PATENT FORAMEN OVALE
TO CLOSE OR NOT TO CLOSE

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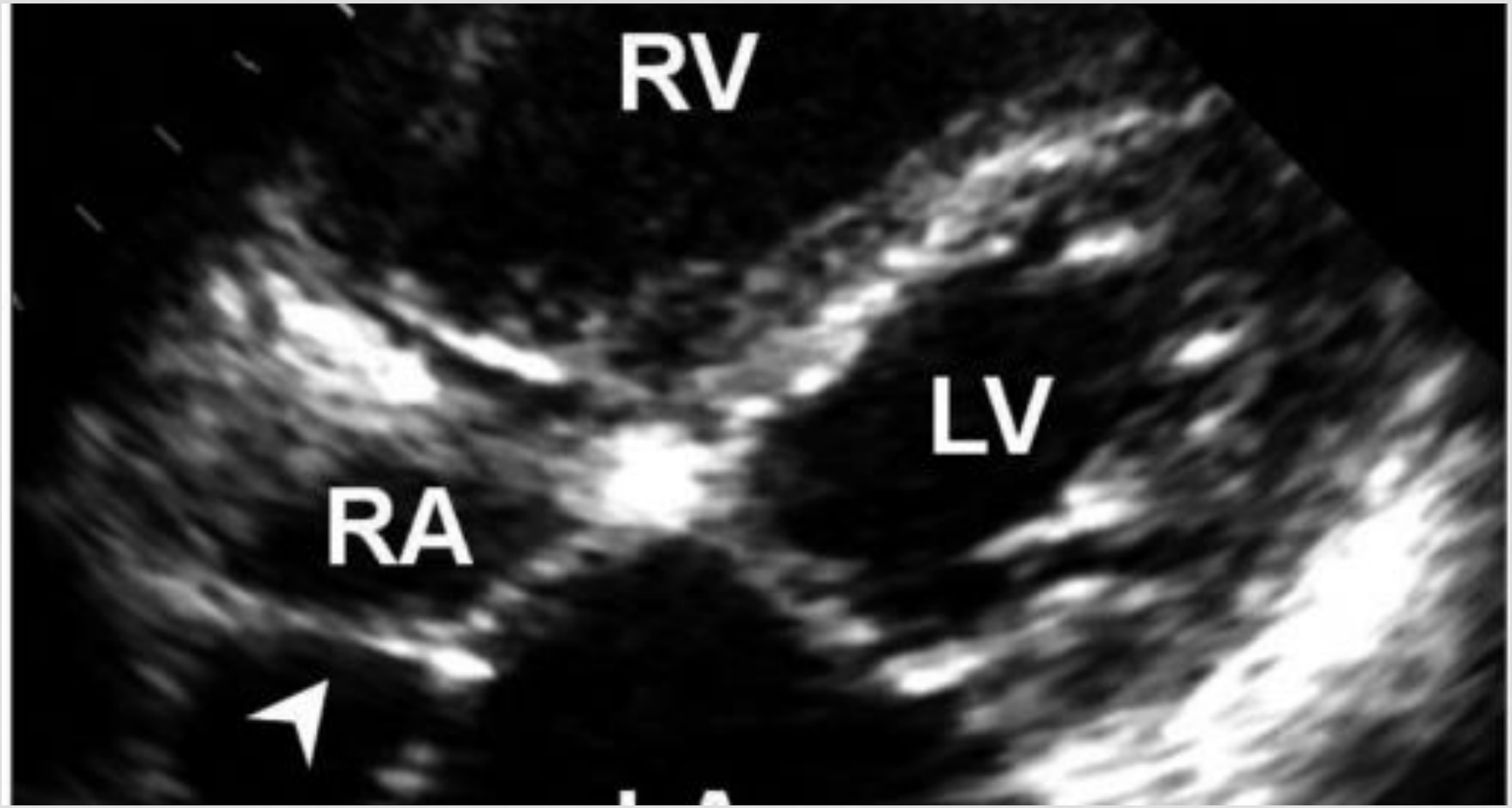
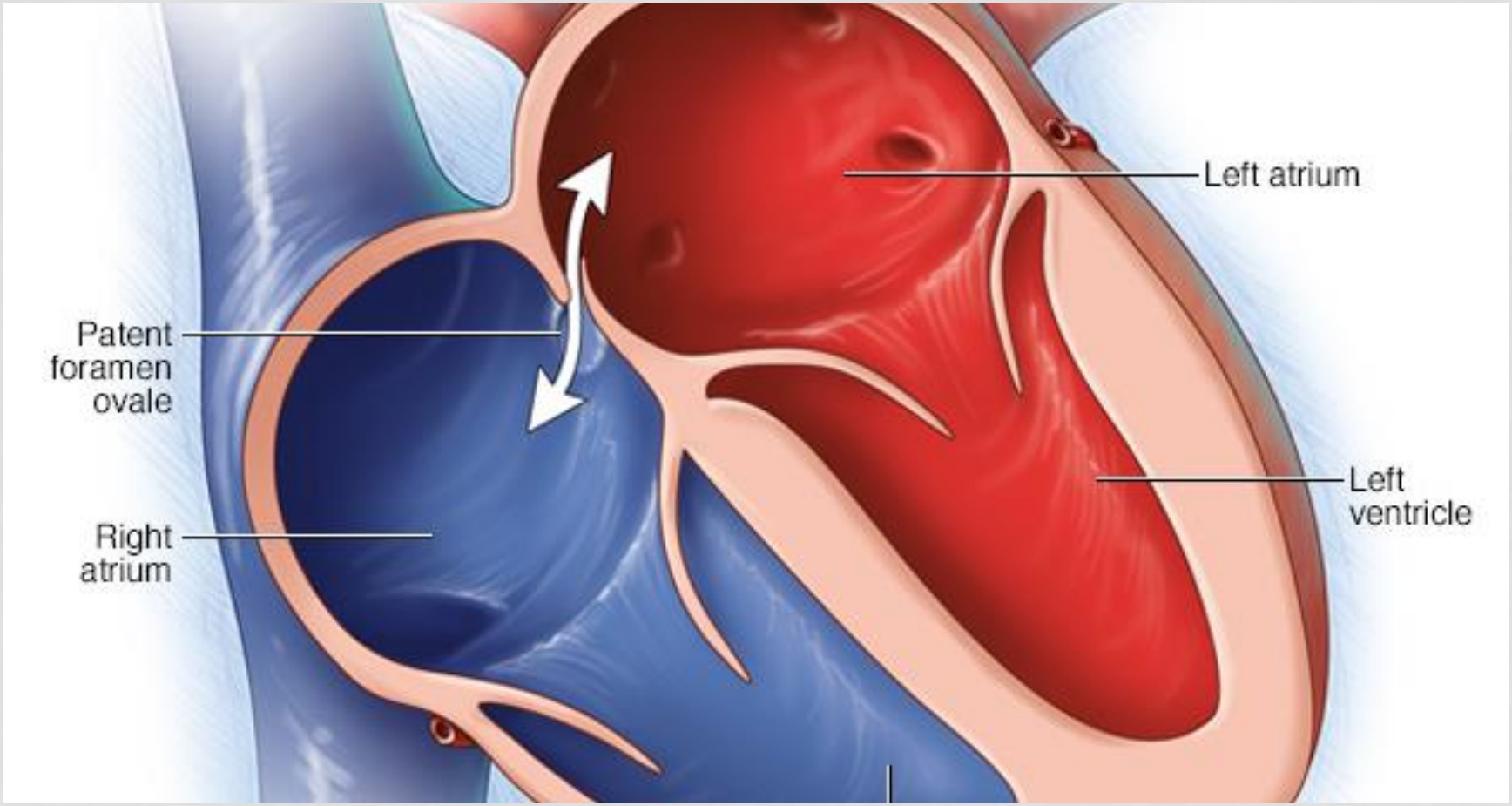
DECEMBER 8, 2017

