PFO Closure for Stroke Prevention

Brain Summit

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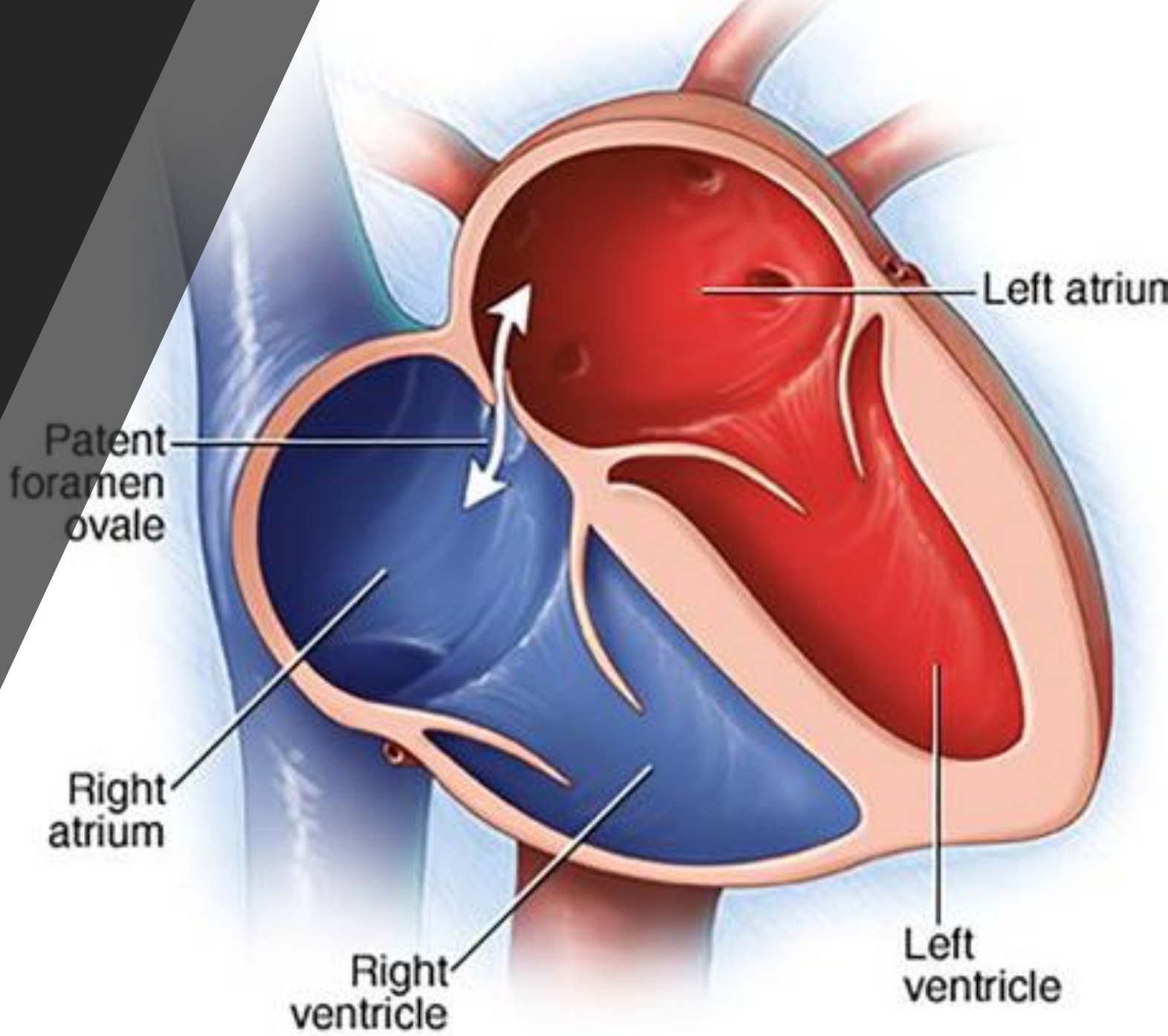


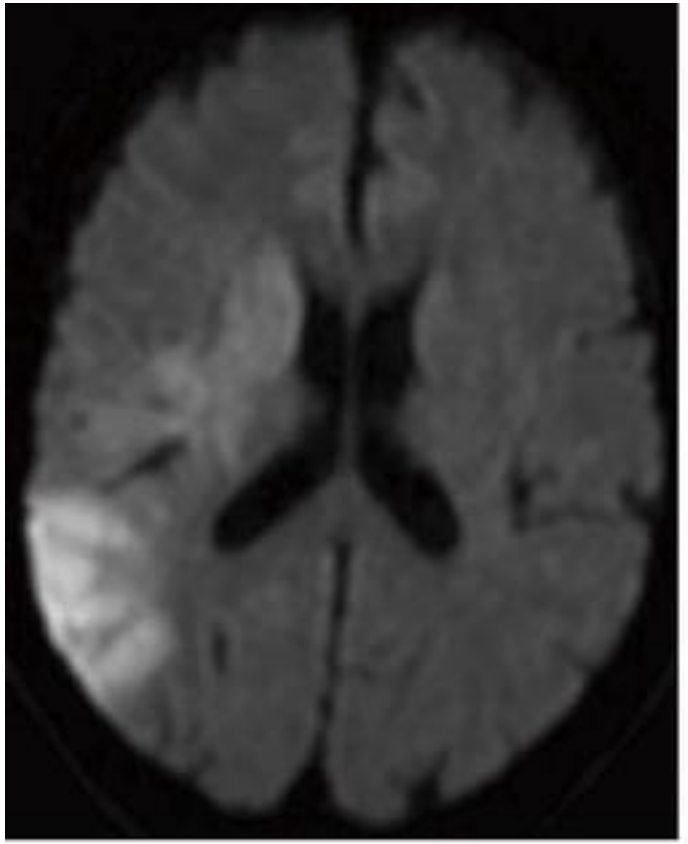
Disclosures

- None

Case

- 43 y/o F with HTN admitted with R MCA stroke 3 months ago
- CTA Head and Neck showed no significant extracranial or intracranial atherosclerotic plaques or stenoses
- TTE w/ bubble during admission reported interatrial shunting (presumed PFO) and normal EF. Lower extremity doppler normal.
- Discharged on aspirin 81mg and atorvastatin 40mg for secondary stroke prevention
- PCP referred to Cardiology clinic. Cardiologist confirmed moderate size PFO on TEE with no septal aneurysm. Planning to schedule closure.

