LA Appendage Closure

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HEALTH

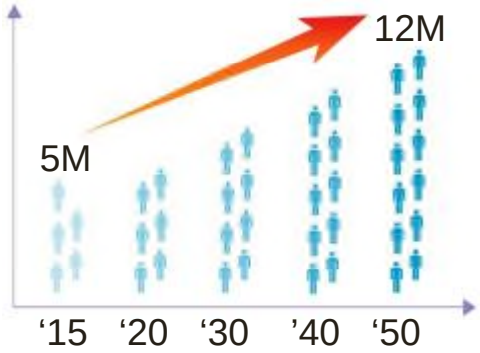
Disclosure Statement of Financial Interest
Brij Maini MD, FACC

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott Vascular
• Consulting Fees/Honoraria	• Medtronic
	• Abiomed
	• SJM
	• Siemens
	• Atritech/Boston Scientific
	• Keystone

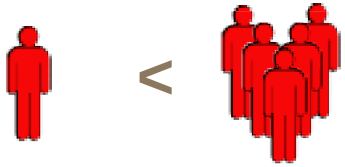
AF is a Growing Problem Associated with Greater Morbidity and Mortality

AF = most common cardiac arrhythmia, and growing



~5 M
people with AF in U.S., expected to more than double by 2050[1]

AF increases risk of stroke

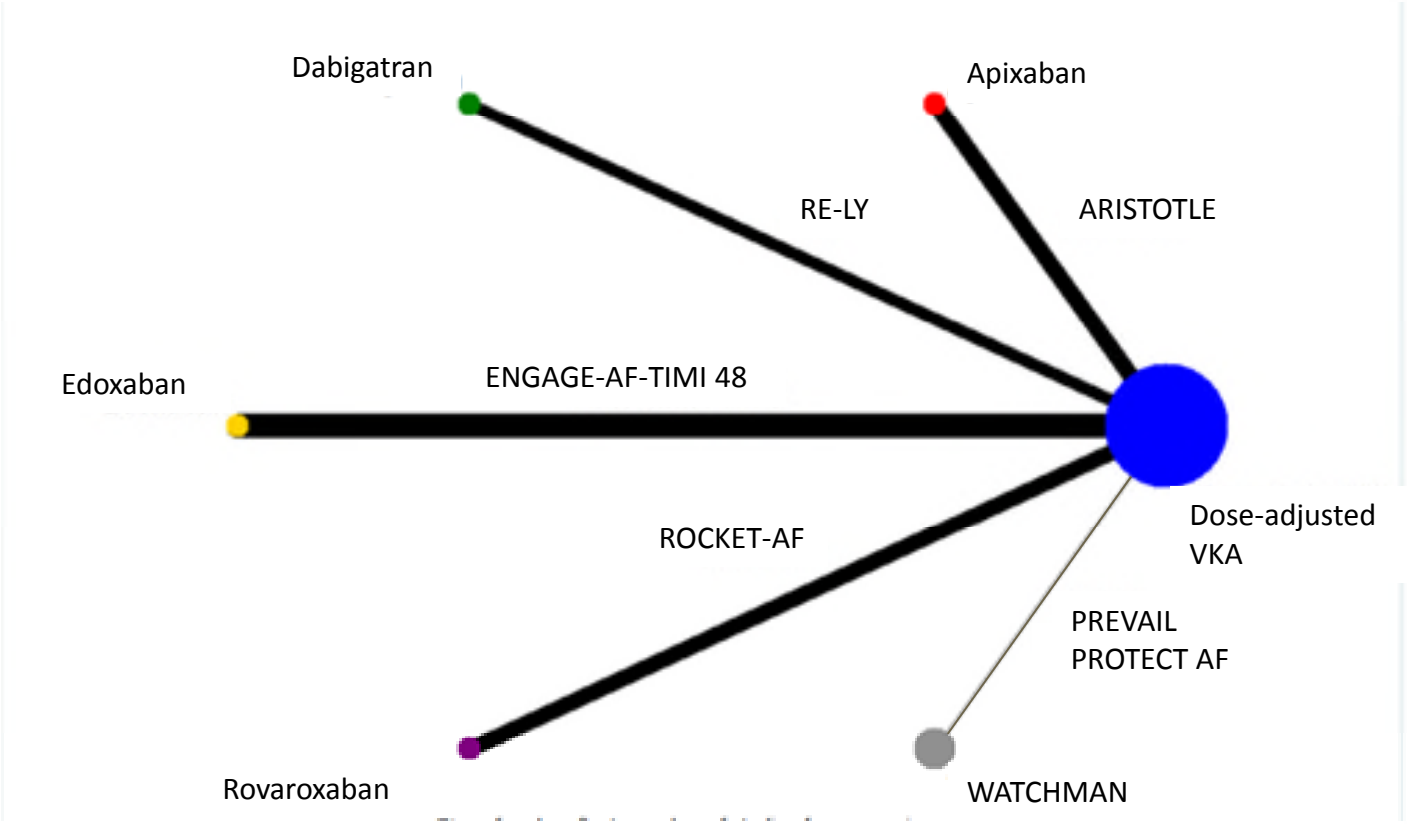


5x
greater risk of stroke with AF[2]

- Higher stroke risk for older patients and those with prior stroke or TIA
- 15-20% of all strokes are AF-related
- AF results in greater disability compared to non-AF-related stroke
- High mortality and stroke recurrence rate

1. Go AS. et al, Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association. Circulation. 2013; 127: e6-e245.
2. Holmes DR, Atrial Fibrillation and Stroke Management: Present and Future, Seminars in Neurology 2010;30:528–536.

Network plot for the stroke prophylaxis network



Size of node reflects number of studies for comparison
Thickness of the edge reflects inverse variance for comparison

Bajaj NS et al., PLOS ONE 2016; doi:org/10.1371/journal.pone.0163608

PROTECT AF 4-Year Results in JAMA

WATCHM
LEFT ATRIAL APP
CLOSURE D

JAMA®
The Journal of the American Medical Association

WATCHMAN™ Met Criteria for both Noninferiority and Superiority for the Primary Composite Endpoint Compared to Warfarin

Table 2. Intention-to-Treat Primary Efficacy and Safety Outcomes According to Treatment Group by Bayesian Model

Event	Device Group (n = 463)		Warfarin Group (n = 244)		Device/Warfarin Rate Ratio (95% Credible Interval)	Posterior Probabilities, %	
	Events/Patient-Years	Observed Rate[a]	Events/Patient-Years	Observed Rate[a]		Noninferiority	Superiority
Primary efficacy end point[b]	39/1720.2	2.3 (1.7-3.2)	34/900.8	3.8 (2.5-4.9)	0.60 (0.41-1.05)	>99	96
Stroke	26/1720.7	1.5 (1.0-2.2)	20/900.9	2.2 (1.3-3.1)	0.68 (0.42-1.37)	>99	83
Ischemic	24/1720.8	1.4 (0.9-2.1)	10/904.2	1.1 (0.5-1.7)	1.26 (0.72-3.28)	78	15
Hemorrhagic	3/1774.2	0.2 (0.0-0.4)	10/916.2	1.1 (0.5-1.8)	0.15 (0.03-0.49)	>99	99
Disabling[c]	8/1771.3	0.5 (0.2-0.8)	11/912.7	1.2 (0.6-1.9)	0.37 (0.15-1.00)	>99	98
Nondisabling[c]	18/1723.7	1.0 (0.7-1.7)	9/907.7	1.0 (0.4-1.7)	1.05 (0.54-2.80)	89	34
Systemic embolization	3/1773.6	0.2 (0.0-0.4)	0/919.5	0	NA		
Cardiovascular or unexplained death	17/1774.3	1.0 (0.6-1.5)	22/919.4	2.4 (1.4-3.4)	0.40 (0.23-0.82)	>99	99
Primary safety end point[d]	60/1666.2	3.6 (2.8-4.6)	27/878.2	3.1 (2.0-4.3)	1.17 (0.78-1.95)	98	20

Abbreviation: NA, not applicable.

[a] Events per 100 patient-years (95% credible interval).

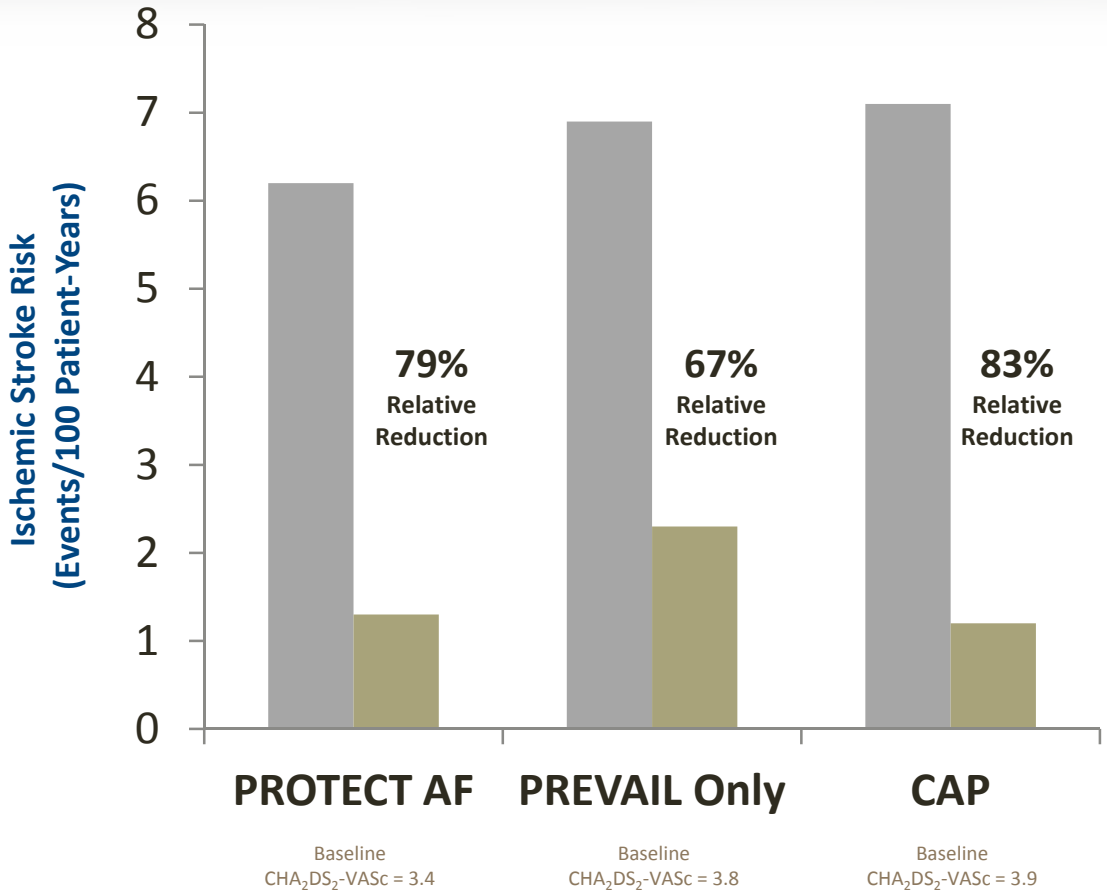
[b] Primary efficacy defined as composite of stroke, systemic embolization, or cardiovascular/unexplained death.

[c] Disabling or fatal strokes were those with a Modified Rankin Score of 3-6 after the stroke. Nondisabling strokes were those with Modified Rankin Scores of 0-2 after the stroke.

[d] Safety defined as procedure-related events (pericardial effusion requiring intervention or prolonged hospitalization, procedure-related stroke, or device embolization) and major bleeding (intracranial or bleeding requiring transfusion).

Reddy, VY et al. JAMA. 2014;312(19):1988-1998.