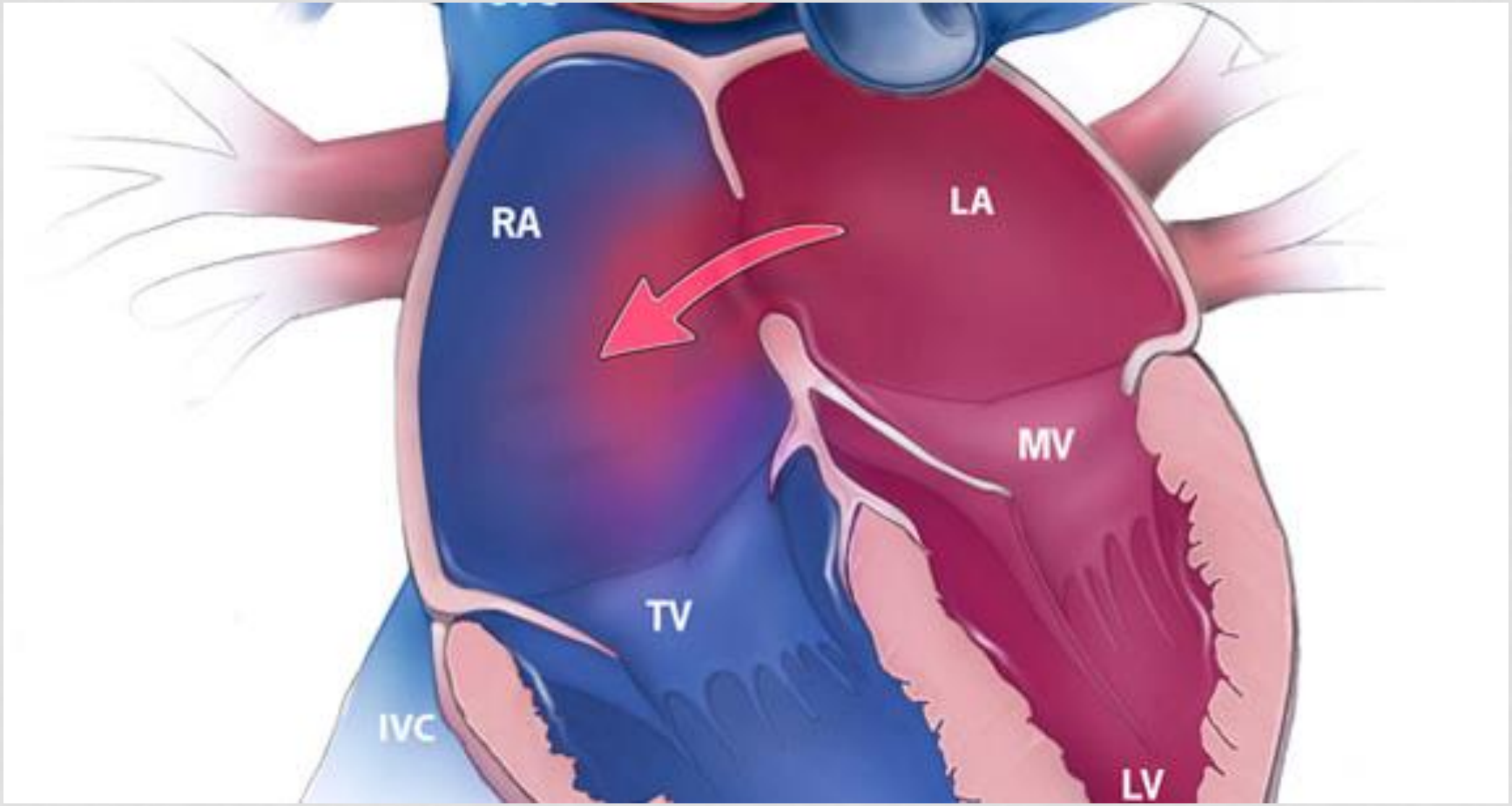
WHAT IS THE FORAMEN OVALE

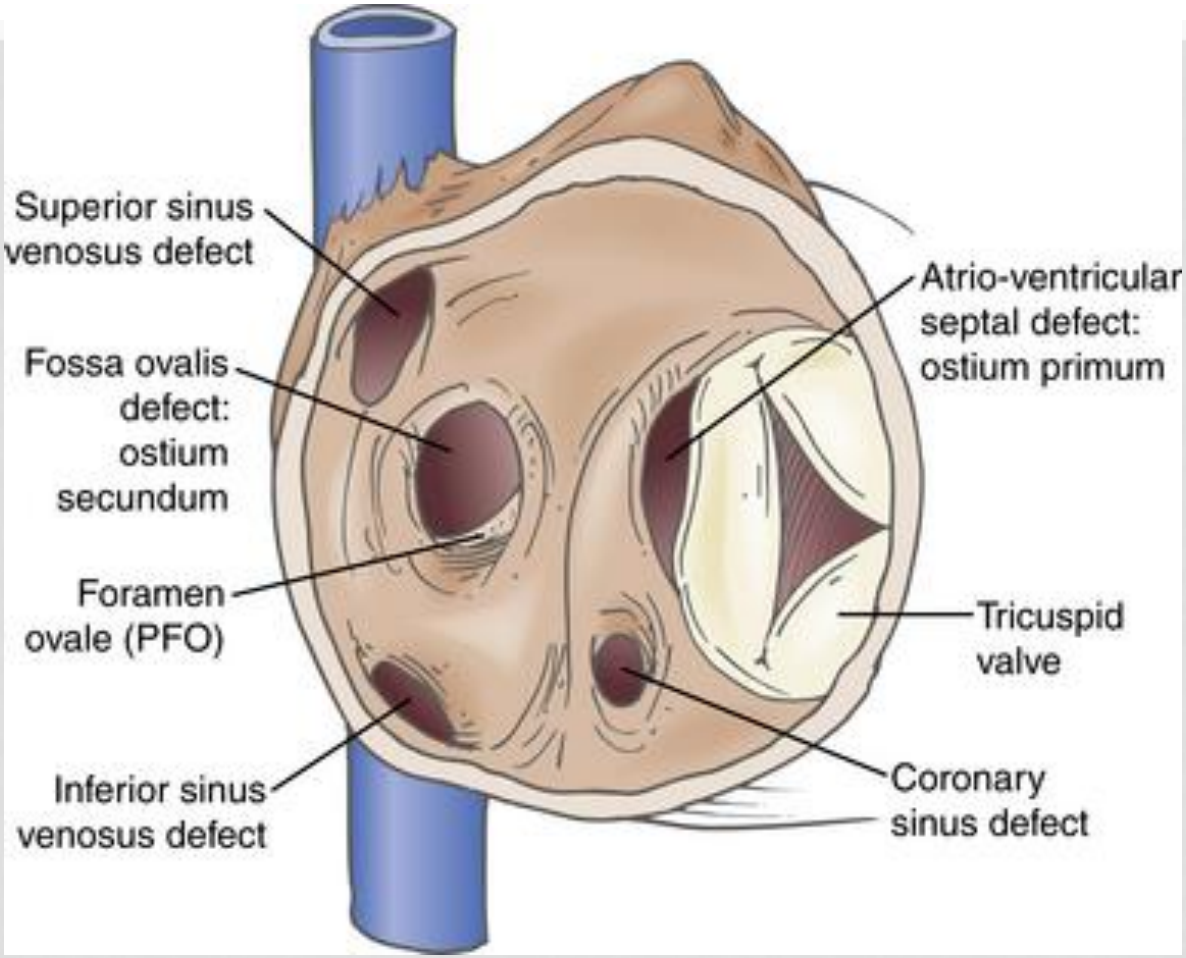
- Normal interatrial shunt during fetal development
  - Flow directed from right atrium to the left
  - Fetal pulmonary circulation bypassed
  - Should close shortly after birth
- PFO is common
  - 25% of population
  - Clinical significance?


