Percutaneous Left Atrial Appendage Occlusion in Patients With Non-valvular Atrial Fibrillation – Are Indications Expanding?

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Disclosures

Sponsored Research
- SJM

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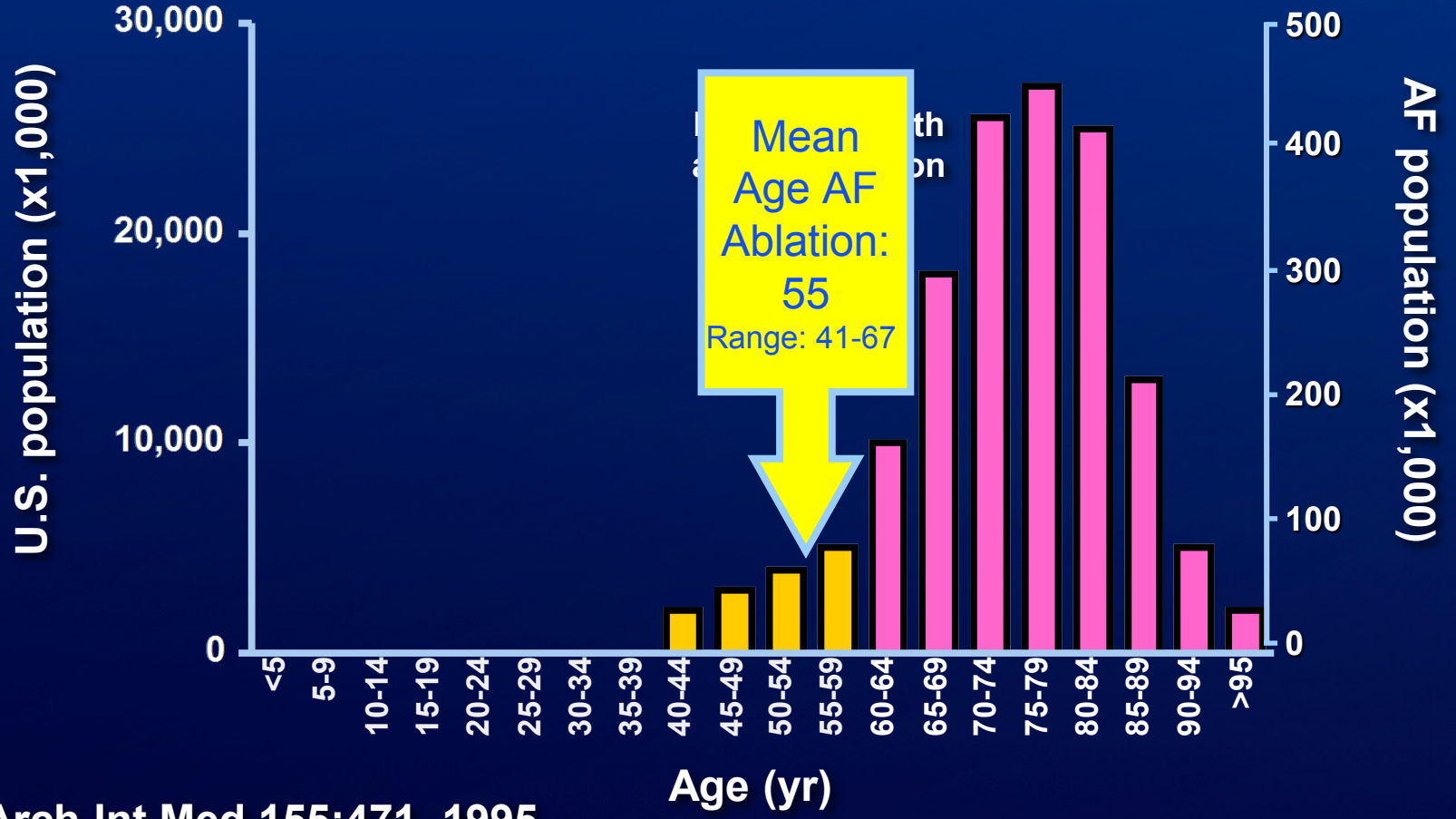
Age Distribution of People with AF



Arch Int Med 155:471, 1995

Meta-analysis AF trials, Calkins, Circ Arrhythm 2009
Including >6900 patients

CHA_2DS_2VASc Score and Stroke Rate

Risk factor	Score
Congestive heart failure/ LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease	1
Age 65-74	1
Sex category (ie, female sex)	1
Maximum score	9

Adjusted Stroke Rate According to CHA2DS2-VASc score

CHA2DS2VASc score	Pt (n=7,329)	Adjusted stroke rate (%/yr)
0	1	0
1	422	1.3
2	1,230	2.2
3	1,730	3.2
4	1,718	4.0
5	1,159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

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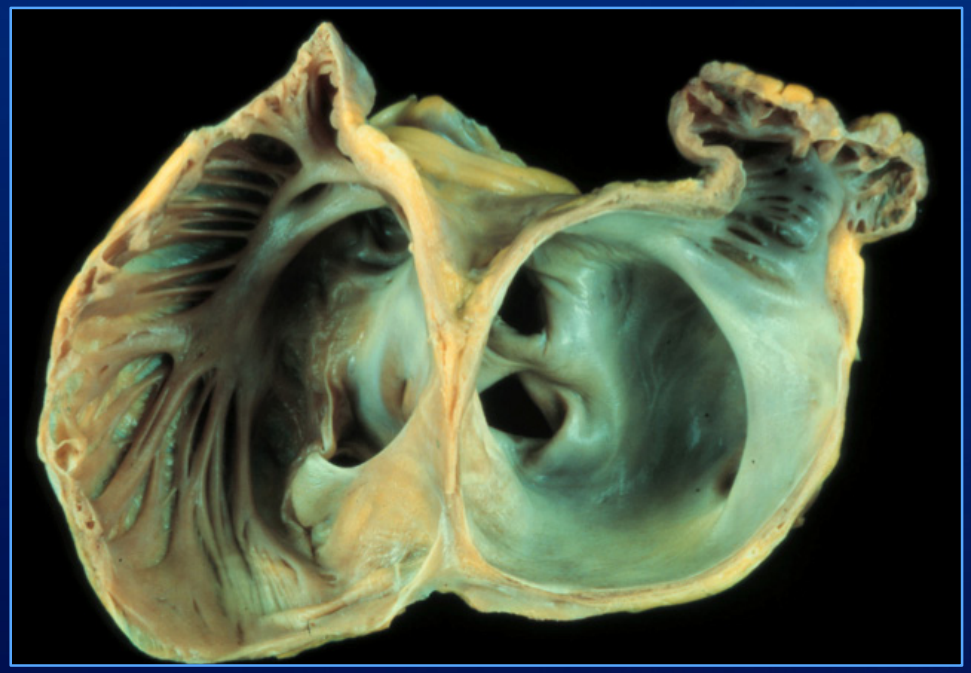
Anticoagulants – Tested in Trials With >60,000 Patients for Stroke Prevention

Bleeding rates

- Major 2-3 %
- Any 15-25%

Discontinuation rates

- 20-25% in major studies



Concept: Avoid “systemic” complications by using “local” approach: & 100% adherence

Possibly control AF?

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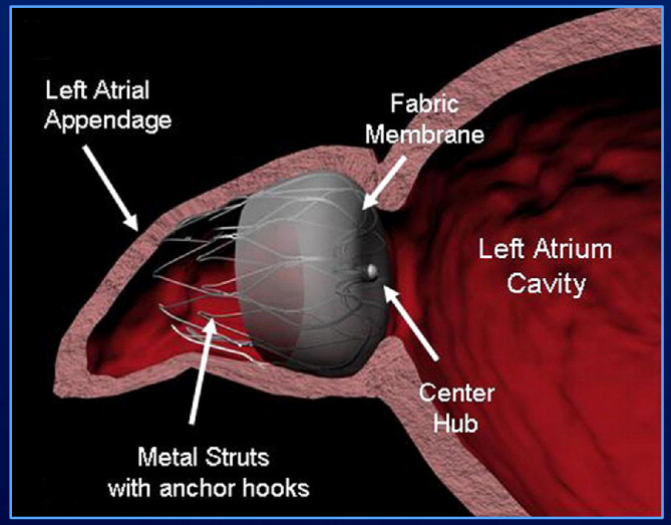
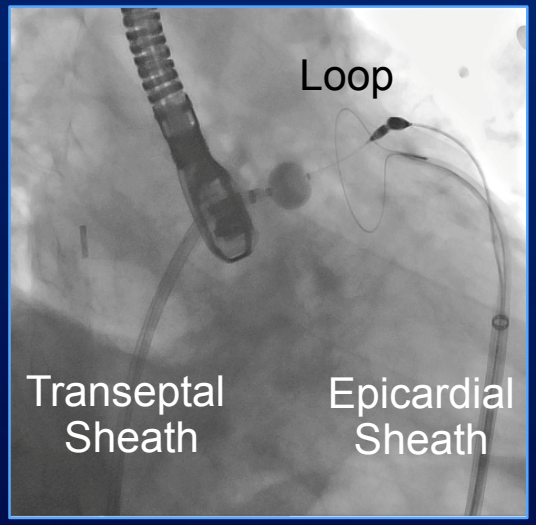
Types of Percutaneous Appendage Closure

Endocardial Plug



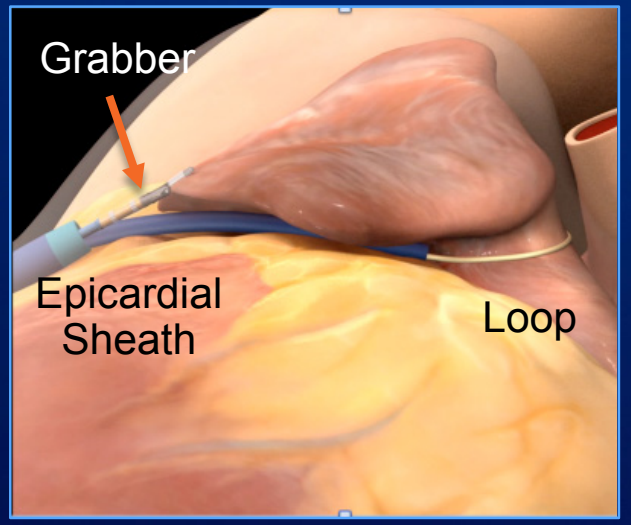
Watchman
WaveCrest
Amplatzer Cardiac Plug

Hybrid Endo/Epi Loop



Lariat

Epicardial Loop



Aegis

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Professional Society Recommendations

Europace (2014) **16**, 1397–1416
doi:10.1093/europace/euu174

EHRA/EAPCI CONSENSUS STATEMENT

EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion

Bernhard Meier (EAPCI Chairperson) (Switzerland)[1], Yuri Blaauw (The Netherlands)[2], Ahmed A. Khattab (Switzerland)[1], Torsten Lewalter (Germany)[3], Horst Sievert (Germany)[4], Claudio Tondo (Italy)[5], Michael Glikson (EHRA Chairperson) (Israel)[6]*

Document Reviewers: Gregory Y. H. Lip (UK), Jose Lopez-Minguez (Spain), Marco Roffi (Switzerland), Carsten Israel (Germany), Dariusz Dudek (Poland), Irene Savelieva (on behalf of EP-Europace, UK)

