# Kryptogenní CMP: uzávěr PFO nebo nic => NIC ?

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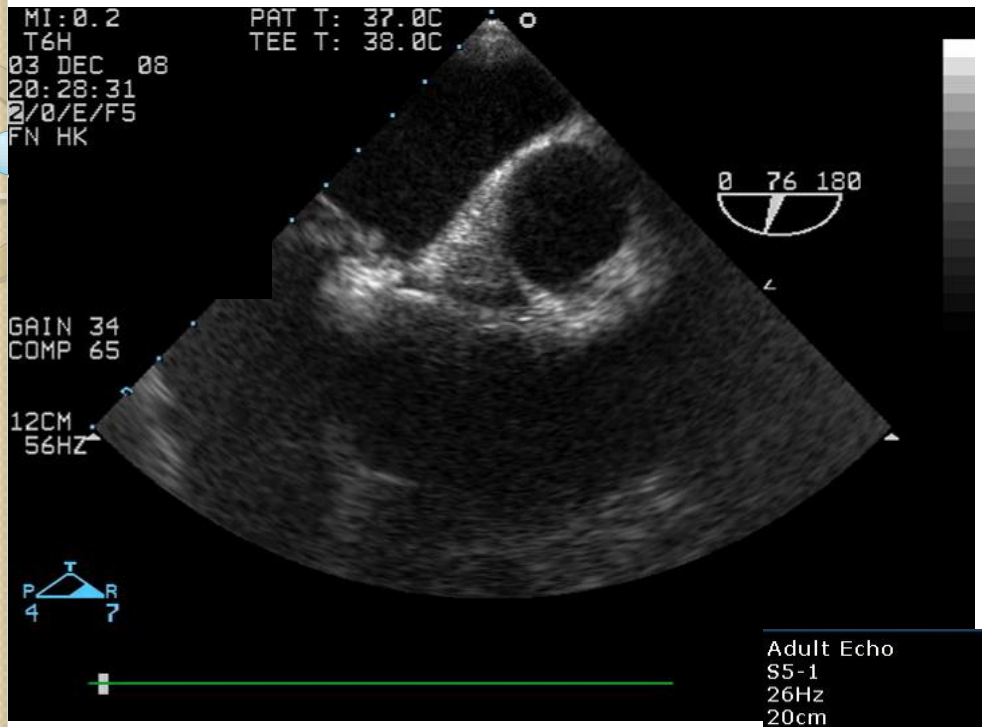
Kardiocentrum

Fakultní nemocnice Hradec Králové

# Katetrizační uzávěr perzistujícího foramen ovale

**Otázky**

- jaká je souvislost a (četnost) mezi PFO a systémových embol.- CMP (CS)?
  (Cohnheim 1877)
- jak vysoké je riziko recidiv SE - CMP u pacientů s PFO?
- existuje efektivní prevence případných SE-CMP?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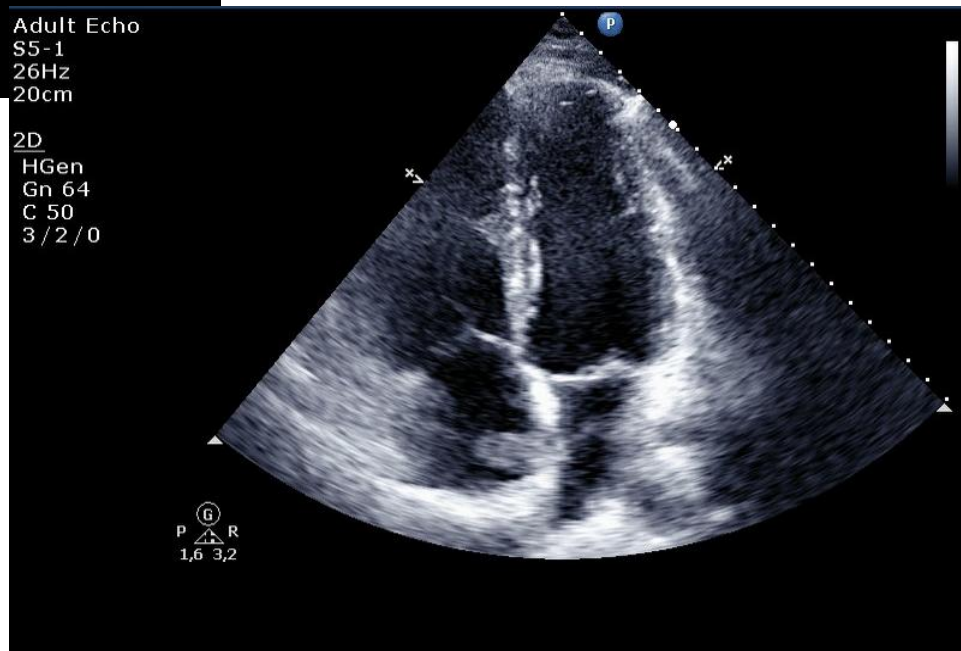
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Gn 64
C 50
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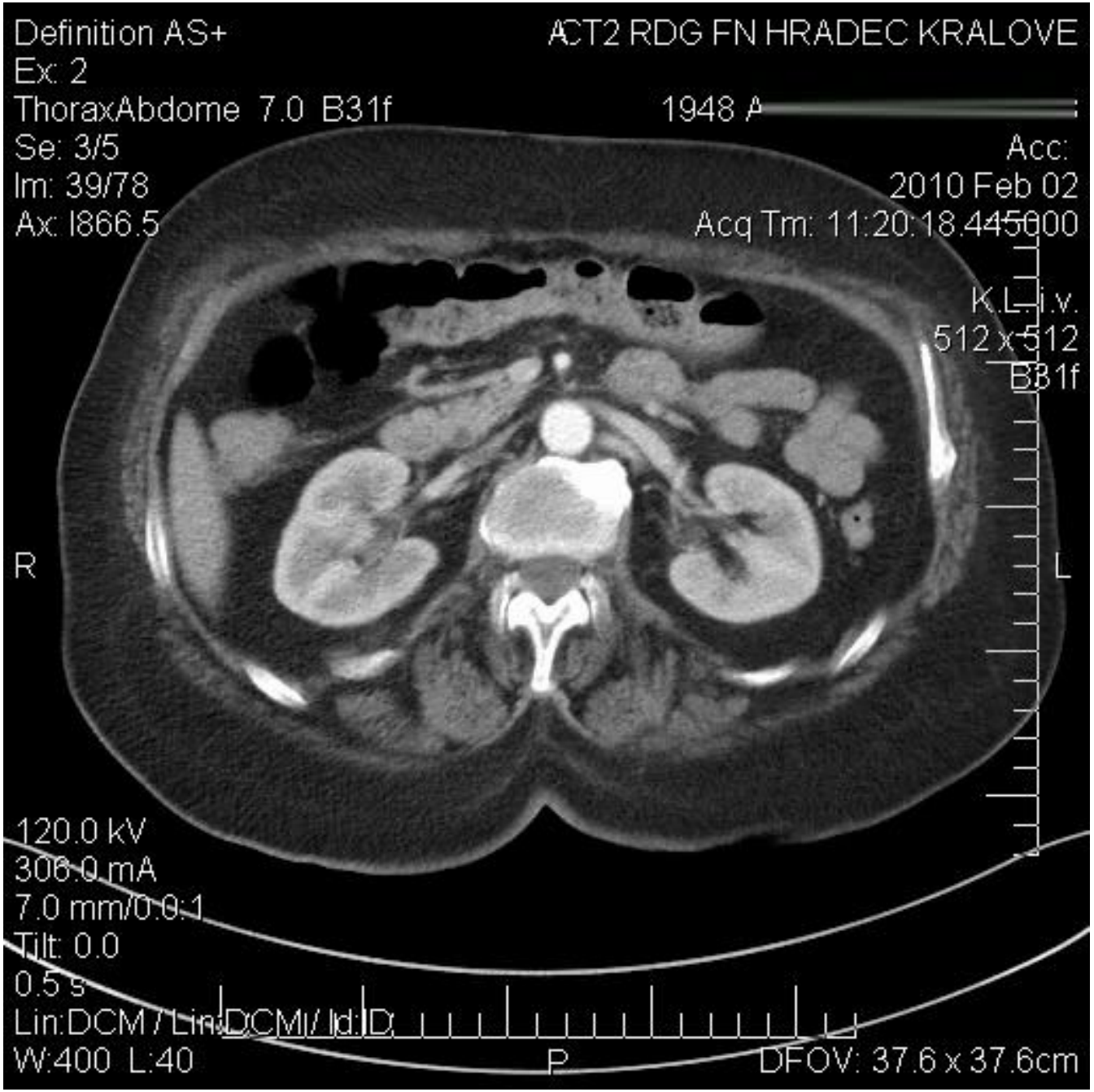
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Im: 39/78
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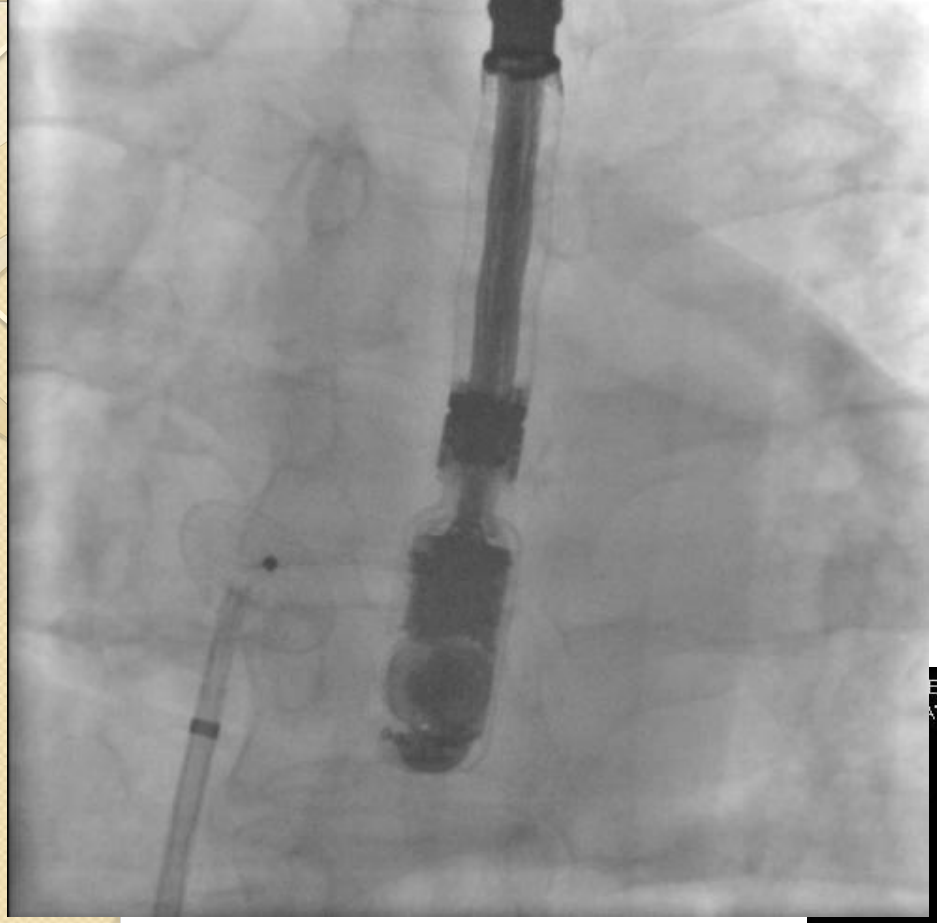