RV
LV
RA


Left atrium
Patent foramen ovale
Left ventricle
Right atrium

IS A PFO AN ASD?




Superior sinus venosus defect
Fossa ovalis defect: ostium secundum
Foramen ovale (PFO)
Inferior sinus venosus defect
Atrio-ventricular septal defect: ostium primum
Tricuspid valve
Coronary sinus defect

ASD VS PFO

- Do ASDs and PFOs share similar treatment indications?
- ASD closure indications
  - Symptoms
  - Right atrial and ventricular dilatation
  - Significant left to right shunt calculated by echo
- Same indications for PFOs?

HOW COMMON IS A PFO IN THE SETTING OF A STROKE

- Study involving over 100 patients with stroke
- Identifiable cause – 21%
- No identifiable cause (with risk factors) – 40%
- No identifiable cause (w/o risk factors) – 54%

STROKE ETIOLOGY

- Must rule out other identifiable causes
  - Structural Cardiac diseases
    - Thrombus, primary cardiac tumors
  - Cerebrovascular disease
  - Hypercoagulable disorders
  - Atherosclerotic disease of the aortic arch
  - Atrial fibrillation

ATRIAL FIBRILLATION

- Frequent etiology in setting of cryptogenic stroke
- EMBRACE Trial
  - Long term (30 days) vs 24 hour cardiac rhythm monitoring
  - 572 patients
  - >55 years with cryptogenic stroke or TIA
  - Mean 72 y/o, median CHADS score of 3
  - Afib detection:
    - 24 hour monitoring 2.2%
    - 30 day 14.8%

HIGH RISK PFO FEATURES

- Large anatomic size (>4mm)
- Greater physiologic size
  - Larger degree of microbubble shunt
- Interatrial septal aneurysm
- Spontaneous right to left shunt at rest

TREATMENT

- How do you lower the risk of recurrent CVA/TIA
  - PFO closure vs medical therapy?
  - Is there an indication for closure?
  - What does the data suggest?

CLOSURE TRIAL

- 2012 NEJM
- 900 patients with CVA or TIA
- Medical therapy found to be just as effective as PFO closure
  - Why?
    - 6% of patients had afib
    - TIA patients enrolled
  - Subpar device?
    - 17% complication rate – device no longer commercially available
    - Procedural success rate only 86.7%
    - Patients only followed for 2 years

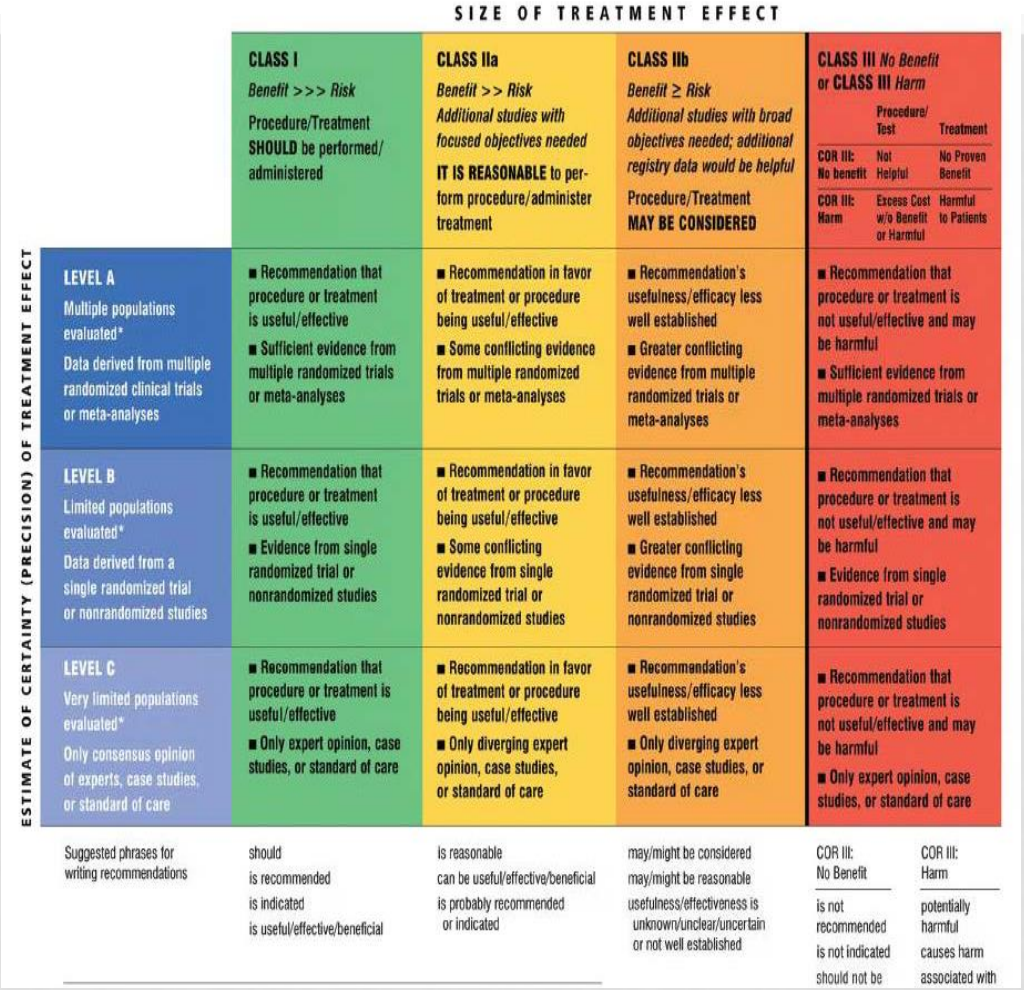
RESPECT TRIAL

- 2013 NEJM
- 980 patients
- Previous CVA only
- Different device (Amplatzer PFO Occluder)
- Closure was superior to medical therapy
- Lower complication rate
  - Higher procedural success rate – 93.5%
- Longer follow up data
  - Mean follow up 2.6 years
  - Long term follow up to 8.1 years

POTENTIAL CLOSURE COMPLICATIONS

- Embolization (air, thrombus)
- Stroke
- Arrhythmia
- Heart block
- Tamponade
- Device embolization
- Device erosions (rare)
- Vascular complications

Definition of Classes and Levels of Evidence Used in AHA/ASA Recommendations



SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit — is not recommended; is not indicated; should not be COR III: Harm — potentially harmful; causes harm; associated with