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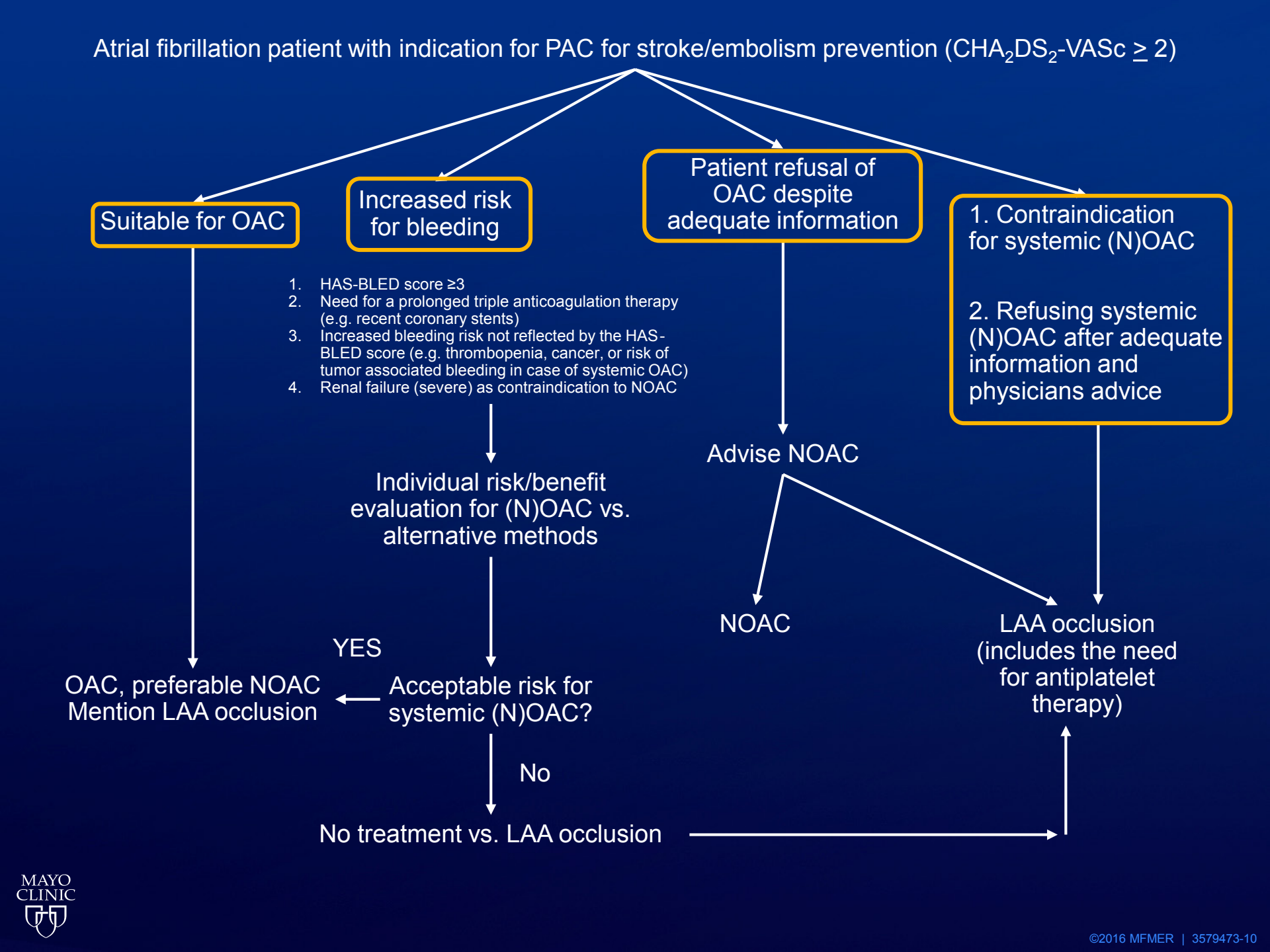
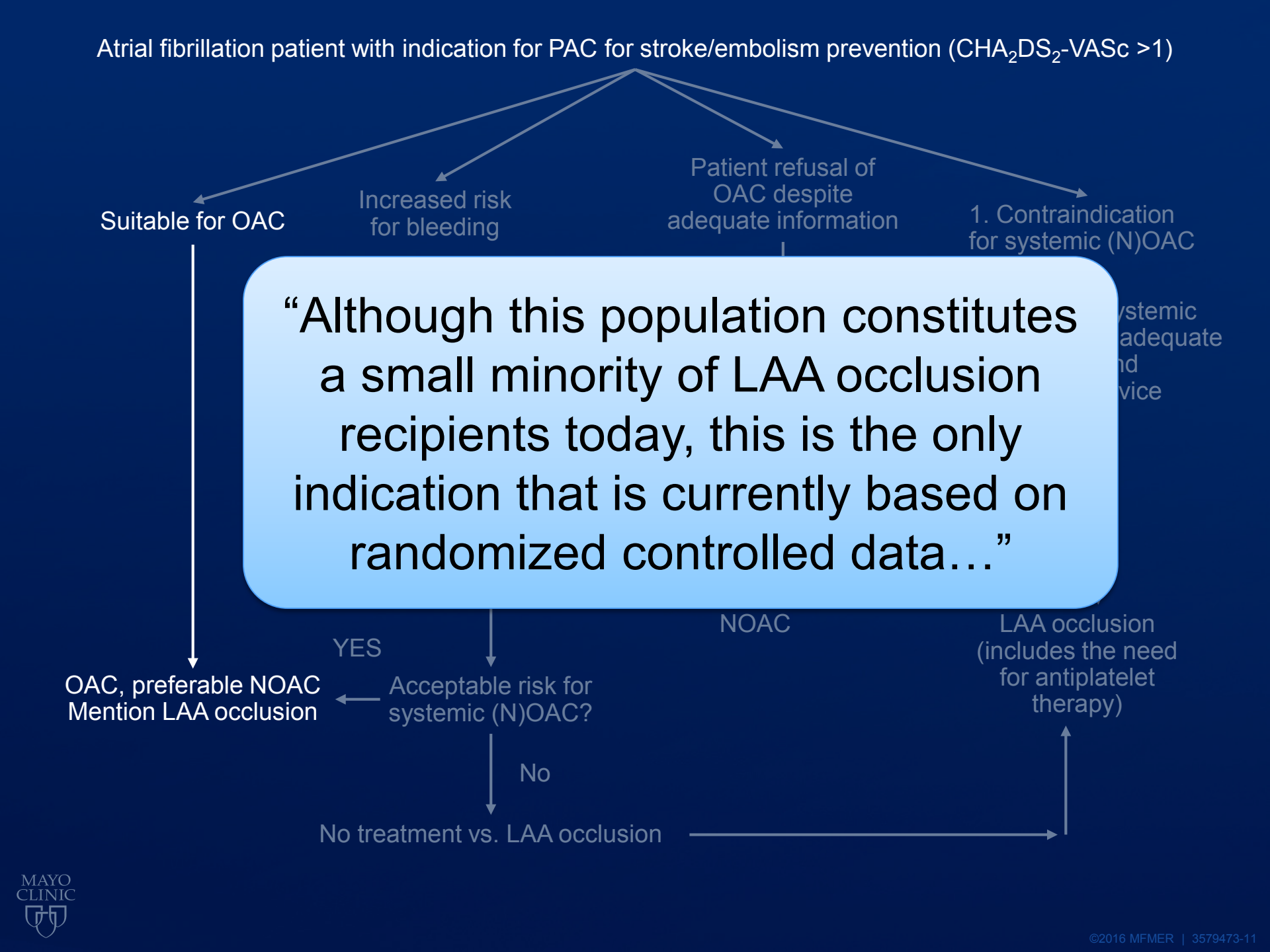
Published online August 29, 2014





Studies of Watchman LAA Closure For **Stroke Prevention** Patient-Level Meta-analysis

PROTECT AF and CAP: Largest Data Sets to Evaluate Totality of Data

	PROTECT AF	PREVAIL	CAP	CAP2	Total
Enrollment	2005-2008	2010-23012	2008-2010	2012-2014	
Enrolled	800	761	566	579	2,406
Randomized	707	407	–	–	1,114
Watchman: warfarin (2:1)	463:244	269:138	566	579	1,877: 382
Mean follow-up (yr)	4.0	2.2	3.7	0.58	N/A
Patient-years	2,717	860	2,022	332	5,931

Warfarin 45 days; ASA + plavix to day 180; ASA

Holmes et al JACC 65(24)2614, 2015

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Patient Demographics Across Trials

	PROTECT AF n=707	PREVAIL n=407	CAP n=566	CAP2 n=579
Age (yr)	72.0±8.9	74.3±7.4	74.0±8.3	75.3±8.0
Male	70.3	70.0	65.5	61.0
Ethnicity/race				
Asian	0.7	0.5	1.6	0.7
Black/African American	1.6	1.7	1.9	1.2
White/Caucasian	91.5	94.4	91.9	94.1
Hispanic/Latino	5.7	2.7	3.5	2.1
Other	0.6	0.7	1.1	1.0
$CHADS_2$ score	2.2±1.2	2.6±1.0	2.4±1.2	2.7±11
$CHADS_2$ risk factors				
CHF	26.9	19.1	23.3	27.1
Hypertension	89.8	88.8	91.4	92.5
≥75 yrs of age	43.1	51.8	53.6	59.7
Diabetes	26.2	24.9	32.4	33.9
Stroke/transient ischemic attack	18.5	30.4	27.8	29.0
CHA_2DS_2-VASc	3.5±1.6	4.0±1.2	3.9±1.5	4.5±1.3
HAS-BLED = 0 (low risk)	6.4	1.7	2.8	2.8
HAS-BLED = 1.2 (moderate risk)	73.7	68.6	61.0	69.9
HAS-BLED = 3+ (high risk)	19.9	29.7	36.2	28.3

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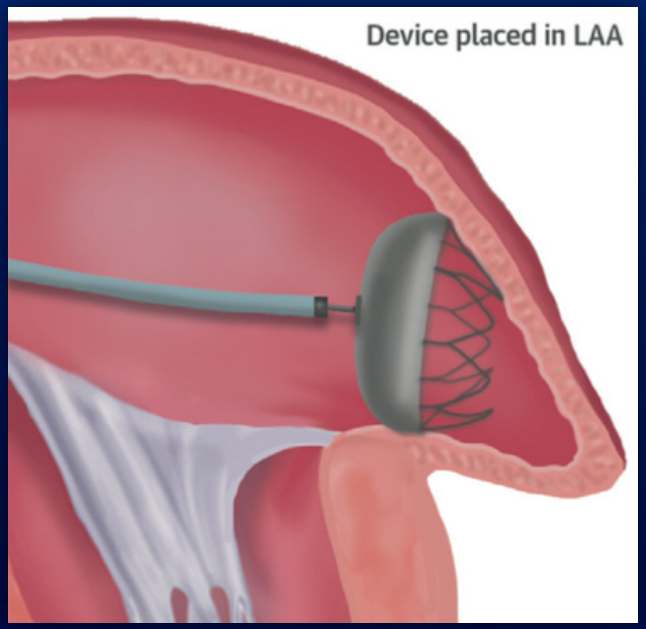
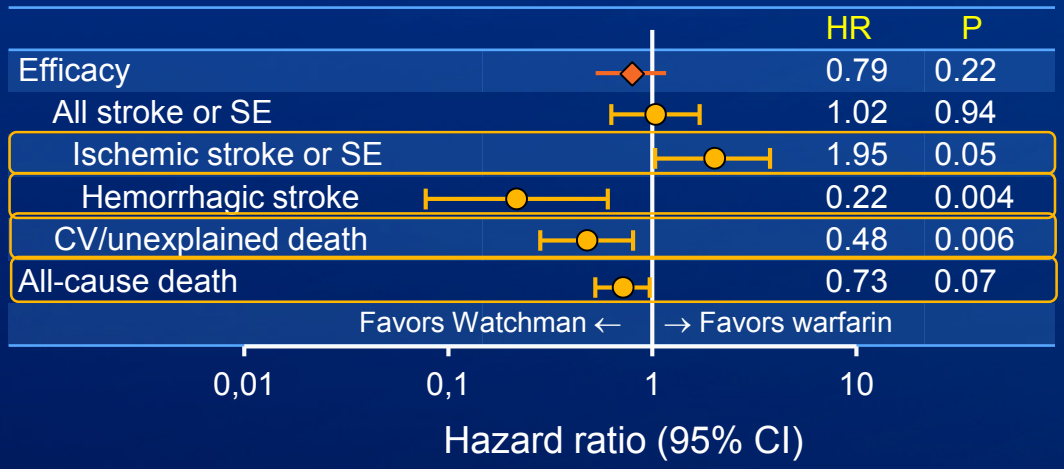
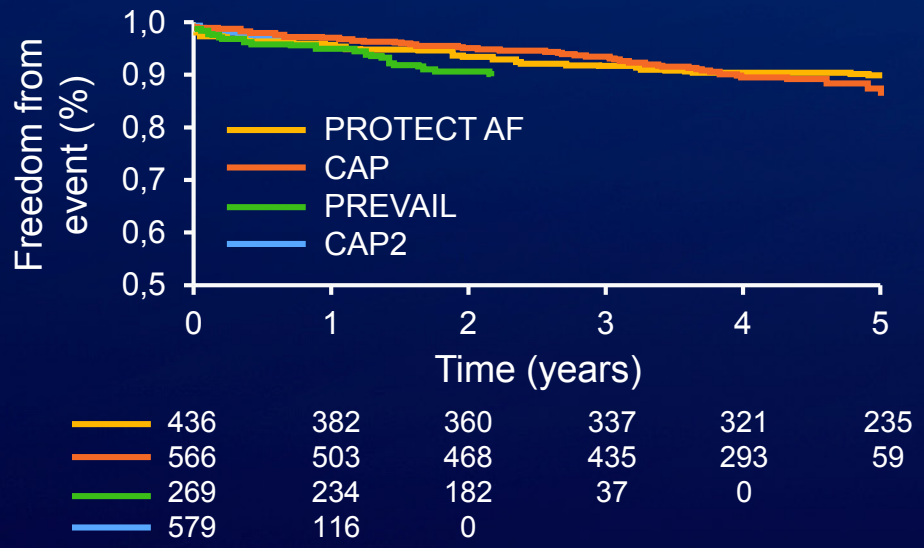
LAA Closure: Patient-Level Meta-Analysis