- Do you agree?



Epidemiology

- Stroke is 5th leading cause of death in U.S.
- Cryptogenic stroke accounts for 1/3 of stroke cases
- PFO prevalence is 25% in general population
- 40% PFO prevalence in patients with cryptogenic stroke
- Prospective observational studies showed no increased risk of stroke conveyed by presence of PFO
- Annual rate of recurrent stroke/TIA per 100 patient years 5.6% in those with PFO vs 5.0% without PFO (p=0.79)

Stroke Etiologies

- TOAST classification

Large-artery atherosclerosis (embolus/thrombosis)

Cardio embolism (high-risk/medium-risk)

Small-vessel occlusion (lacunae)

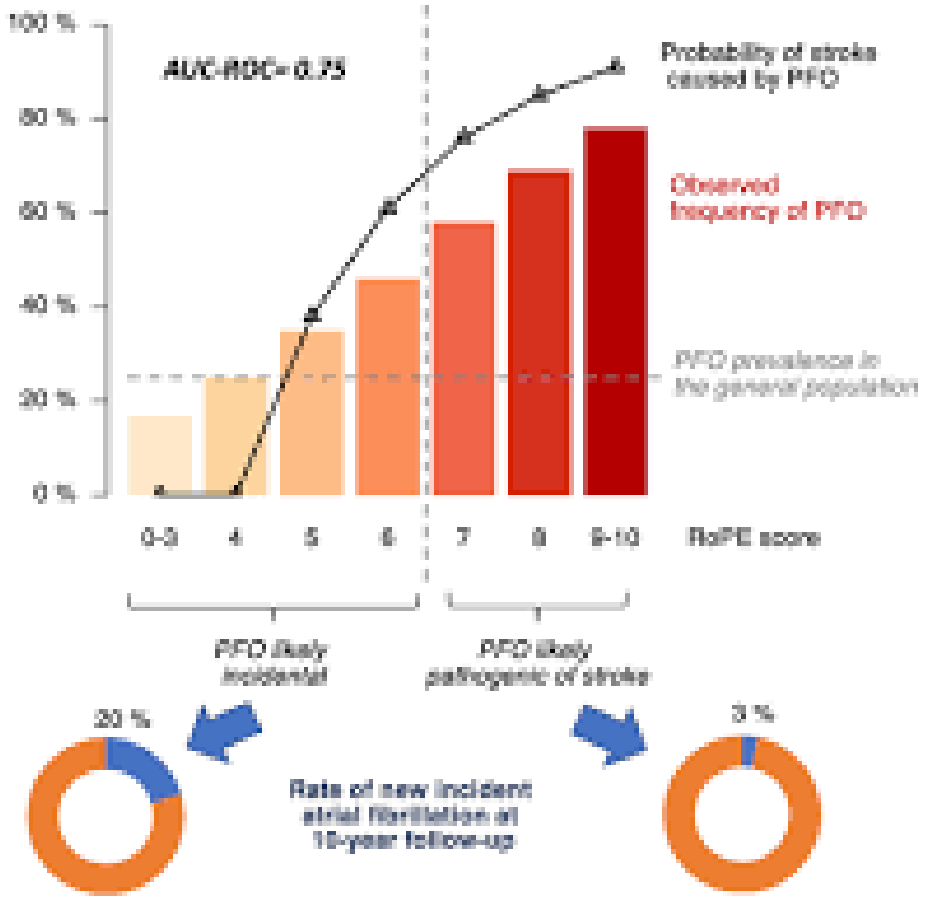
Stroke of other determined aetiology

Stroke of undetermined aetiology
  a) Two or more causes identified
  b) Negative evaluation
  c) Incomplete evaluation

Table 3 Cryptogenic Stroke Workup

Condition	Recommended Testing
Hypercoagulable disorder	CBC (hemoglobin and platelet count), factor V Leiden, protein C, protein S, antithrombin III, homocysteine levels, prothrombin G20210A mutation, and antiphospholipid antibodies
Paroxysmal atrial fibrillation	≥30-day continuous cardiac monitoring
Cardiac thrombus, vegetation, or tumor; mitral stenosis	TTE followed by TEE (if TTE is normal); cardiac CT or MRI can be considered if high suspicion
Carotid atherosclerotic disease	Carotid duplex ultrasound, CTA, or MRA of the neck and head
Cerebral vascular atherosclerotic disease	CTA or MRA of the head
Aortic arch atheroma	TEE or CTA of the chest
Arterial dissection	CTA of the chest and neck

ROPE score



Patient characteristics	Points
No history of hypertension	+1
No history of diabetes	+1
No history of stroke or TIA	+1
Non-smoker	+1
Cortical infarct on imaging	+1
Age (years)	
18-29	+5
30-39	+4
40-49	+3
50-59	+2
60-69	+1

