	2:1	1:1:1
Průběh	2003-8	2000-9	2003-11	2008-15	2016
Rok publikace	2012	2013	2017	2017	2017
Prům. věk	46	44	46	45	44
Indikace	kCMP/TIA	kCMP/TIA MRI/perif.	kCMP	kCMP/TIA MRI	kCMP
Doba sled.	2	4,1	5,9	3,2	5,4
Okluder	Starflex	Amplatzer	Amplatzer	Helex/Gore	Různé (59% Amplatzer)

Publikované 14.9.2017

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Věk pro zařazení: 18-60 (18-59)

Randomizované studie
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Metaanalýza (2018)

„… who have their PFO closed, ischemic stroke recurrence is less frequent compared with patients receiving medical treatment.“

Closure of Patent Foramen Ovale Versus Medical Therapy in Patients With Cryptogenic Stroke or Transient Ischemic Attack

Updated Systematic Review and Meta-Analysis

George Ntaios, MD; Vasileios Papavasileiou, MD; Dimitrios Sagris, MD; Konstantinos Makaritsis, MD; Konstantinos Vemmos, MD; Thorsten Steiner, MD; Patrik Michel, MD

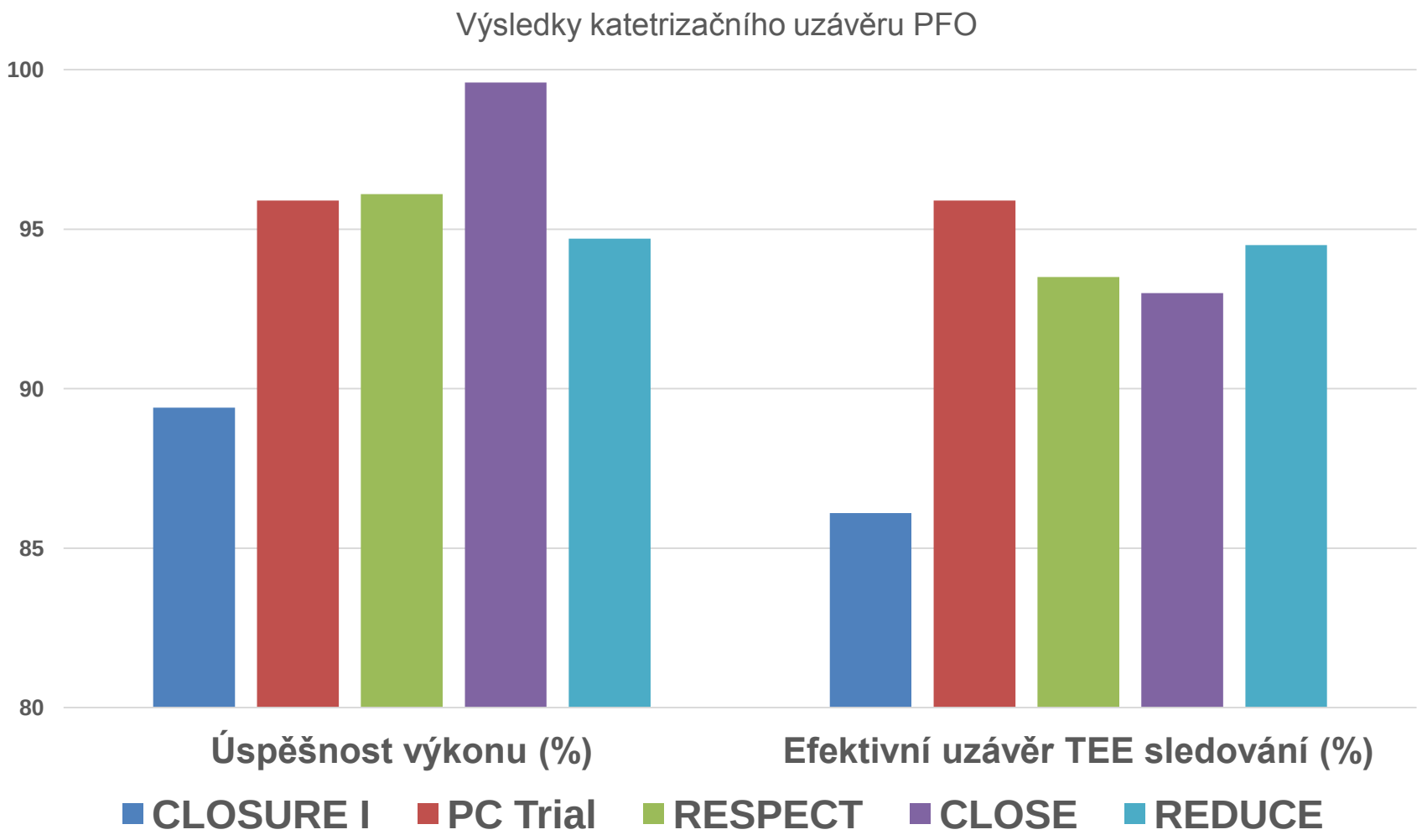
Conclusions—In patients with cryptogenic stroke/TIA and PFO who have their PFO closed, ischemic stroke recurrence is less frequent compared with patients receiving medical treatment. Atrial fibrillation is more frequent but mostly transient. There is no difference in TIA, all-cause mortality, or myocardial infarction. **(*Stroke*. 2018;49:412-418. DOI: 10.1161/STROKEAHA.117.020030.)**

Jak byla hodnocena efektivita?