Stroke Prevention in Nonvalvular Atrial Fibrillation With LAA Closure







Holmes DR et al: J Am Coll Cardiol 65(24):2614, 2015

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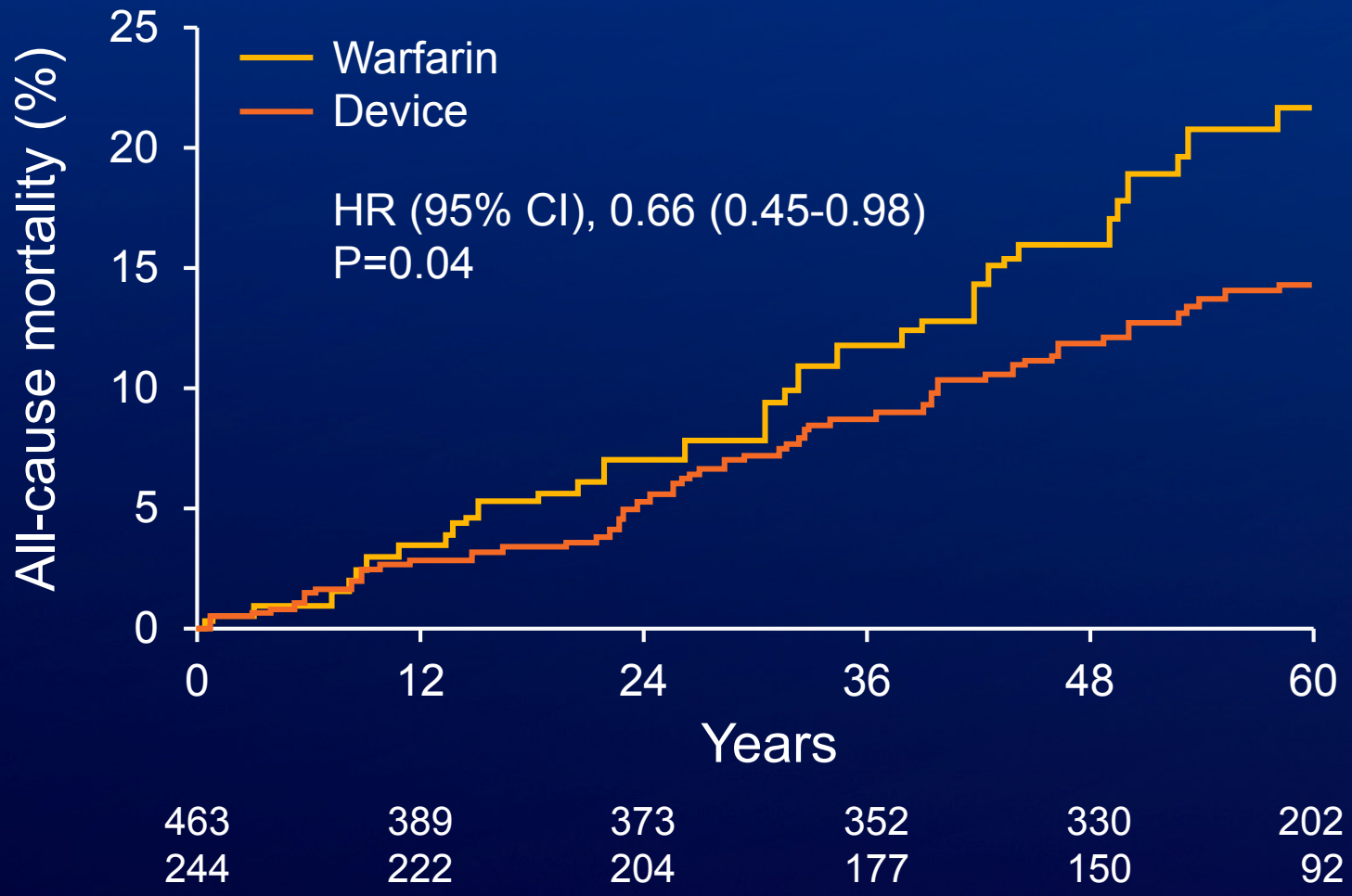
All Cause Mortality: 4 Year Follow-Up



Reddy et al: JAMA 312(19):1988, 2014

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US FDA Approved Indication

- This device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:
  - Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2 VASc scores and are recommended for anticoagulation;
  - 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.

http://www.accessdata.fda.gov/cdrh_docs/pdf13/p130013a.pdf (March 13, 2015)

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Cumulative Device Experience

Procedural complications reduced since PROTECT AF, and similar to registry experience

	PROTECT AF device group n/attempted (%)	CAP registry n/attempted (%)	PREVAIL device group n/attempted (%)
Implant success	408/449 (90.9)	534/566 (94.3)	252/265 (95.1)
Procedure related death	0 (0)	0 (0)	0 (0)
Procedure related ischemic stroke	5/449 (1.1)	0/566 (0.0)	1/265 (0.4)
Cardiac perforation (surgical repair)	7/449 (1.6)	1/566 (0.2)	1/265 (0.4)
Pericardial effusions with tamponade (pericardiocentesis)	13/449 (2.9)	7/566 (1.2)	4/265 (1.5)
Device embolization	3/449 (0.7)	1/566 (0.2)	2/265 (0.8)

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CMS Approved Indication

- This device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who
  - A $CHADS_2$ score ≥ 2 or CHA_2DS^2-VASc score ≥ 3
  - A formal shared decision making interaction with an independent non-interventional physician using an evidence-based decision tool on oral anticoagulation in patients with NVAF prior to LAAC.
  - A suitability for short-term warfarin but deemed unable to take long term oral anticoagulation following the conclusion of shared decision making, as LAAC is only covered as a second line therapy to oral anticoagulants

Decision memo: CAG-00445N (March 13, 2015)

MAYO CLINIC

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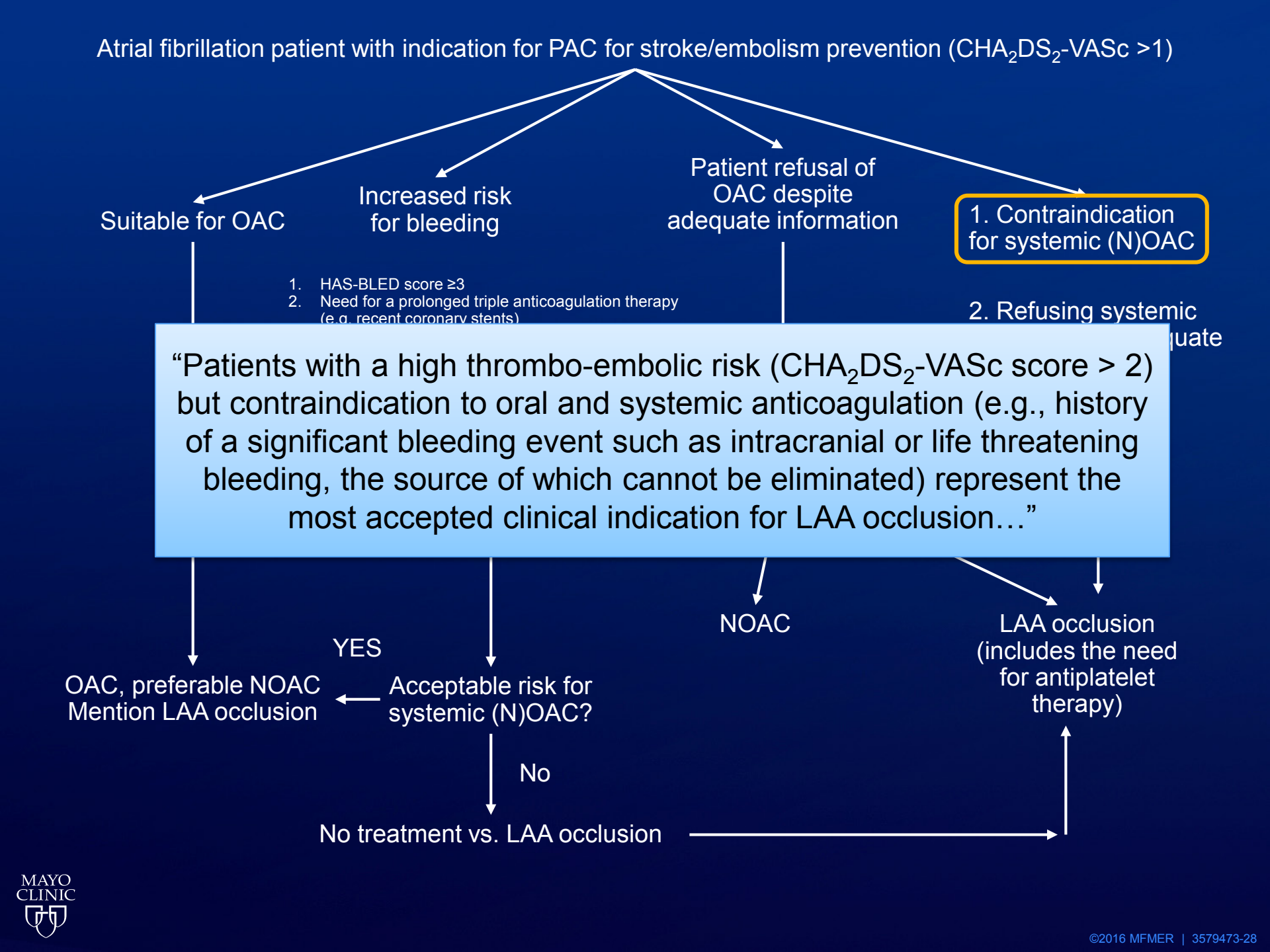
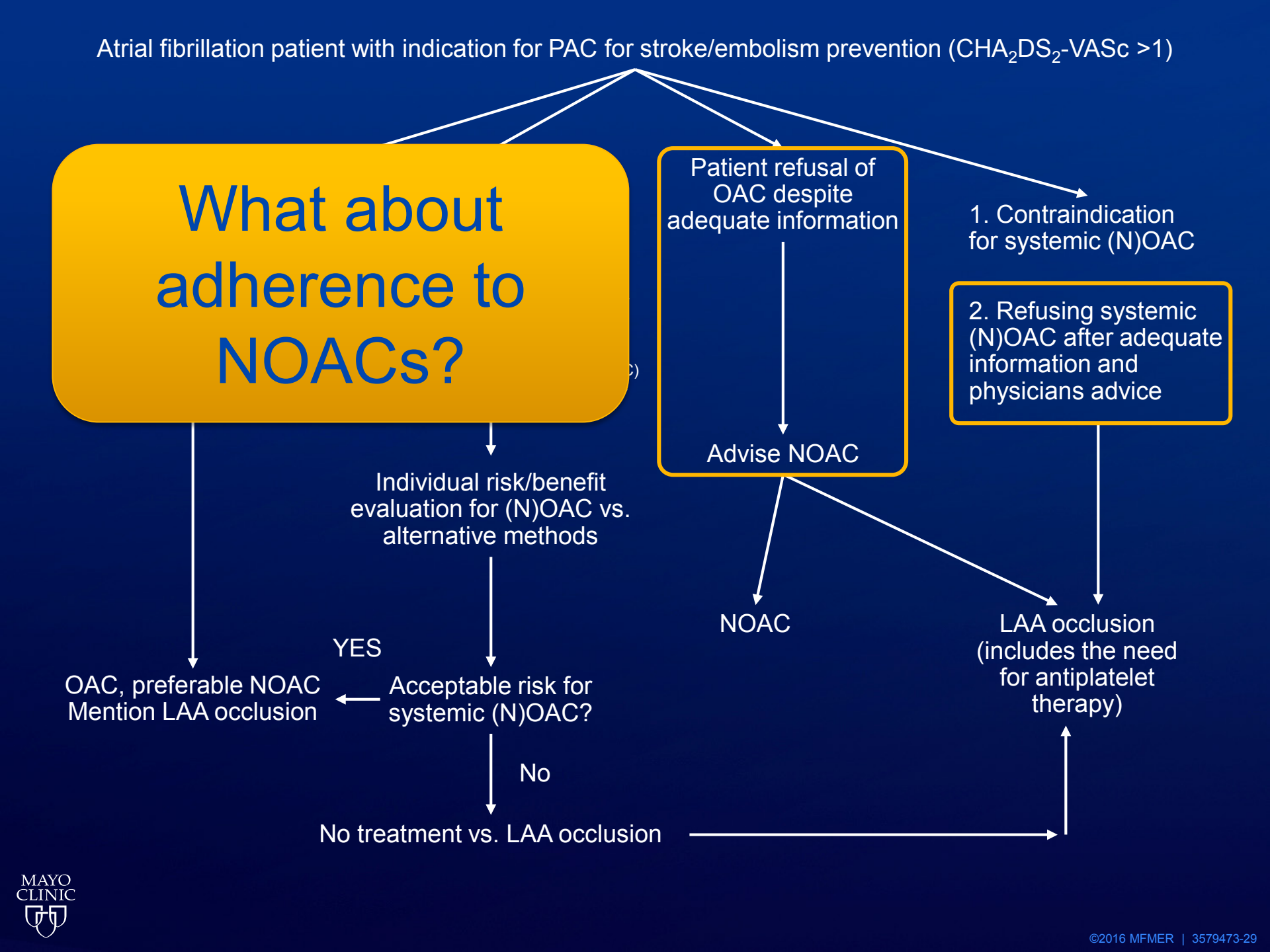
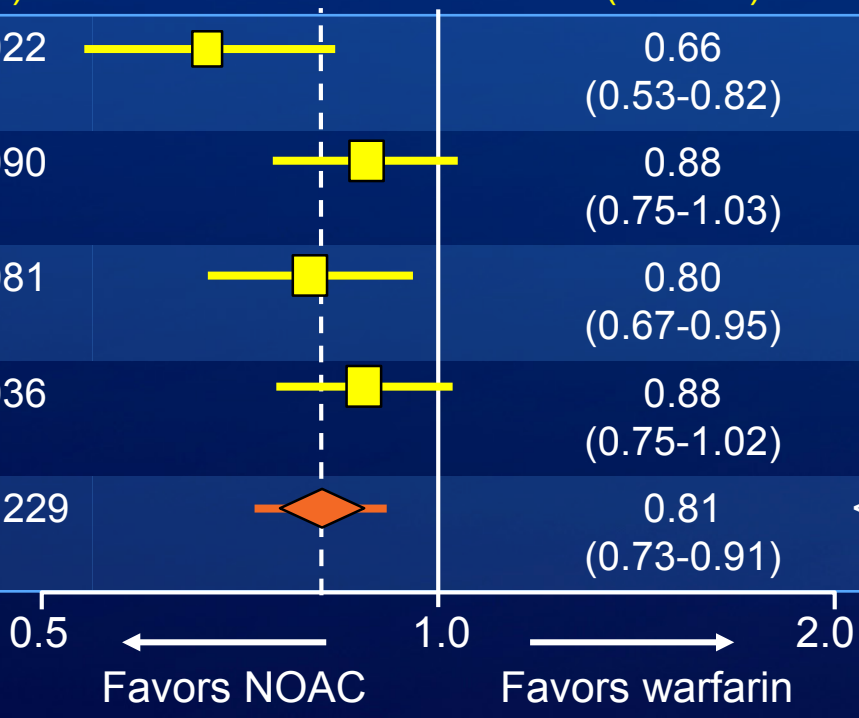