EC KRALOVE I.Interni klinika
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AV,MIROSLAV 43Years M 690617/3208
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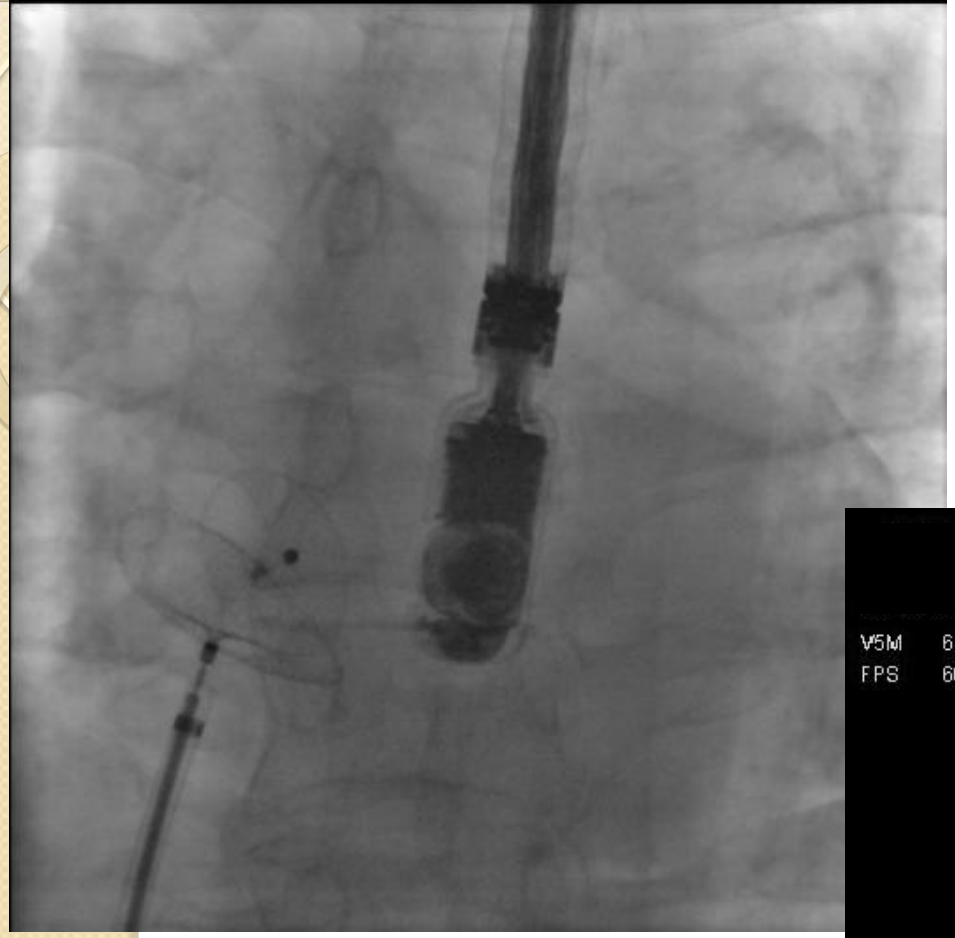


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V5M 6.0
FPS 66s
90
2D 60/1/30

# Katetrizační uzávěr perzistujícího foramen ovale

**PFO výskyt**

- sekce 15 – 30%
- TEE 10 - 15%

**!! Ischem.CMP < 55let 45 - 66% !!**

**Kryptogenní CMP+ASA = 86% PFO (Agmon)**

2001

# Blinded Adjudication of Stroke Cause Using ASCOD Phenotyping

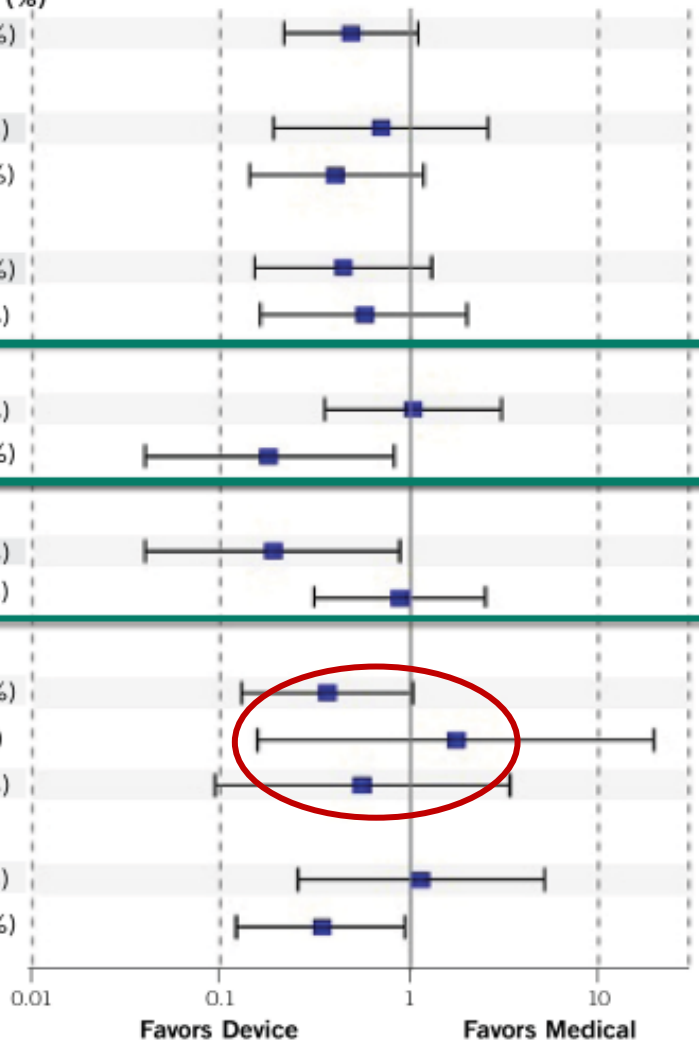
- ASCOD coding captures presence of possible stroke etiologies, and assigns a probability of relatedness (post-hoc)
- Five phenotypes:
  - A = atherosclerosis
  - S = small vessel disease
  - C = cardiac pathology
  - O = other cause
  - D = dissection
- Recurrent strokes classified as either cryptogenic or of known cause