WATCHMAN™ Device Reduces Ischemic Stroke Over No Therapy

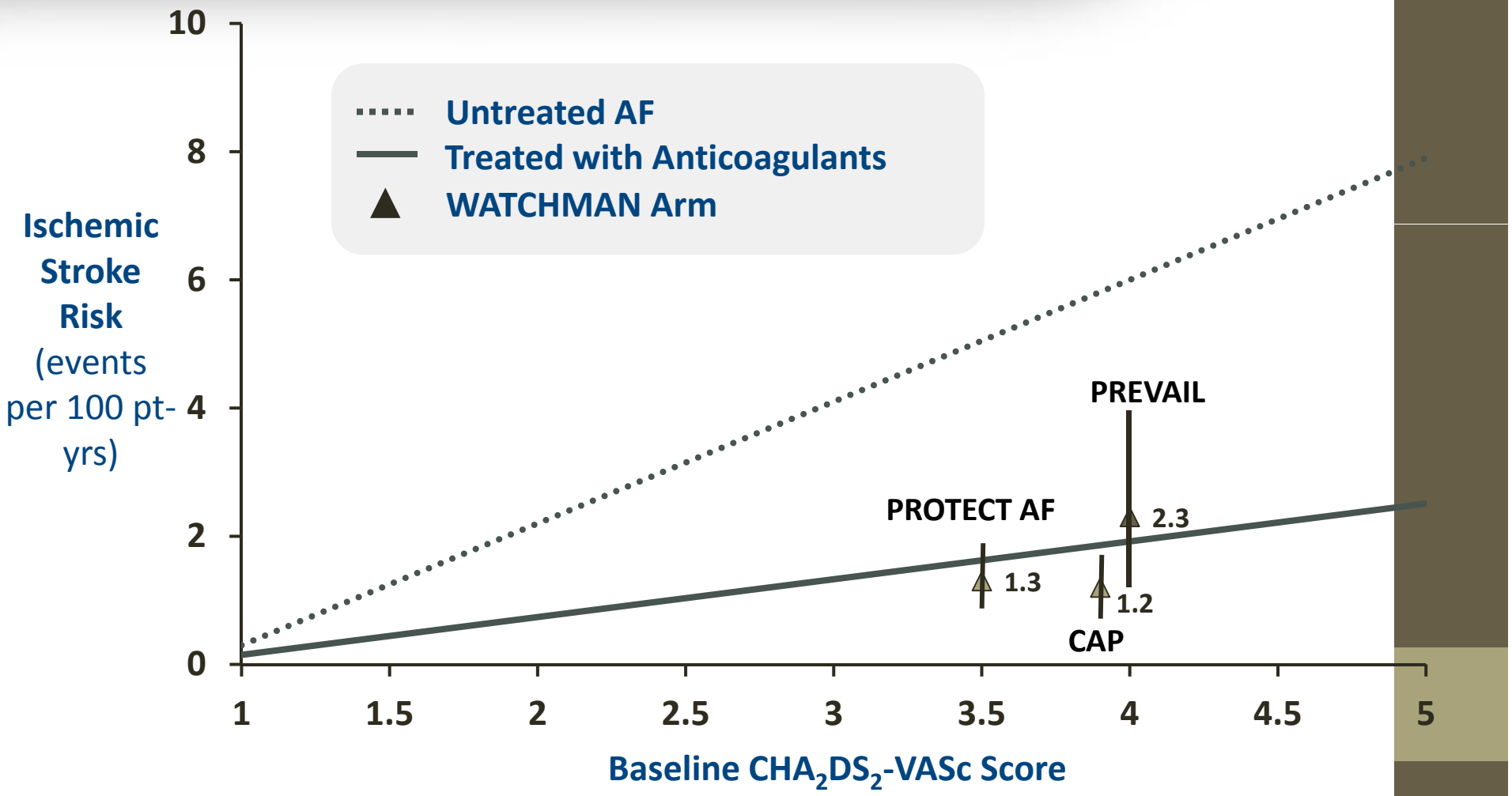


- Imputed Ischemic Stroke Rate*
- Observed WATCHMAN Ischemic Stroke Rate

* Imputation based on published rate with adjustment for CHA_2DS_2-VASc score (3.0); Olesen JB. Thromb Haemost (2011)

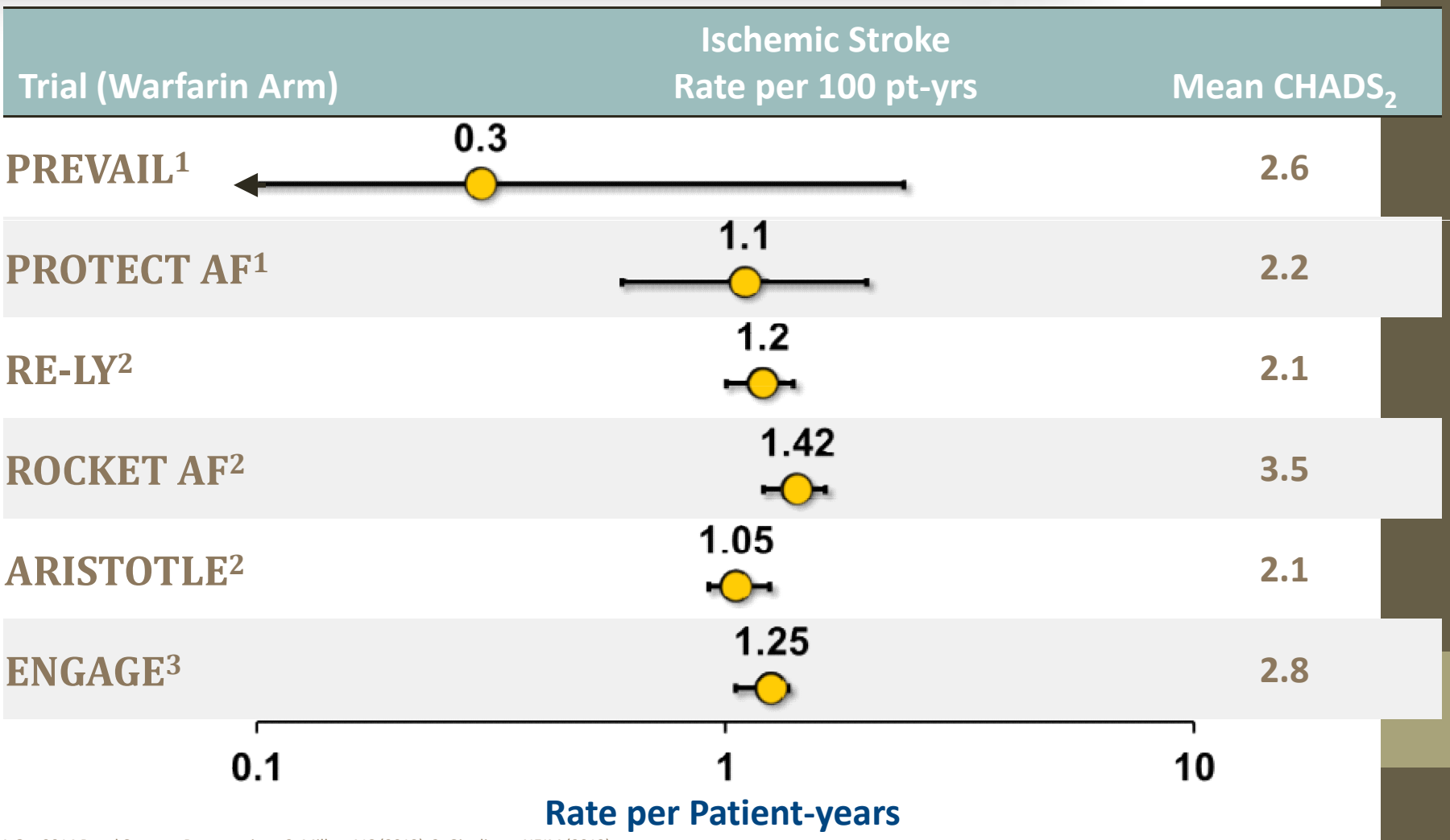
FDA Oct 2014 Panel Sponsor Presentation. Hanzel G, et al. TCT 2014 (abstract)

WATCHMAN™ Ischemic Stroke Rate Aligns with Expected Rate Based on Risk Score



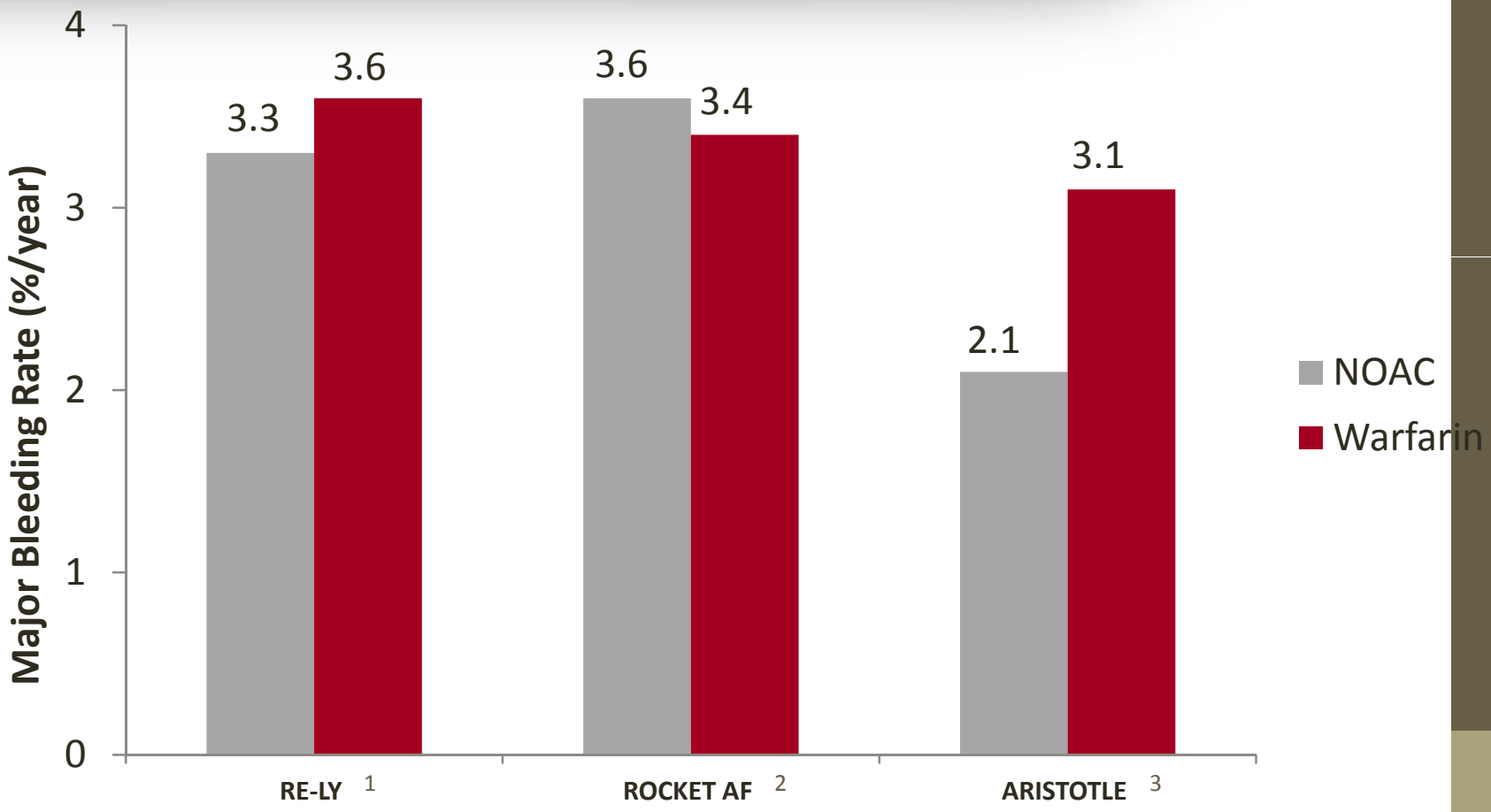
Source: Friberg L. et al. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182,678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J (2012). NICE UK (2014)