Diagnosing PFO

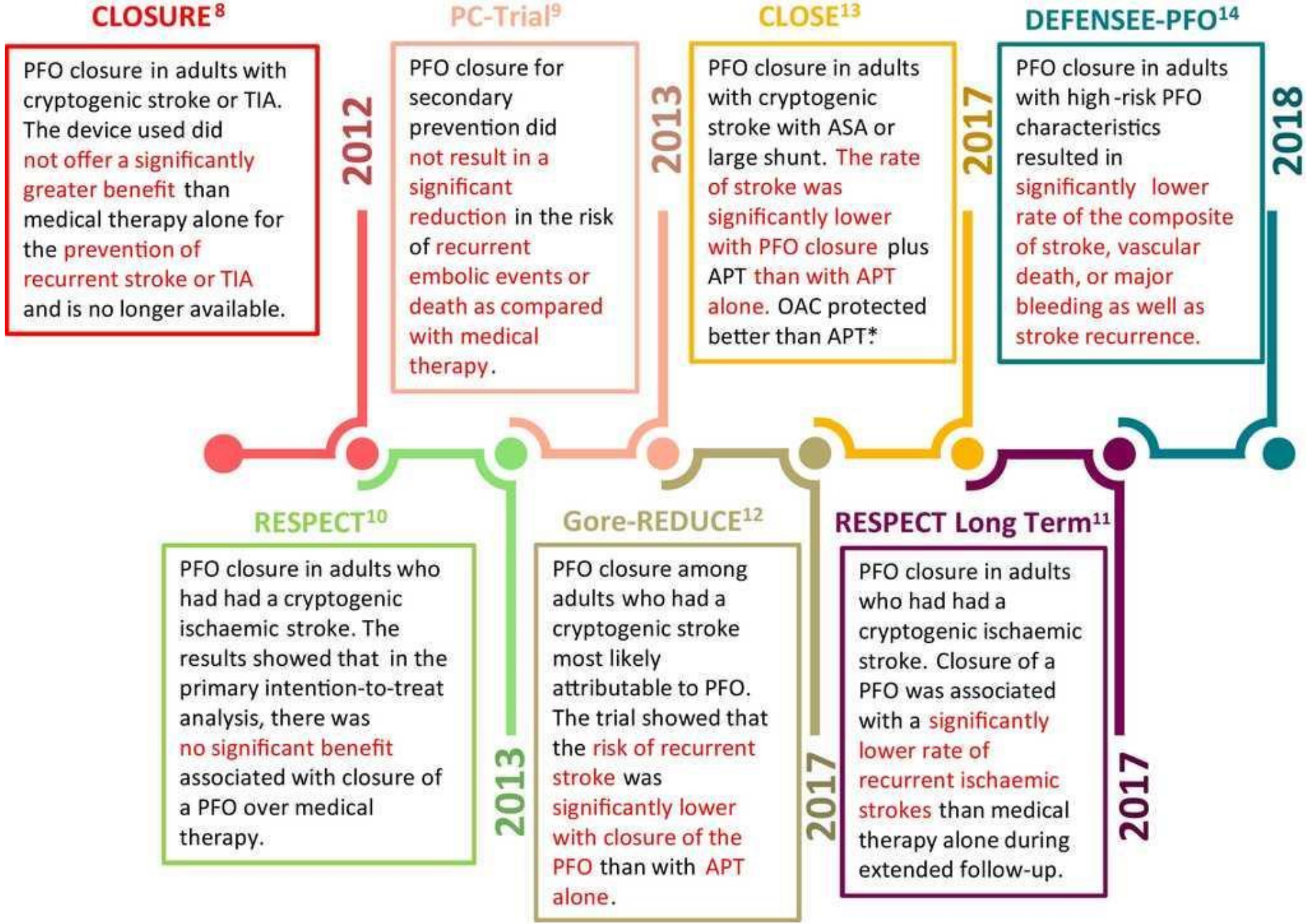
- Transthoracic Echo w/ bubble
  - Early vs late bubbles
  - Rest and Valsalva
  - Number of bubbles -> size of PFO
- Average diameter 4.9 mm in adults (1-19 mm)
  - Large >_ 4mm
  - Medium 2 - 3.9mm
  - Small < 2 mm
- High risk features: Long tunnel, atrial septal aneurysm, thick septum secundum, multiple orifices in the left atrium, Eustachian valve or Chiari network

Diagnosing PFO

- Transesophageal Echo vs Transcranial Doppler
- TEE is considered “gold standard”
- Visualize PFO and anatomic details
- TCD is more sensitive (95%) but less specific (75%)
  - Detects intracardiac and intrapulmonary shunts
  - Less invasive

Trials

- CLOSURE I (2012): PFO closure with STARFLEX device vs medical management with warfarin, aspirin, or both
- RESPECT (2017): PFO closure with Amplatzer device vs medical management with aspirin, clopidogrel, aspirin-dipyridamole, or warfarin
- REDUCE (2017): PFO closure with HELEX or Cardioform device vs medical management with aspirin, clopidogrel, or aspirin-dipyridamole
- CLOSE (2017): PFO (w/ large shunt or septal aneurysm) closure with chosen devices vs antiplatelet alone vs anticoagulant alone