Amarenco et al. *Cerebrovasc Dis* 2013;36:1-5

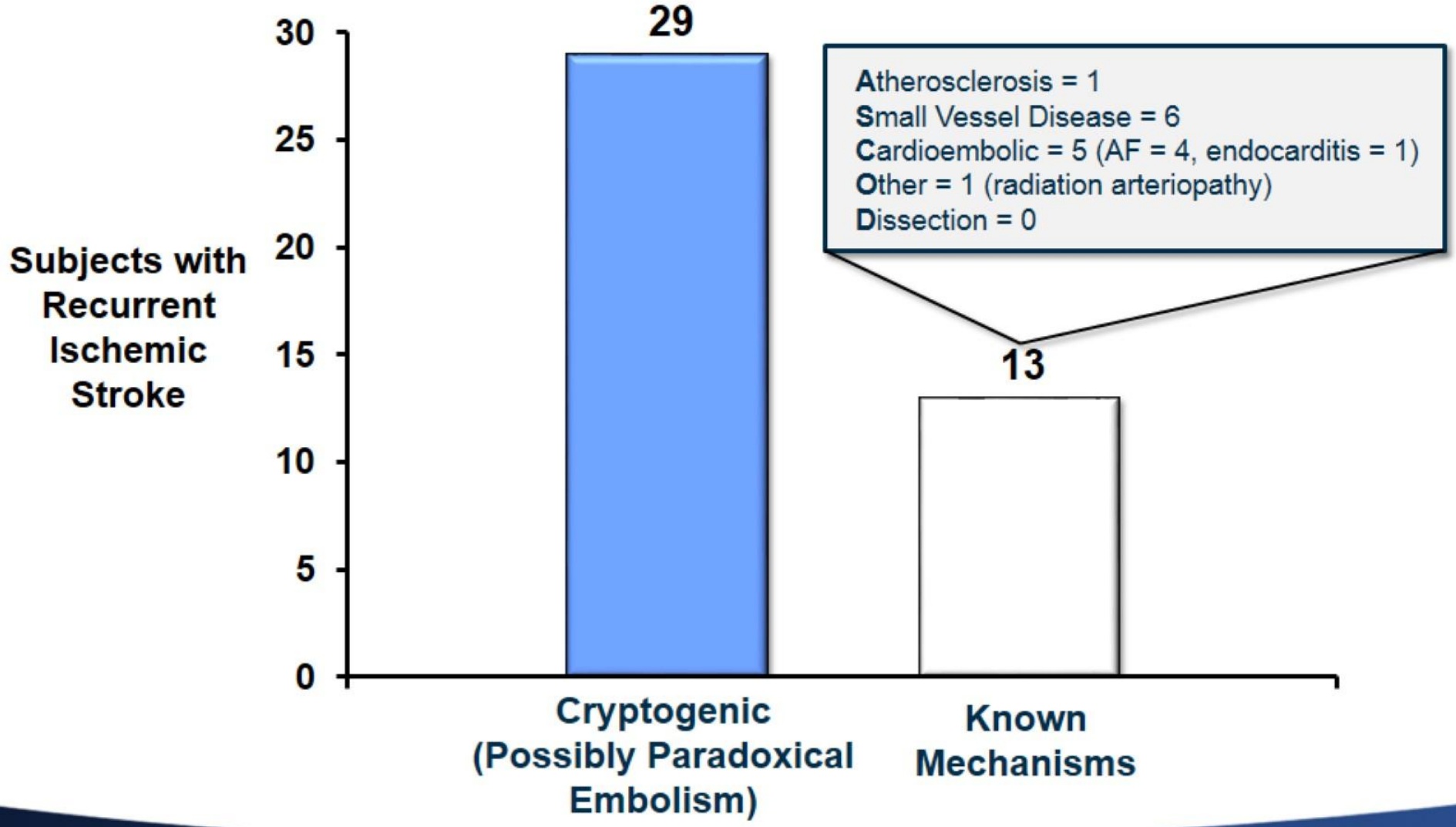
# Subpopulation Differential Treatment Effect

RESPECT CLINICAL TRIAL

| Subgroup | Device Group | Medical Group | Hazard Ratio and 95% CI | | Pvalue (Log Rank) | Interaction Pvalue |
|---|---|---|---|---|---|---|
| | no. of patients/total number (%) | | | | | |
| **Overall** | 9/499 (1.8%) | 16/481 (3.3%) | | 0.492 (0.217, 1.114) | 0.0825 | |
| **Age** | | | | | | 0.5156 |
| - 18-45 | 4/230 (1.7%) | 5/210 (2.4%) | | 0.698 (0.187, 2.601) | 0.5901 | |
| - 46-60 | 5/262 (1.9%) | 11/266 (4.1%) | | 0.405 (0.140, 1.165) | 0.0828 | |
| **Sex** | | | | | | 0.7312 |
| - Male | 5/268 (1.9%) | 10/268 (3.7%) | | 0.448 (0.153, 1.311) | 0.1321 | |
| - Female | 4/231 (1.7%) | 6/213 (2.8%) | | 0.571 (0.161, 2.024) | 0.3789 | |
| **Shunt Size** | | | | | | 0.0667 |
| - None, trace or moderate | 7/247 (2.8%) | 6/244 (2.5%) | | 1.034 (0.347, 3.081) | 0.9527 | |
| - Substantial | 2/247 (0.8%) | 10/231 (4.3%) | | 0.178 (0.039, 0.813) | 0.0119 | |
| **Atrial septal aneurysm** | | | | | | 0.1016 |
| - Present | 2/180 (1.1%) | 9/169 (5.3%) | | 0.187 (0.040, 0.867) | 0.0163 | |
| - Absent | 7/319 (2.2%) | 7/312 (2.2%) | | 0.889 (0.312, 2.535) | 0.8259 | |
| **Index infarct topography** | | | | | | 0.3916 |
| - Superficial | 5/280 (1.8%) | 12/269 (4.5%) | | 0.366 (0.129, 1.038) | 0.0487 | |
| - Small Deep | 2/57 (3.5%) | 1/70 (1.4%) | | 1.762 (0.156, 19.93) | 0.6429 | |
| - Other | 2/157 (1.3%) | 3/139 (2.2%) | | 0.558 (0.093, 3.340) | 0.5167 | |
| **Planned medical regimen** | | | | | | 0.1966 |
| - Anticoagulant | 4/132 (3.0%) | 3/121 (2.5%) | | 1.141 (0.255, 5.098) | 0.8628 | |
| - Antiplatelet | 5/367 (1.4%) | 13/359 (3.6%) | | 0.336 (0.120, 0.944) | 0.0299 | |