Patent Foramen Ovale Recommendations

2014 Recommendation	Revisions (2011)
For patients with an ischemic stroke or TIA and a PFO who are not on anticoagulation therapy, antiplatelet therapy is recommended. (Class I, LOE B)	Class changed from IIa to I
For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics. (Class I, LOE A). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (Class IIa, LOE C).	New Recommendations
For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data does not support a benefit for PFO closure. (Class III, LOE A)	Revised Recommendation
In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT. (Class IIb, LOE C)	New Recommendation

REDUCE TRIAL

- The Gore REDUCE Clinical Study
  - Randomized, controlled, open-label Trial
- 63 multinational sites, 664 subjects with cryptogenic stroke and PFO randomized in a 2:1 ratio to:
  - Antiplatelet therapy + PFO closure with Gore septal occluder
  - Control arm – antiplatelet therapy alone
- Subjects prospectively followed for up to 5 years
- Neuroimaging required for all subjects at baseline and at 2 years or study exit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STUDY OBJECTIVE

- The REDUCE Study aims to establish superiority of PFO closure in conjunction with antiplatelet therapy over antiplatelet therapy alone in reducing the risk of recurrent clinical ischemic stroke or new brain infarct in patients who have had a cryptogenic stroke

ENDPOINTS

- 2 primary endpoints
  - Freedom for recurrent clinical ischemic stroke through at least 24 months post randomization
  - Incidence of new brain infarct (clinical ischemic stroke or silent brain infarct noted on imaging) through 24 months

TRIAL DEMOGRAPHICS

- Age 18–59 years
- Cryptogenic ischemic stroke within 180 days
  - Ischemic stroke = clinical symptoms ≥ 24 hours or with MRI evidence of infarction
  - Cryptogenic
- No stenosis > 50 percent or ulcerated plaque in relevant intra- or extra-cranial vessels
- No atrial fibrillation or high-risk source of cardioembolism
- Non-lacunar (based on syndrome and / or size)
- No evidence of hypercoagulable disorder
- No other known cause of stroke
- PFO
  - Confirmed by transesophageal echocardiography (TEE / TOE) with bubble study demonstrating right-to-left shunt at rest or during Valsalva maneuver
- No indication for anticoagulation
- No uncontrolled diabetes mellitus, hypertension, autoimmune disease, alcohol or drug abuse

EXPECTED MEDICAL MANAGEMENT

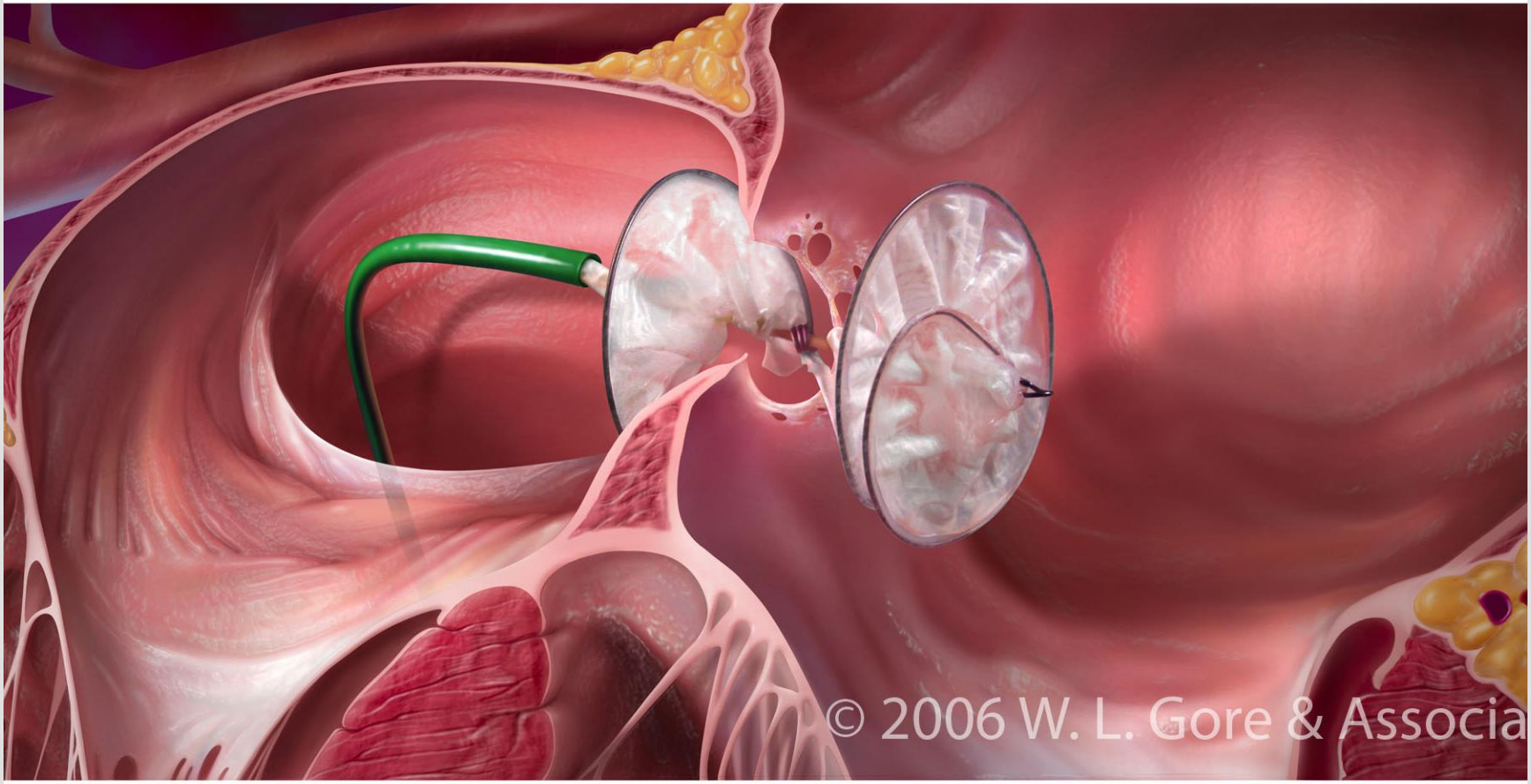
- Medical therapy options:
  - Aspirin alone (75-325mg daily)
  - Combination aspirin and dipyridamole (225 – 400mg daily)
  - Plavix 75mg daily
  - Other cominations of antiplatelet therapy
  - Anticoagulants not permitted
- Prescribed for all subjects of both control and test arm

PRIMARY ENDPOINT RESULT

- 77% relative reduction in clinical stroke with PFO closure
- 49% relative risk reduction in new brain infarct with PFO closure at 2 years
- PFO closure effect similar across subgroups
  - Age, sex, shunt size
- Number needed to treat – 28 at 2 years