PREVAIL: Warfarin Ischemic Stroke Rate Differs from Other Trials



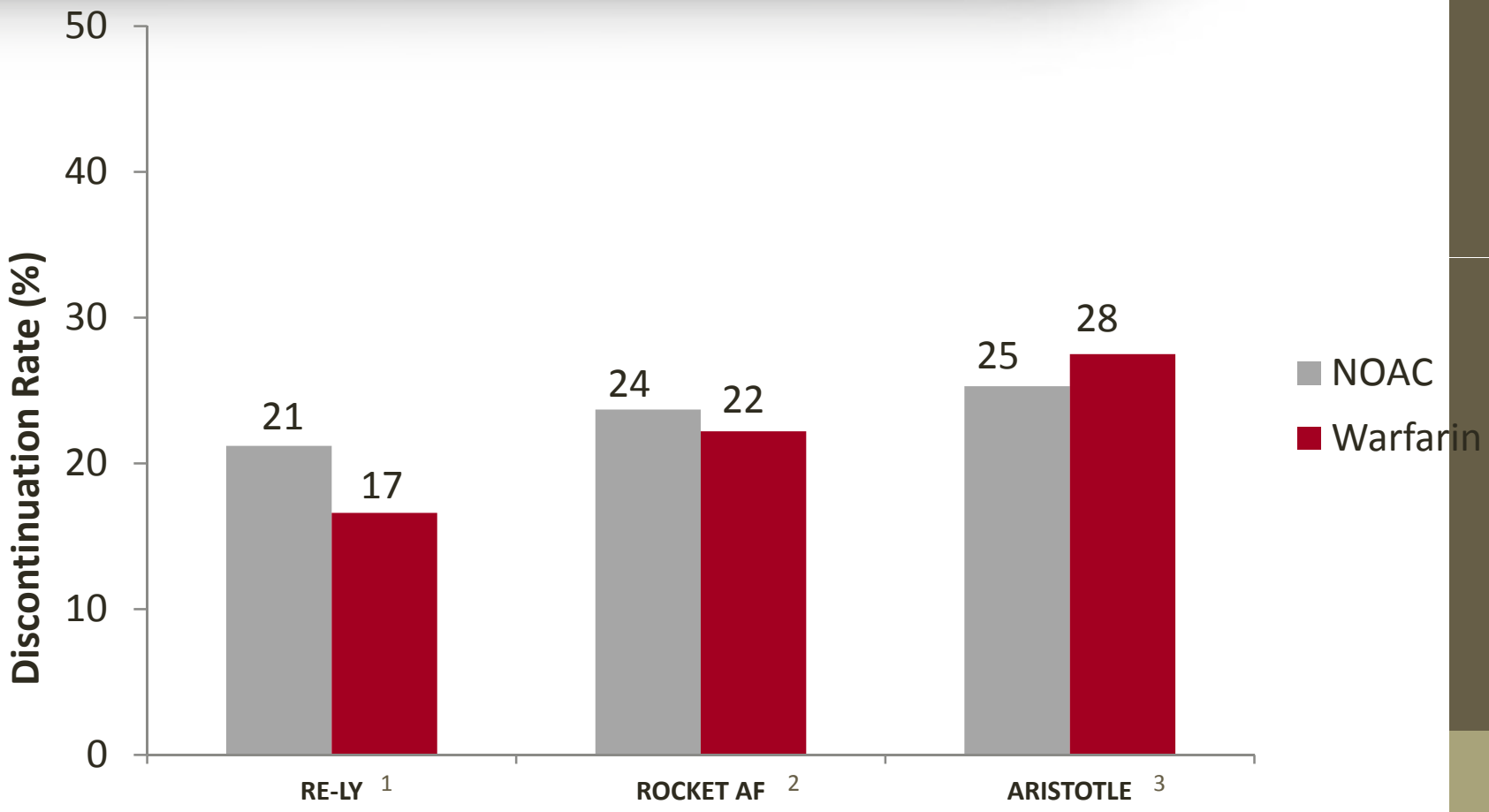
1. FDA Oct 2014 Panel Sponsor Presentation. 2. Miller. AJC (2012) 3. Giugliano. NEJM (2013)

Rate of Major Bleeding in NOAC Trials



[1]Connolly, S. NEJM 2009; 361:1139-1151 – 2 yrs f-up (Corrected) 150 mg [2]Patel, M. NEJM 2011; 365:883-891 – 1.9 yrs f-up, ITT [3]Granger, C NEJM 2011; 365:981-992 – 1.8 yrs f-up

Rate of Discontinuation in NOAC Trials



[1]Connolly, S. NEJM 2009; 361:1139-1151 – 2 yrs f-up (Corrected), 150 mg [2]Patel, M. NEJM 2011; 365:883-891 – 1.9 yrs f-up, ITT [3]Granger, C NEJM 2011; 365:981-992 – 1.8 yrs f-up

ABBREVIATED STATEMENT
WATCHMAN™ Left Atrial Appendage Closure Device with Delivery System and WATCHMAN Access System

INDICATIONS FOR USE

The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

The WATCHMAN Access System is intended to provide vascular and transseptal access for all WATCHMAN Left Atrial Appendage Closure Devices with Delivery Systems.

CONTRAINDICATIONS

Do not use the WATCHMAN Device if:

- Intracardiac thrombus is visualized by echocardiographic imaging.
- An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present.
- The LAA anatomy will not accommodate a device. See **Table** 46 in the DFU.
- Any of the customary contraindications for other percutaneous catheterization procedures (e.g., patient size too small to accommodate TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) are present.
- There are contraindications to the use of warfarin, aspirin, or clopidogrel.
- The patient has a known hypersensitivity to any portion of the device material or the individual components (see Device Description section) such that the use of the WATCHMAN Device is contraindicated.

WARNINGS

- Device selection should be based on accurate LAA measurements obtained using fluoro and ultrasound guidance (TEE recommended) in multiple angles (e.g., 0º, 45º, 90º, 135º).
- Do not release the WATCHMAN Device from the core wire if the device does not meet all release criteria.
- If thrombus is observed on the device, warfarin therapy is recommended until resolution of thrombus is demonstrated by TEE.
- The potential for device embolization exists with cardioversion <30 days following device implantation. Verify device position post-cardioversion during this period.
- Administer appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.
- For single use only. Do not reuse, reprocess, or resterilize.

PRECAUTIONS

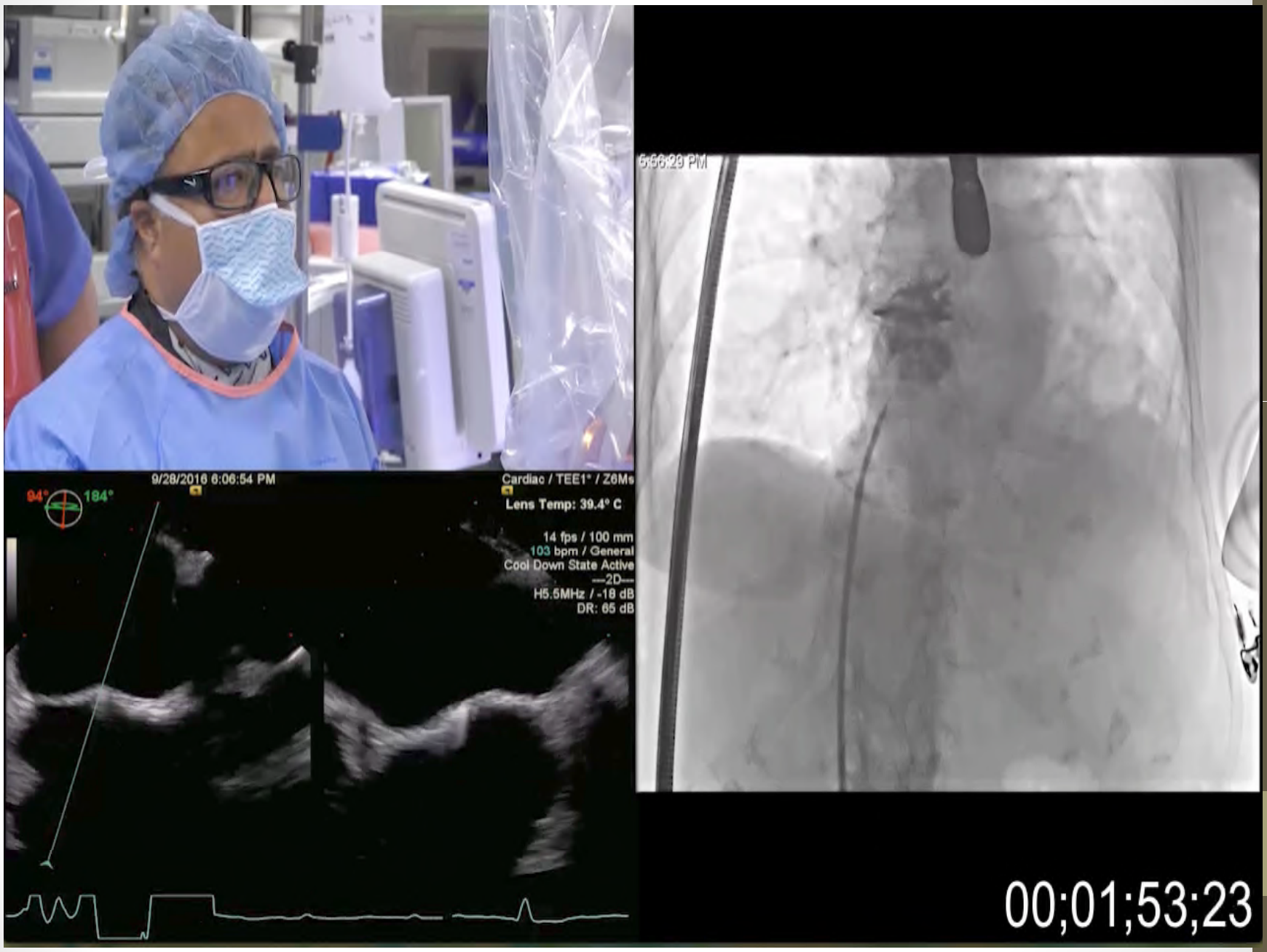
- The safety and effectiveness (and benefit-risk profile) of the WATCHMAN Device has not been established in patients for whom long-term anticoagulation is determined to be contraindicated.
- The LAA is a thin-walled structure. Use caution when accessing the LAA and deploying the device.
- Use caution when introducing the WATCHMAN Access System to prevent damage to cardiac structures.
- Use caution when introducing the Delivery System to prevent damage to cardiac structures.
- To prevent damage to the Delivery Catheter or device, do not allow the WATCHMAN Device to protrude beyond the distal tip of the Delivery Catheter when inserting the Delivery System into the Access Sheath.
- If using a power injector, the maximum pressure **should not** exceed 100 psi.
- In view of the concerns that were raised by the RE-ALIGN[1] study of dabigatran in the presence of prosthetic mechanical heart valves, caution should be used when prescribing oral anticoagulants other than warfarin in patients treated with the WATCHMAN Device. The WATCHMAN Device has only been evaluated with the use of warfarin post-device implantation.