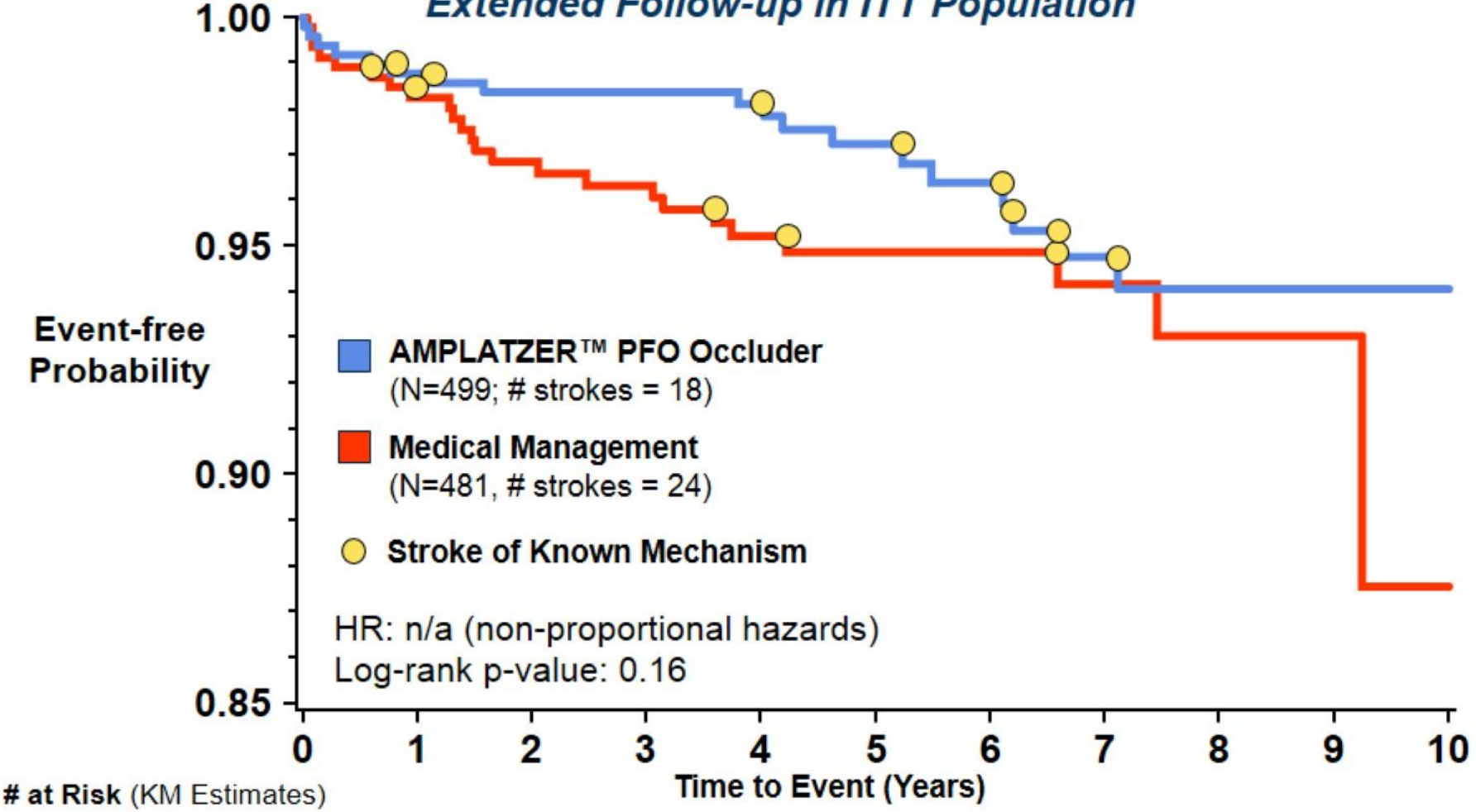


# Nearly 1/3 of Recurrent Strokes in Extended Follow-up Are of Known Mechanism



# 1 out of 3 Recurrent Strokes Had Mechanism That PFO Closure Cannot Prevent

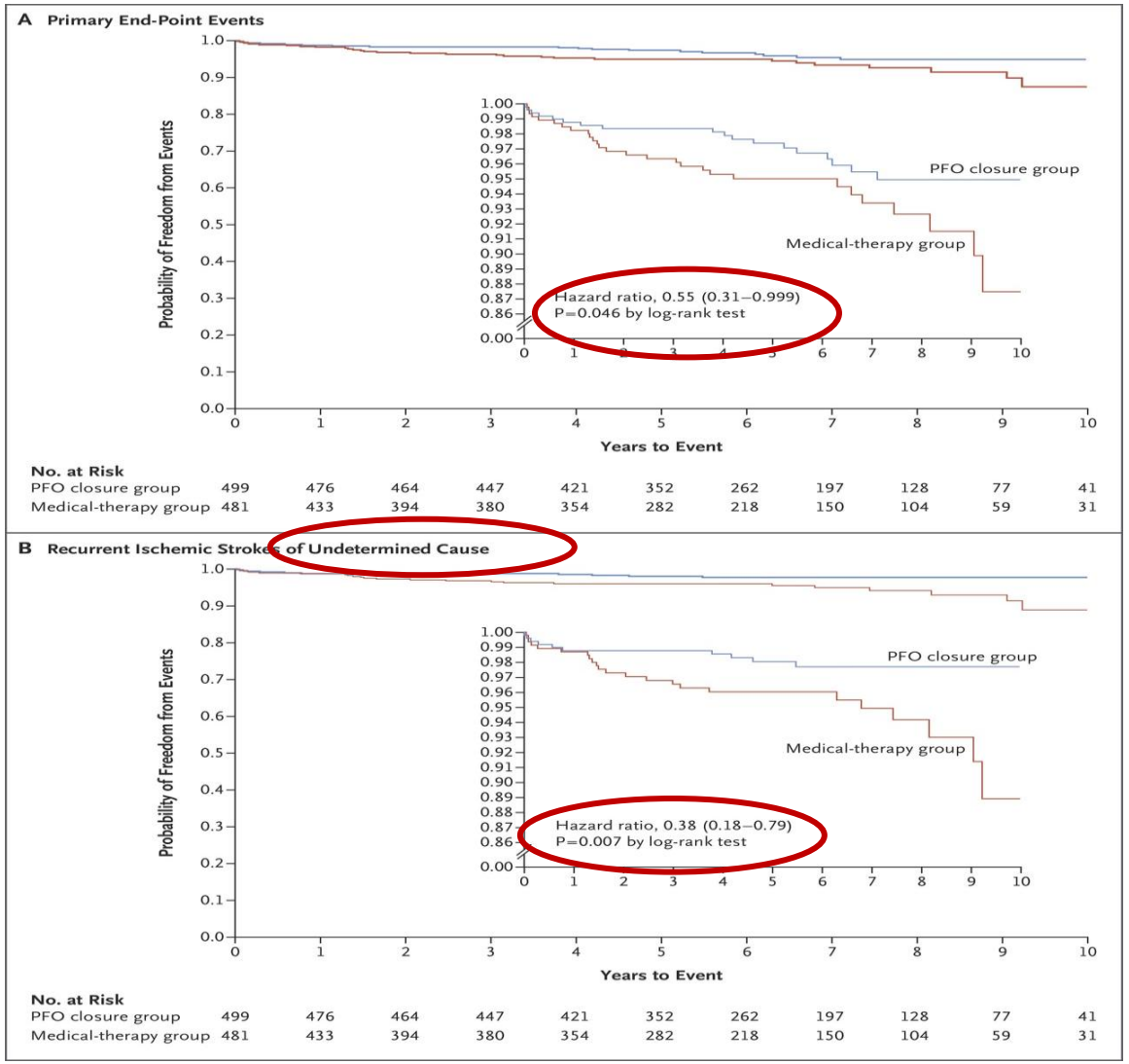
***Extended Follow-up in ITT Population***




**# 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%) |

# RESPECT



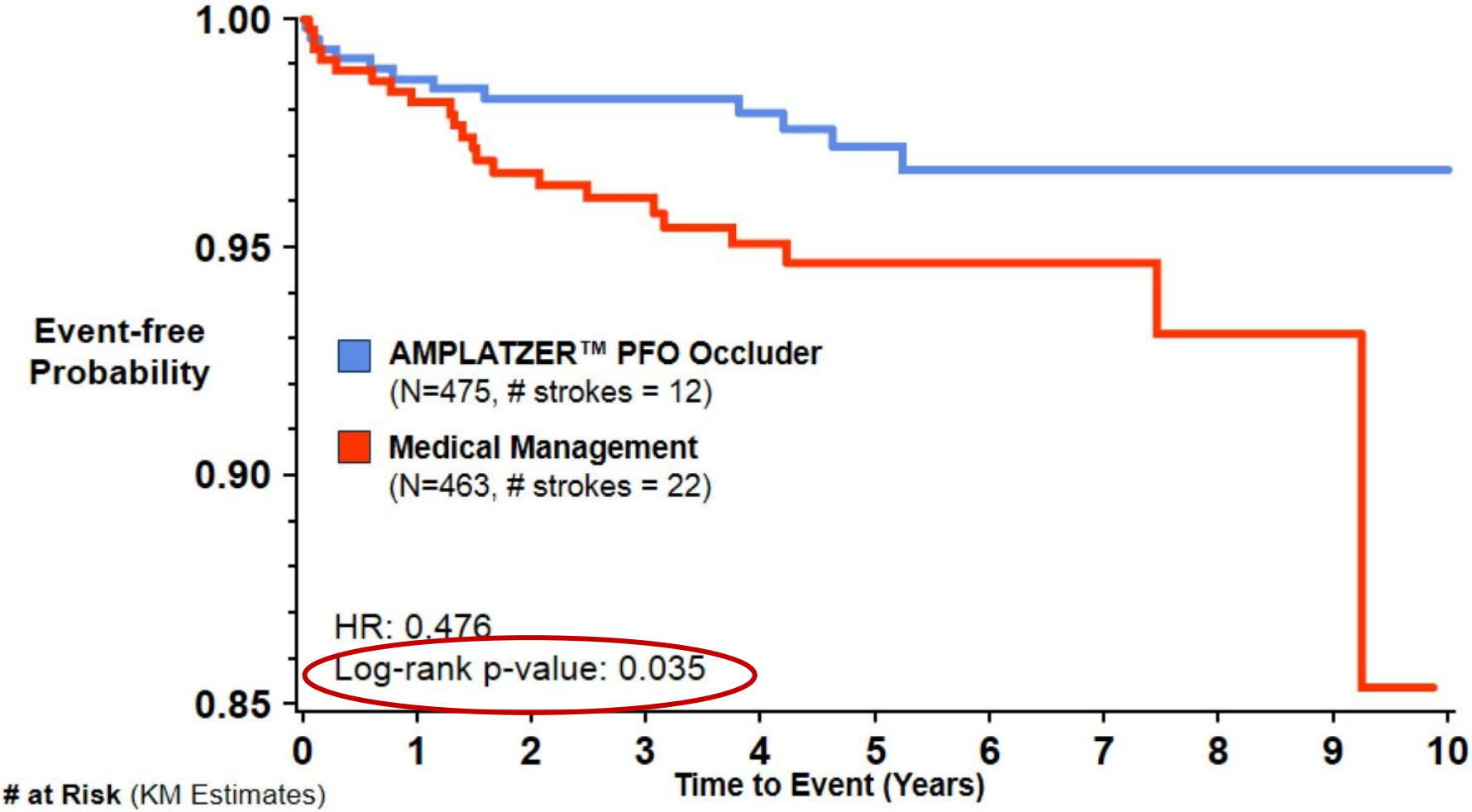

**Saver JL et al. N Engl J Med 2017;377:1022-1032**

# 1 out of 5 Patients Were >60 Years in Extended Follow-up Analysis

- As patients age, increase in non-cryptogenic strokes expected
- PFO closure can only reduce risk for recurrent strokes mediated by paradoxical embolism
  - Appropriate clinical interpretation of trials requires adjudication for stroke mechanism

# Freedom from Recurrent Stroke of Any Mechanism: <60 Yrs

## *52% Relative Risk Reduction in ITT Sensitivity Analysis*




**# at Risk** (KM Estimates)

| | | | | | | |
|---|---|---|---|---|---|---|
| **AMPLATZER** | **475** (0%) | **417** (1.8%) | **308** (2.1%) | **166** (3.3%) | **69** (3.3%) | **15** (3.3%) |
| **MM** | **463** (0%) | **353** (3.4%) | **254** (4.9%) | **124** (5.4%) | **51** (6.9%) | **9** (14.7%) |