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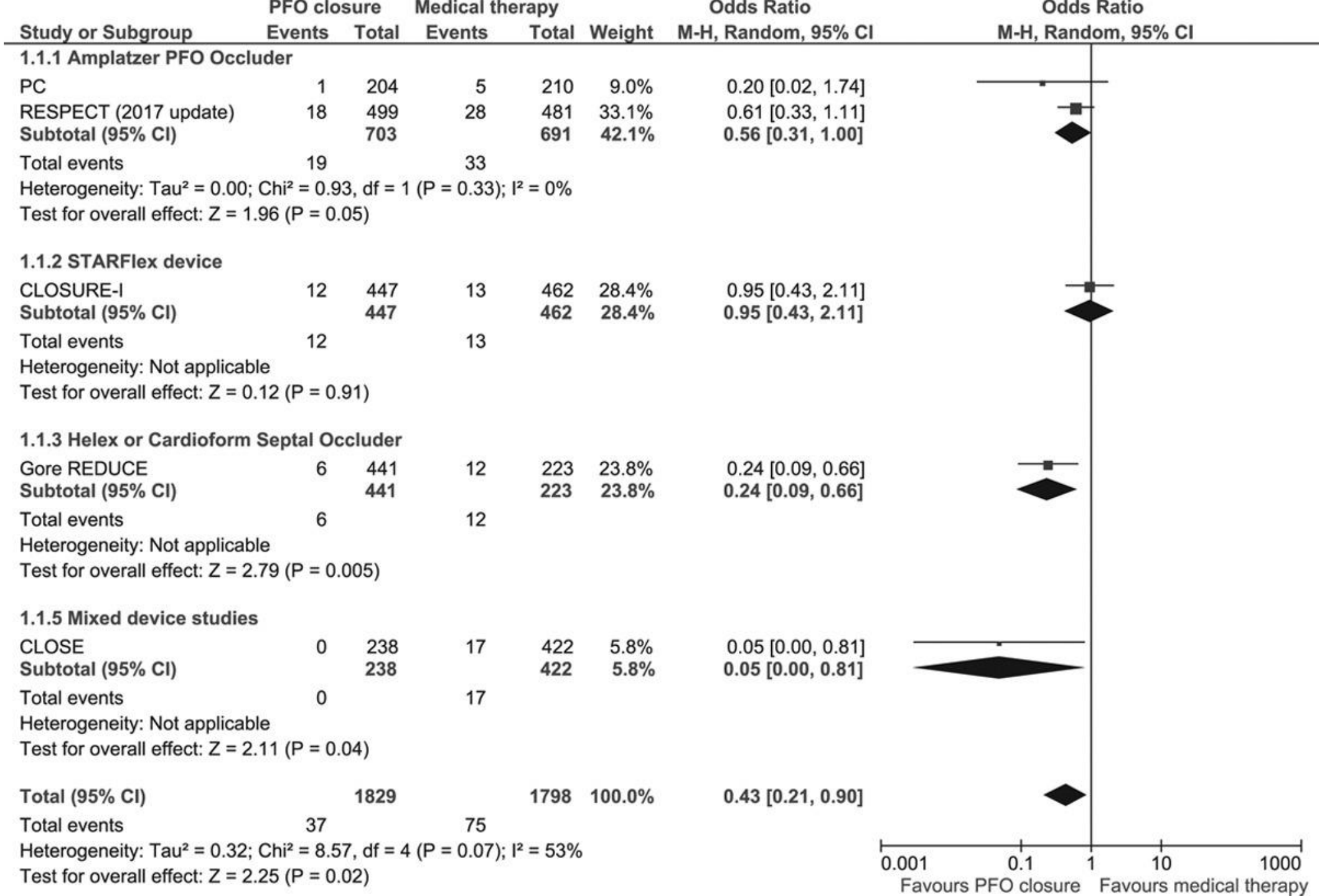
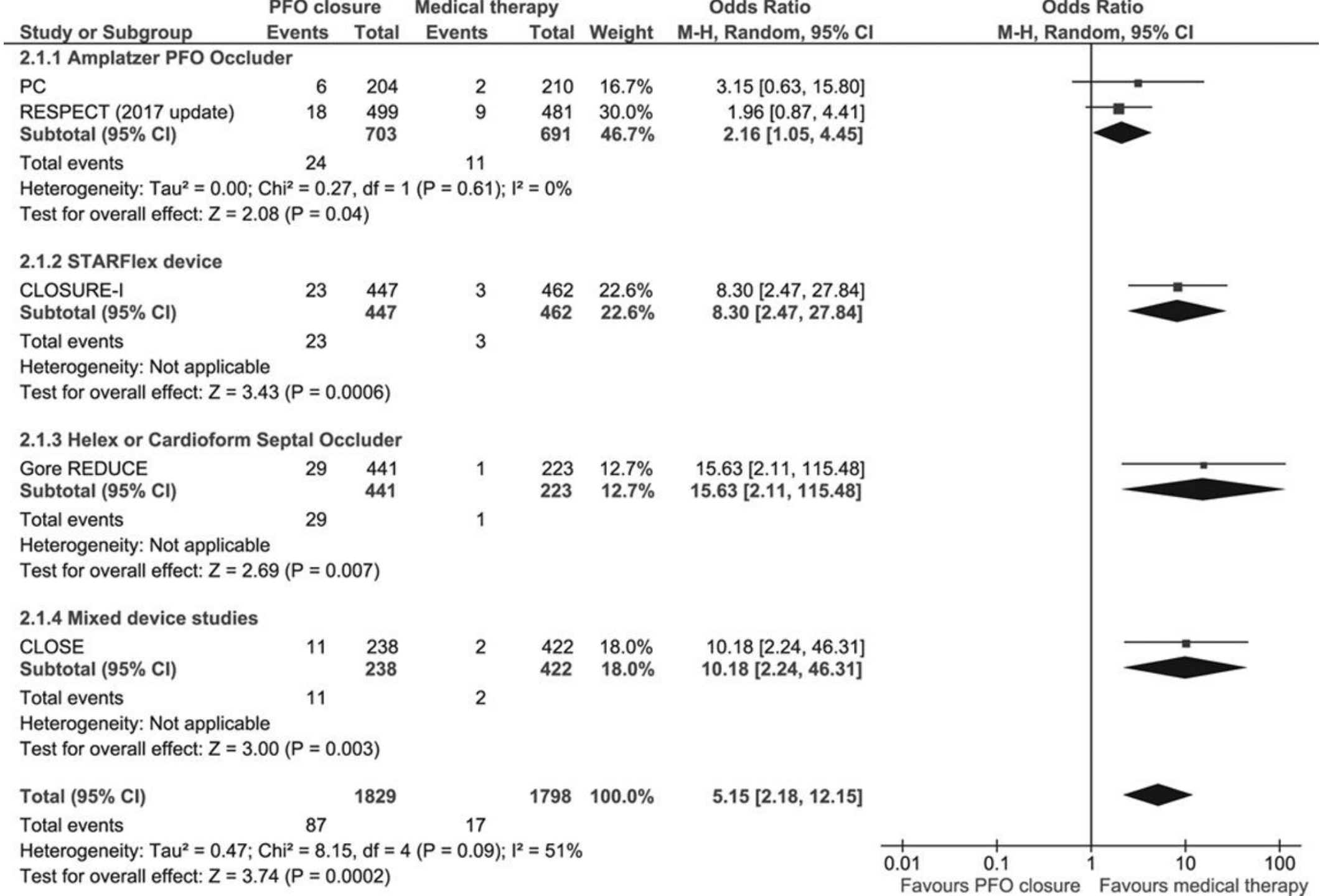
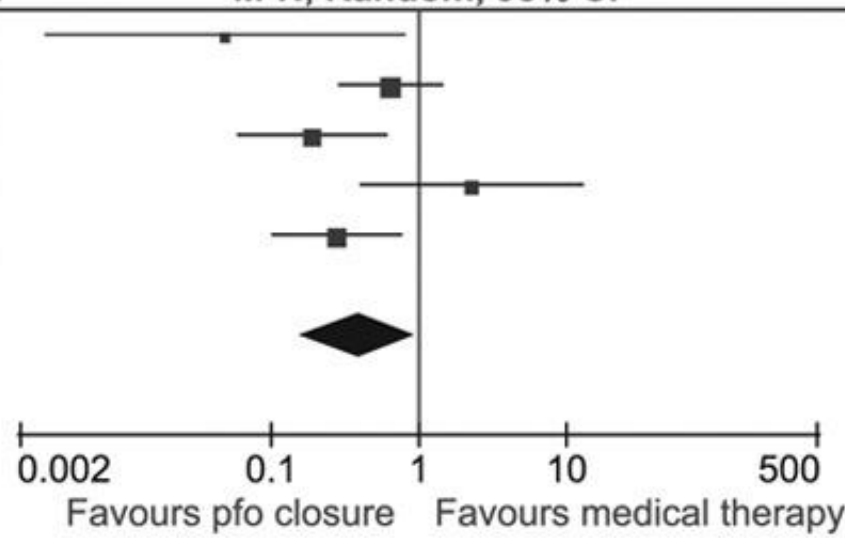