NOACS vs Warfarin
Stroke or Systemic Embolism

	NOAC (events)	Warfarin (events)	RR (95% CI)	P
RE-LY	134/6,076	199/6,022	0.66 (0.53-0.82)	0.0001
ROCKET AF	269/7,081	306/7,090	0.88 (0.75-1.03)	0.12
ARISTOTLE	212/9,120	265/9,081	0.80 (0.67-0.95)	0.012
ENGAGE-TIMI 48	296/7,035	337/7,036	0.88 (0.75-1.02)	0.10
Combined (random)	911/29,312	1,107/29,229	0.81 (0.73-0.91)	<0.0001



Stroke or systemic embolism was significantly reduced in the trials of apixaban (ARISTOTLE) and dabiagtran (RE-LY)

Ruff et al: Lancet, Dec 2013

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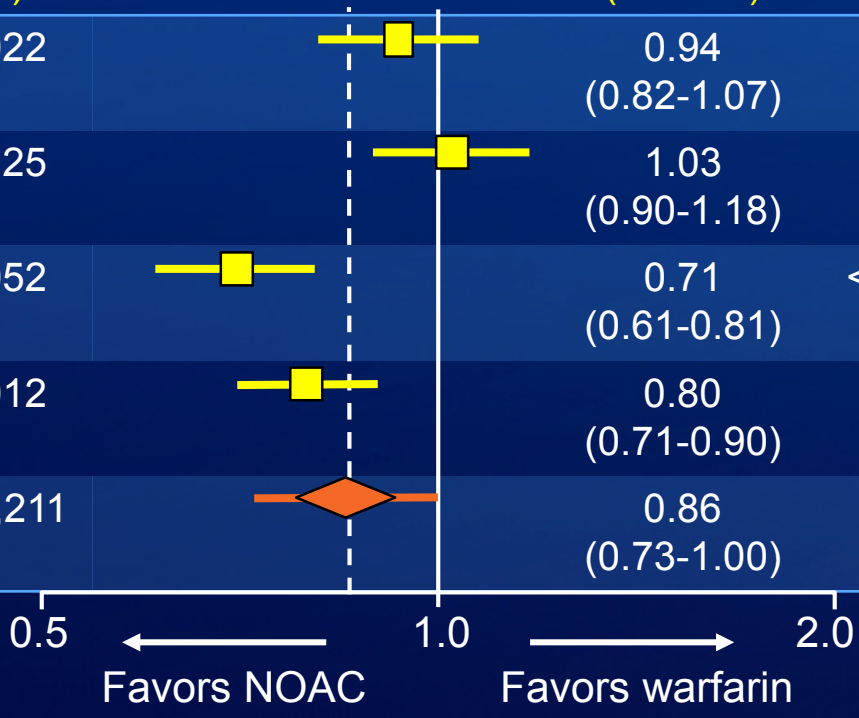
NOACS vs Warfarin
Risk of Major Bleeding

	NOAC (events)	Warfarin (events)	RR (95% CI)	P
RE-LY	375/6,076	397/6,022	0.94 (0.82-1.07)	0.34
ROCKET AF	395/7,111	386/7,125	1.03 (0.90-1.18)	0.72
ARISTOTLE	327/9,088	462/9,052	0.71 (0.61-0.81)	<0.0001
ENGAGE-TIMI 48	444/7,012	557/7,012	0.80 (0.71-0.90)	0.0002
Combined (random)	1,541/29,287	1,802/29,211	0.86 (0.73-1.00)	0.06



Risk of major bleeding was lower in trials of apixaban (ARISTOTLE) and edoxoban (ENGAGE AF)

Ruff et al: Lancet, Dec 2013

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How adherent are patients to NOACs?

- Retrospective analysis of administrative claims data (privately insured and Medicare Advantage enrollees)
- Patients (n=64,661) with atrial fibrillation who initiated treatment with warfarin, dabigatran, rivaroxaban, or apixaban between November 1, 2010 and December 31, 2014 were identified
- Endpoint: adherence ≥80%

	Apixaban n=3900 (%)	Dabigatran n=10,235 (%)	Rivaroxaban n=12,336 (%)	All NOACs n=26,471 (%)	Warfarin n=38,190 (%)	P value (All NOACs Pooled vs Warfarin)
Unadjusted adherence*						
All	61.9	38.5	50.5	47.5	40.2	<0.001
CHA_2DS_2-VASc score 0 or 1	50.1	24.6	36.5	32.6	27.1	<0.001
CHA_2DS_2-VASc score 2 or 3	62.0	40.3	52.8	49.1	38.1	<0.001
CHA_2DS_2-VASc score ≥4	64.0	42.4	53.2	51.1	42.3	<0.001

Yao X et al: J Am Heart Assoc, 2016

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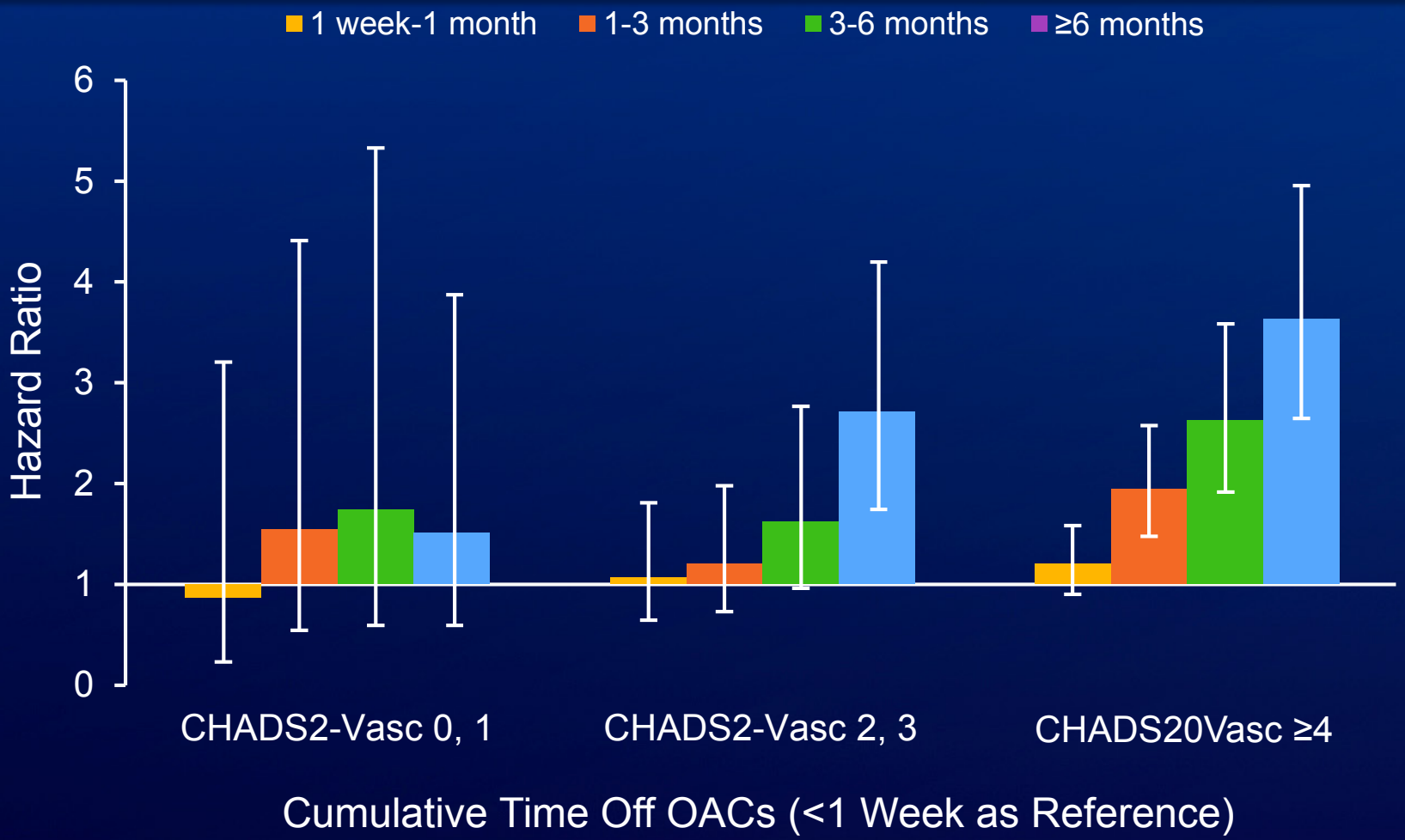
Stroke of Systemic Embolism

Adherence: Warfarin 40.2%, NOAC 47.5% at 1.1 years



Yao X et al: J Am Heart Assoc, 2016

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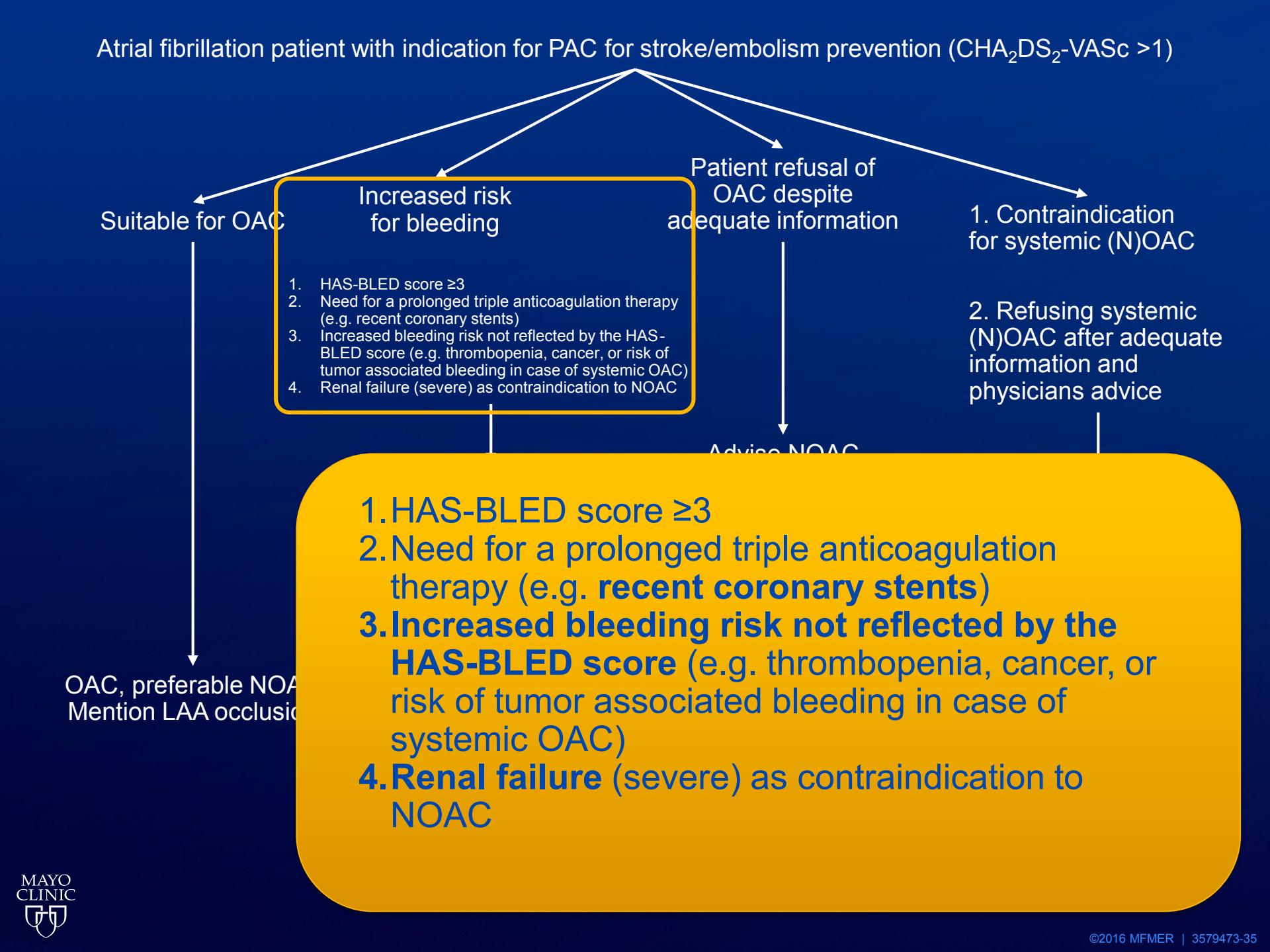