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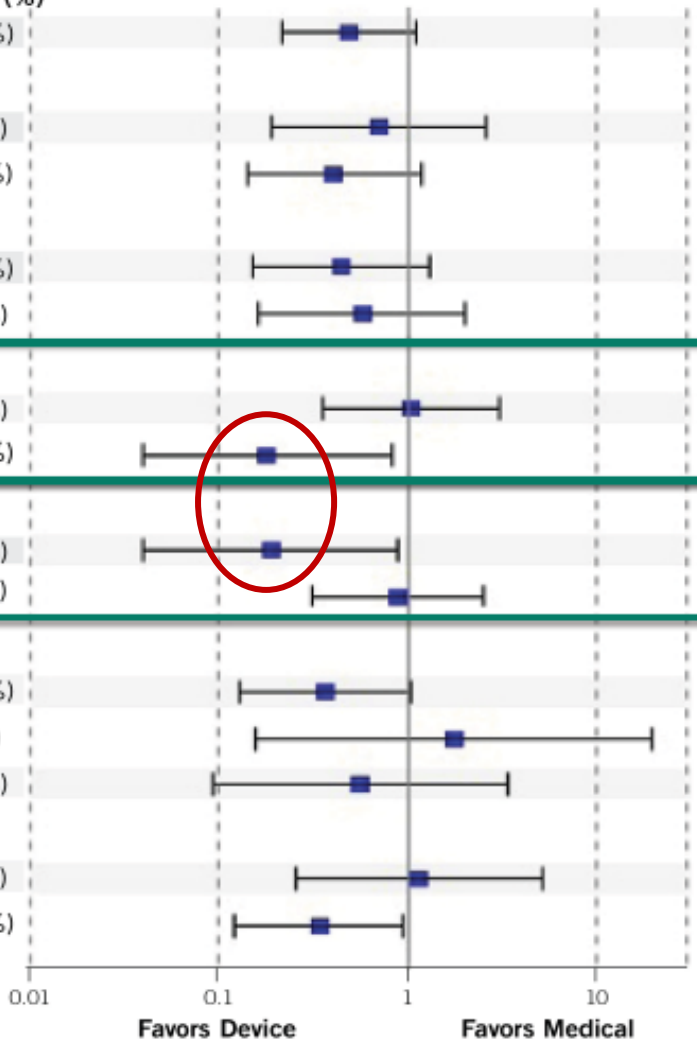
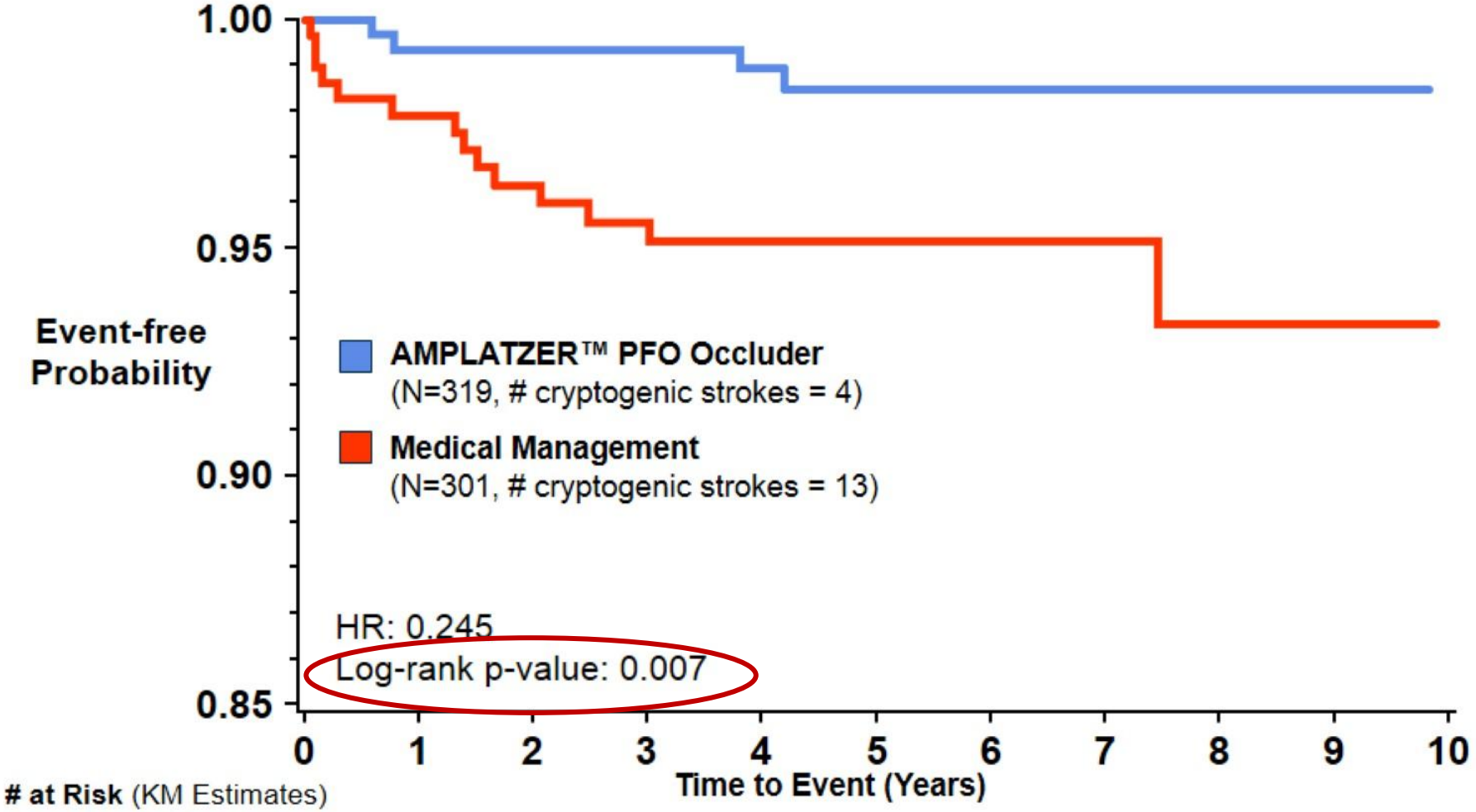


# Greater Benefit in Substantial Shunt or ASA Subgroup

*75% Relative Risk Reduction in Recurrent Cryptogenic Stroke in ITT Population*




**# at Risk** (KM Estimates)

| | | | | | | |
|---|---|---|---|---|---|---|
| **AMPLATZER** | **319** (0%) | **299** (0.6%) | **229** (1.0%) | **134** (1.5%) | **52** (1.5%) | **11** (1.5%) |
| **MM** | **301** (0%) | **243** (3.6%) | **186** (4.8%) | **105** (4.8%) | **45** (6.6%) | **7** (6.6%) |

# CLOSE - Conclusions

- Among patients who had had a recent cryptogenic stroke attributed to ***PFO with an associated atrial septal aneurysm or large interatrial shunt***, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to ***antiplatelet therapy alone.***
- ***PFO closure was associated with an increased risk of atrial fibrillation***.