PFO closure
Medical therapy
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.1 Amplatzer PFO Occluder
PC 1 204 5 210 9.0% 0.20 [0.02, 1.74]
RESPECT (2017 update) 18 499 28 481 33.1% 0.61 [0.33, 1.11]
Subtotal (95% CI) 703 691 42.1% 0.56 [0.31, 1.00]
Total events 19 33
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 1.96 (P = 0.05)
1.1.2 STARFlex device
CLOSURE-I 12 447 13 462 28.4% 0.95 [0.43, 2.11]
Subtotal (95% CI) 447 462 28.4% 0.95 [0.43, 2.11]
Total events 12 13
Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.91)
1.1.3 Helex or Cardioform Septal Occluder
Gore REDUCE 6 441 12 223 23.8% 0.24 [0.09, 0.66]
Subtotal (95% CI) 441 223 23.8% 0.24 [0.09, 0.66]
Total events 6 12
Heterogeneity: Not applicable
Test for overall effect: Z = 2.79 (P = 0.005)
1.1.5 Mixed device studies
CLOSE 0 238 17 422 5.8% 0.05 [0.00, 0.81]
Subtotal (95% CI) 238 422 5.8% 0.05 [0.00, 0.81]
Total events 0 17
Heterogeneity: Not applicable
Test for overall effect: Z = 2.11 (P = 0.04)
Total (95% CI) 1829 1798 100.0% 0.43 [0.21, 0.90]
Total events 37 75
Heterogeneity: Tau² = 0.32; Chi² = 8.57, df = 4 (P = 0.07); I² = 53%
Test for overall effect: Z = 2.25 (P = 0.02)
0.001
0.1
1
10
1000
Favours PFO closure
Favours medical therapy


PFO closure
Medical therapy
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.1.1 Amplatzer PFO Occluder
PC 6 204 2 210 16.7% 3.15 [0.63, 15.80]
RESPECT (2017 update) 18 499 9 481 30.0% 1.96 [0.87, 4.41]
Subtotal (95% CI) 703 691 46.7% 2.16 [1.05, 4.45]
Total events 24 11
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)
2.1.2 STARFlex device
CLOSURE-I 23 447 3 462 22.6% 8.30 [2.47, 27.84]
Subtotal (95% CI) 447 462 22.6% 8.30 [2.47, 27.84]
Total events 23 3
Heterogeneity: Not applicable
Test for overall effect: Z = 3.43 (P = 0.0006)
2.1.3 Helex or Cardioform Septal Occluder
Gore REDUCE 29 441 1 223 12.7% 15.63 [2.11, 115.48]
Subtotal (95% CI) 441 223 12.7% 15.63 [2.11, 115.48]
Total events 29 1
Heterogeneity: Not applicable
Test for overall effect: Z = 2.69 (P = 0.007)
2.1.4 Mixed device studies
CLOSE 11 238 2 422 18.0% 10.18 [2.24, 46.31]
Subtotal (95% CI) 238 422 18.0% 10.18 [2.24, 46.31]
Total events 11 2
Heterogeneity: Not applicable
Test for overall effect: Z = 3.00 (P = 0.003)
Total (95% CI) 1829 1798 100.0% 5.15 [2.18, 12.15]
Total events 87 17
Heterogeneity: Tau² = 0.47; Chi² = 8.15, df = 4 (P = 0.09); I² = 51%
Test for overall effect: Z = 3.74 (P = 0.0002)
0.01
0.1
1
10
100
Favours PFO closure
Favours medical therapy

Study or Subgroup	PFO closure Events	Total	Medical therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
CLOSE	0	238	17	422	8.0%	0.05 [0.00, 0.81]
CLOSURE-I	10	231	15	228	28.5%	0.64 [0.28, 1.46]
Gore REDUCE	4	348	10	173	22.8%	0.19 [0.06, 0.61]
PC	4	47	2	51	15.5%	2.28 [0.40, 13.06]
RESPECT (2017 update)	5	247	16	231	25.2%	0.28 [0.10, 0.77]
Total (95% CI)		**1111**		**1105**	**100.0%**	**0.39 [0.16, 0.96]**
Total events	23		60			

Heterogeneity: Tau² = 0.56; Chi² = 9.55, df = 4 (P = 0.05); I² = 58%

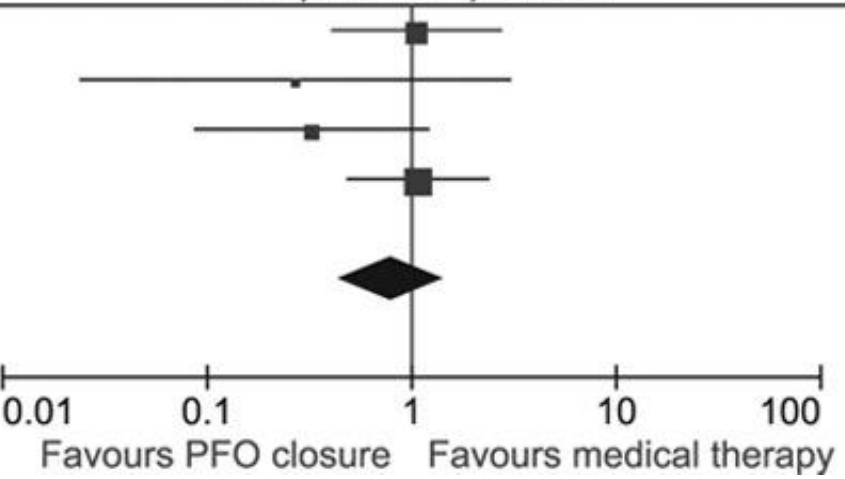
Test for overall effect: Z = 2.06 (P = 0.04)