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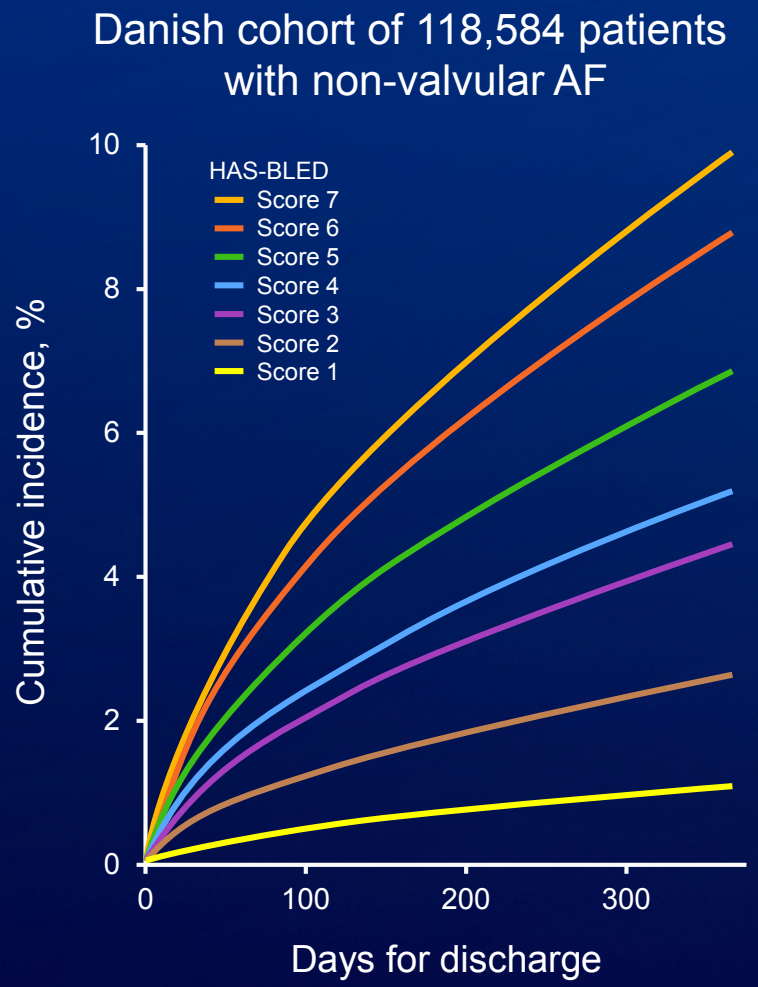
HAS-BLED Score

- H: hypertension
- A: abnormal renal/liver function
- S: stroke
- B: bleeding history
- L: labile INR
- E: elderly
- D: drug consumption/alcohol abuse

1-year bleeding rate on VKA
- 0-1: 2.66% (95% CI: 2.40-2.94)
- 2: 5.54% (95% CI: 5.15-5.96)
- ≥3: 8.11% (95% CI: 7.61-8.64)



Olesen JB et al: J Thromb Haemost 9: 1460, 2011

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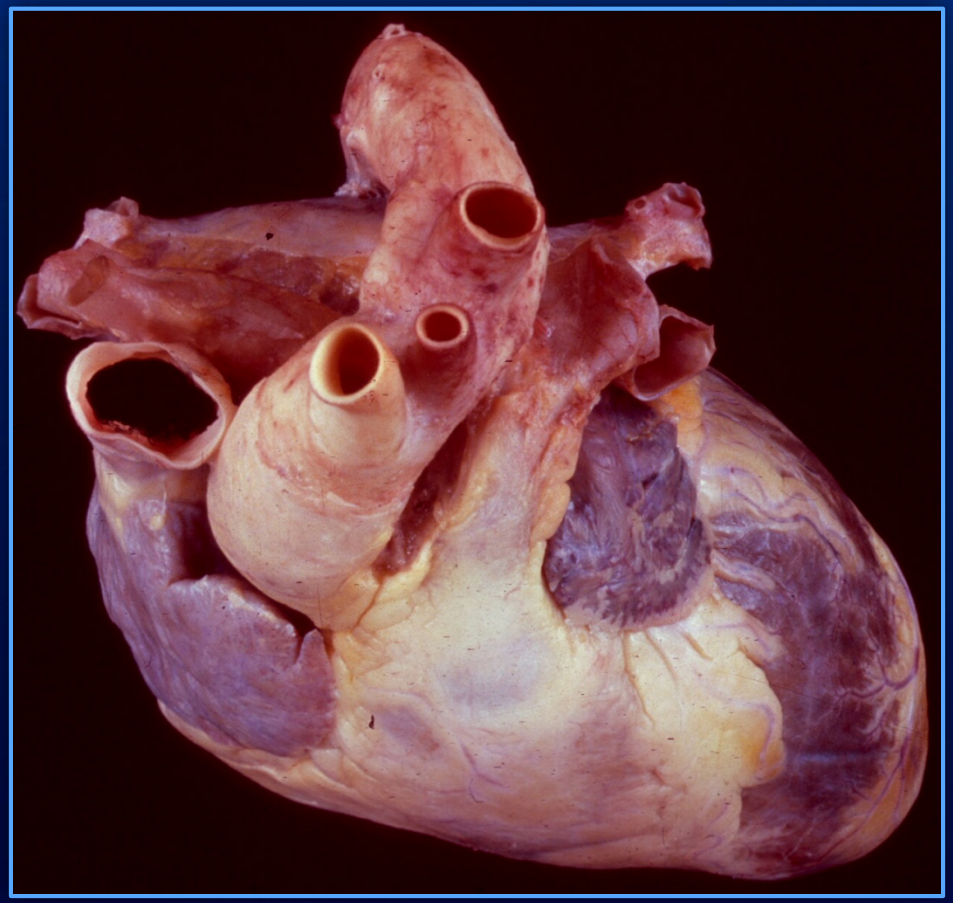
Normal Heart
External Topography



Superior View

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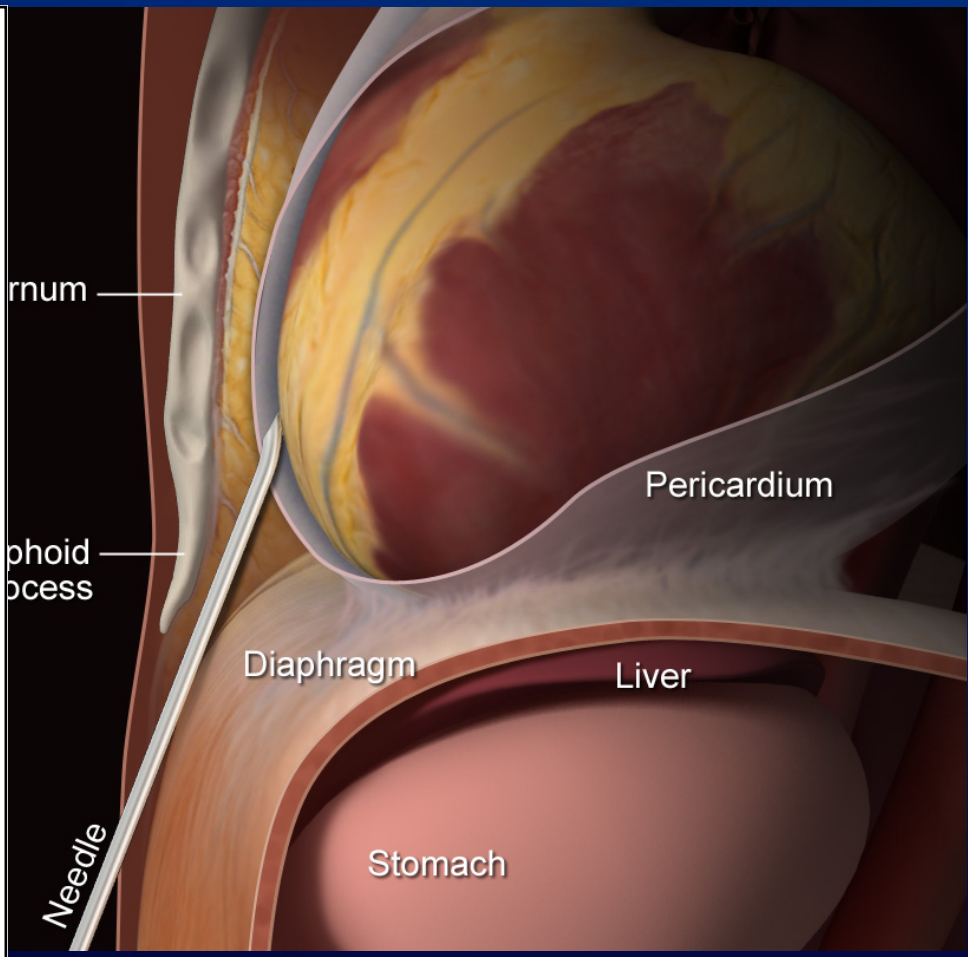
Lateral View – Percutaneous epicardial access

head



feet

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Hybrid:
- No foreign body
- Ostial shape less important
- Post op A/C may not be needed
- May control Atrial Fibrillation

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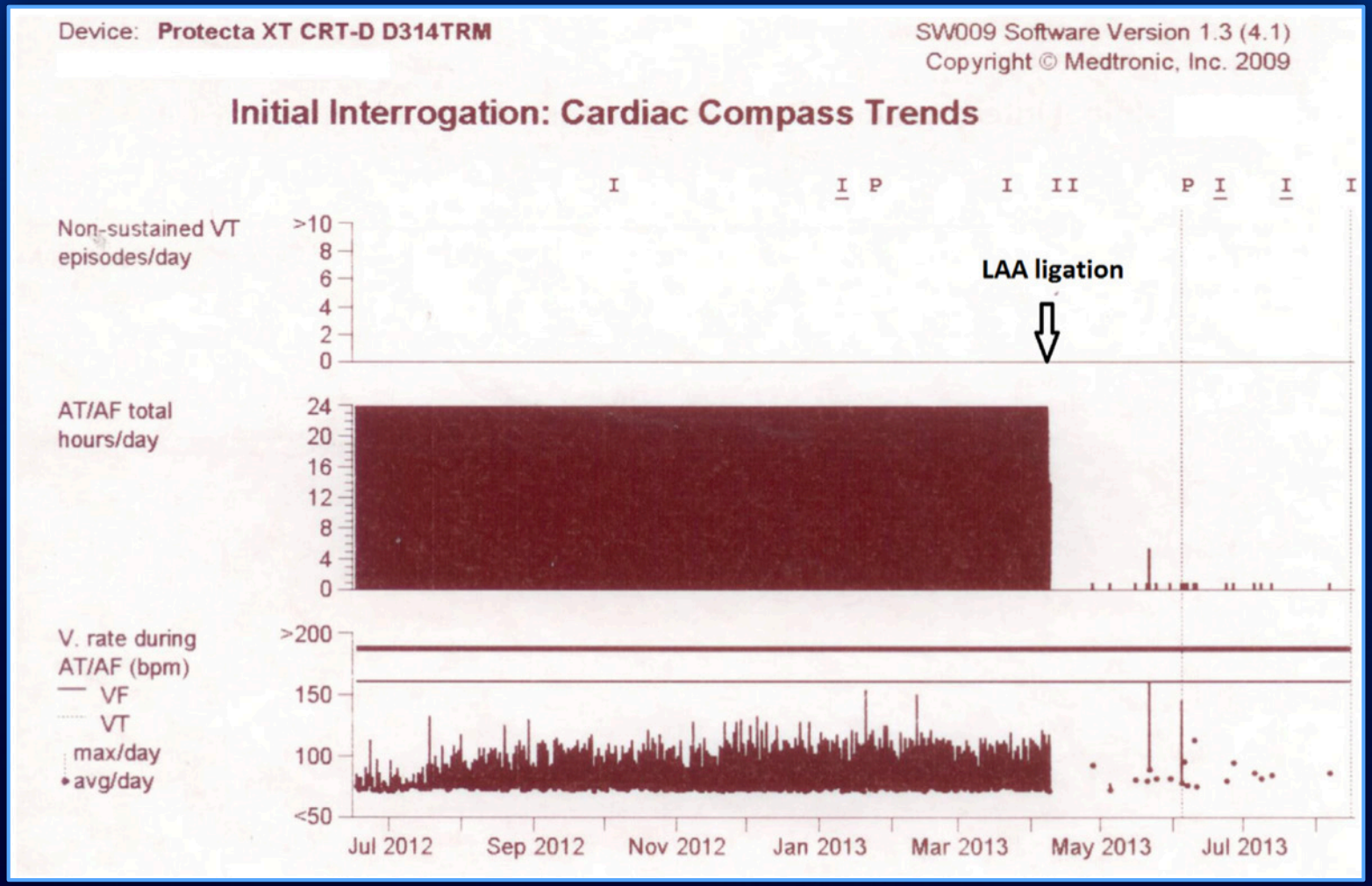
Potential New Indication: AF Control



Afzal et al: Heart Rhythm 2015;12:52-59

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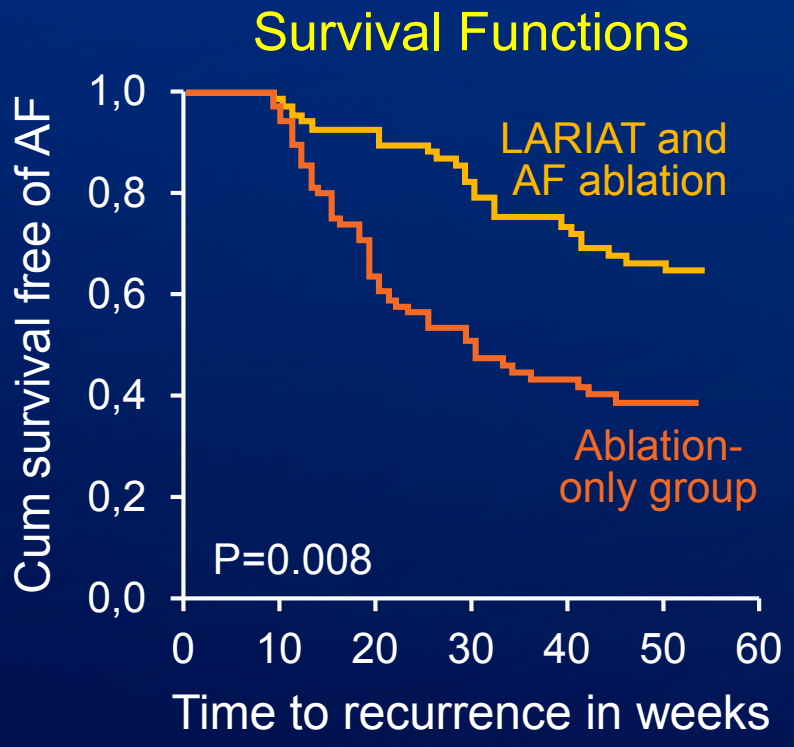
LAALA-AF Registry: Ablation and Ligation