- Prevence recidivy CMP/TIA

- ~~Kompletní uzávěr při implantaci~~
- Kompletní uzávěr při TEE sledování
  - Stupeň zkratu 0
- Efektivní uzávěr při TEE sledování
  - Stupeň zkratu 0 a 1 (< 10 bublin)

Efektivita


Výsledky katetrizačního uzávěru PFO
100
95
90
85
80
Úspěšnost výkonu (%)
Efektivní uzávěr TEE sledování (%)
CLOSURE I
PC Trial
RESPECT
CLOSE
REDUCE

Metanalýza studií – Rekurence CMP

- **Roční riziko** 1,16% při konzervativní léčbě
  - Selekce nemocných v RCT

- Implantace okluderu → Redukce rizika o 68%

- **Velký zkrat → větší benefit uzávěru** (0,90 vs. 0,33)
- NNT – prevence 1 CMP za 1 rok
  - NNT 178 v celé populaci
  - NNT 96 u velkých zkrat

- Přítomnost aneuryzmatu septa síní nemá vliv na výsledky
- Fibrilace síní je **častější po uzávěru** (roční riziko 1,38%)

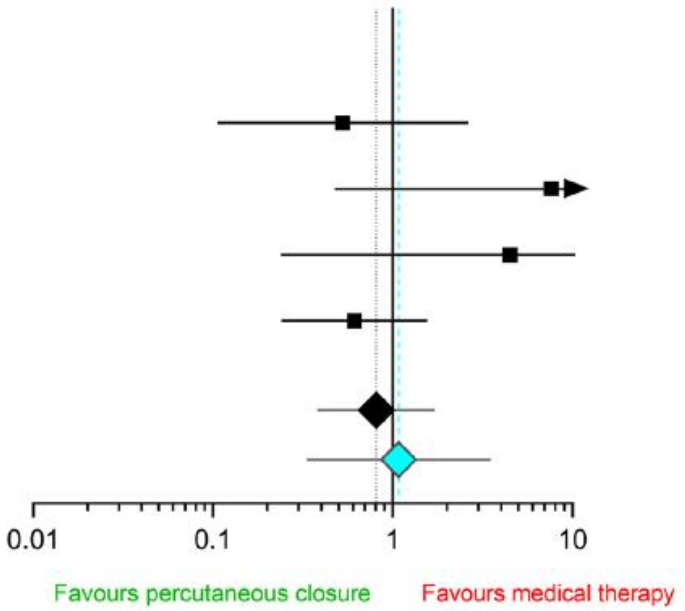
European Heart Journal (2018) 0,
doi: 10.1093/eurheartj/ehy121