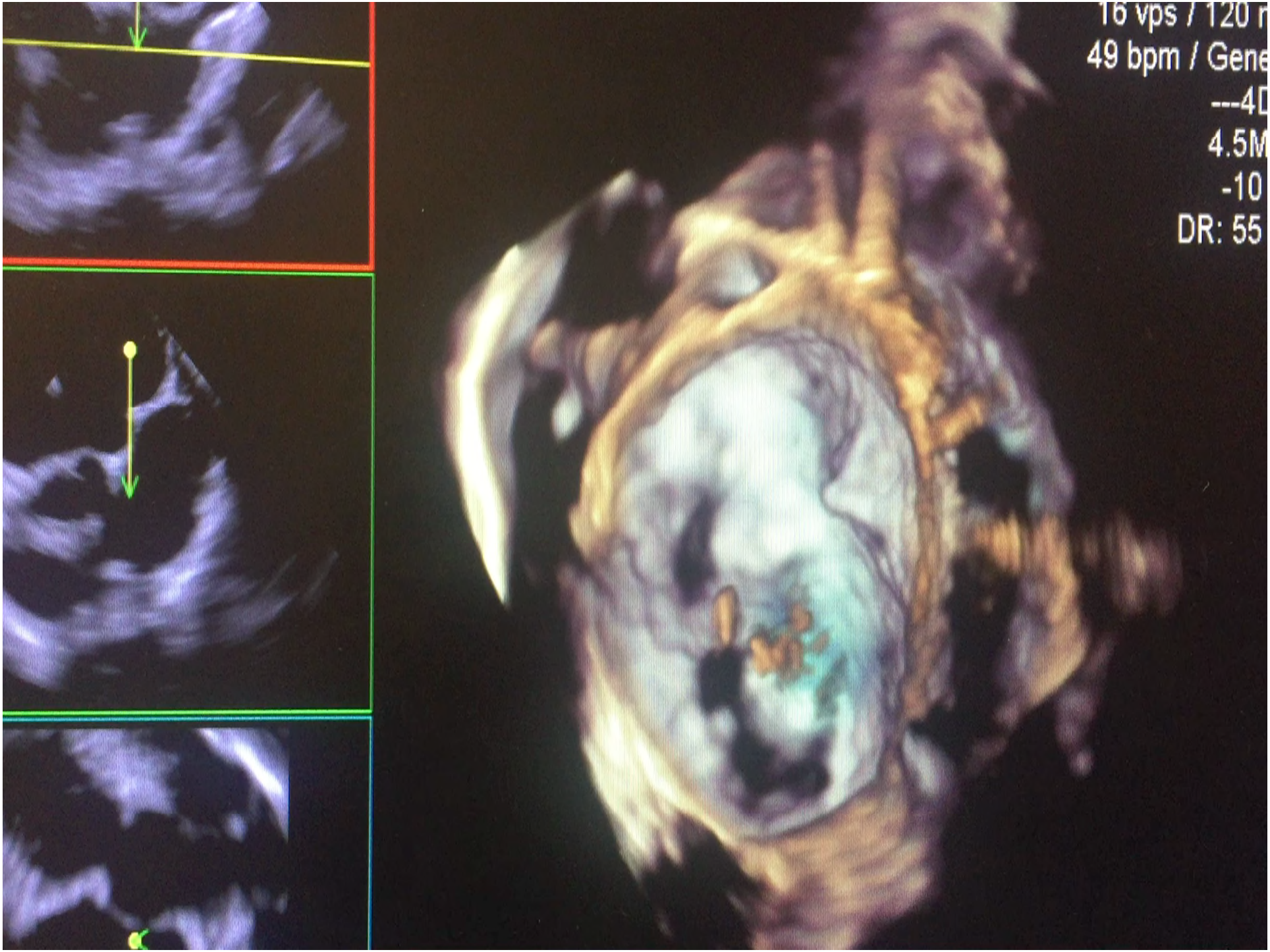
ADVERSE EVENTS

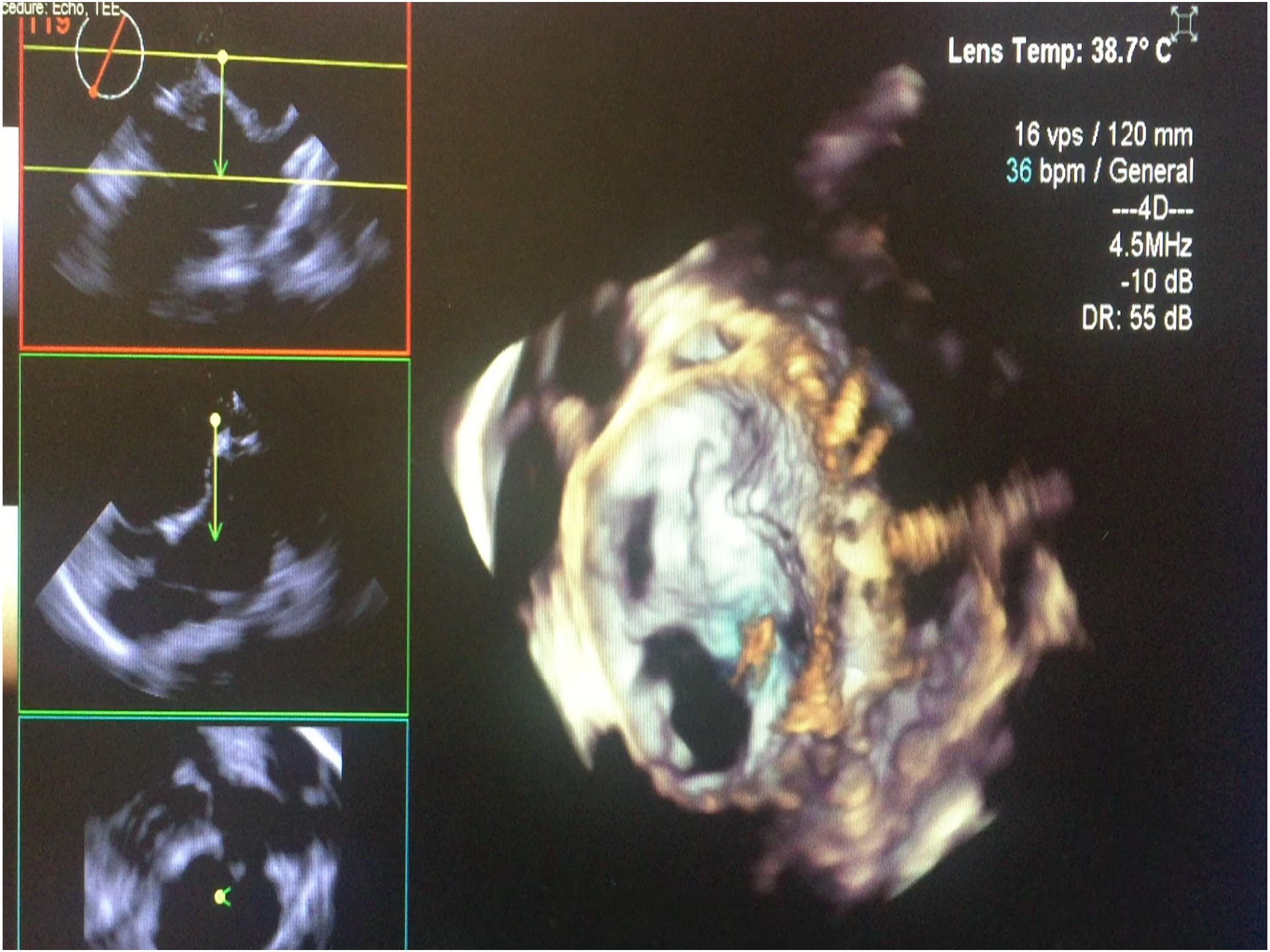
Potential adverse events (in alphabetical order) which may be associated with the use of a left atrial appendage closure device or implantation procedure include but are not limited to:
Air embolism, Airway trauma, Allergic reaction to contrast media/medications or device materials, Altered mental status, Anemia requiring transfusion, Anesthesia risks, Angina, Anoxic encephalopathy, Arrhythmias, Atrial septal defect , AV fistula , Bruising, hematoma or seroma, Cardiac perforation , Chest pain/discomfort, Confusion post procedure, Congestive heart failure, Contrast related nephropathy, Cranial bleed, Decreased hemoglobin, Deep vein thrombosis, Death, Device embolism, Device fracture, Device thrombosis, Edema, Excessive bleeding, Fever, Groin pain, Groin puncture bleed, Hematuria, Hemoptysis, Hypotension, Hypoxia, Improper wound healing, Inability to reposition, recapture, or retrieve the device, Infection / pneumonia, Interatrial septum thrombus, Intratracheal bleeding, Major bleeding requiring transfusion, Misplacement of the device / improper seal of the appendage / movement of device from appendage wall, Myocardia erosion, Nausea, Oral bleeding, Pericardial effusion / tamponade, Pleural effusion, Prolonged bleeding from a laceration, Pseudoaneurysm, Pulmonary edema, Renal failure, Respiratory insufficiency / failure, Surgical removal of the device, Stroke – Ischemic , Stroke – Hemorrhagic, Systemic embolism, TEE complications (throat pain, bleeding, esophageal trauma), Thrombocytopenia, Thrombosis, Transient ischemic attack (TIA), Valvular damage, Vasovagal reactions
There may be other potential adverse events that are unforeseen at this time.

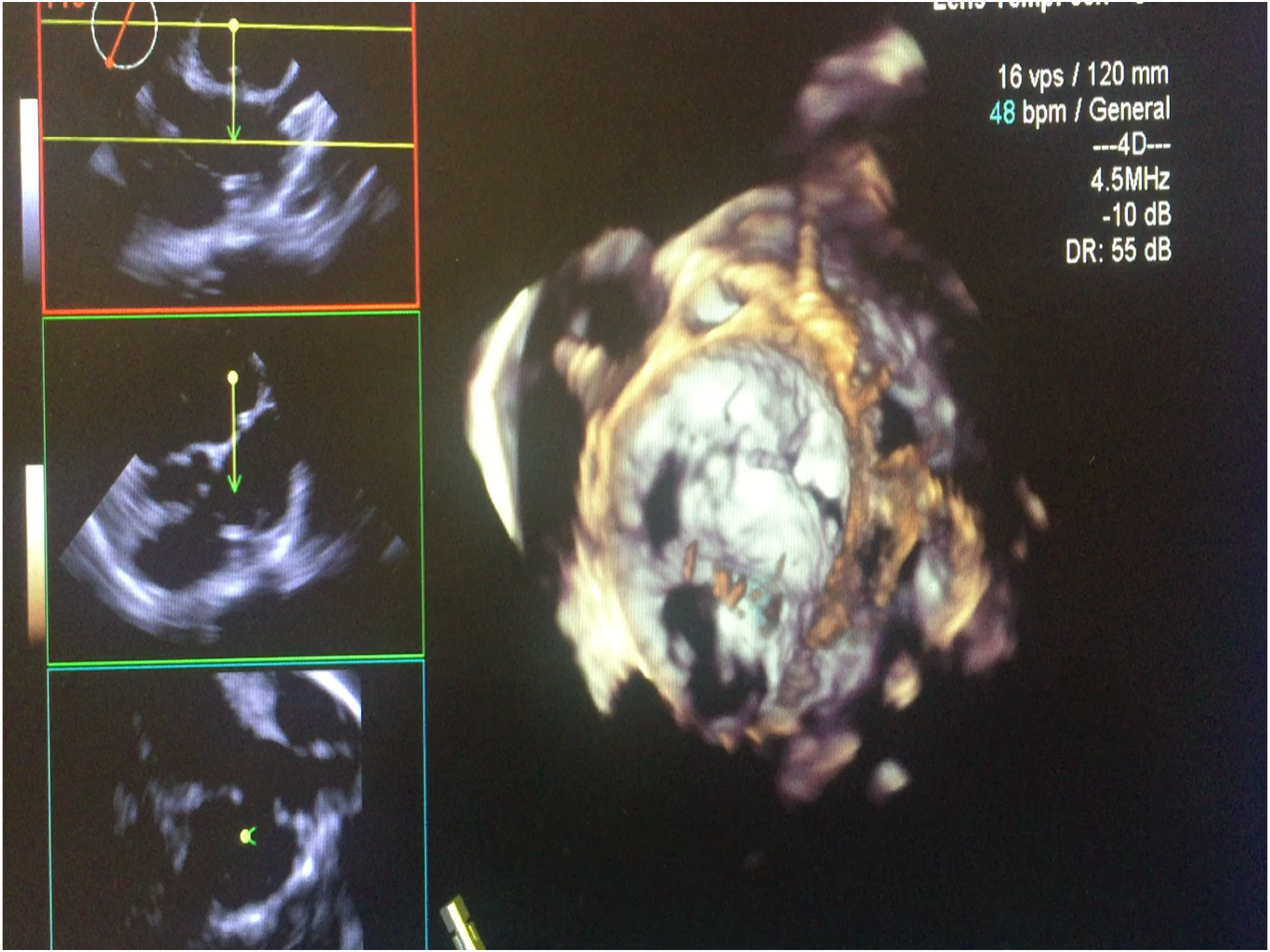
CAUTION: *Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete "Directions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator's Instructions.*

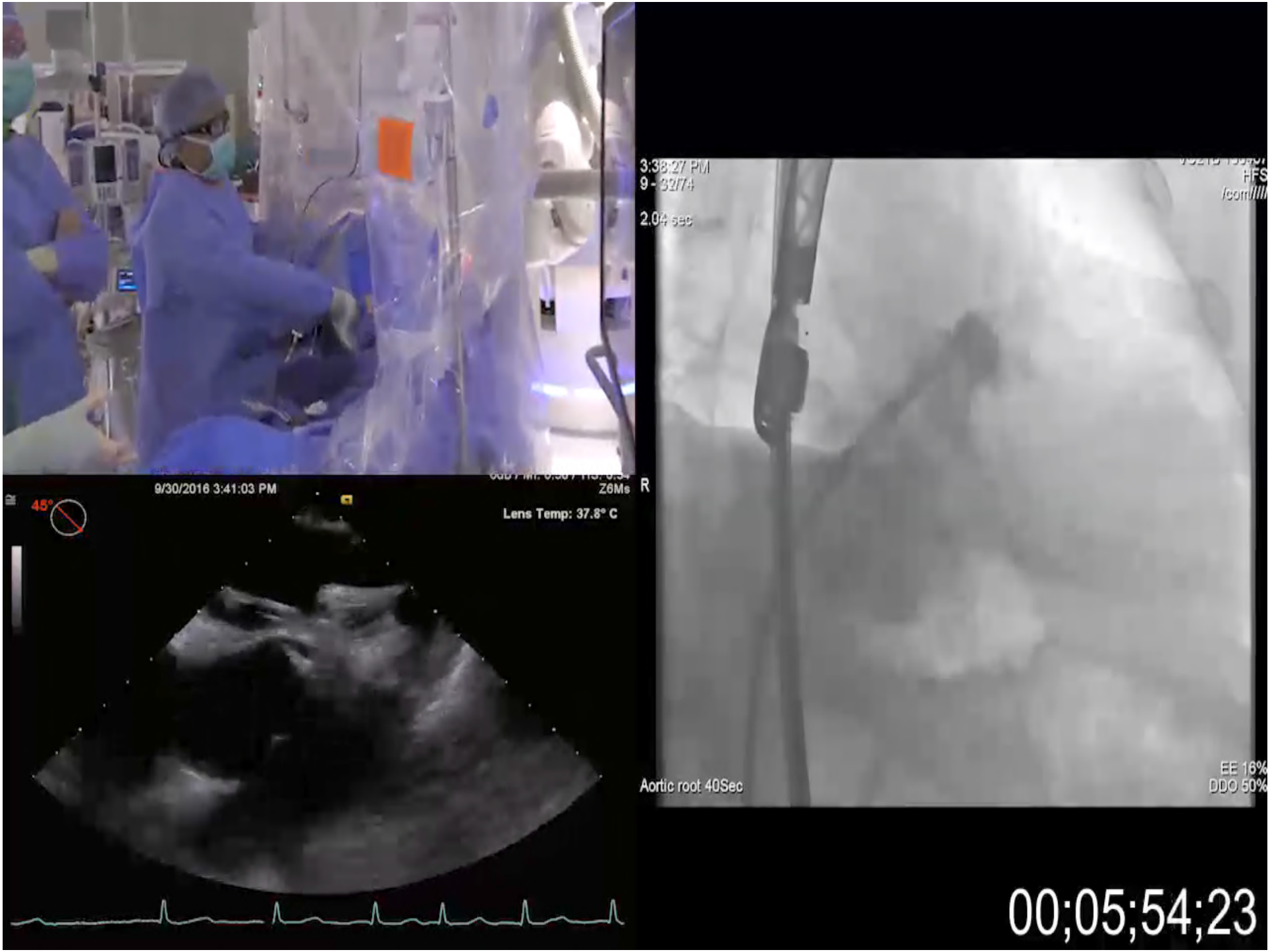
[1]Eikelboom JW, Connolly SJ, Brueckmann M, et al. N Engl J Med 2013;369:1206-14.