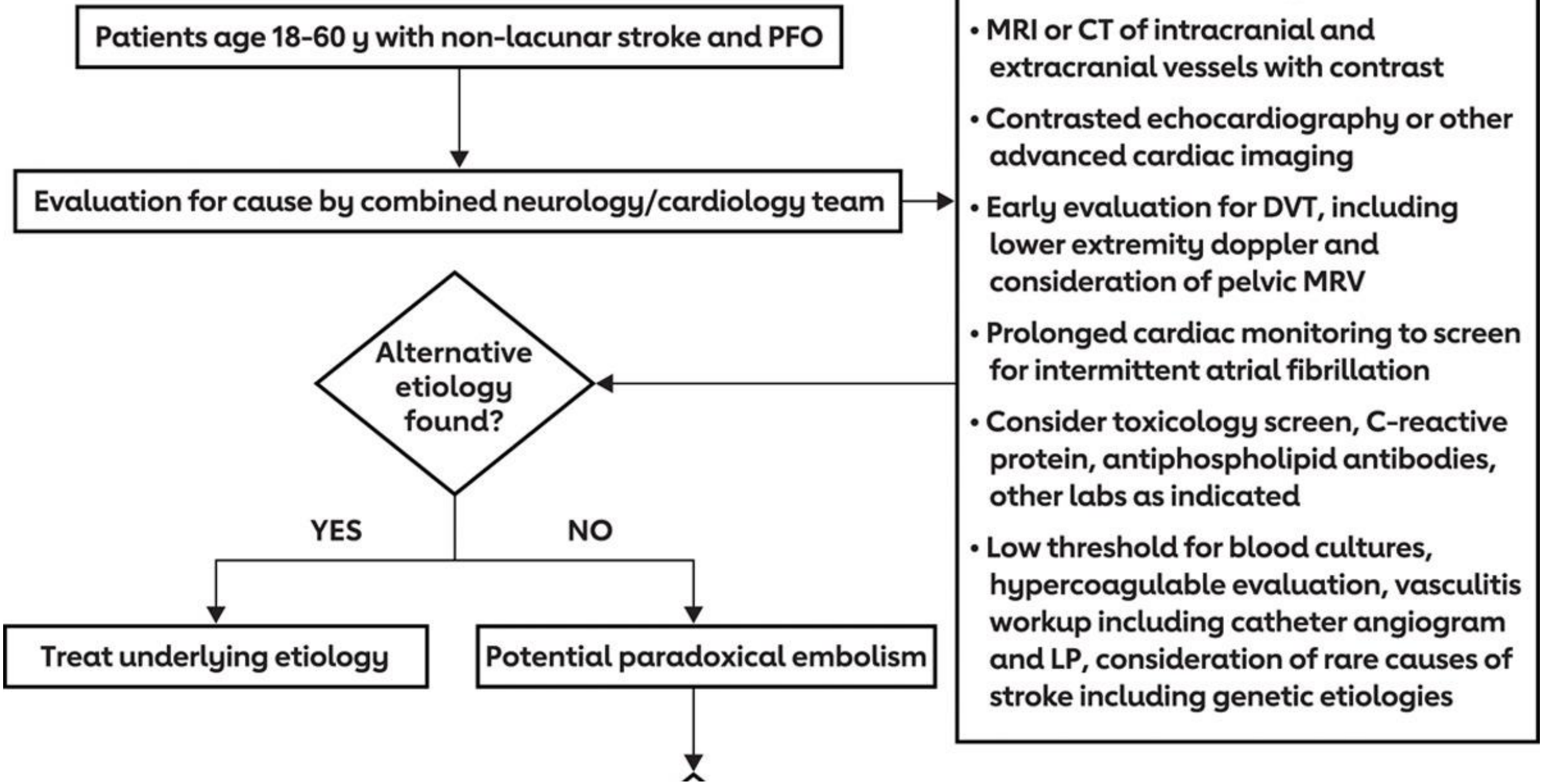


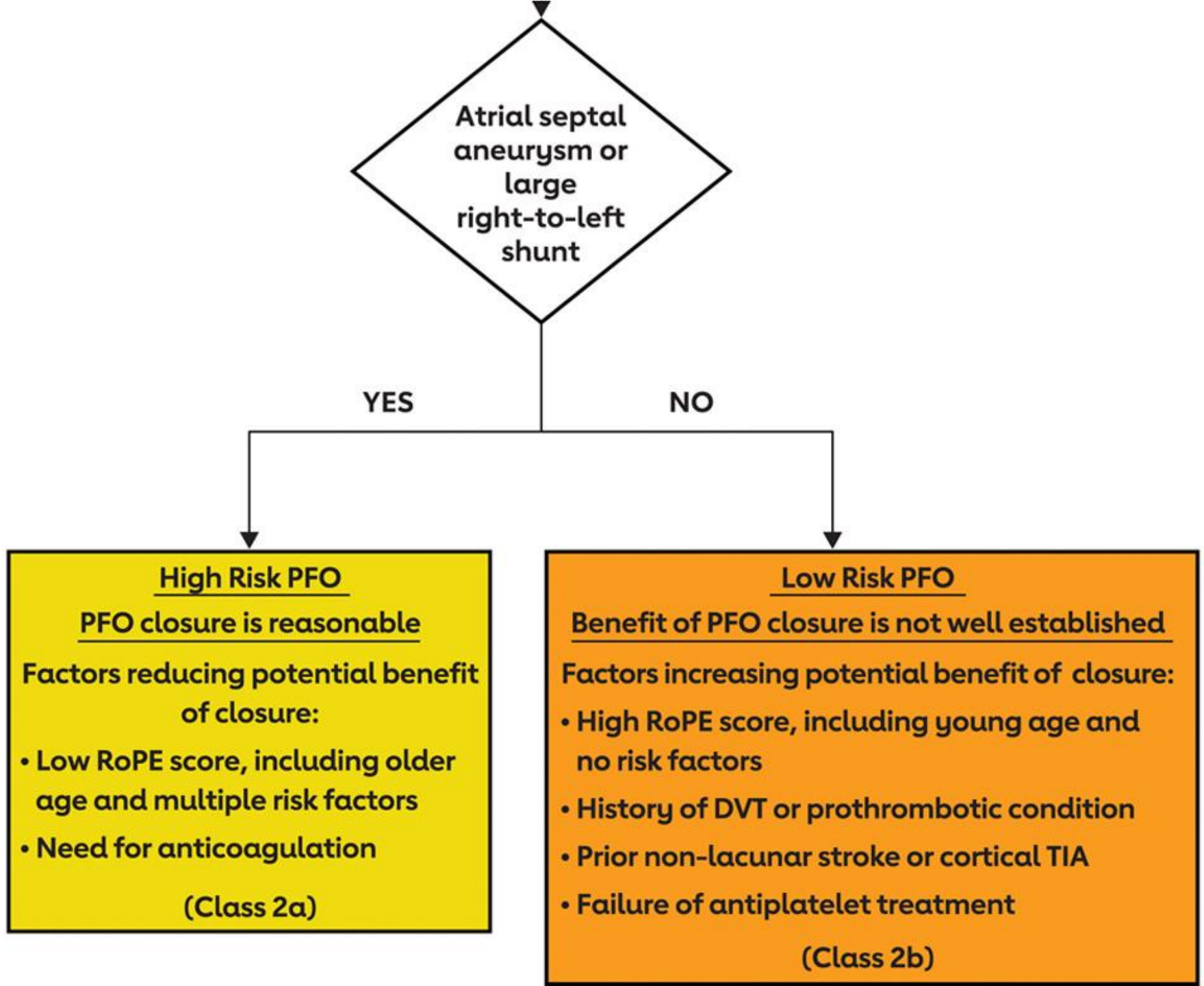
Study or Subgroup	PFO closure Events	Total	Medical therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
CLOSURE-I	8	118	10	155	32.4%	1.05 [0.40, 2.76]
Gore REDUCE	1	77	2	43	5.9%	0.27 [0.02, 3.06]
PC	3	157	9	159	18.4%	0.32 [0.09, 1.22]
RESPECT (2017 update)	13	247	12	244	43.3%	1.07 [0.48, 2.40]
Total (95% CI)		**599**		**601**	**100.0%**	**0.79 [0.43, 1.43]**
Total events	25		33			