Celková mortalita

B Death

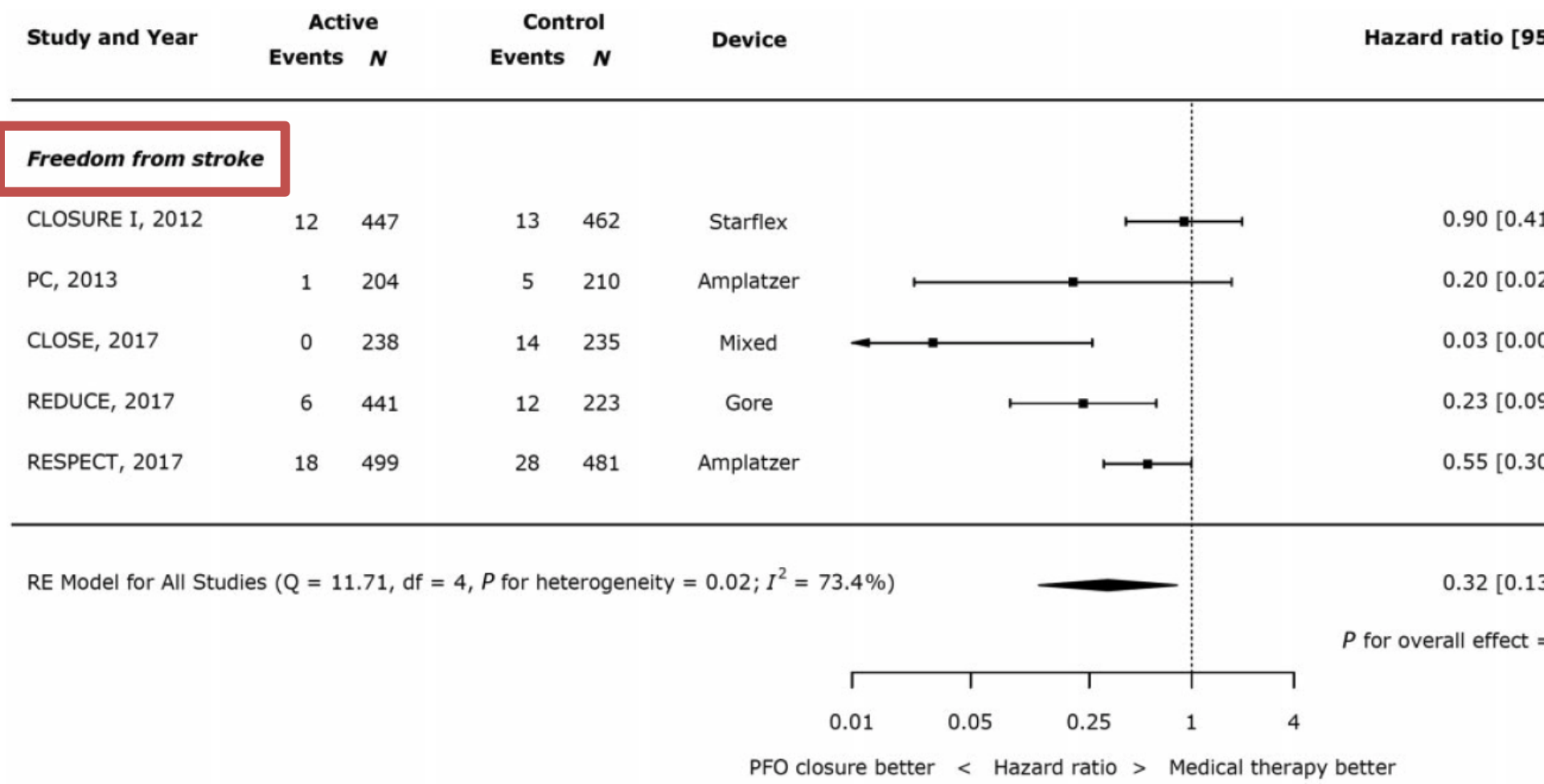
Trial	Closure Events	Closure Total	Medical Events	Medical Total	OR [95%- CI]
CLOSE	0	238	0	235	NA NA
CLOSURE I	2	447	4	462	0.53 [0.11-2.63]
PC	2	204	0	210	7.65 [0.48-122.71]
REDUCE	2	441	0	223	4.52 [0.24-85.17]
RESPECT	7	499	11	481	0.61 [0.24-1.56]
Total	**13**	**1829**	**15**	**1611**	
Fixed effect model					**0.81 [0.38-1.71]**
Random effects model					**1.08 [0.33-3.51]**

Heterogeneity: I^2 =32.5% [0.0% -76%]
Test for overall effect (fixed effect): z= -0.55, (p=0.58)
Test for overall effect (random effects): z= -0.13, (p=0.90)