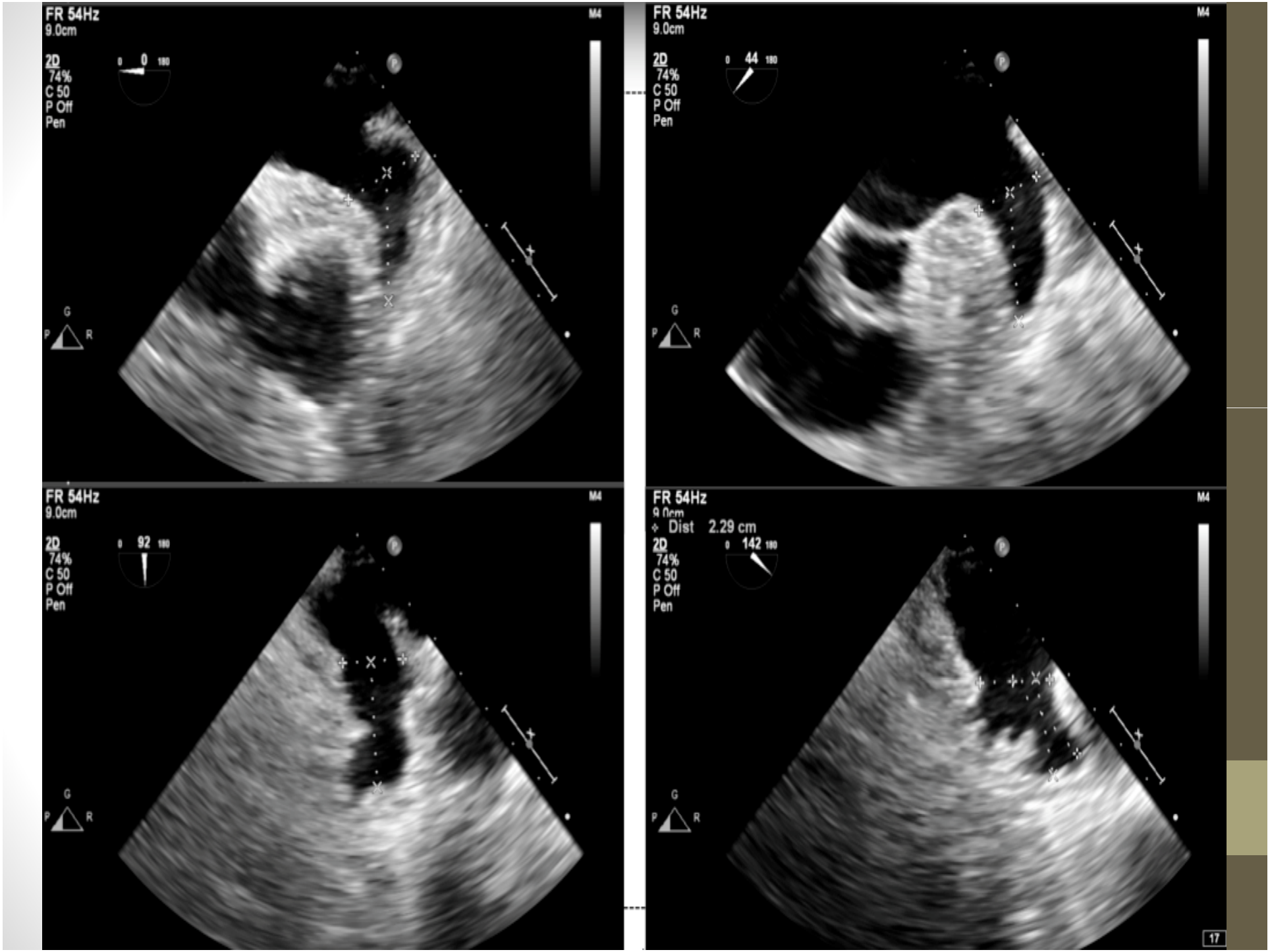

9/28/2016 6:06:54 PM
Cardiac / TEE1° / Z6Ms
Lens Temp: 39.4° C
94°
184°
14 fps / 100 mm
103 bpm / General
Cool Down State Active
2D
H5.5MHz / -18 dB
DR: 65 dB
00;01;53;23

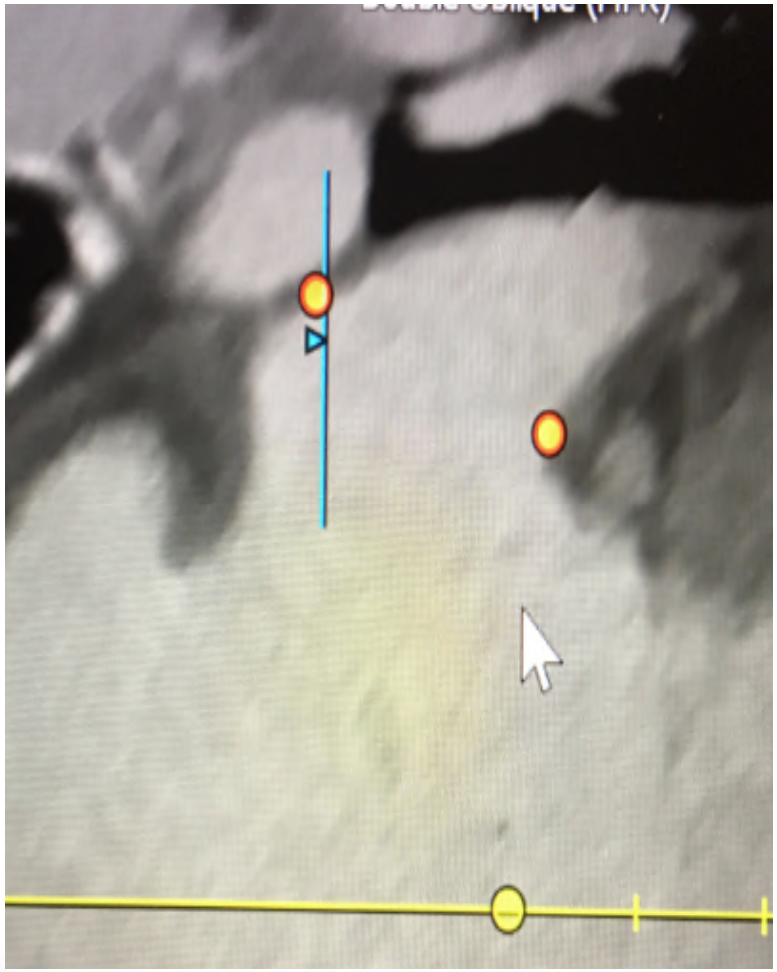

16 vps / 120 r
49 bpm / Gene
---4D
4.5M
-10
DR: 55

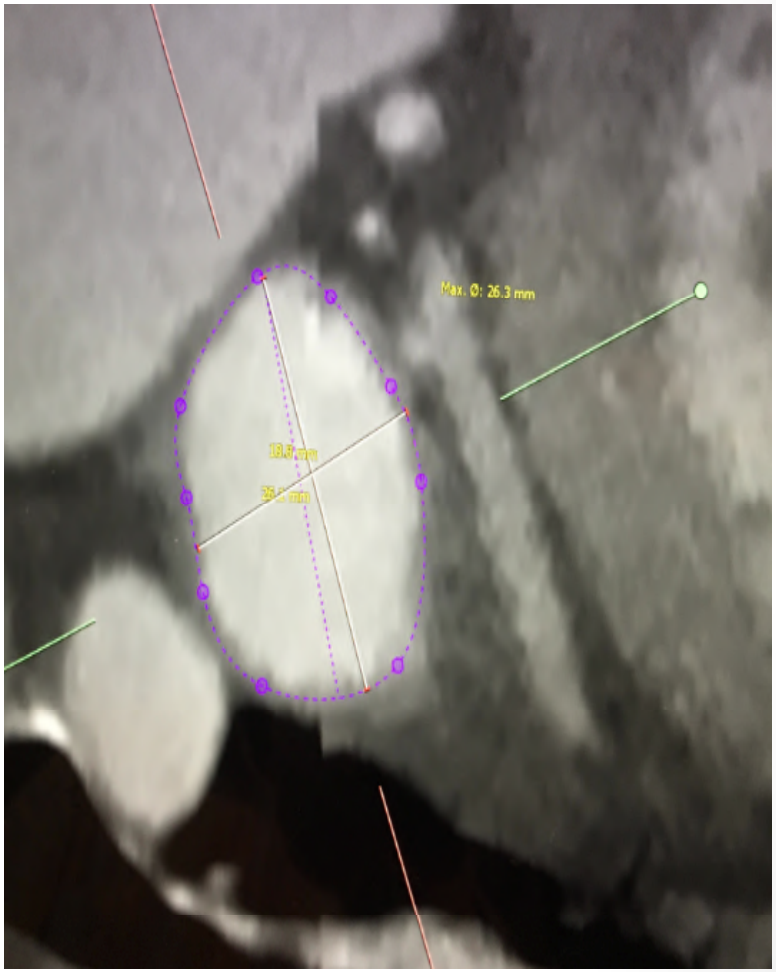

Lens Temp: 38.7° C
16 vps / 120 mm
36 bpm / General
---4D---
4.5MHz
-10 dB
DR: 55 dB


16 vps / 120 mm
48 bpm / General
---4D---
4.5MHz
-10 dB
DR: 55 dB


9/30/2016 3:41:03 PM
Z6Ms
45°
Lens Temp: 37.8° C
R
3:38:27 PM
9 - 32/74
2.04 sec
HFS
Aortic root 40Sec
EE 16%
DDO 50%
00;05;54;23


FR 54Hz
9.0cm
M4
2D
74%
C 50
P Off
Pen
0
0
180
G
P
R
FR 54Hz
9.0cm
M4
2D
74%
C 50
P Off
Pen
0
44
180
G
P
R
FR 54Hz
9.0cm
M4
2D
74%
C 50
P Off
Pen
0
92
180
G
P
R
FR 54Hz
M4
Dist 2.29 cm
2D
74%
C 50
P Off
Pen
0
142
180
G
P
R
17




Max. Ø: 26.3 mm

Post-FDA Approval, Initial US Clinical Experience with Watchman Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation

Vivek Y. Reddy MD[1]*, Douglas N. Gibson MD[2], Saibal Kar[3], William O'Neill MD[4], Shephal K. Doshi MD[5], Rodney P. Horton MD[6], Maurice Buchbinder MD[7], Nicole T. Gordon BSEE[8], David R. Holmes MD[9]