OUTCOMES

- 98% procedural success rate
- Low risk of device/procedure related serious adverse events
- Higher rates of atrial fibrillation in closure group vs medical therapy (6.6% vs 0.4%)
  - Majority resolved within two weeks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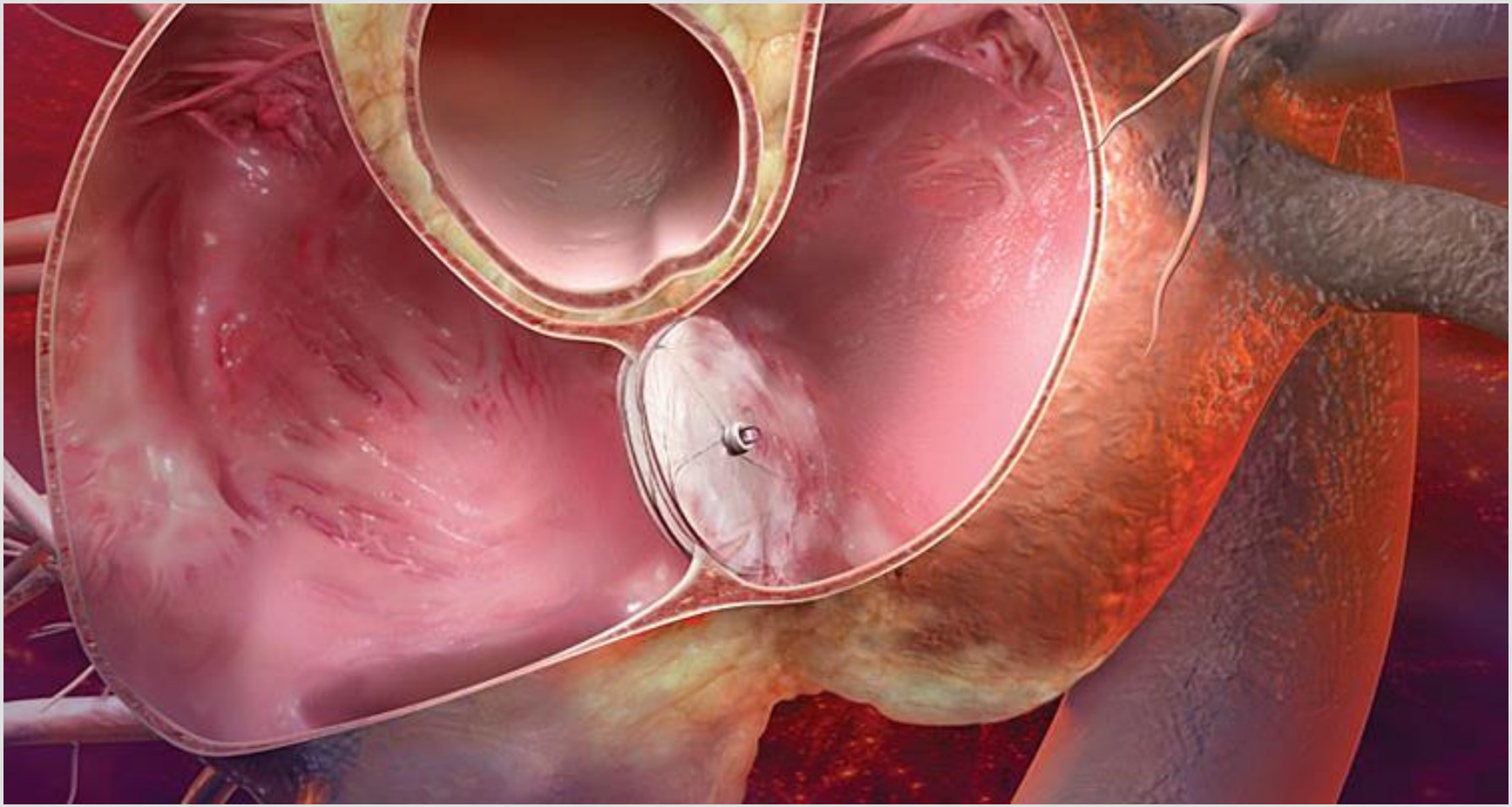