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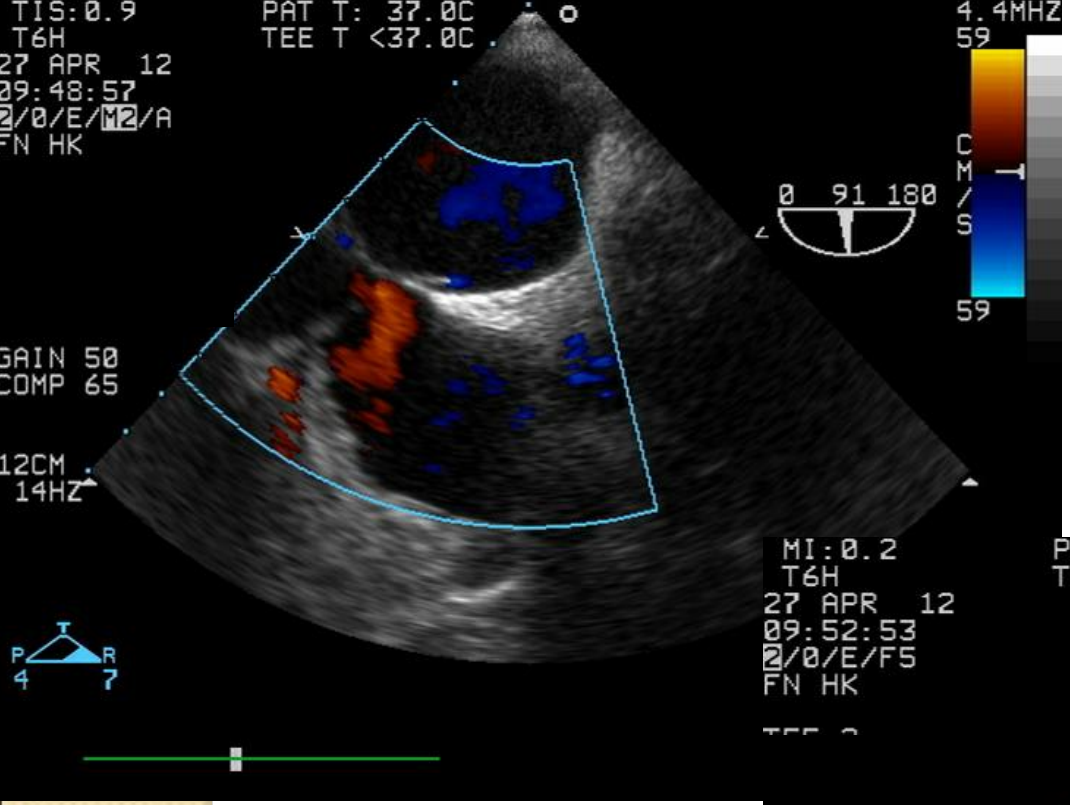
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COMP 65
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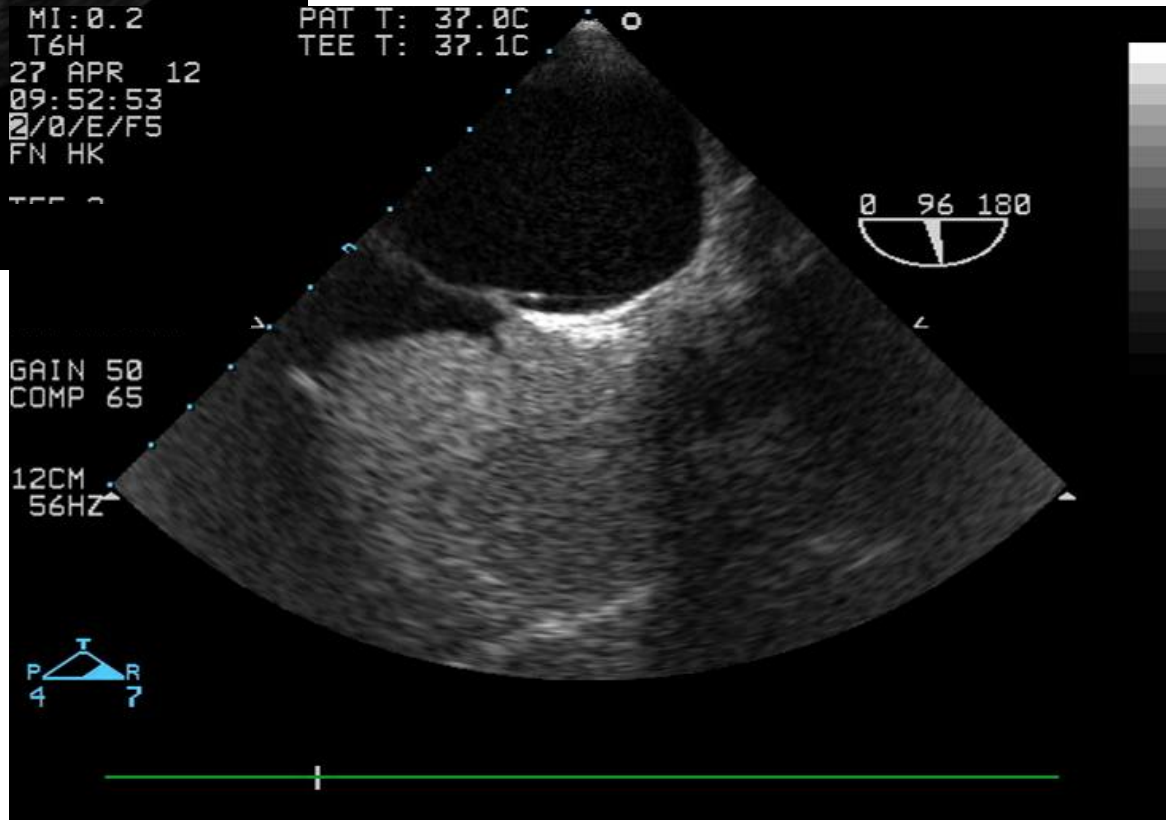
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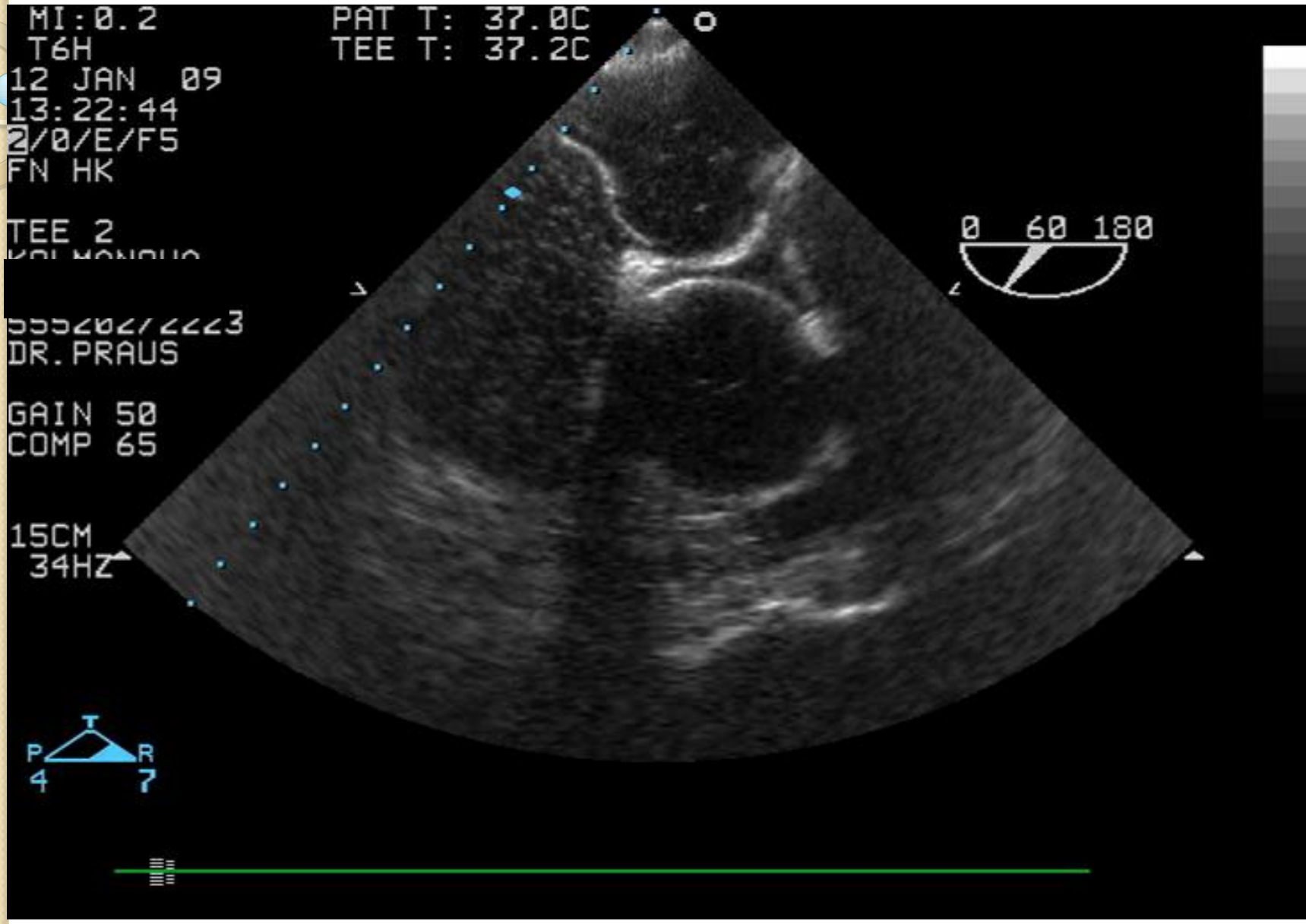
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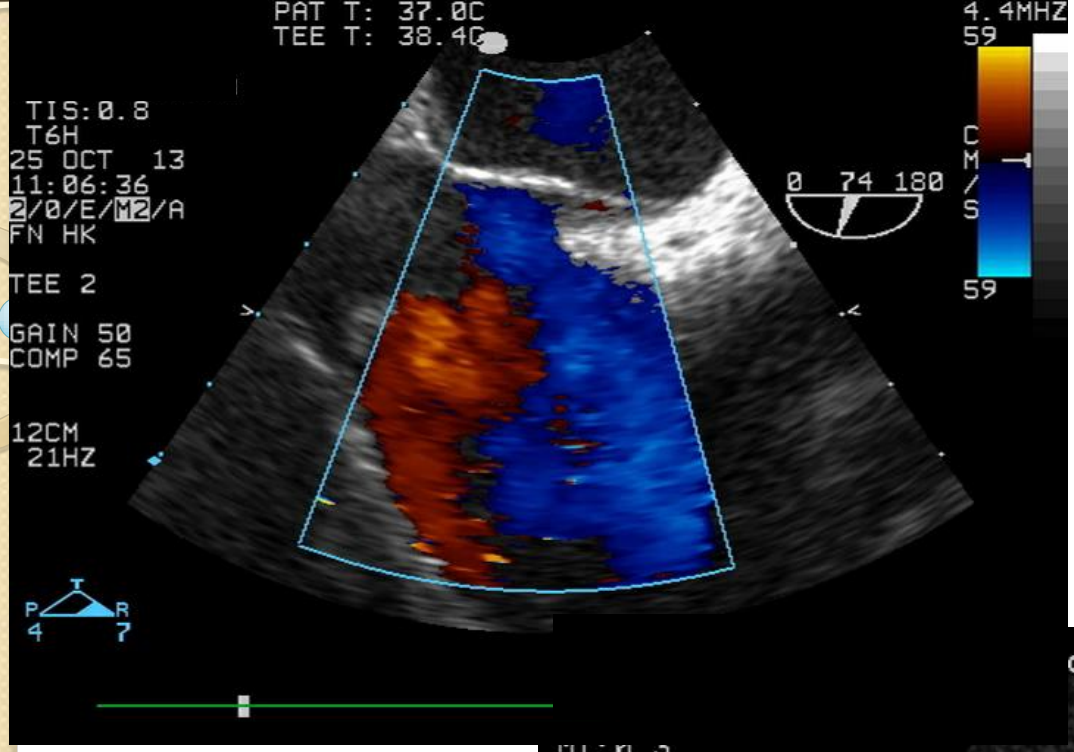
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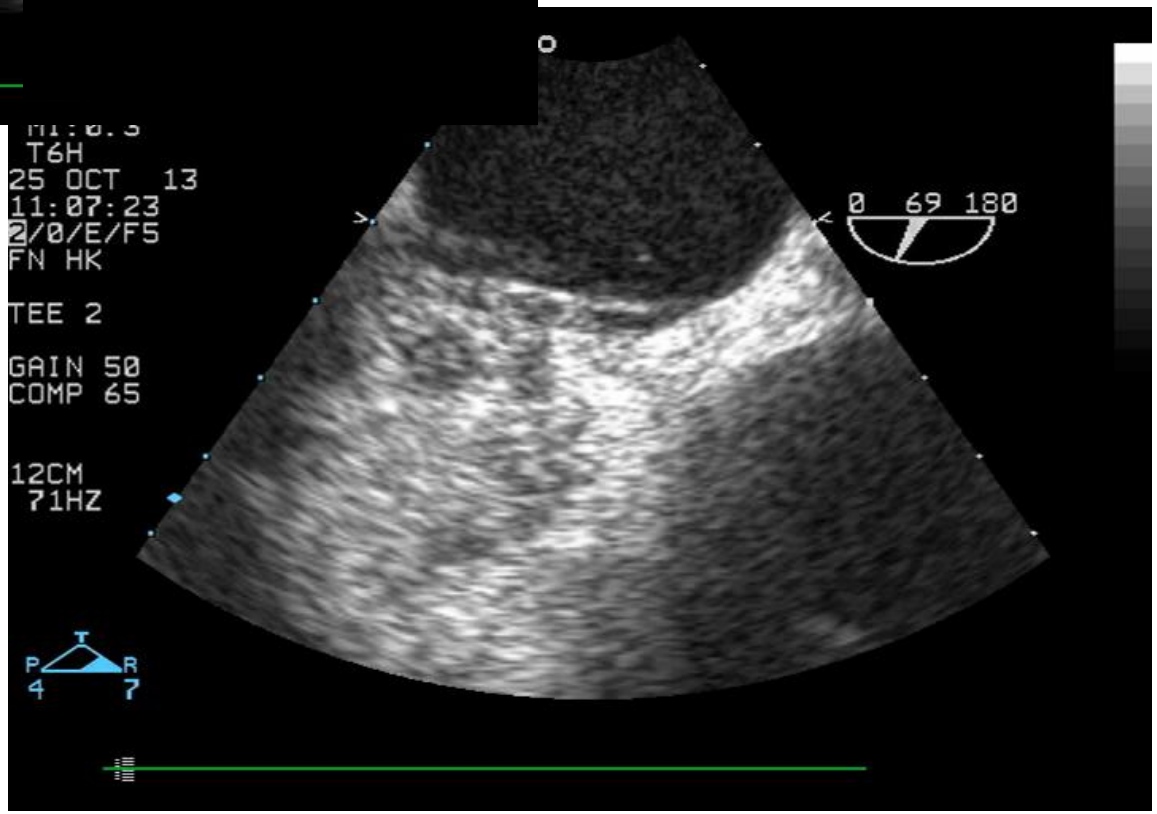
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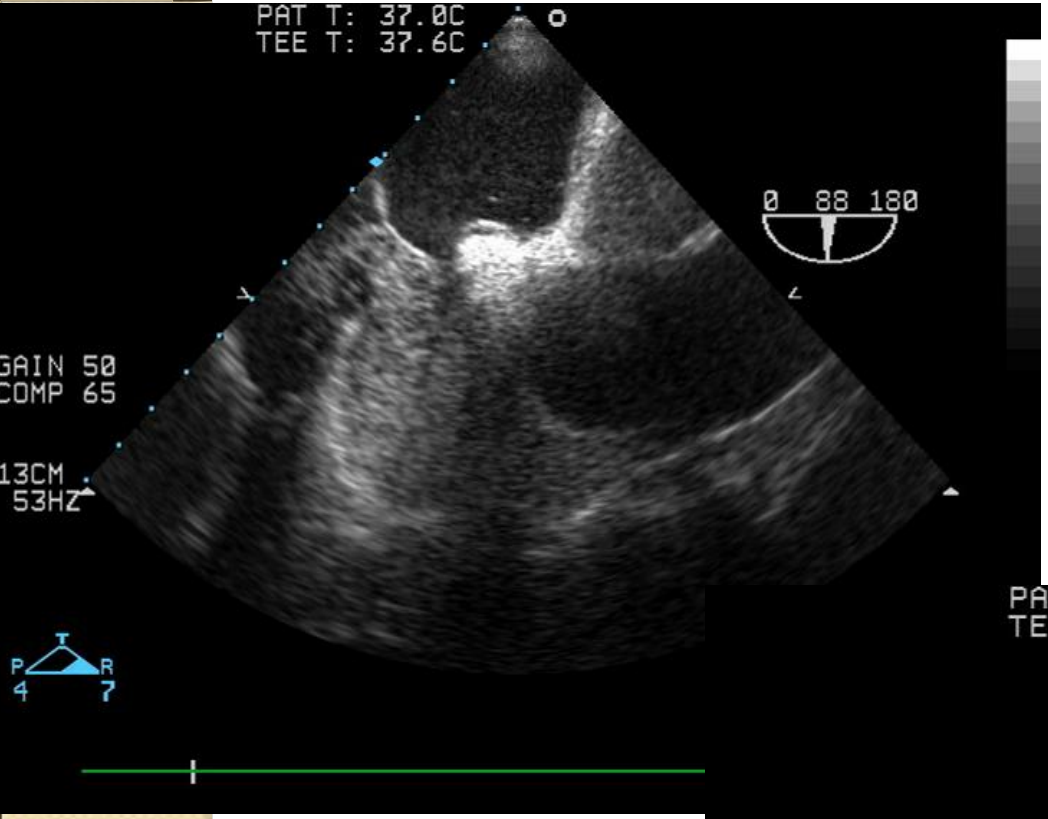
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PAT T: 37.0C
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GAIN 45
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# RESPECT