Heterogeneity: Tau² = 0.05; Chi² = 3.38, df = 3 (P = 0.34); I² = 11%

Test for overall effect: Z = 0.78 (P = 0.44)




Patients age 18-60 y with non-lacunar stroke and PFO
Evaluation for cause by combined neurology/cardiology team
• MRI of brain confirming ischemic stroke
• MRI or CT of intracranial and extracranial vessels with contrast
• Contrasted echocardiography or other advanced cardiac imaging
• Early evaluation for DVT, including lower extremity doppler and consideration of pelvic MRV
• Prolonged cardiac monitoring to screen for intermittent atrial fibrillation
• Consider toxicology screen, C-reactive protein, antiphospholipid antibodies, other labs as indicated
• Low threshold for blood cultures, hypercoagulable evaluation, vasculitis workup including catheter angiogram and LP, consideration of rare causes of stroke including genetic etiologies
Alternative etiology found?
YES
NO
Treat underlying etiology
Potential paradoxical embolism

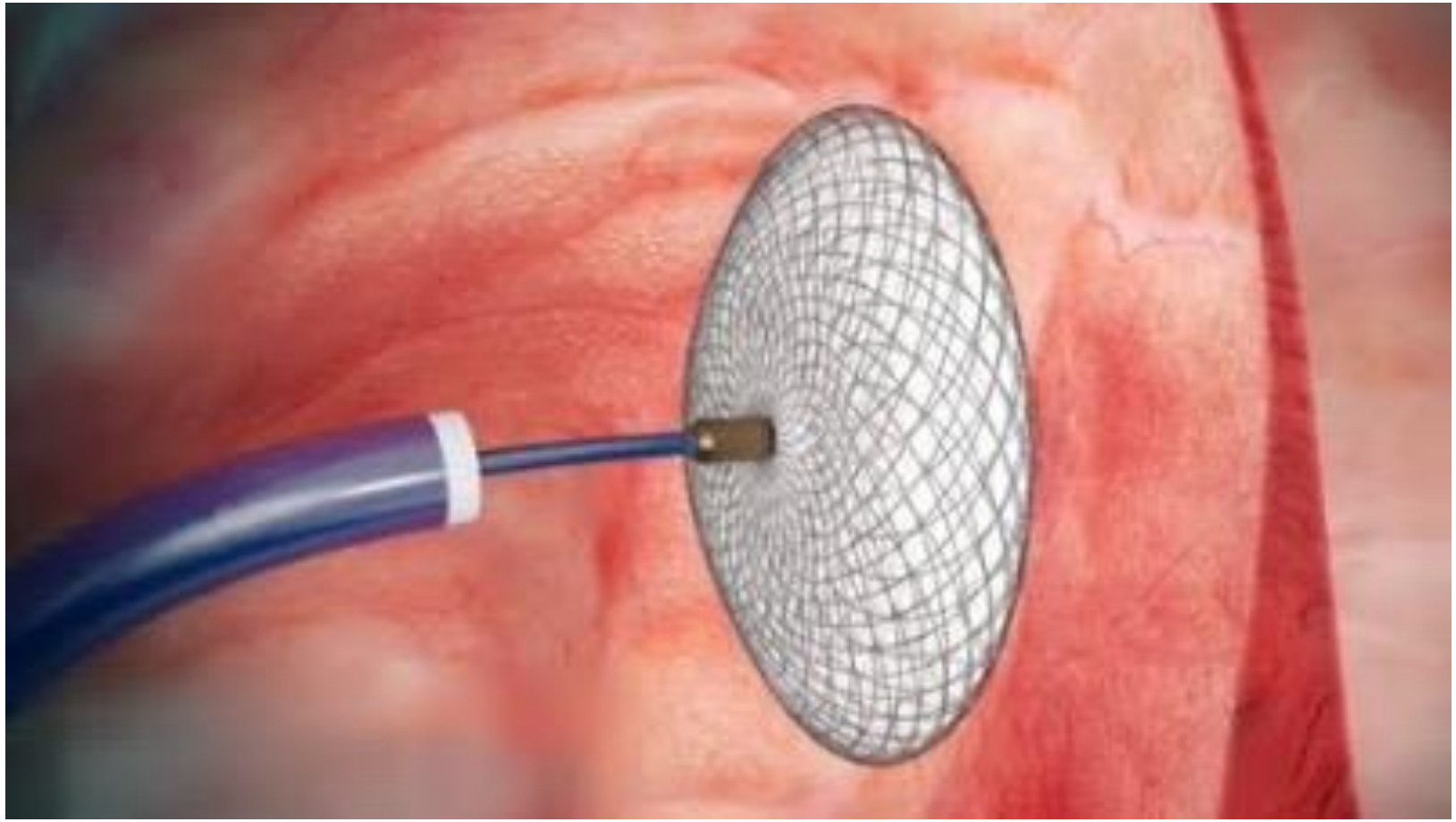

Atrial septal aneurysm or large right-to-left shunt
YES
NO
High Risk PFO
PFO closure is reasonable
Factors reducing potential benefit of closure:
• Low RoPE score, including older age and multiple risk factors
• Need for anticoagulation
(Class 2a)
Low Risk PFO
Benefit of PFO closure is not well established
Factors increasing potential benefit of closure:
• High RoPE score, including young age and no risk factors
• History of DVT or prothrombotic condition
• Prior non-lacunar stroke or cortical TIA
• Failure of antiplatelet treatment
(Class 2b)