Both authors contributed equally to the development of this manuscript

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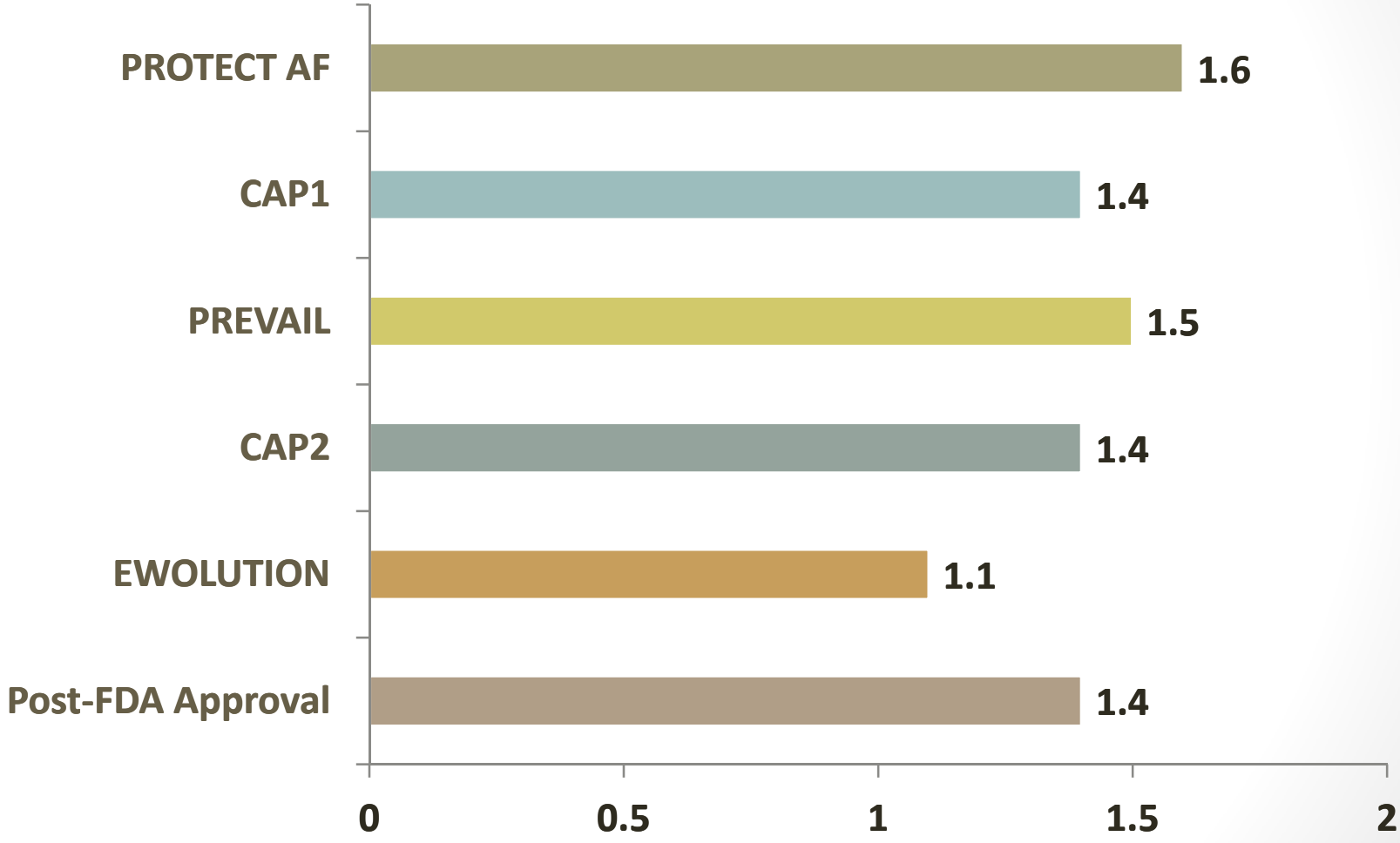
Procedural Success

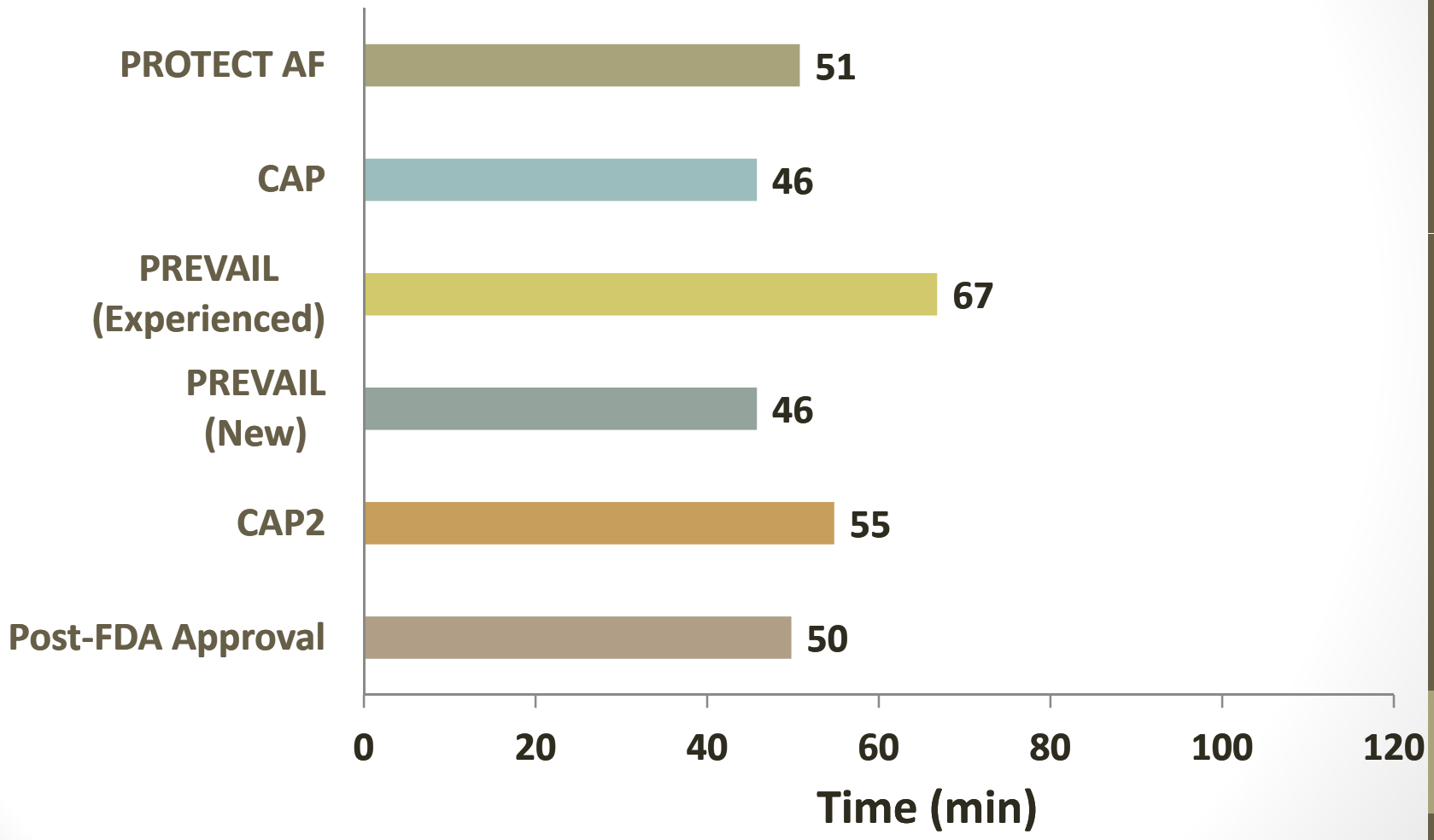
Implant success defined as deployment and release of the device into the LAA; no leak ≥ 5 mm

Devices per Case[1-2]



1 WATCHMAN FDA Panel Sponsor Presentation. Oct 2014; 2 Boersma, L.et al. *EHJ*; published online Jan 2016 *in press*

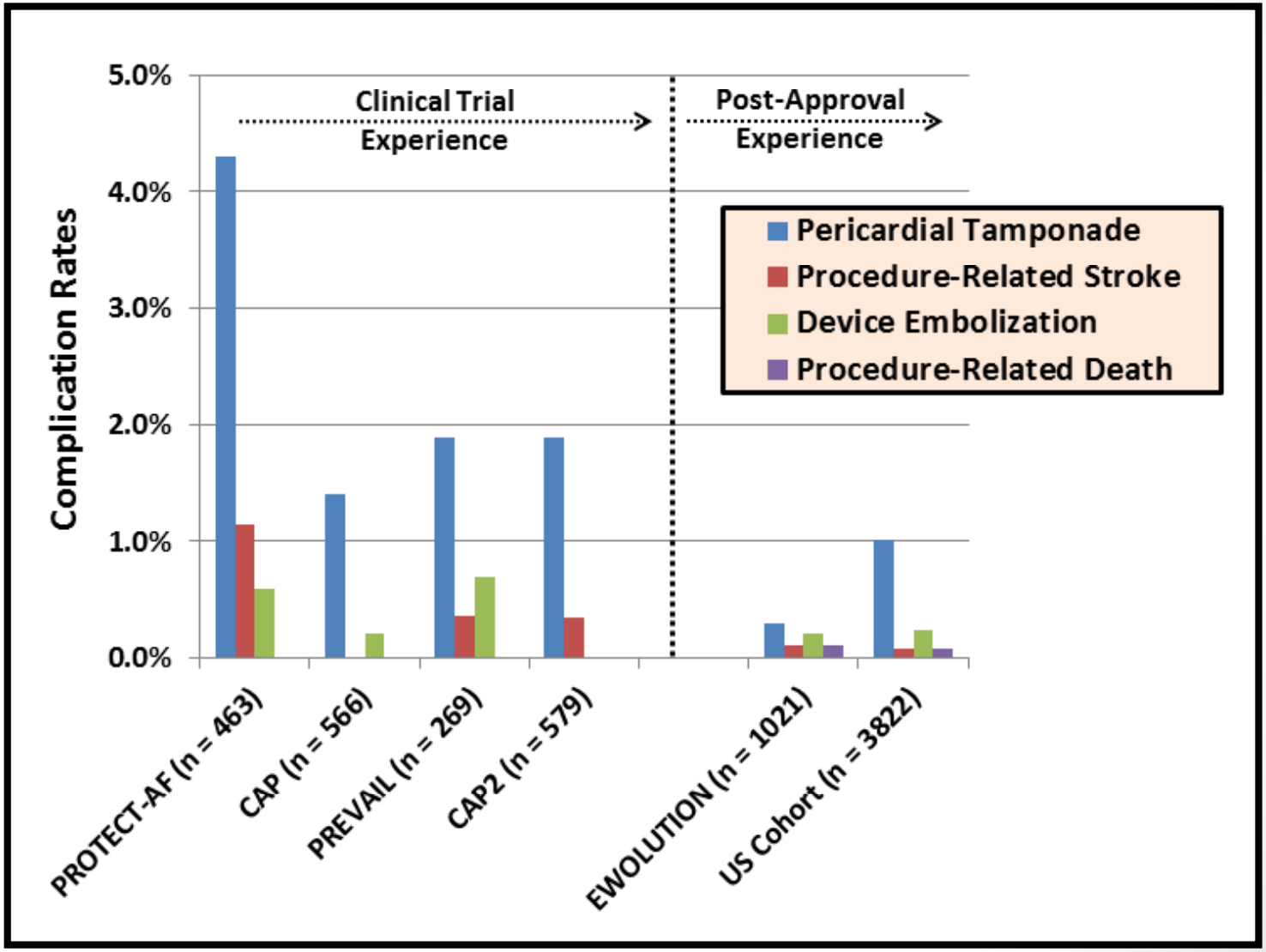
Procedure Duration



Outcomes in the Post-FDA Approval Watchman Experience N=3822

	Post-FDA Approval Experience
Complications	
Pericardial Tamponade	39 (1.02%)
Treated with Pericardiocentesis	24 (0.63%)
Treated Surgically	12 (0.31%)
Resulted in Death	3 (0.078%)
Pericardial Effusion – No Intervention	11 (0.29%)
Procedure-Related Stroke	3 (0.078%)
Device Embolization	9 (0.24%)
Removed Percutaneously	3
Removed Surgically	6
Death	
Procedure-Related Mortality	3 (0.078%)
Additional Mortality within 7 days	1 (0.026%)

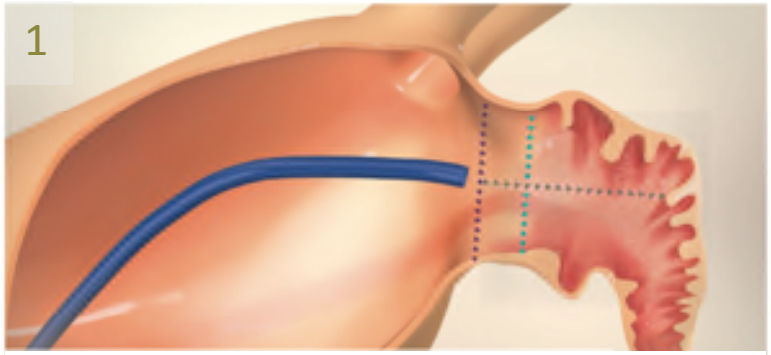
Comparison of Procedural Complications Across Watchman Studies



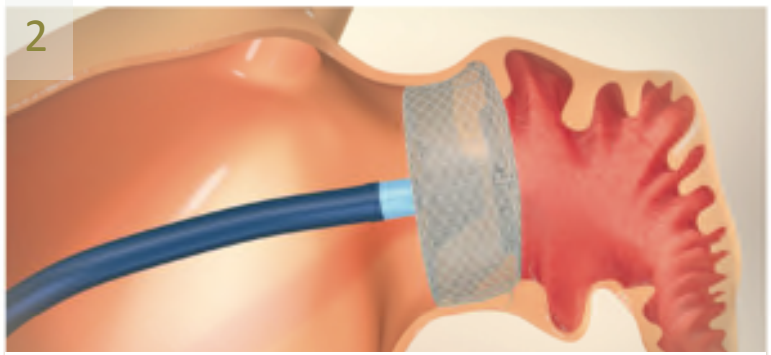
Conclusion

- In the real-world post-FDA approval experience of Watchman LAAC, procedural success was high and complication rates low.
- Complications were low even with ~50% of the operators being new to the procedure. This demonstrates that early procedure learnings can be transferred through rigorous training.