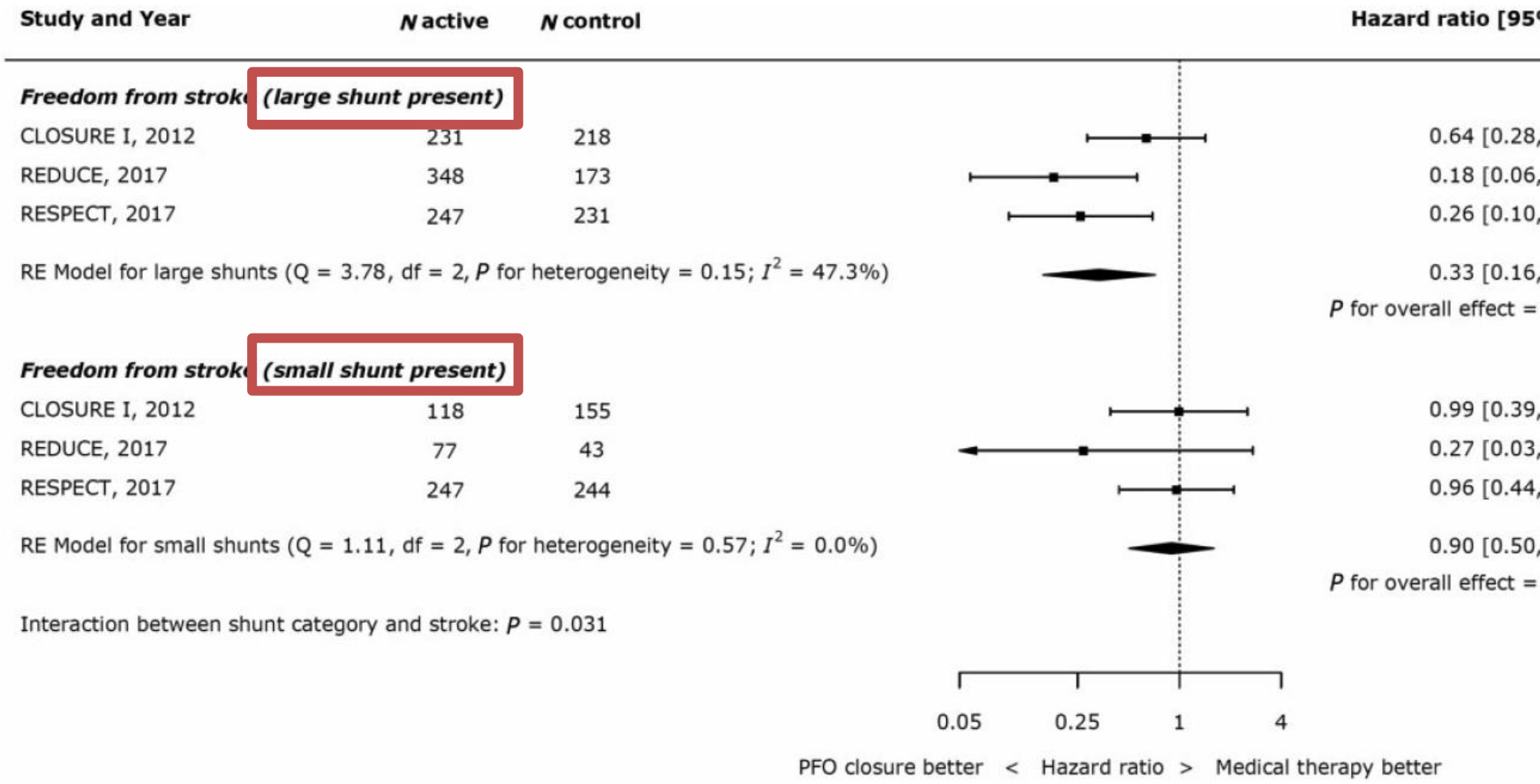
Clinical Research in Cardiology
https://doi.org/10.1007/s00392-018-1246-y

Prevence rekurence CMP



European Heart Journal (2018) 0,
doi: 10.1093/eurheartj/ehy121

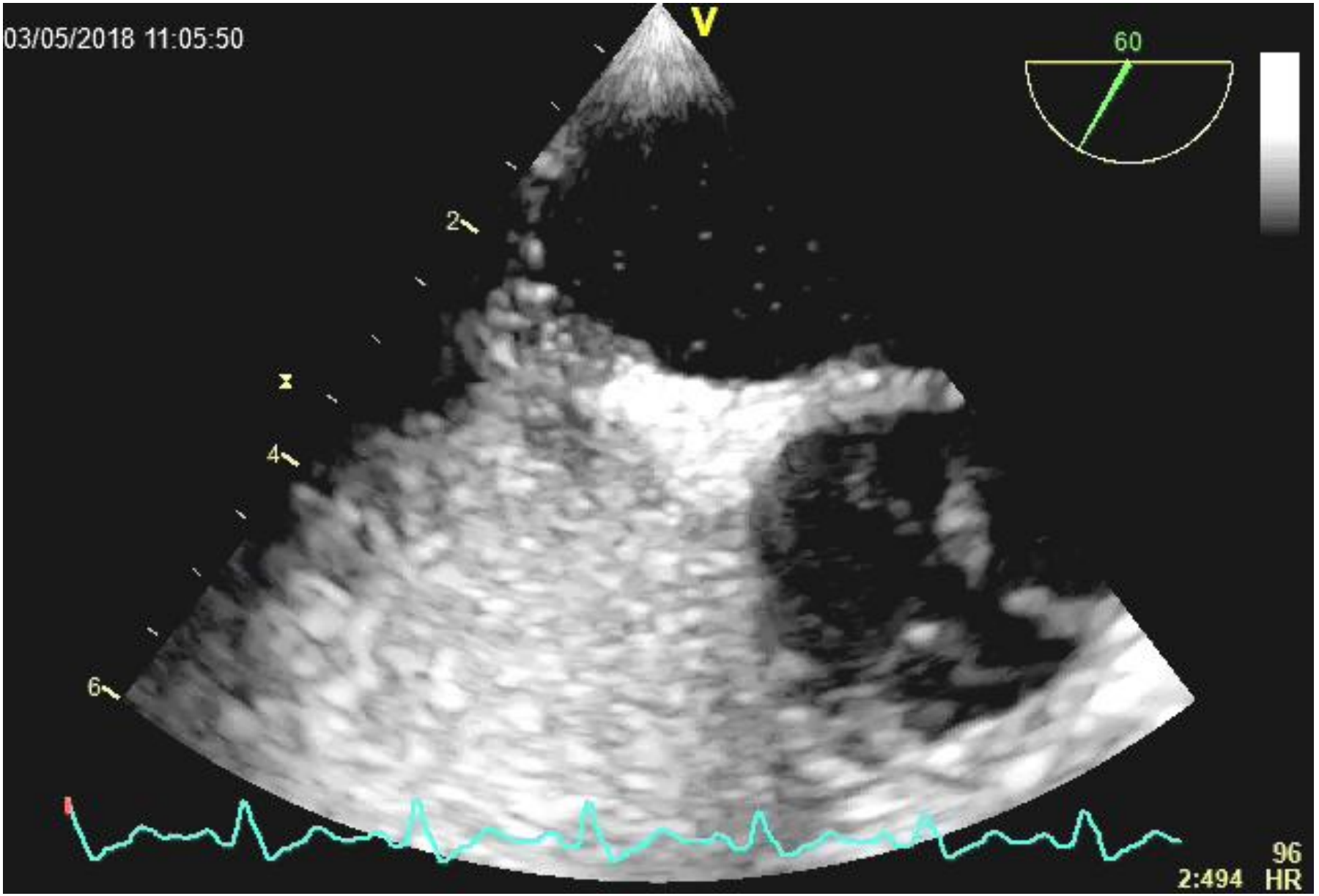
Velikost zkratu ovlivňuje efekt PFO uzávěru na rekurenci CMP