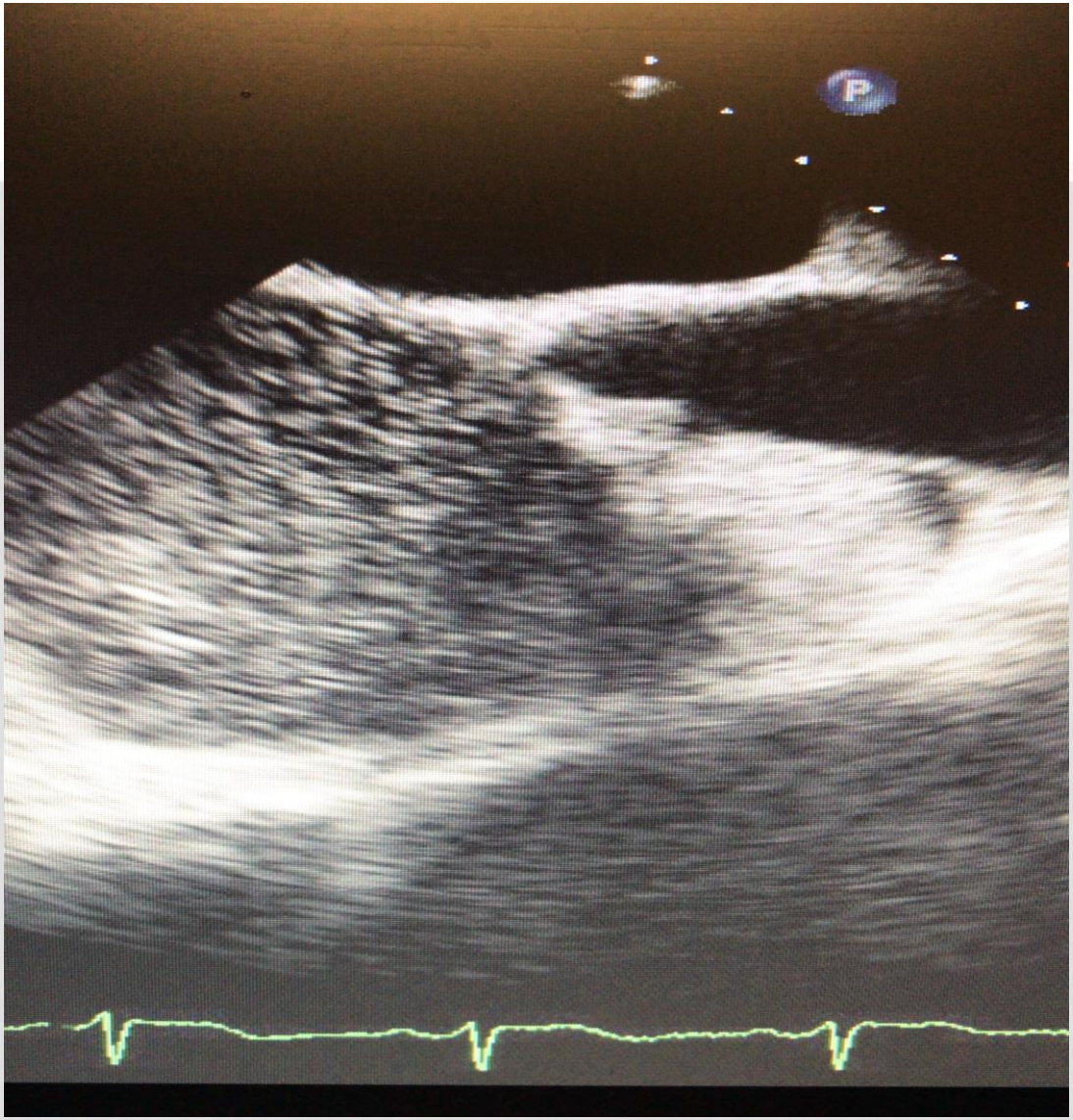
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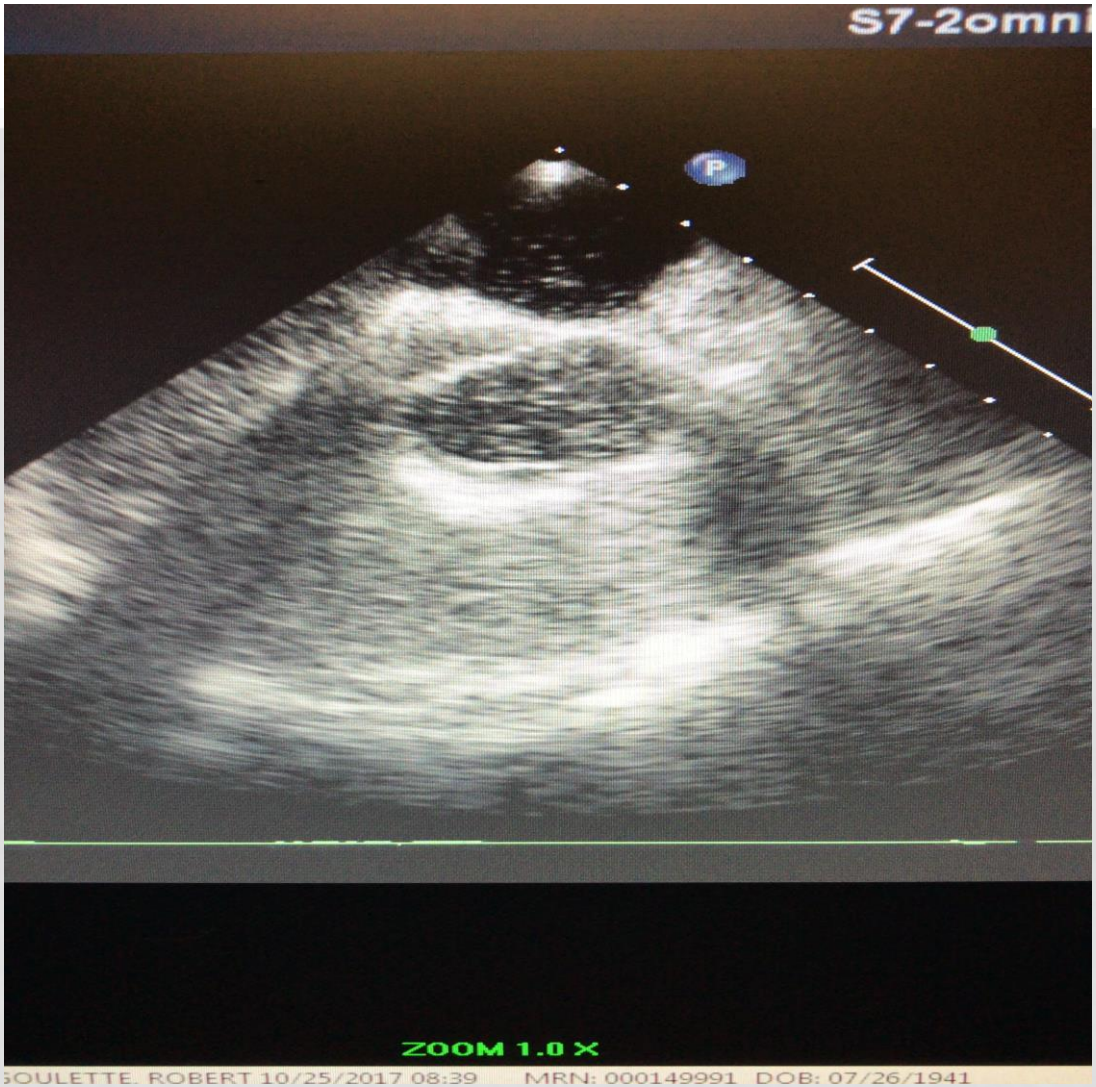
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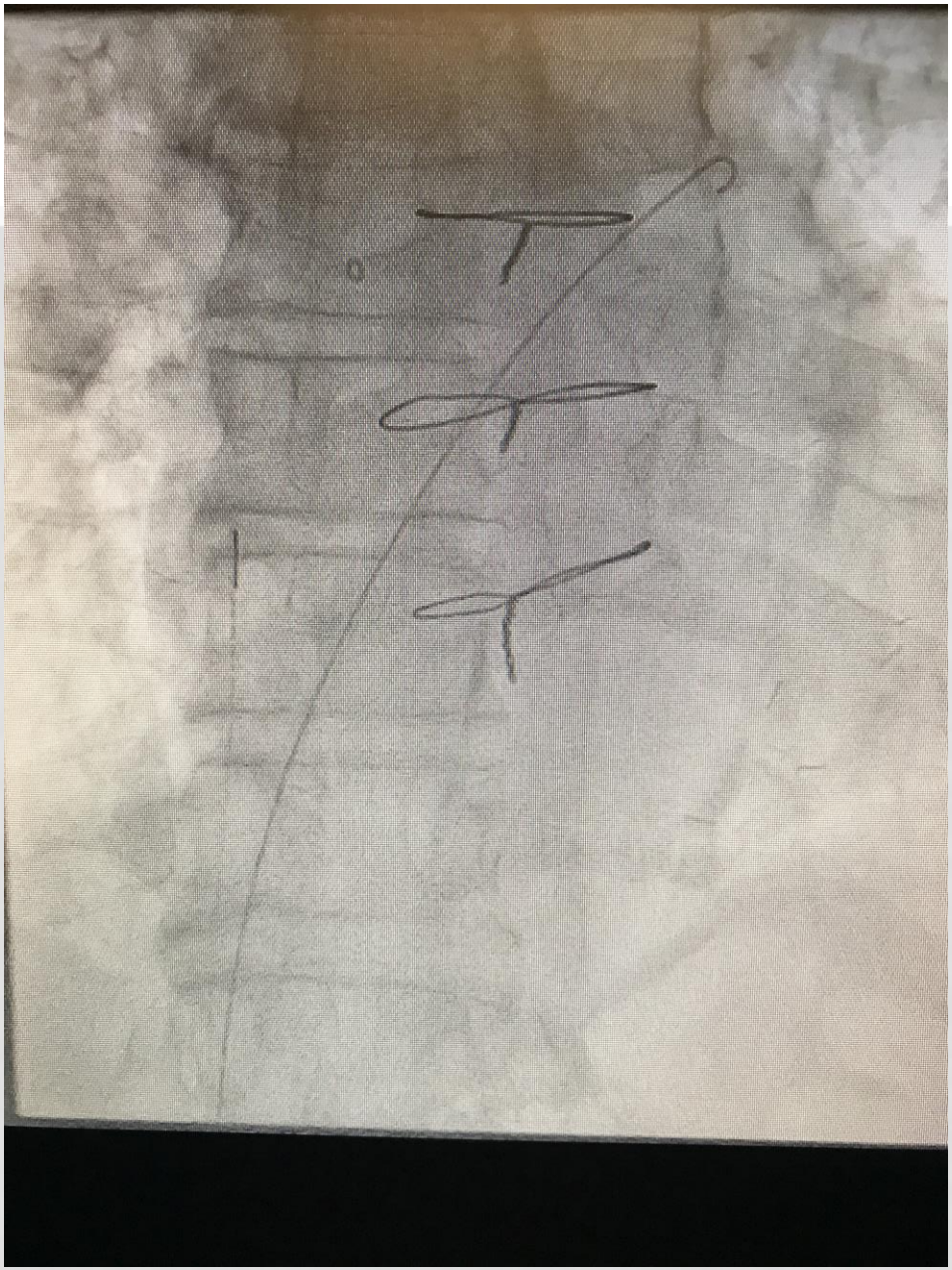