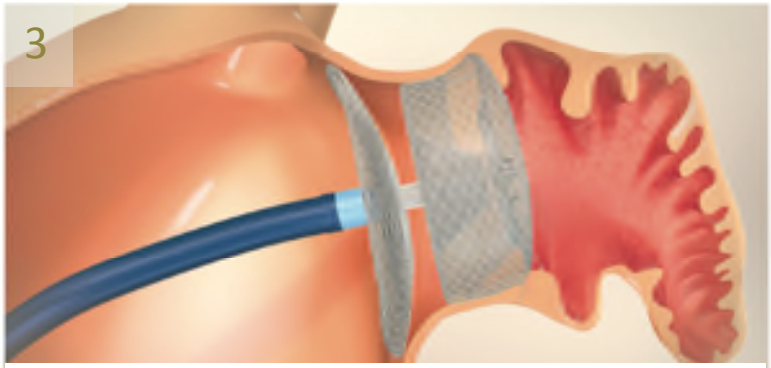
Amplatzer™ Amulet™ Device Implant Procedure



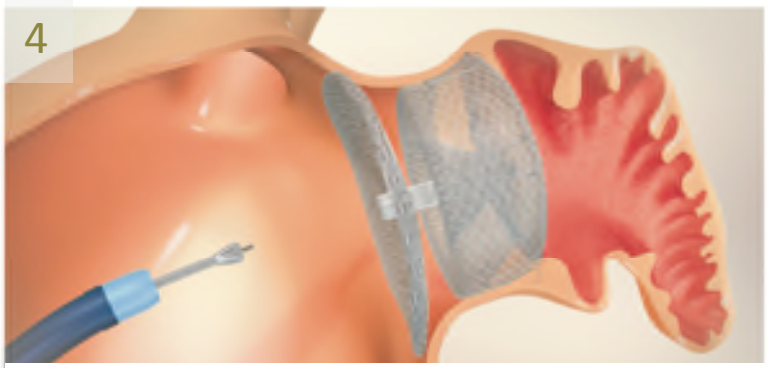
Measure LAA orifice, landing zone, depth



Deploy LOBE in landing zone



Deploy the DISC, to cover the ostium

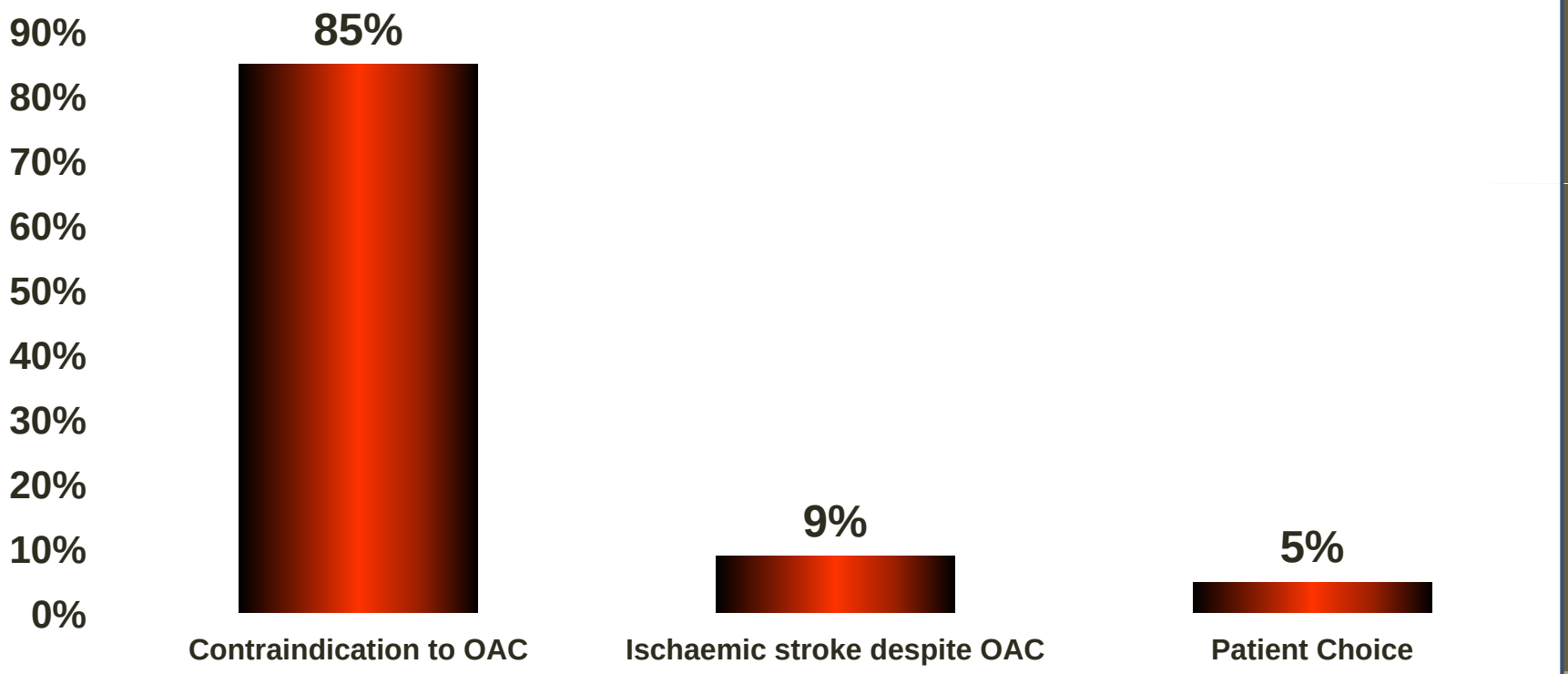


Release

Results: Patient Population

	Mean ± SD or % n=1071*
Age (years)	75 ± 8
Gender - Female	35.6%
Prior Stroke	27.1%
Prior TIA	10.6%
Heart Failure	17.4%
Diabetes	31.4%
Hypertension	84.2%
Prior History of Major Bleeding	72.5%
CHA_2DS_2-VASc Score $\geq$ 4	65%
HAS-BLED $\geq$ 3	58%

Results: Indication for Procedure (N = 610)



18% of patients on (N)OAC at time of consent

Implant Procedure

Imaging modality	% (n)
Intracardiac echo	10% (107)
Transoesophageal echo	90% (966)

Device Selection	% (n)
First device selected implanted	93% (995)

Implant Success

Implant	No.	%
Implant Success Defined as successful implantation of the Amulet device in the LAA.	**1060/1073**	**98.8%**

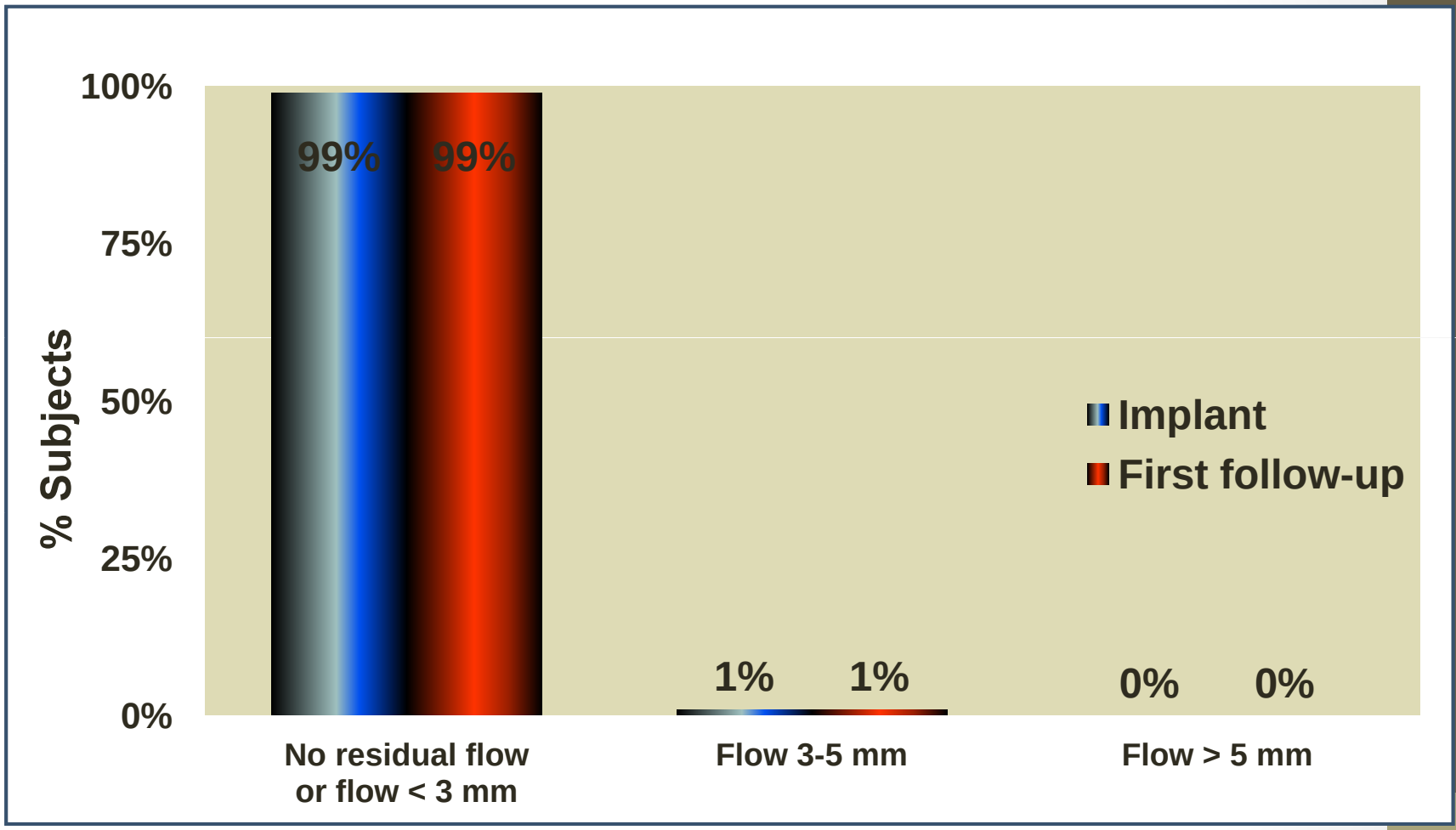
Major Adverse Events

Device/Procedure Related MAE	No.	%
Death	3	0.3%
Related to Cardiac Perforation	*1*	*0.1%*
Related to Myocardial Infarction	*1*	*0.1%*
Related to Cardiorespiratory Arrest	*1*	*0.1%*
Stroke	3	0.3%
Pericardial Effusion	5	0.5%
Resulted in Pericardiocentesis	*4*	*0.4%*
Resulted in Surgical Intervention	*1*	*0.1%*
Embolization	1	0.1%
Bleeding	10	0.9%
Other	7	0.7%
TOTAL	**29**	**2.7%**

Antiplatelet and Anticoagulant therapy
(1-3 months F/U)

	Baseline N = 1073	Discharge N = 1058	1-3 Month F/U N = 719
None	40.6%	14.7%	6.5%
Single Antiplatelet	20.5%	23.8%	31.3%
Dual Antiplatelet	14.4%	41.8%	45.6%
(N)OAC only	15.8%	7.3%	4.7%
(N)OAC plus Single Antiplatelet	1.5%	1.9%	1.3%
Triple Therapy	0.7%	2.2%	2.4%

TEE verified LAA Closure Rate



Comparison to Other Studies

	ACP Registry[1]	Watchman EWOLUTION[2]	Amulet (Current Study)
Implant Success	97.3%	98.5%	98.8%
LAA Closure Rate (1-3 months) ≤ 5 mm	98.1%	99.3%	100.0%
Device or Procedure-Related Complications	5.0%	2.7%	2.7%
Early Mortality	0.8% (30-day)	0.7% (30-day)	0.3% (7-day)

[1] Tzikas et al. EuroIntervention. 2015;10

[3] Boersma et al. Eur Heart J. 2016 Aug;37(31):2465-74.