- 72,7% pacientů mělo kompletní uzávěr a 93,5% mělo efektivní uzávěr
- SAE  uzávěr 23,0% x medikace 21,6% (p=0,65)

- **vyšší ochrana uzávěru**
  - **velký P-L zkrat (HR 0,18; 95% CI 0,04-0,81)**
  - **síňové aneurysma (HR 0,19; 95% CI 0,04-0,87)**
  - **CMP do povrchových vrstev (HR 0,37; 95% CI 0,13-1,04)**

Carroll et al. NEJM 2013

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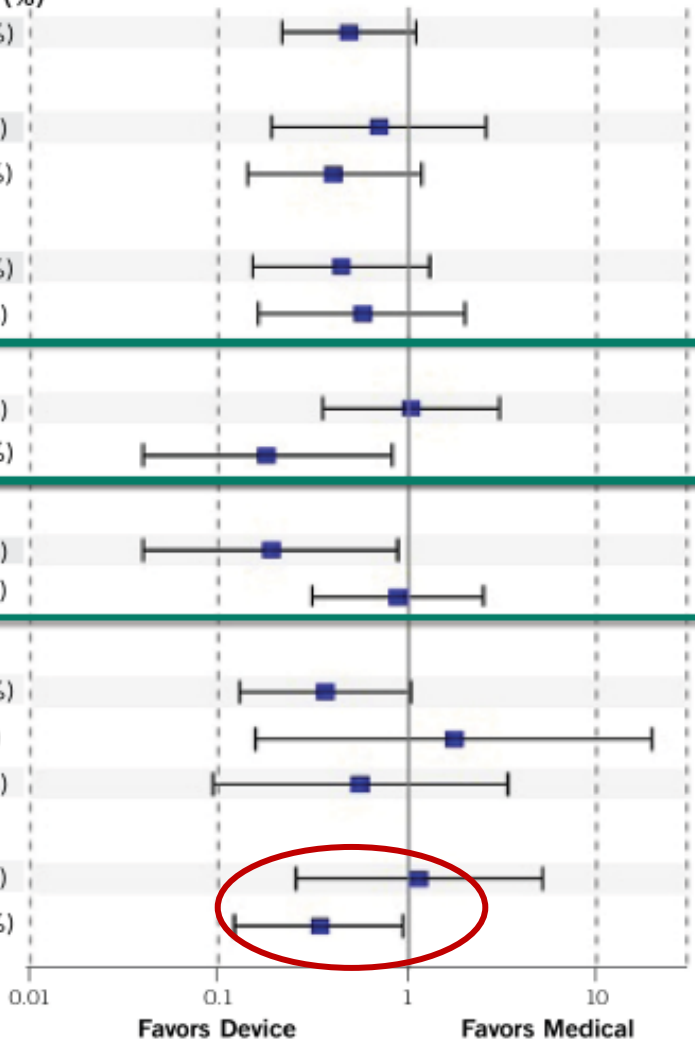

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# Totality of Evidence and NNT

## 46.6%-72.7% risk reduction of stroke in favor of device

RESPECT CLINICAL TRIAL

### Totality of Evidence

| Analysis | Risk Reduction | P-Value[1] |
|---|---|---|
| Intent to Treat Raw Count | 46.6% | 0.157 |
| Intent to Treat KM | 50.8% | 0.083 |
| Per Protocol KM | 63.4% | 0.032 |
| As Treated KM | 72.7% | 0.007 |