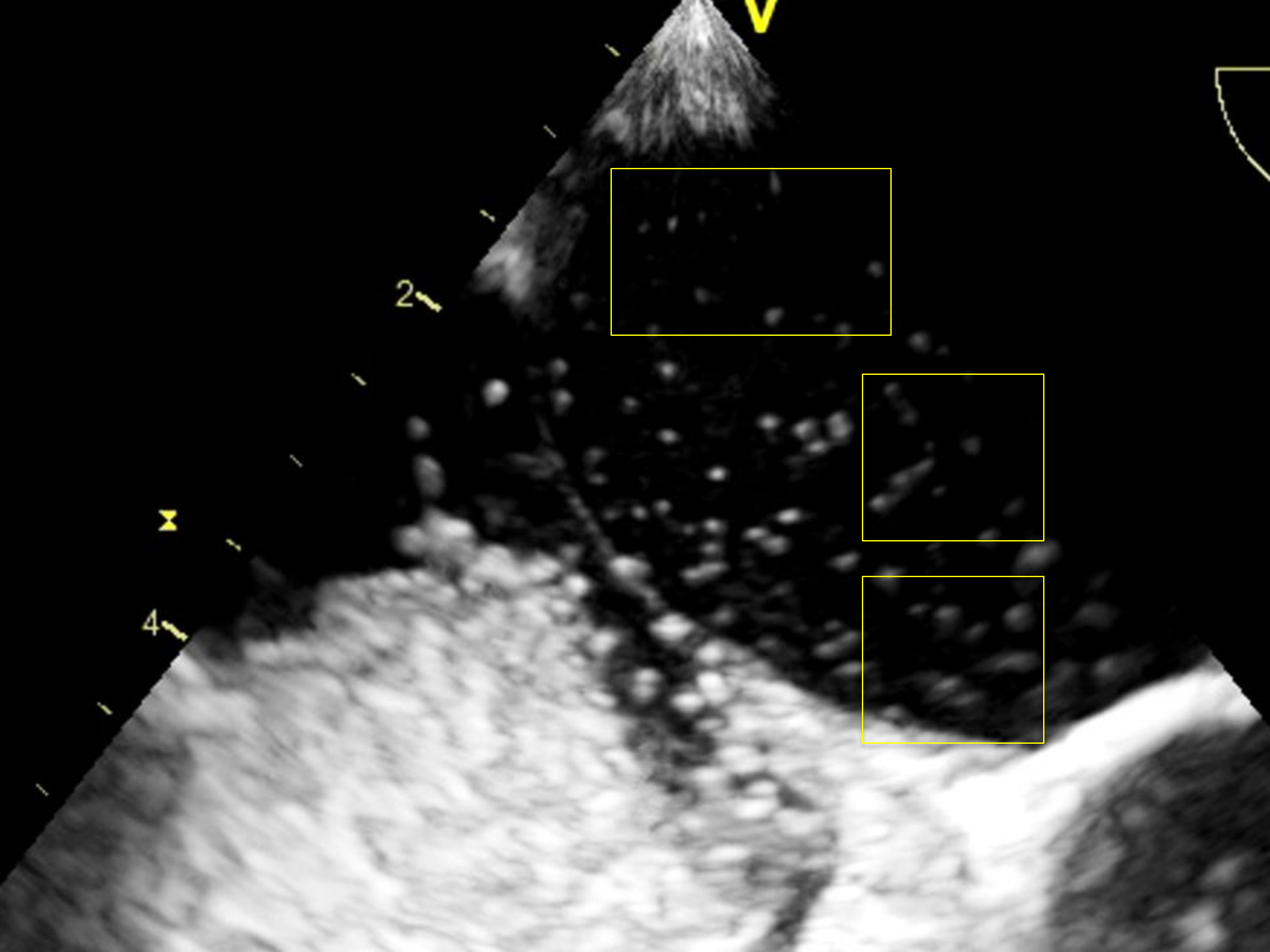


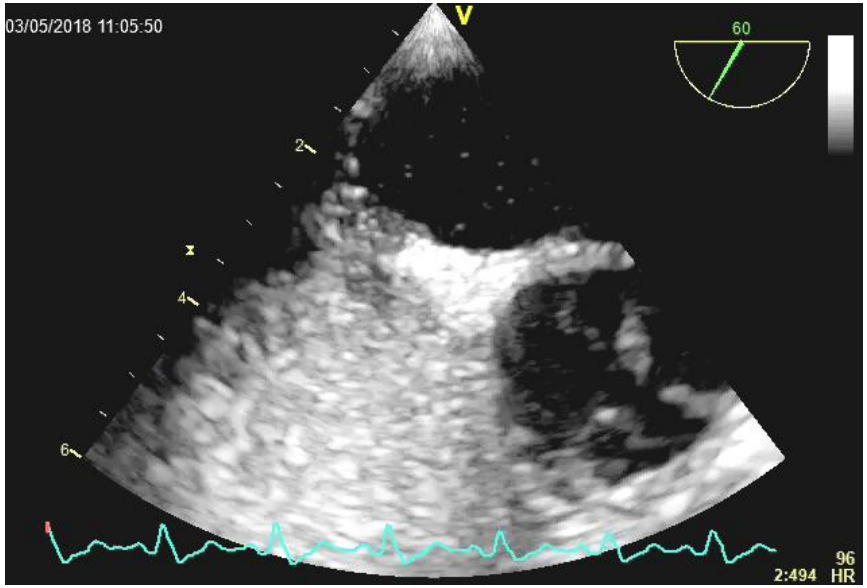
European Heart Journal (2018) 0,
doi: 10.1093/eurheartj/ehy121

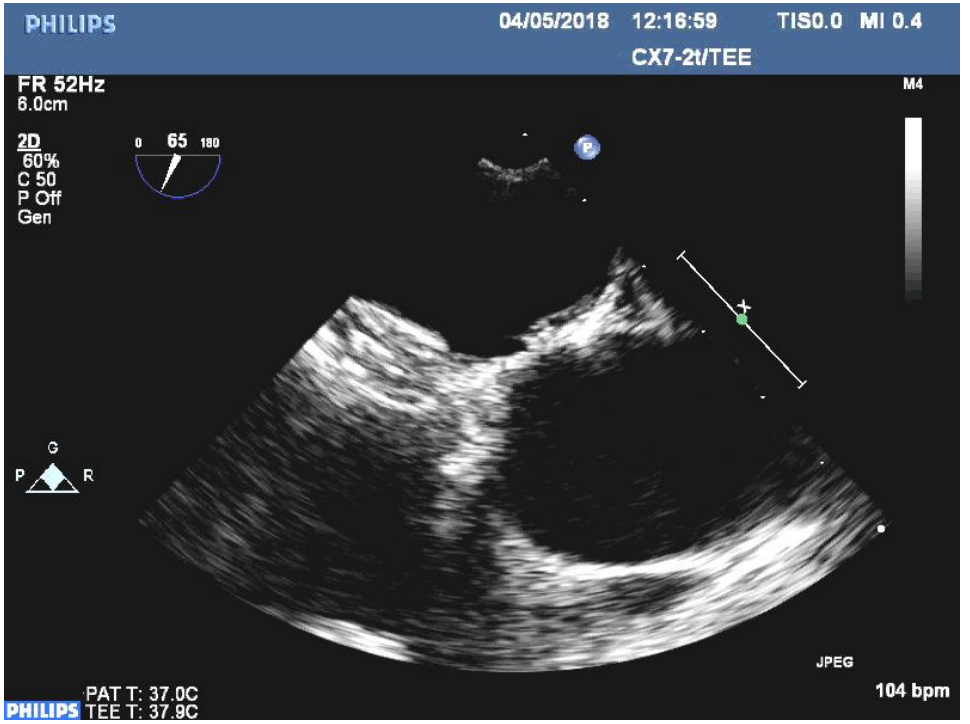
Výskyt a definice „velkého“ zkratu v RCT

	CLOSURE 1	PC TRIAL	RESPECT	REDUCE	CLOSE
Definice velkého zkratu (počet bublin)	>25	>20	>20	>25	>30
Pacienti s velkým zkratem		22%	49%	41%	66%
	53% velký a střední				