- Prospective observation study
- Persistent AF
- LAA ligation (LARIAT) before AF ablation (n=69)
- Controls: only ablated (n=69)



"In patients with persistent AF, addition of LAA ligation with the LARIAT device to conventional ablation appears to improve the success rate of AF ablation" → AMAZE trial prospectively studying

Lakkireddy et al: J Am Coll Cardiol EP; 1:153, 2015

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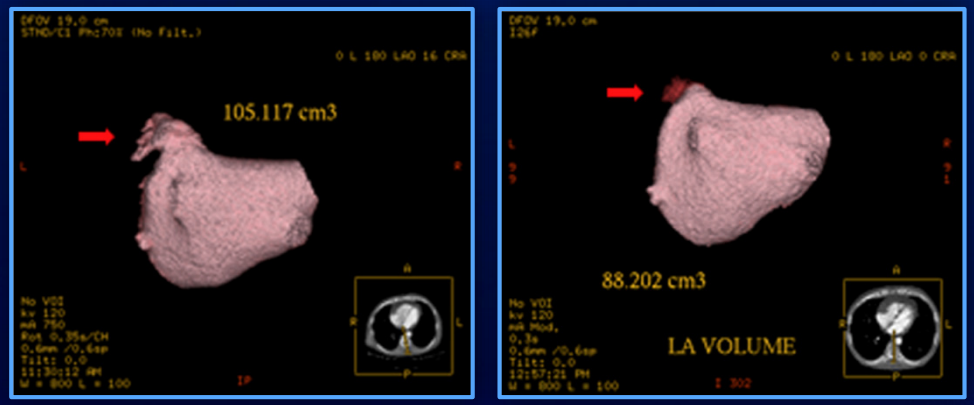
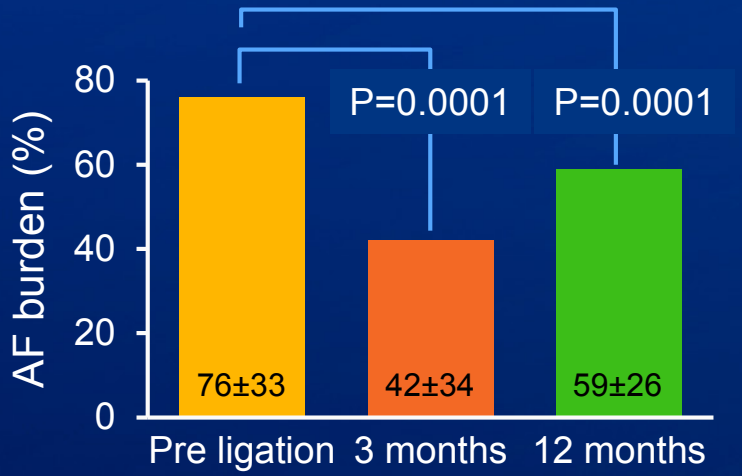
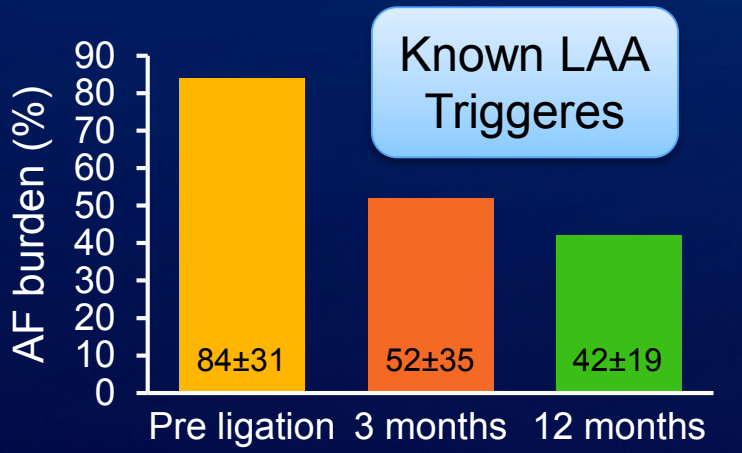
AF Burden Reduction with LAA Ligation

- 50 patients with AF and CIED
- Burden assess baseline, 3 months, 12 months







Afzal et al: Heart Rhythm; 12:52, 2015

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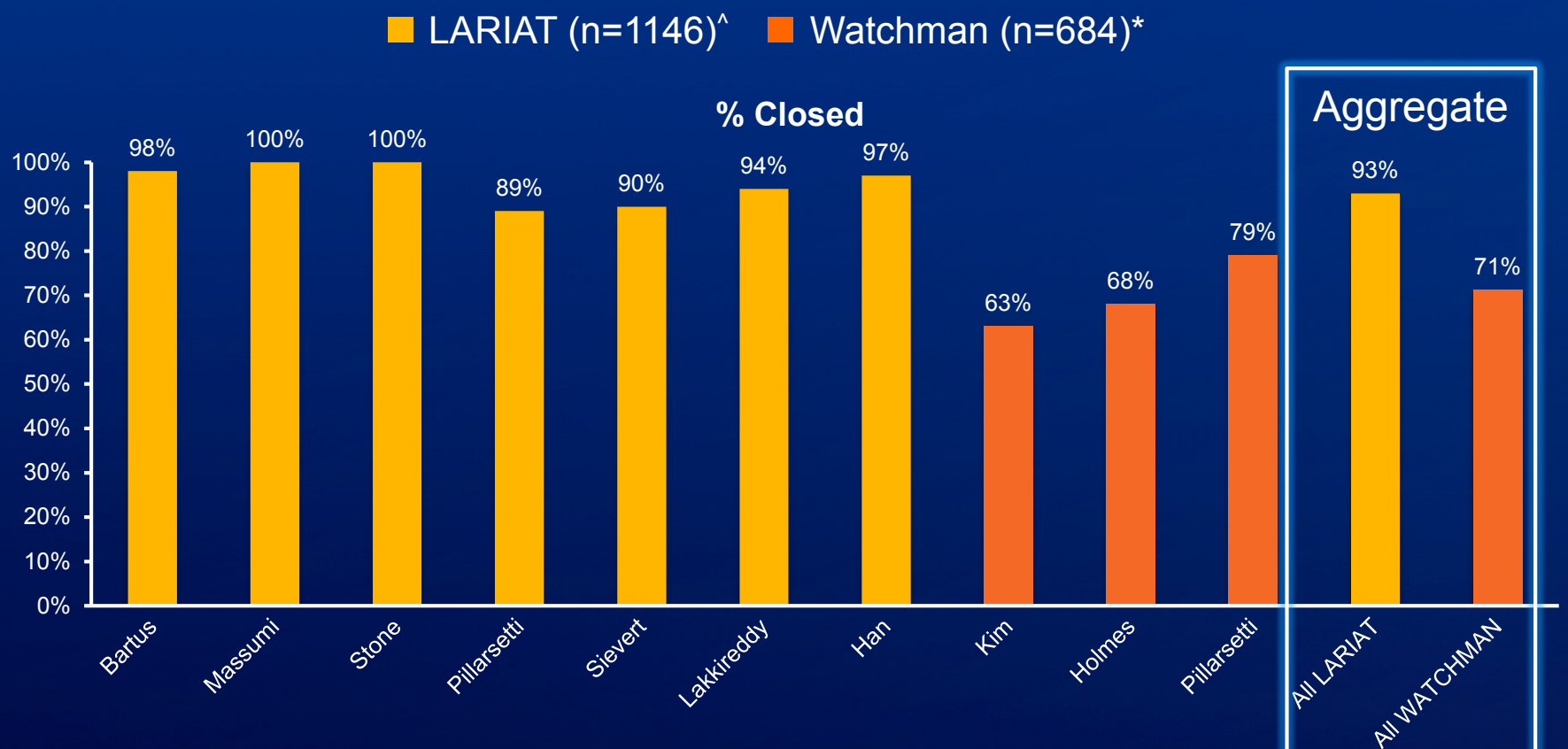
LARIAT vs Watchman Closure Rates



Author	Bartus[7]	Massumi[5]	Stone[6]	Pillarsetti[11]	Sievert[9]	Lakkireddy[12]	Han[13]	Kim[20]	Holmes[15]	Pillarsetti[11]	LARIAT	WATCHMAN
% Closed	98%	100%	100%	89%	90%	94%	97%	63%	68%	79%	93%	71%
F/U Period	12m	96d	45d	12m	12m	12m	12m	3m	12m	12m	9m	9m
N=	65	17	22	259	117	480	68	46	419	219	1028	684

- LARIAT left atrial appendage closure is associated with a lower rate of leaks at long-term follow up as compared to Watchman.
- LARIAT is the only LAA closure device where a leak may be corrected.

^LARIAT leak rate data only includes papers that followed >90% of subjects at 1yr

*Watchman leak rate data only includes papers that measured actual leak rates versus Watchman closure success criteria of <5mm leaks

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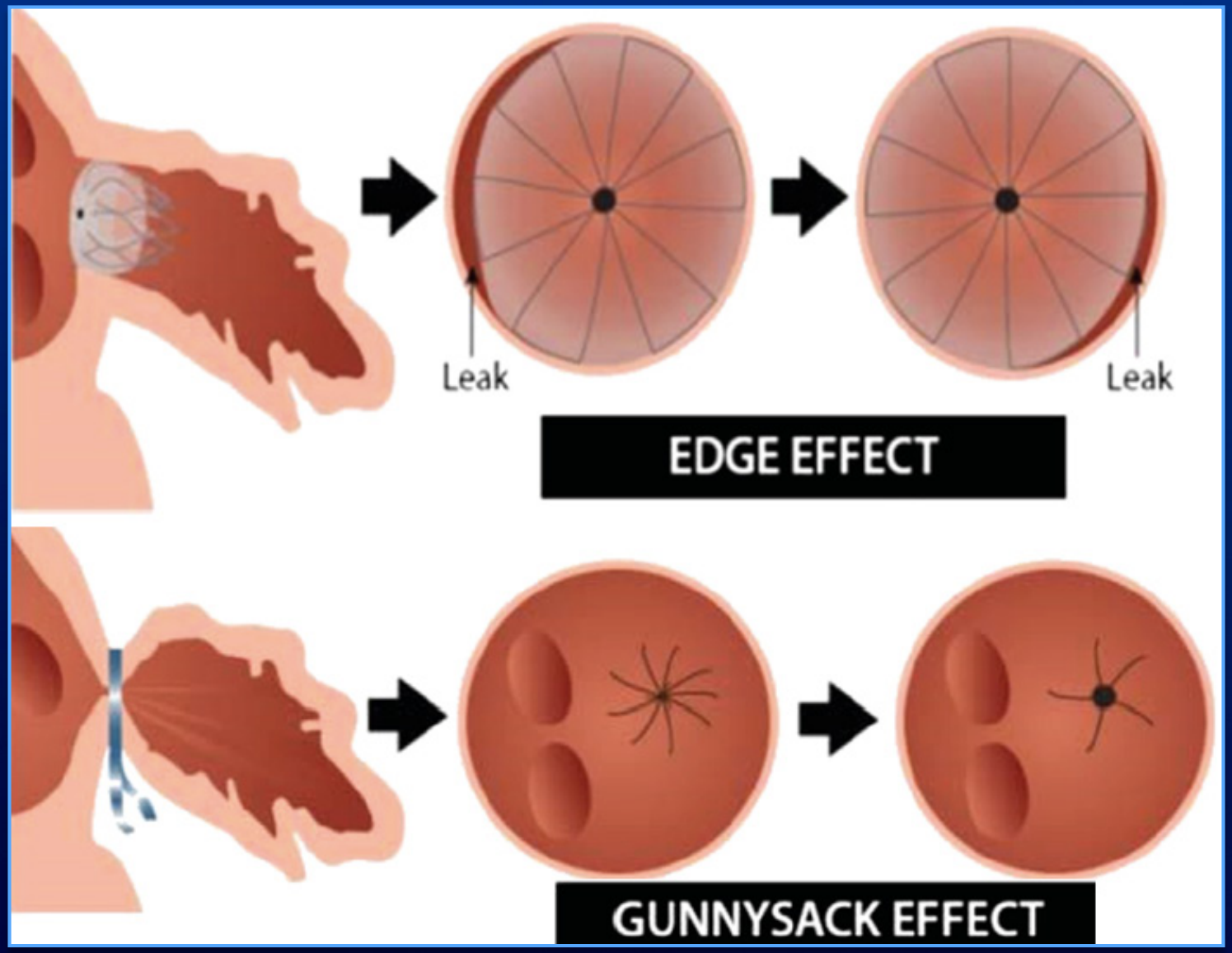