Case continued…

- TEE confirmed PFO with no high risk features
- ROPE score = 7
- Hypercoagulable work-up negative
- 30-day cardiac event monitoring negative for afib

> Select patients being considered for PFO closure though to be at risk of atrial fibrillation should receive prolonge cardiac monitoring for at least 28 days. (Risk factors for atrial fibrillation include age ≥50 years, hypertension, obesity, sleep apnea, enlarged left atrium, elevated NT-proBNP, frequent premature atrial contractions, and increased P wave dispersion. Recently published guideli from the American Heart Association, American College Cardiology, and Heart Rhythm Society recommend prolo ECG monitoring following cryptogenic stroke for patient older than 40 years, although more research is needed t define the yield in unselected young patients, and in pat with PFO.[14])

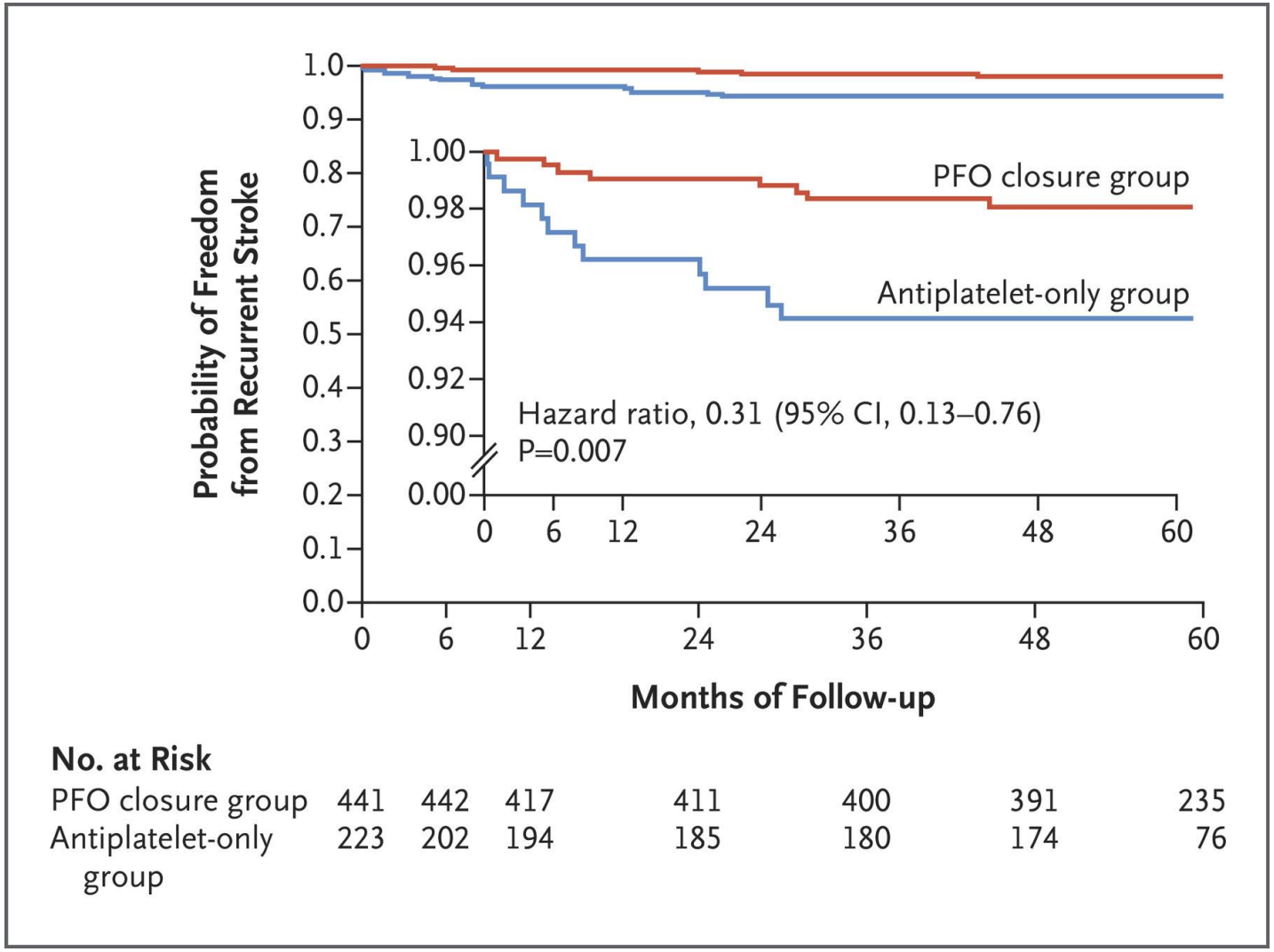
Closure Procedure with Amplatzer device



Post-Procedure

- Antiplatelets resumed after device placed at discretion of the physician
- Low rates of infection reported but dental procedures should be avoided
- 7% adverse outcome rate after PFO closure (afib rate highest at 1.2% vs 0.8 % in medical management)
- Repeat TTE to confirm closure. Less than 1% with persistent shunting after closure in recent studies.
- Less than 1% with thrombus formation on the device

LONG TERM OUTCOMES



Future Studies

- New closure devices
- Cost effectiveness data
- Trials in patients with PFO and age>60 (DEFENSE-ELDERLY)
- Comparison of PFO closure to long term anticoagulation
- PFO closure in low risk PFO
- Registry for long term risks associated with closure

References

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