### Number Needed to Treat (NNT)

| | NNT[2] | Device Group Event Rate[3] | Medical Group Event Rate[3] |
|---|---|---|---|
| 1 Year | 250 | 1.33% | 1.73% |
| 2 Year | 70.4 | 1.60% | 3.02% |
| 5 Year | 23.9 | 2.21% | 6.40% |

1. P-values: ITT Raw Count is calculated using Fisher's Exact test; all other P-values are calculated using log-rank test
2. The NNT is the average number of subjects that need to be treated with the AMPLATZER™ PFO Occluder in order to prevent one stroke in the respective time intervals. The NNT is calculated as the reciprocal of the difference between the control arm and device arm event rates
3. Calculated using the Kaplan-Meier estimated event rates for each treatment group

# Recurrent Cerebral Infarct Size[1]

## Methods pre-specified; analysis post-hoc

RESPECT CLINICAL TRIAL

| Event | Device Group n/N (%) | Medical Group n/N (%) | P-value[2] |
|---|---|---|---|
| Larger infarct >1.5cm | 1/7 (14%) | 9/13 (69%) | P=0.0573 |
| Smaller infarct ≤ 1.5cm | 6/7 (86%) | 4/13 (31%) | |

- This exploratory analysis of site-reported recurrent cerebral infarct size is provocative in suggesting that recurrent ischemic strokes in the medical versus device group are not only more frequent but also larger

1. Recurrent infarct size reported on primary endpoint population
2. P-value based on Fisher's Exact test

# Komplikace

- embolizace, malpozice instrumentária
- perforace srdečních struktur, tamponáda
- reziduální zkrat
- lokální trombóza
- vzduchová embolizace
- alergie na nikl
- infekční endokarditida

# CLOSE - Conclusions

- Among patients who had had a recent cryptogenic stroke attributed to ***PFO with an associated atrial septal aneurysm or large interatrial shunt***, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to ***antiplatelet therapy alone.***
- ***PFO closure was associated with an increased risk of atrial fibrillation***.

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# CLOSE

**Table 3. Procedural Complications and Serious Adverse Events.***

| Complication or Event | Randomization Groups 1 and 2 | | | Randomization Groups 1 and 3 | | |
|---|---|---|---|---|---|---|
| | PFO Closure Group (N=238) | Antiplatelet-Only Group (N=235) | P Value | Anticoagulant Group (N=187) | Antiplatelet-Only Group (N=174) | P Value |
| | *no. of patients (%)* | | | *no. of patients (%)* | | |
| Major or fatal device-related or procedure-related complication† | 14 (5.9) | NA | NA | NA | NA | NA |
| Major or fatal bleeding complication | 2 (0.8) | 5 (2.1) | 0.28 | 10 (5.3) | 4 (2.3) | 0.18 |
| Atrial fibrillation or flutter‡ | 11 (4.6)§ | 2 (0.9) | 0.02 | 0 | 2 (1.1) | 0.23 |
| Death | 0 | 0 | NA | 1 (0.5)¶ | 0 | 0.65 |
| At least one serious adverse event | 85 (35.7) | 78 (33.2) | 0.56 | 62 (33.2) | 59 (33.9) | 0.88 |

* Definitions of major or fatal device-related or procedure-related complications, definitions of major or fatal bleeding complications, and a full list of serious adverse events are provided in the Supplementary Appendix.

† Major or fatal device-related or procedure-related complications in the PFO closure group are listed for those that occurred within 30 days after the procedure and included atrial fibrillation (9 patients), atrial flutter (1 patient), supraventricular tachycardia (2 patients), air embolism (1 patient), and hyperthermia resulting in prolongation of hospitalization (1 patient).

‡ Atrial fibrillation or flutter was classified as cases that required treatment for more than 1 month.

§ In 10 patients, atrial fibrillation or flutter occurred within 30 days after the procedure.

¶ The one death was due to pancreatic cancer.

**Mas J-L et al. N Engl J Med 2017;377:1011-1021**

# Katetrizační uzávěr perzistujícího foramen ovale

**Co je nutné vědět před indikací indikací uzavření PFO od:**

*1/ neurologa*

*- pokud možno přesné určení etiologie CMP*

*2/ klinika*

*- pokud možno přesné určení etiologie SE*

*2/ kardiologa (ECHO)*

*- nejen průkaz PFO*

*- pokud možno nejlepší zobrazení morfologie síňového septa v klidu, hlubším dýchání a při zátěži (Vlsalva m.)*

# Závěry:

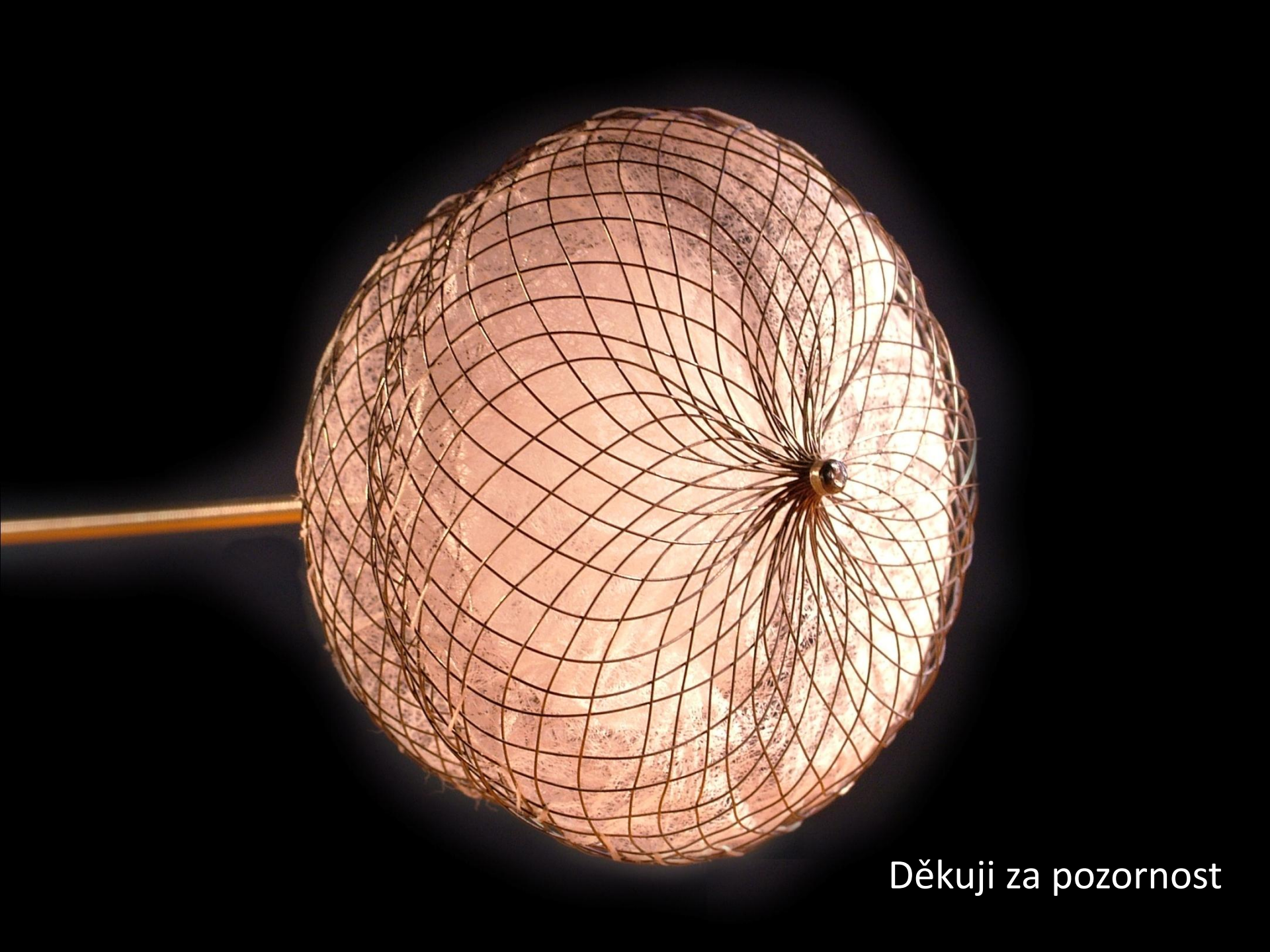
- **U pacientů s kryptogenní CMP uzavření PFO snižuje výskyt opakovaných CMP proti medikamentózní léčbě (antiagregace)**

- **Vysoká úspěšnost uzávěru PFO, nízký výskyt komplikací, *ale není bez komplikací***

- **Vyšší výskyt FIS (periprocedurální období)**

# Závěry:

- **Maximální snaha o průkaz souvislosti mezi PFO a SE-CMP**
- **Efekt u „rizikových“ PFO, nutné max. přesné posouzení rizikovosti PFO =>TEE**
- ***Pokud neprokážeme vysokou pravděpodobnost souvislosti SE-CMP s PFO a je přítomen „triviální“ PFO – uzávěr PFO není indikován !!!***
- ***U starších nemocných (> 60 let) a u nemocných s nutnosti trvalé antikoagulace je nutné uzávěr PFO velmi zvážit a případná indikace musí být přísně individuální!!!***


Děkuji za pozornost