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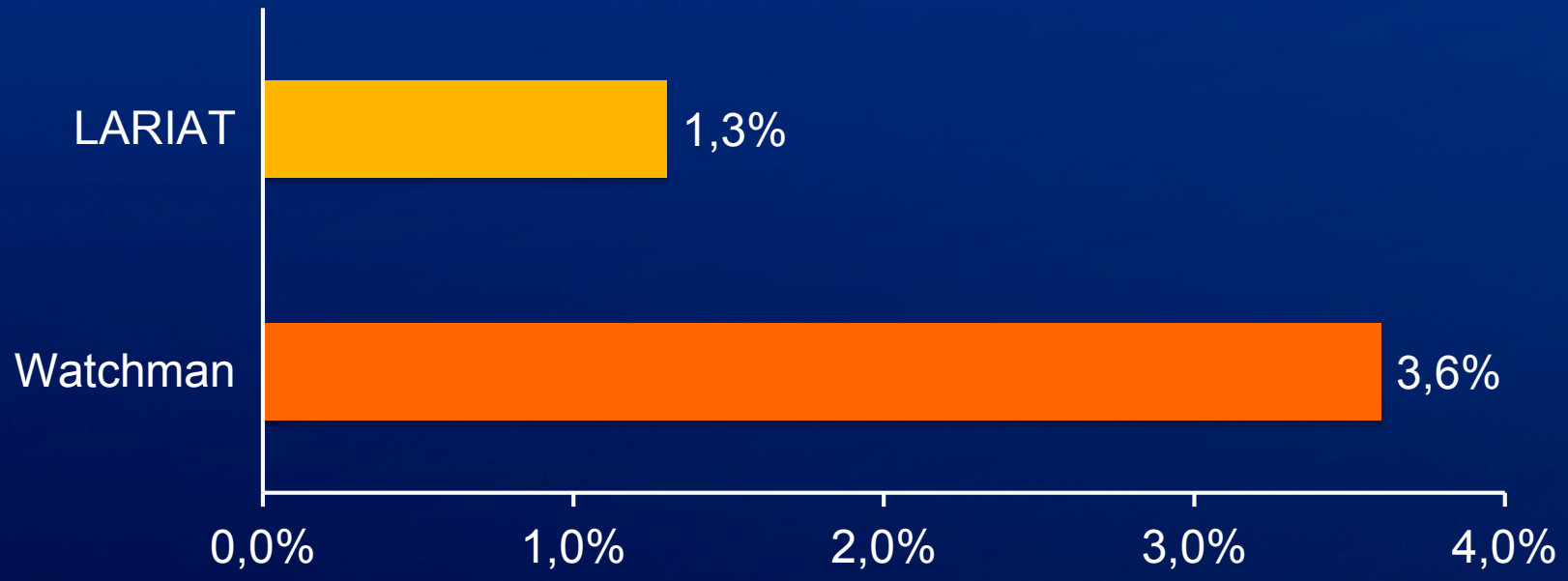
LARIAT vs Watchman Thrombus Rates



LARIAT n=259
OAC: 0-45d (31%)
APT: 6mo (30%)
>6mo: Operator discretion

Watchman n=219
Warfarin: 45d (100%)
APT: 6mo (100%)
>6mo: Operator discretion

Source: Pillarisetti J., et al., Endocardial (Watchman) versus Epicardial (LARIAT) Left Atrial Appendage Exclusion Devices: Understanding the Differences in the Locations and Type Leaks and their Clinical Implications. Heart Rhythm. 2015 Jul;12(7):1501-7.

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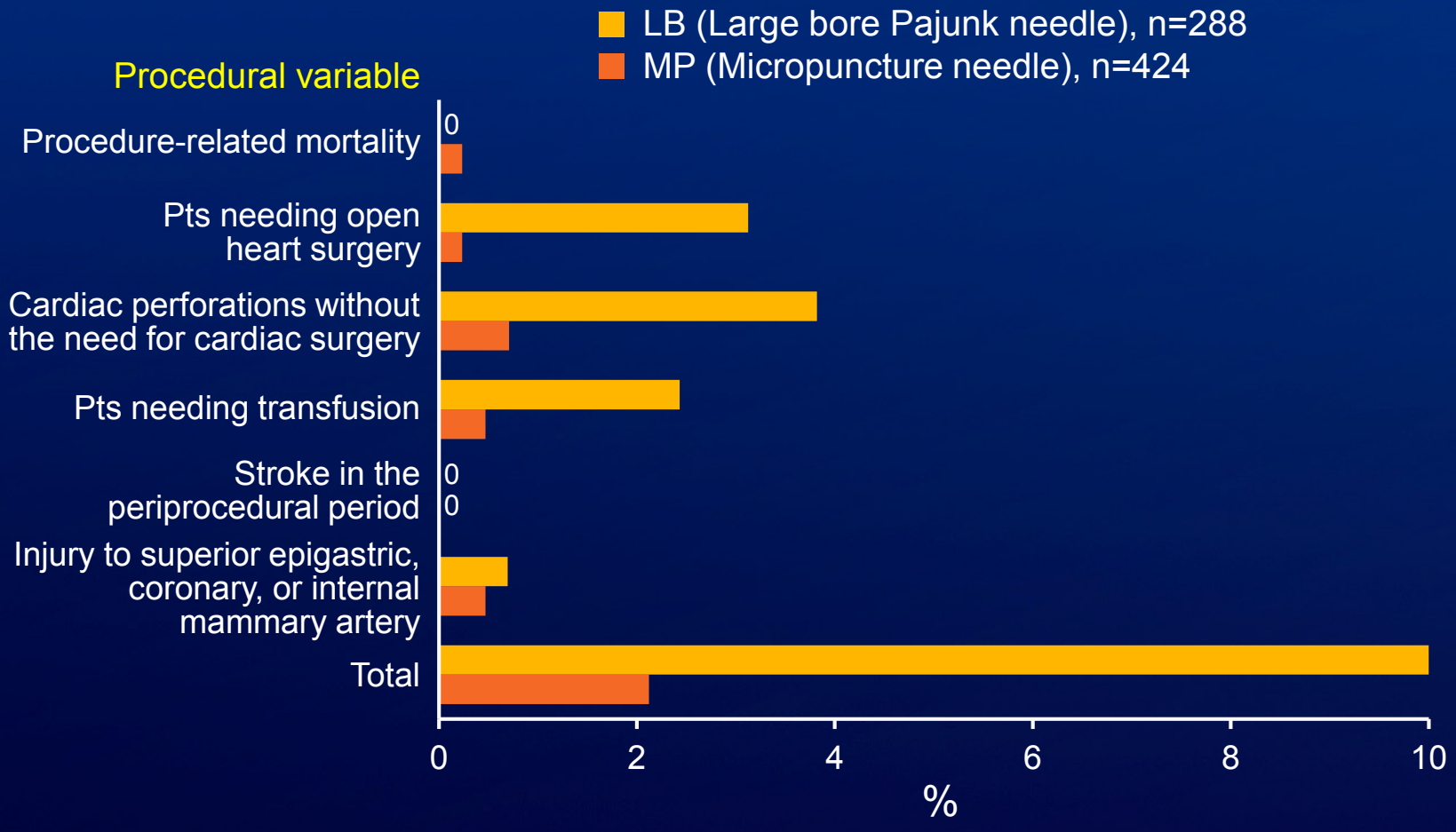
LARIAT: Acute Procedural Complications Importance of Micropuncture Needle



Lakkireddy et al: Heart Rhythm 13:3010, 2016

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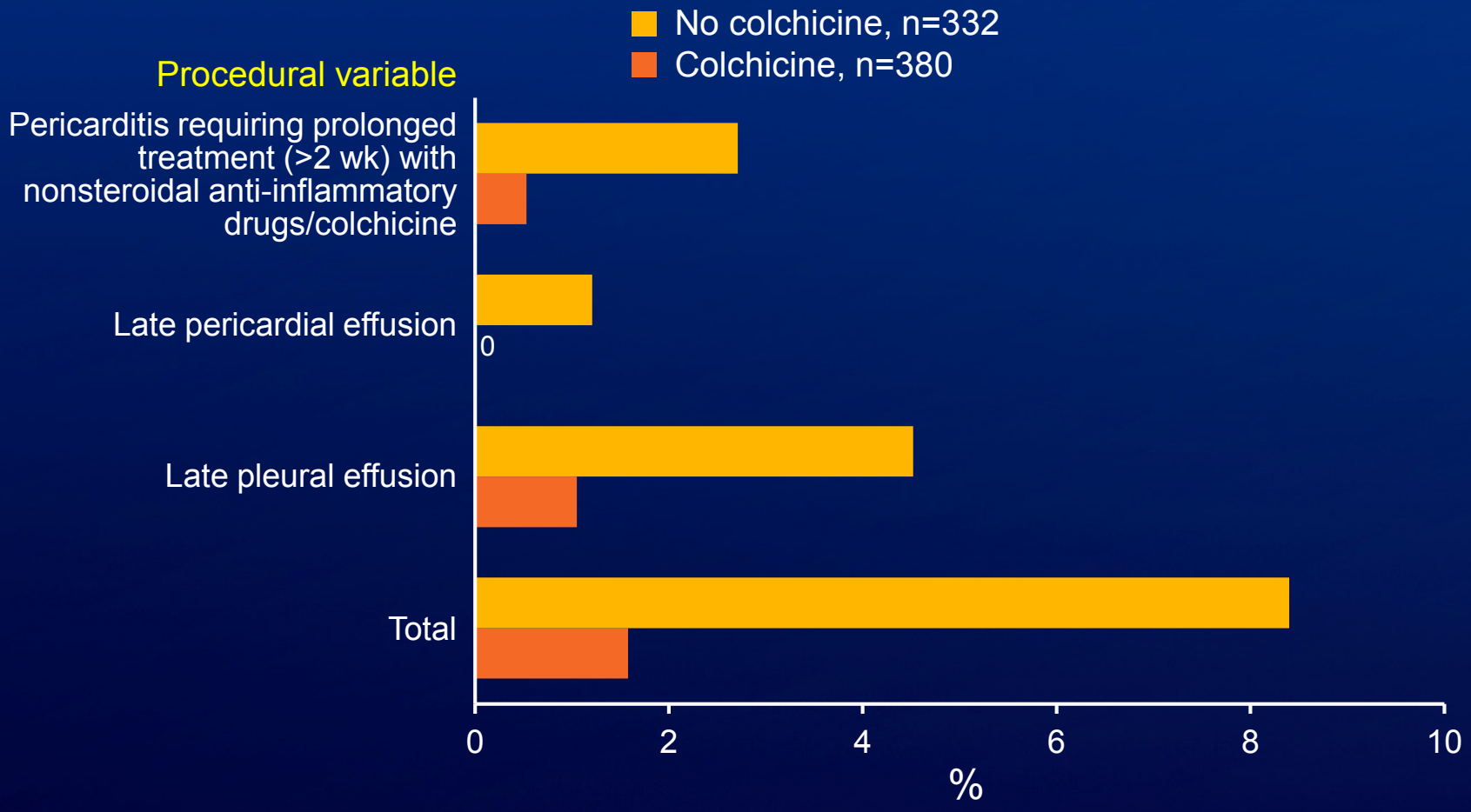
LARIAT: Impact of Use of Periprocedural Colchicine on Delayed Complications



Lakkireddy et al: Heart Rhythm 13:3010, 2016

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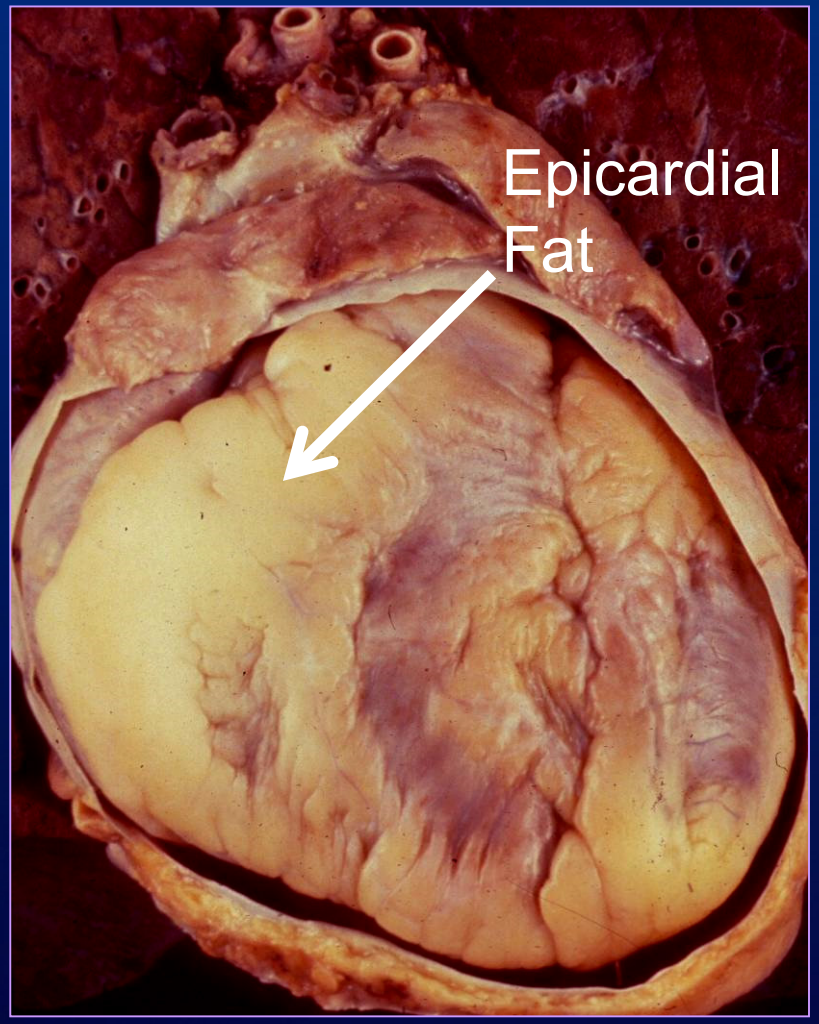
Heparin and bleeding in LAA closure