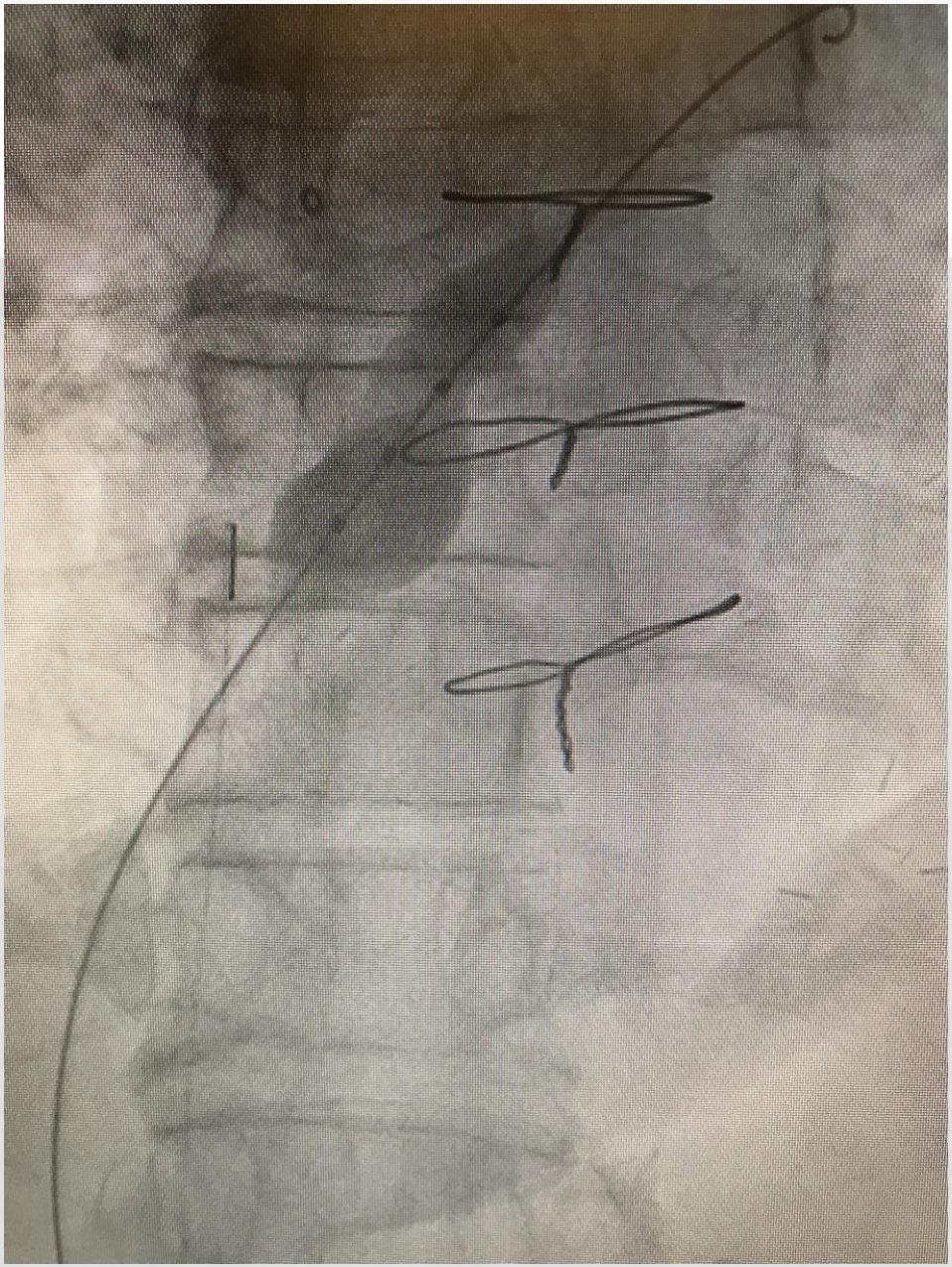

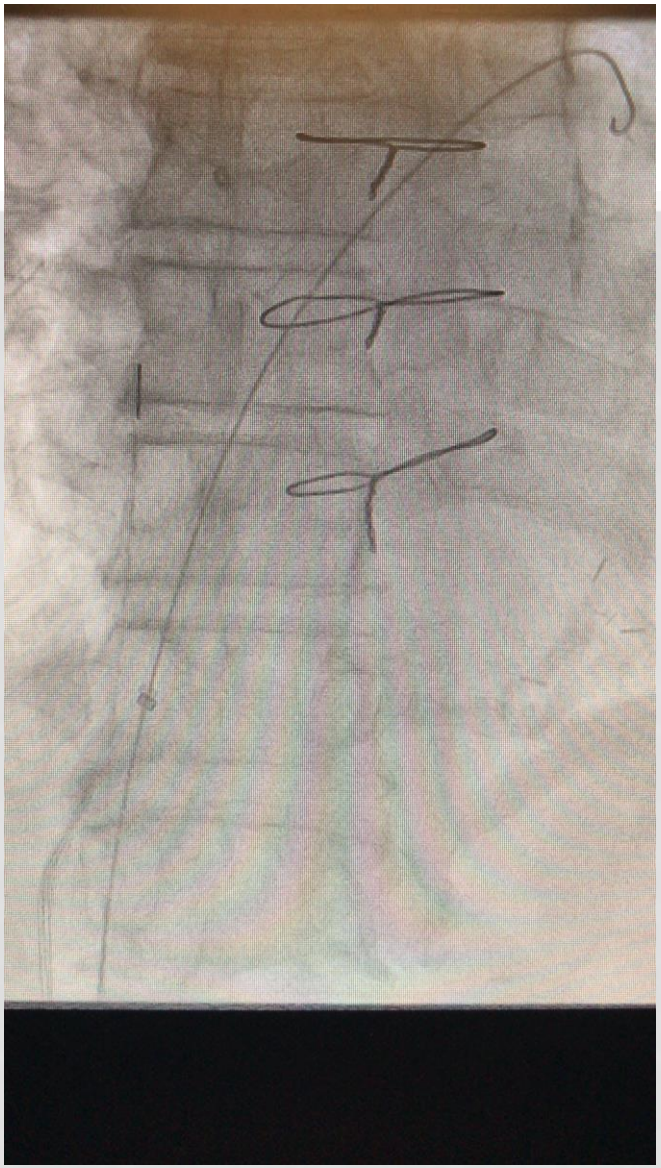

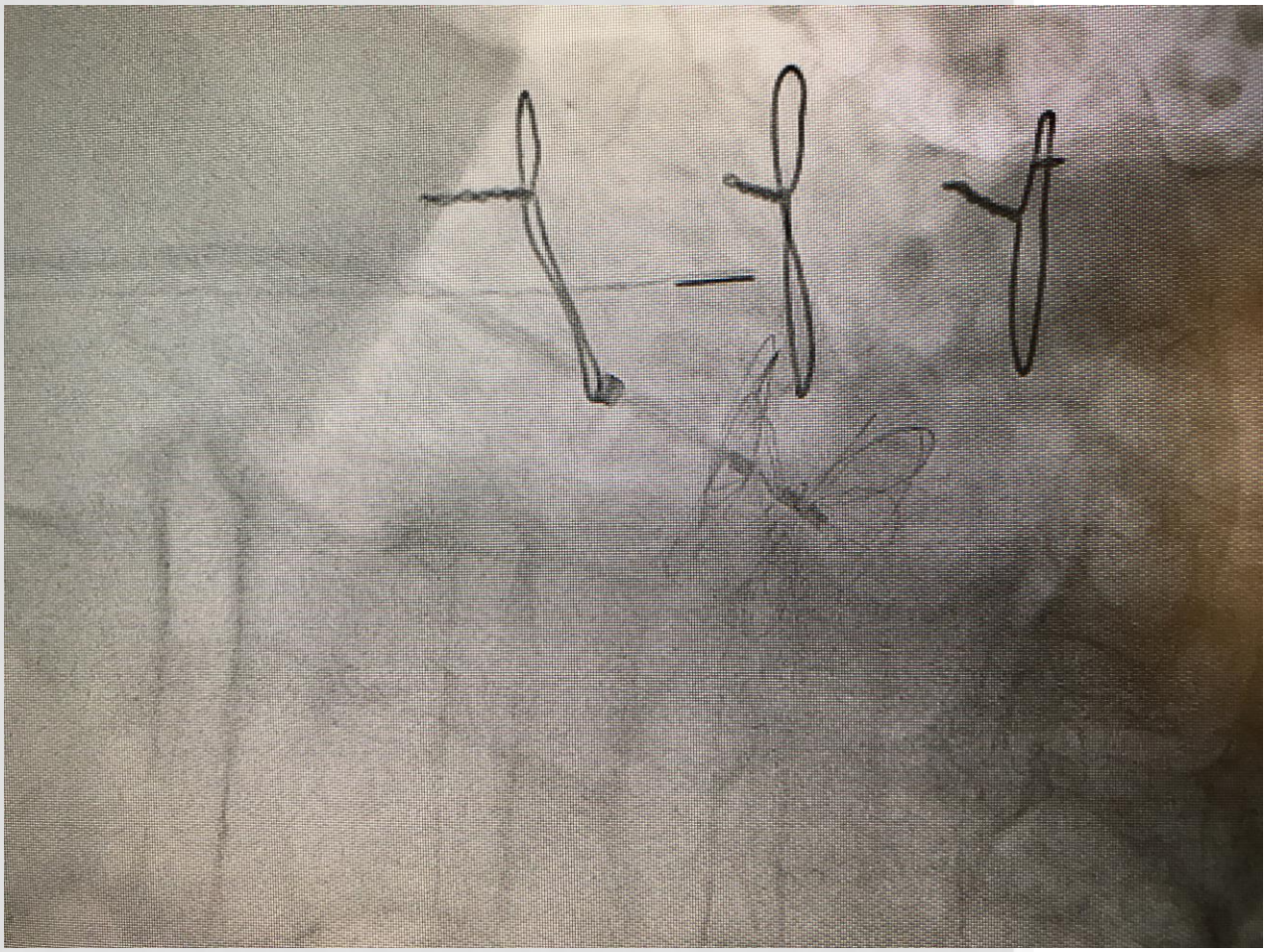

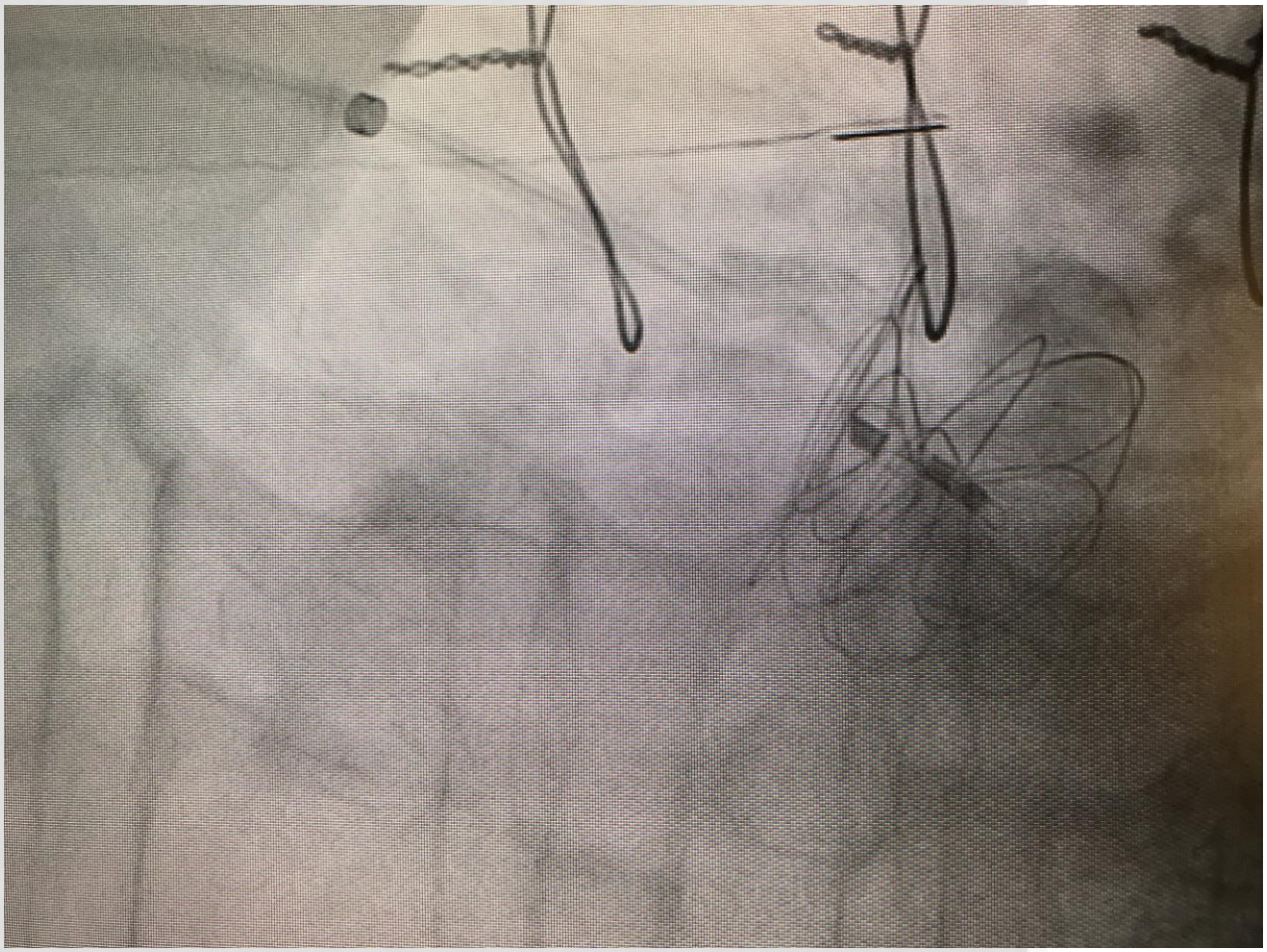

POST OP MANAGEMENT

- Post procedure vascular access management
  - hemostasis
- Echo
- Antiplatelet therapy
  - Specified duration of antiplatelet therapy?