Conclusions

- The Amplatzer Amulet device has very high technical implant success rates
- Implantation is associated with low rates of peri-procedural and early adverse events
- Amulet demonstrated high closure rates
- Antiplatelet therapy is appears to be a reasonable treatment strategy post-implantation in the short-term
- Additional long-term data will be collected to confirm these promising early findings

SJM Amulet Trial Highlights

https://clinicaltrials.gov/ct2/show/NCT02879448?term=amulet&rank=1

1. **Enrollment – 1:1 randomization of 1600 pts @ 150 sites**
2. **Efficacy endpoints**
   a. **Ischemic stroke or systemic embolism**
   b. **Device closure at 45 days**
3. **Safety composite endpoint**
   - **All cause death; or**
   - **Major bleeding; or**
   - **Procedure and device related complications requiring percutaneous or surgical intervention**
4. **Inclusion highlights:**
   a. **$CHADS_2$>2 or CHA_2DS_2-VASc>3**
   b. **Suitable for short term warfarin therapy but unable to take long term oral anticoagulation following the conclusion of shared decision making**
   c. **Deemed suitable for LAA closure by a multidisciplinary team of medical professionals (including an independent non-interventional physician) involved in the formal and shared decision making process, and by use of an evidence-based decision tool on oral anticoagulation**
5. **Exclusion: Chronic P2Y12 platelet inhibitor therapy**
6. **Adjunctive Pharma**
   - **Watchman: per IFU**
   - **Amulet: 0 – 45 days, aspirin and either clopidogrel or any approved OAC**

ASAP-TOO

https://clinicaltrials.gov/ct2/show/NCT02928497?term=NCT02928497

- Patients (N=888) deemed by 2 physicians unsuitable for oral anti-coagulation therapy.
- Randomized 2 Watchman vs. 1 Control (single antiplatelet or no tx)
- Sequential Design Allows early looks; potential to stop early for benefit

Device Group Pharma

Visit Interval	Aspirin	Clopidogrel
0 – 3 months	Yes, 75 – 100 mg	Yes 75 mg
3 – 12 months	Yes, 75 – 100 mg	No, unless other indication
> 12 months	No, unless other indication	No, unless other indication

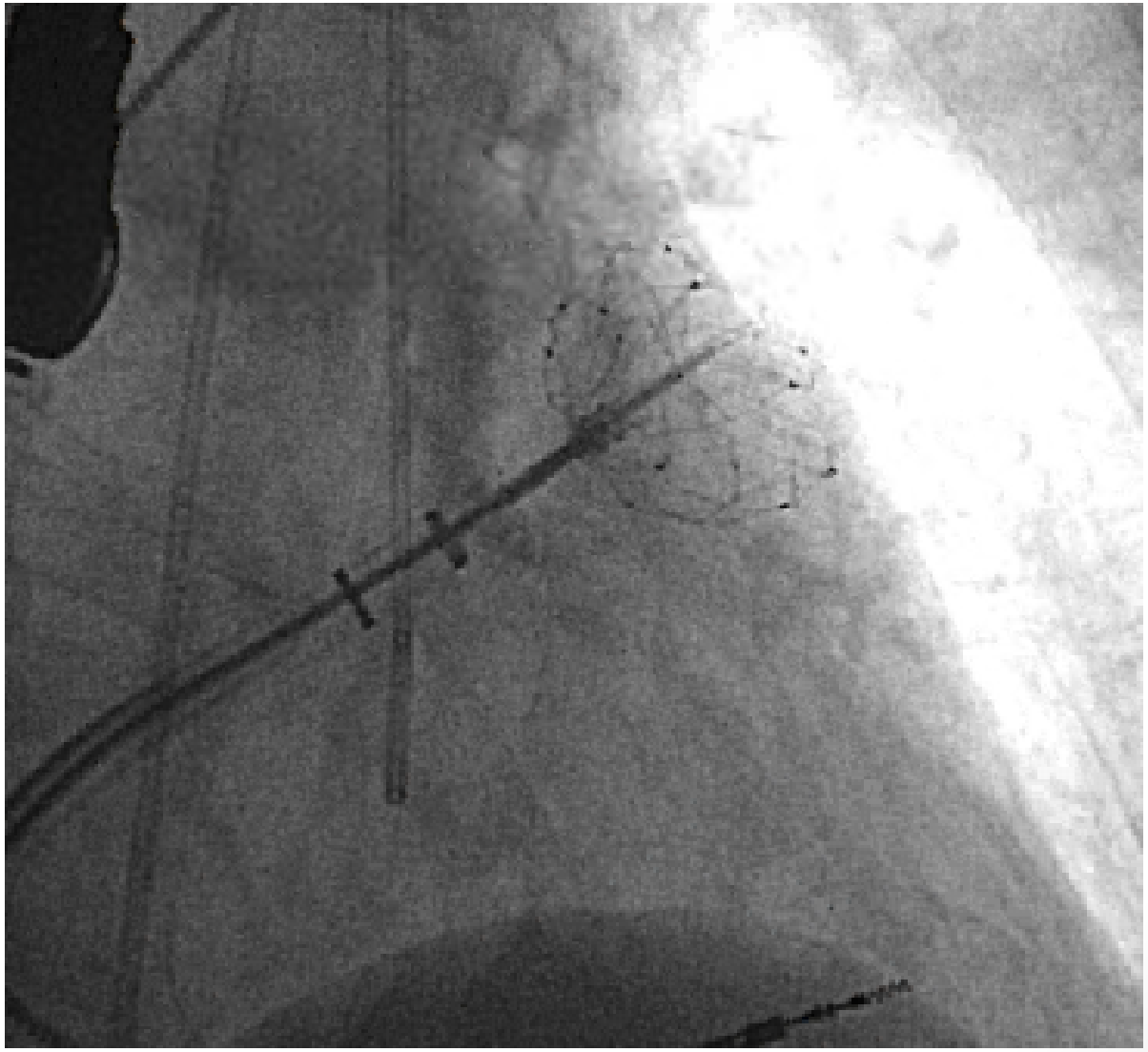
Potential pivotal data

- Define the absolute benefit of LAA closure.
- Evidence of no OAC transition and longterm LAA occlusion without antiplatelet tx
- Extend benefit to CHA_2DS_2-VASc ≥ 2

However, Many physicians have declined participation

- Difficult to define population that can tolerate DAPT but not 6 wks OAC
- Ethics of withholding therapy in high stroke risk patients

WAVECREST:



WAVECREST II

Pivotal IDE Approval Trial

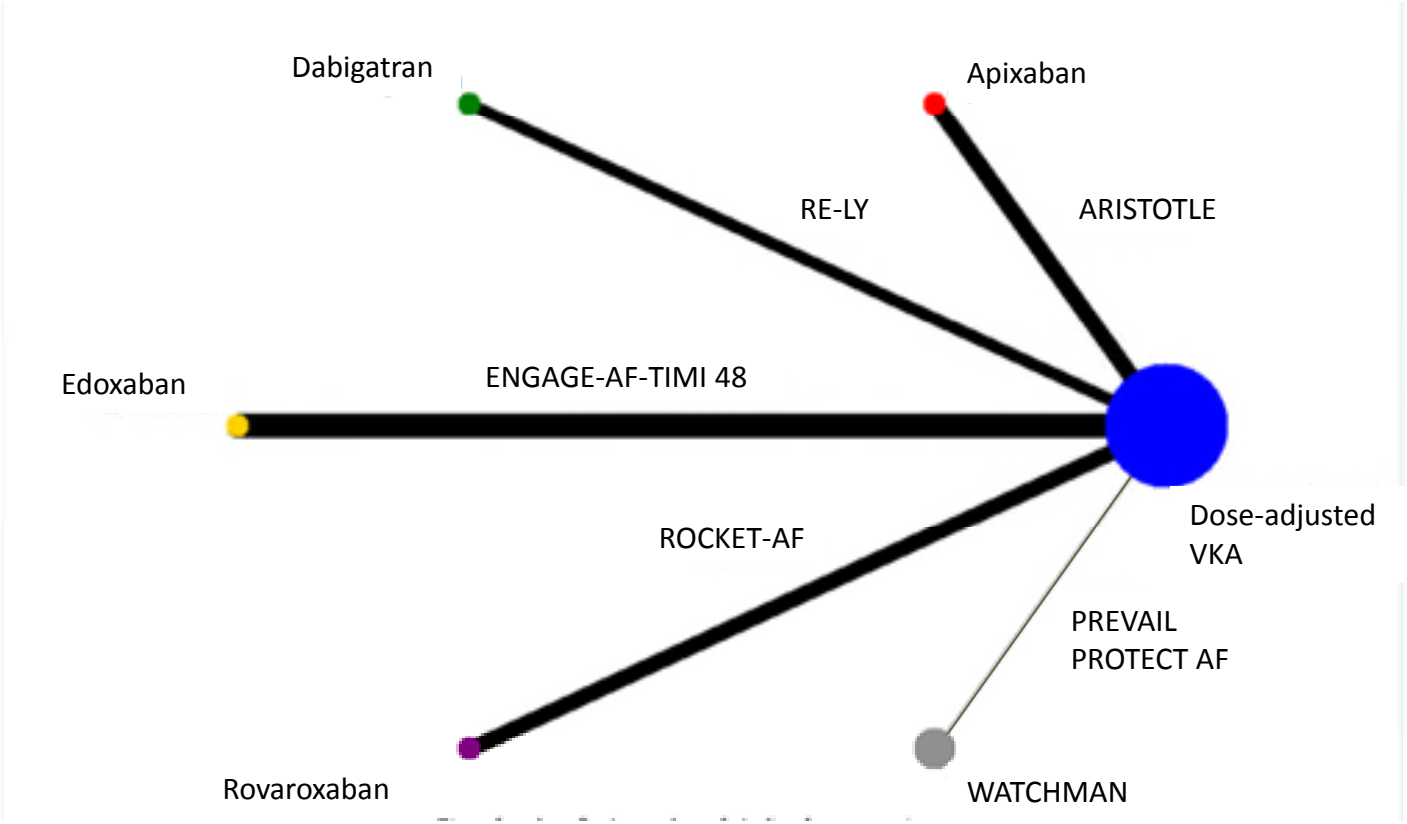
1250 Patients Randomized
(+ up to 5 roll-Ins per site)

625 WaveCrest

625 Watchman

- **Primary effectiveness endpoint:** Ischemic stroke or systemic embolization at 2 years
- **Primary safety endpoint:** All-cause death, procedure or device-related complications requiring percutaneous or surgical intervention through 45 days post-procedure, or major bleeding
- Powered for non-inferiority
- Anticipated start Q1 2017

Network plot for the stroke prophylaxis network



Size of node reflects number of studies for comparison
Thickness of the edge reflects inverse variance for comparison

Bajaj NS et al., PLOS ONE 2016; doi:org/10.1371/journal.pone.0163608

Should the New Oral Anticoagulants Change the Equation vs LAA Closure?

Not until further trials are completed

We HAVE COME A LONG WAY FROM LAAC BEING CONSIDERED A FOOL'S ERRAND TO IT BEING A VIABLE THERAPEUTIC OPTION AND MAY BECOME THE FIRST LINE THERAPY FOR STROKE PROPHYLAXIS IN PATIENTS WITH ATRIAL FIBRILLATION.

THANK YOU