Heparin may augment:

- Bleeding due to sheath contact with epicardial fat
- Small tears of LAA or other structures (4.8% effusion in Protect AF)
- Disruption of “bridging veins” in pericardial space
- Post op pain *due to blood in pericardium & inflammation*



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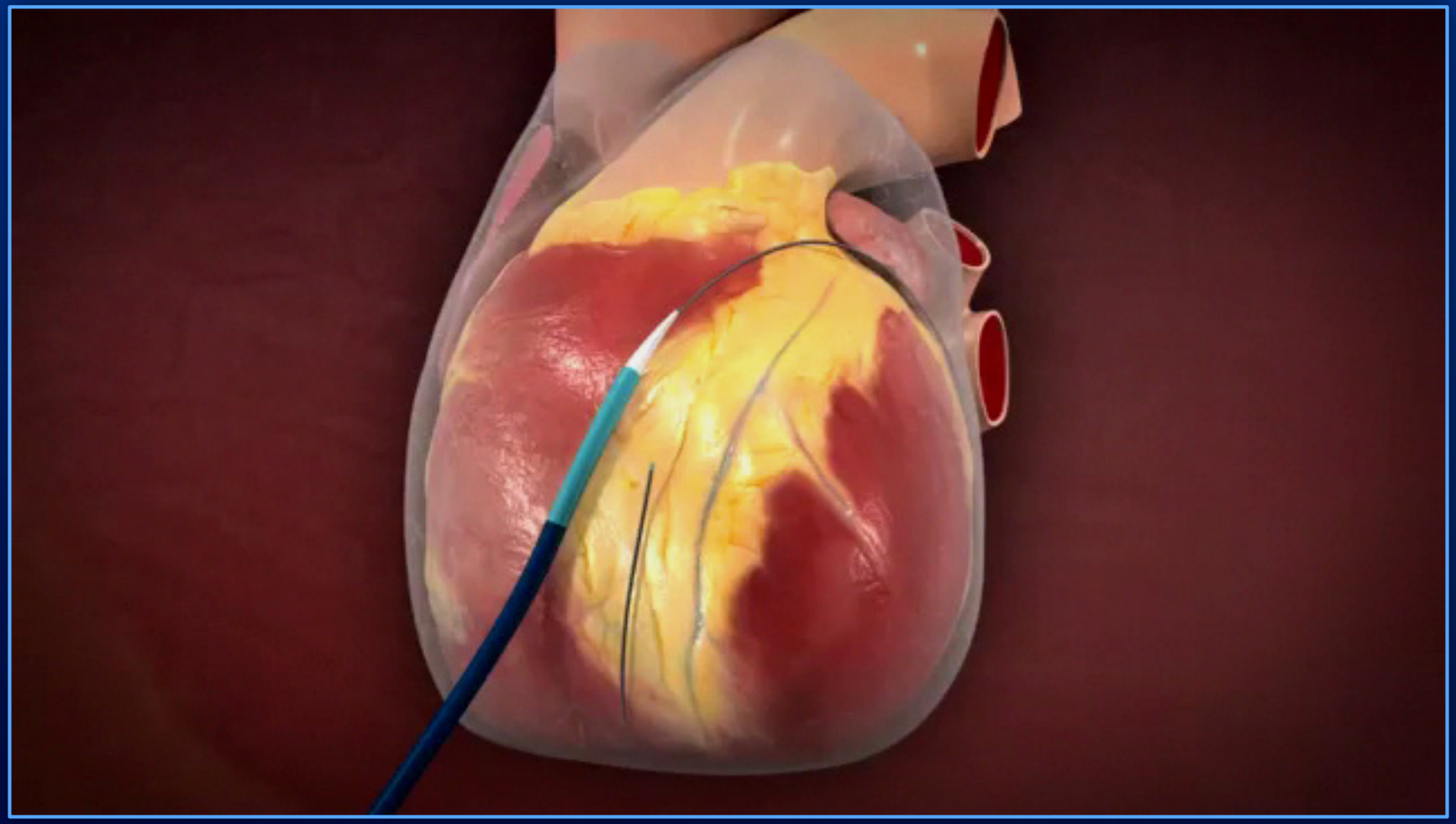

Epicardial only:
- Eliminate transeptal puncture
- Eliminate heparin
- Eliminate metal frame around suture
- Electrogram navigation/confirmation

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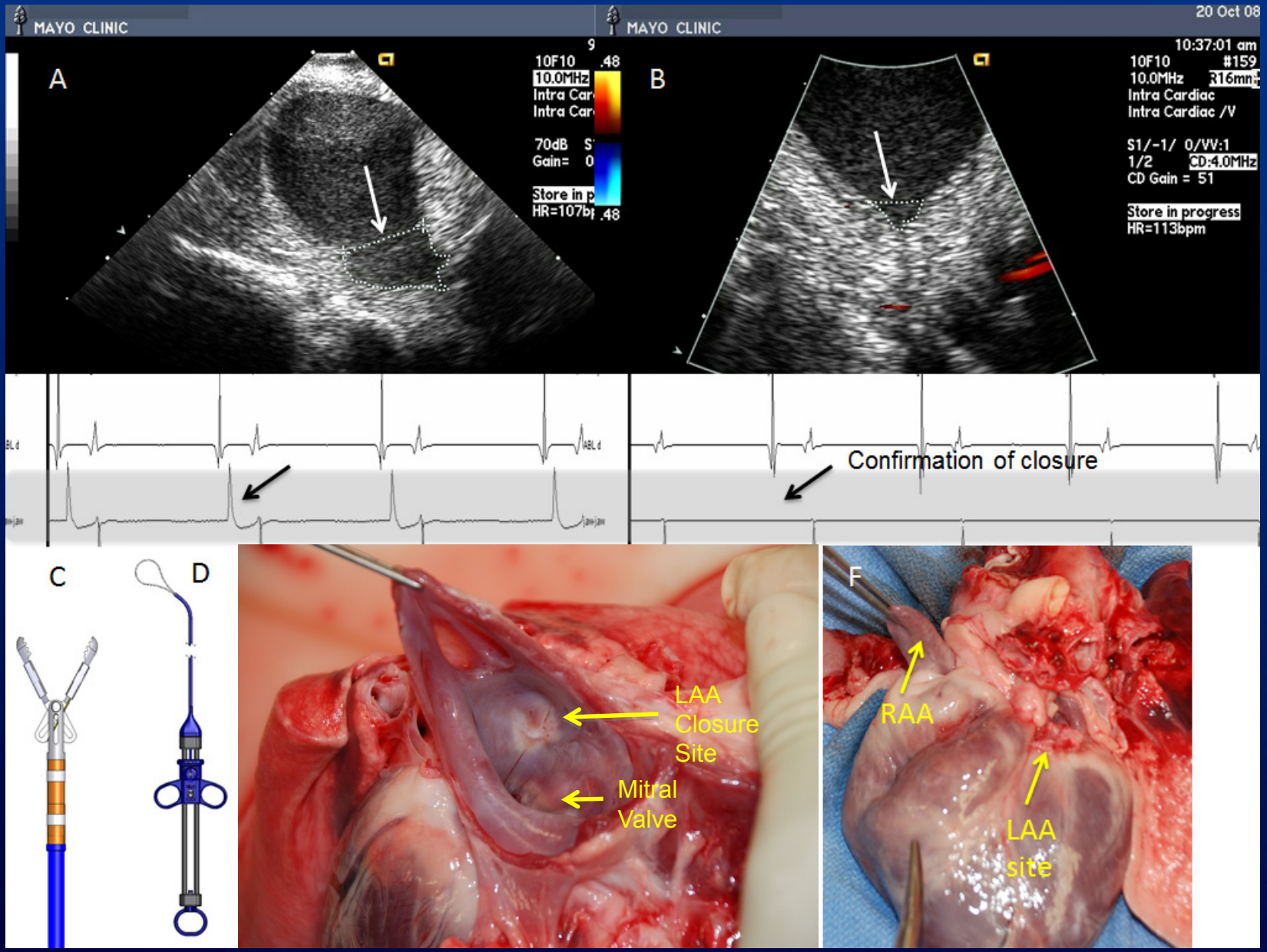

Friedman et al: JCE, 2009; Bruce et al: JCE, 2010

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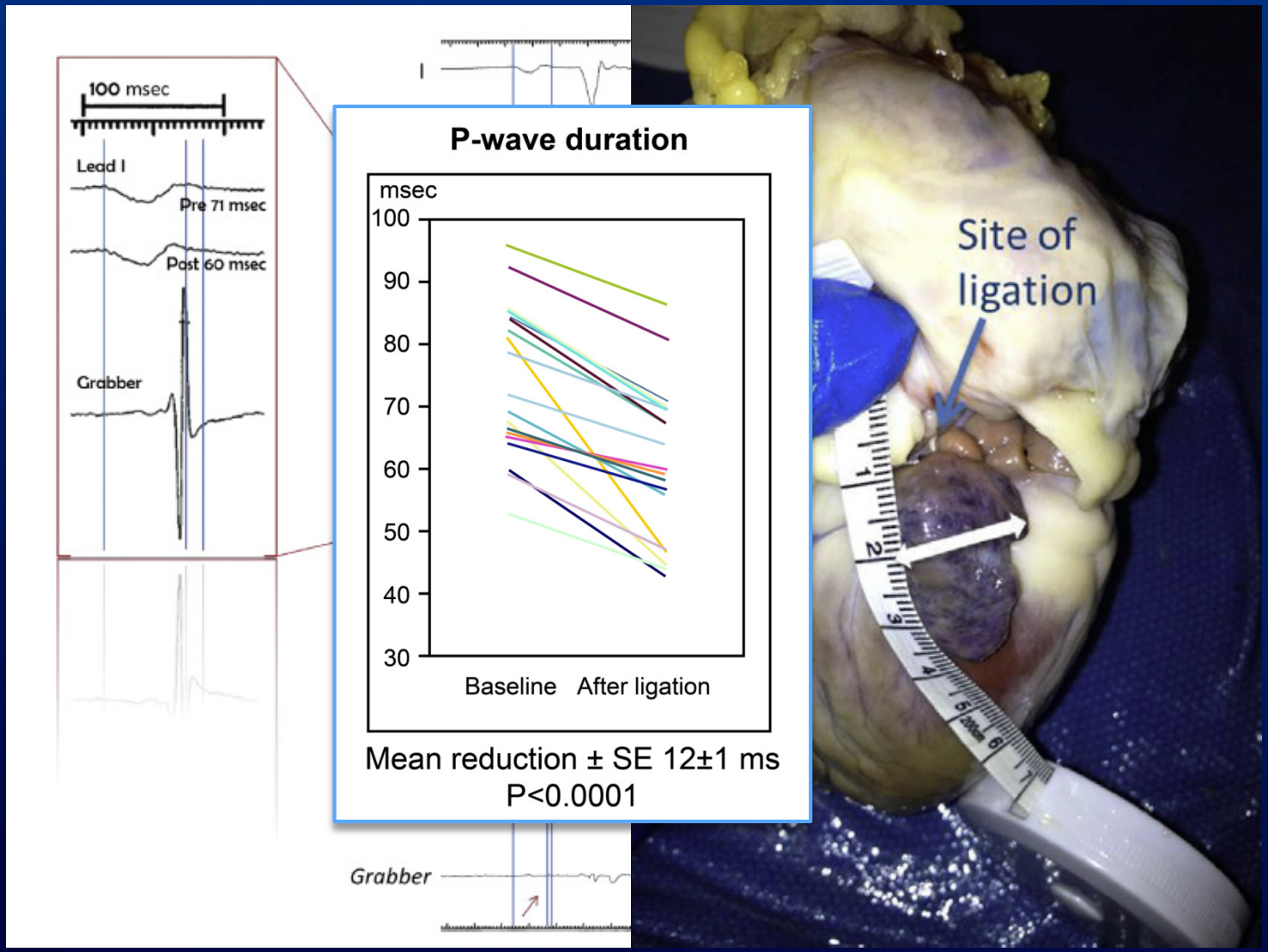
Atrial Remodeling



Syed…Friedman Translational Research; 165:365, 2015

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Aegis Epicardial Human Early Feasibility

Patient No.	$CHADS_2$ Score	Procedure Time (min)	Fluoro Time (min)	Technical Success	Ligating Devices Delivered	Adverse Event	Acute Closure*	1 Month Closure*
1	1	97	57.8	Yes	1	No	Yes	Yes
2	1	18	7.7	Yes	1	No	Yes	Yes
3	2	20	N/A	Yes	1	No	Yes	Yes
4	2	33	N/A	Yes	2	No	Yes	Yes
5	1	15	6.6	Yes	1	No	Yes	Yes
6	2	32	14.6	Yes	2	No	Yes	Yes
7	2	28	17.3	Yes	2	No	Yes	Yes

Average procedure time <35 minutes
First procedure 97 min, subsequent 15-33 minutes.
Fluoro time average 20.8 minutes (range 6.6 to 57.8)

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Conclusions

- N/OAC is well established for stroke reduction in AF
- For patients who cannot or prefer not to take N/OAC, LAA closure is an increasingly attractive option
  - It is at least equivalent to warfarin
  - Benefit accrues over time due to reduction in bleeding complications
- Patient selection critical: CHADSVASC3 in US
- External ligation may have particular role for rhythm control and some anatomies

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