03/05/2018 11:05:50
60
2
4
6
96
2:494 HR


2
4

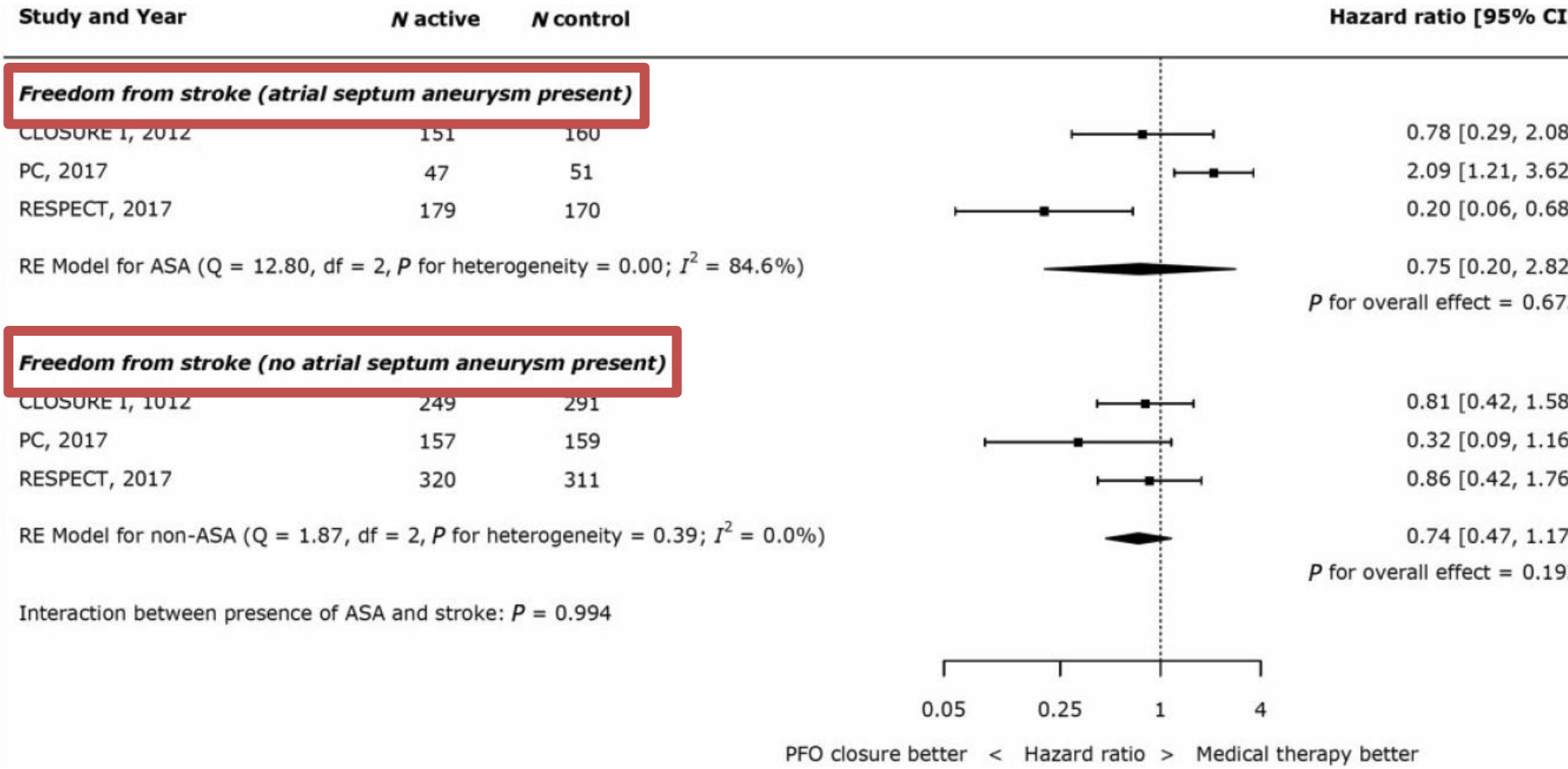




Stav po uzávěru: TEE sledování v 6/12 měsících

	CLOSURE 1	PC TRIAL	RESPECT	REDUCE	CLOSE
Efektivní uzávěr	86%	95,9%	93,5%	94,5%	93%
Kompletní uzávěr			72,7%	76%	

Přítomnost aneuryzmatu septa síní nemá vliv na na rekurenci CMP po uzávěru PFO



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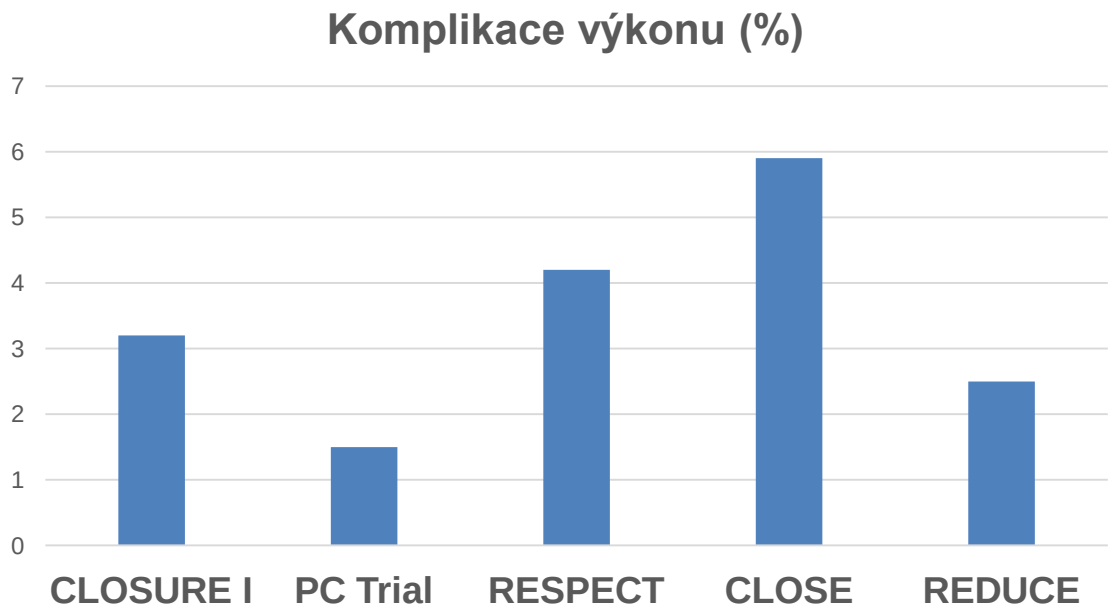
doi: 10.1093/eurheartj/ehy121

Komplikace



Periprocedurální úmrtí: 0
Periprocedurální CMP: 0

Komplikace výkonu

Frekvence 2-4%

- Vaskulární komplikace
- Krvácivé komplikace bez závislosti na výkonu

Frekvence < 0,4%:

- Tamponáda
- Embolizace okluderu
- Trombus na okluderu

Frekvece 3 – 6%

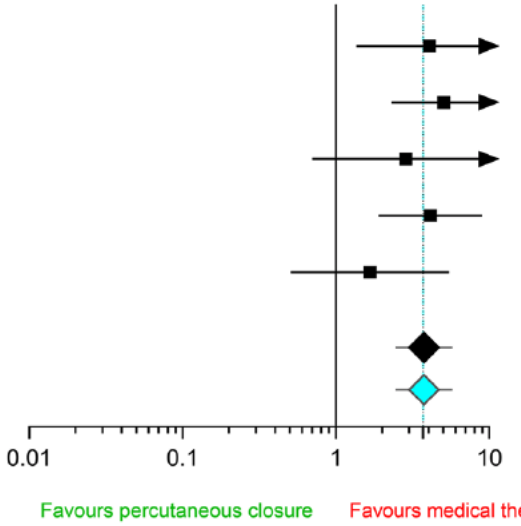
- Fibrilace/Flutter síní

Výskyt fibrilace síní po uzávěru PFO

A Atrial fibrillation

Trial	Closure Events	Closure Total	Medical Events	Medical Total	OR [95%- CI]	Weight fixed	Weight random
CLOSE	11	238	2	235	4.09 [1.36-12.29]	15.4%	15.6%
CLOSURE I	23	447	3	462	5.03 [2.31-10.98]	30.7%	31.1%
PC	6	204	2	210	2.85 [0.70-11.53]	9.6%	9.70%
REDUCE	29	441	1	223	4.13 [1.90-8.96]	31.1%	31.5%
RESPECT	7	499	4	481	1.67 [0.51-5.49]	13.2%	12.2%
	76	**1829**	**12**	**1611**			
Fixed effect model					**3.75 [2.44-5.78]**	**100%**	--
Random effects model					**3.75 [2.44-5.78]**	--	**100%**

Heterogeneity: I^2 = 0% [0% - 73%]
Test for ove rall effect (fixed effect): z = 6.00, (p <0.01)
Test for overa ll effect (random effects): z = 6.00, (p <0.01)



Výskyt fibrilace síní po uzávěru PFO

	Device group	*Control group*
• REDUCE	6.6%	0.4%
• CLOSURE-1	5.7%	0.7%
• PC Trial	2.9%	1.0%
• RESPECT	3.0%	1.5%
• CLOSE	4.6%	0.9%

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„… 71% případů AF se objevilo bezprostředně nebo časně po uzávěru. Byly přechodné nebo ustoupily během 30-45 dní.“ (Alushi et, Clin Resear Cardiol 2018)

REDUCE: 83% Fis/FluS během 45 dní po uzávěru, 59% zmizelo během 2 týdnů
CLOSE: 10 z 11 případů AF se objevilo během 30 dní po implantaci okluderu
RESPECT: 7 periprocedurálních případů AF zmizelo před dimisí. Následně již nebyl rozdíl mezi výskytem AF ve obou skupinách
PC trial: ze 6 pacientů (5 verze, 1 přetrvávala)

EuroIntervention 2018;14-online publish-ahead-of-print August 2018

European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism

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? Reklasifikace etiologie CMP

- Pacient s „kryptogenní“ CMP a PFO ➔ kardioembolizační CMP při PFO