8th Annual Emirates Cardiac Society Conference

ACC Middle East Conference 2017

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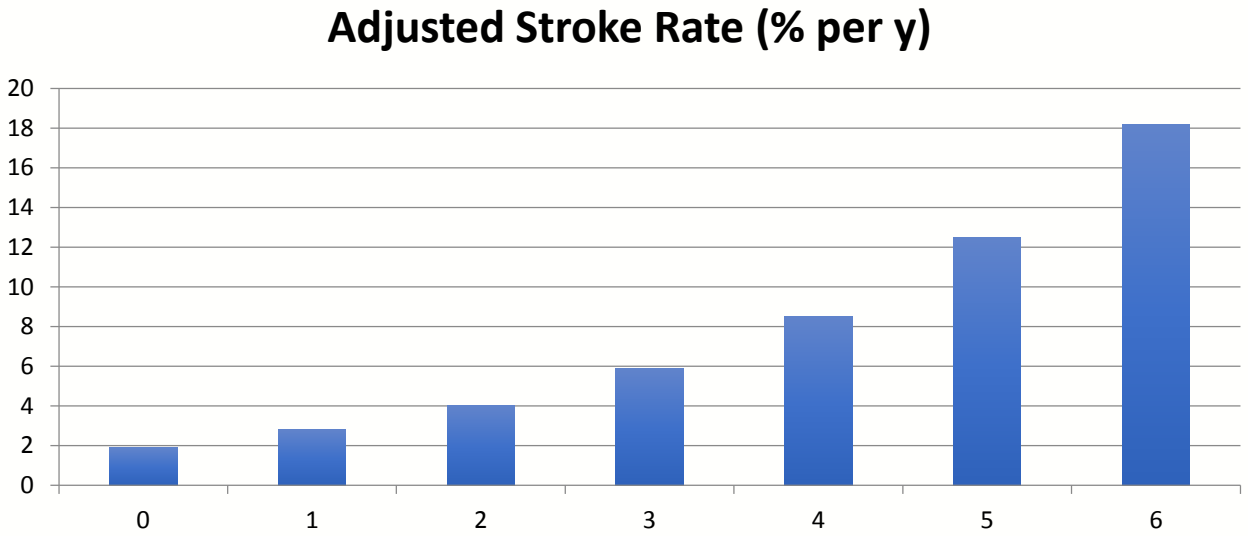
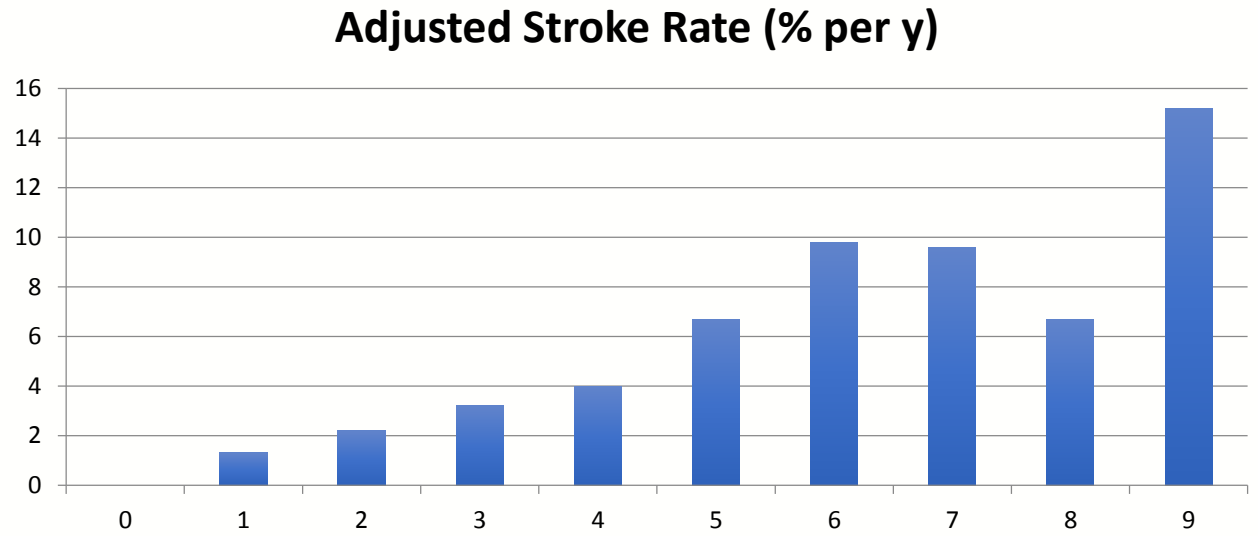
Gauging stroke risk across the AF spectrum and selecting the appropriate patient for LAA closure

Miguel Valderrábano, MD

ACC Middle East Conference 2017

Risk of Stroke in Atrial Fibrillation
$CHADS_2$-CHA_2DS_2-VASc Scores





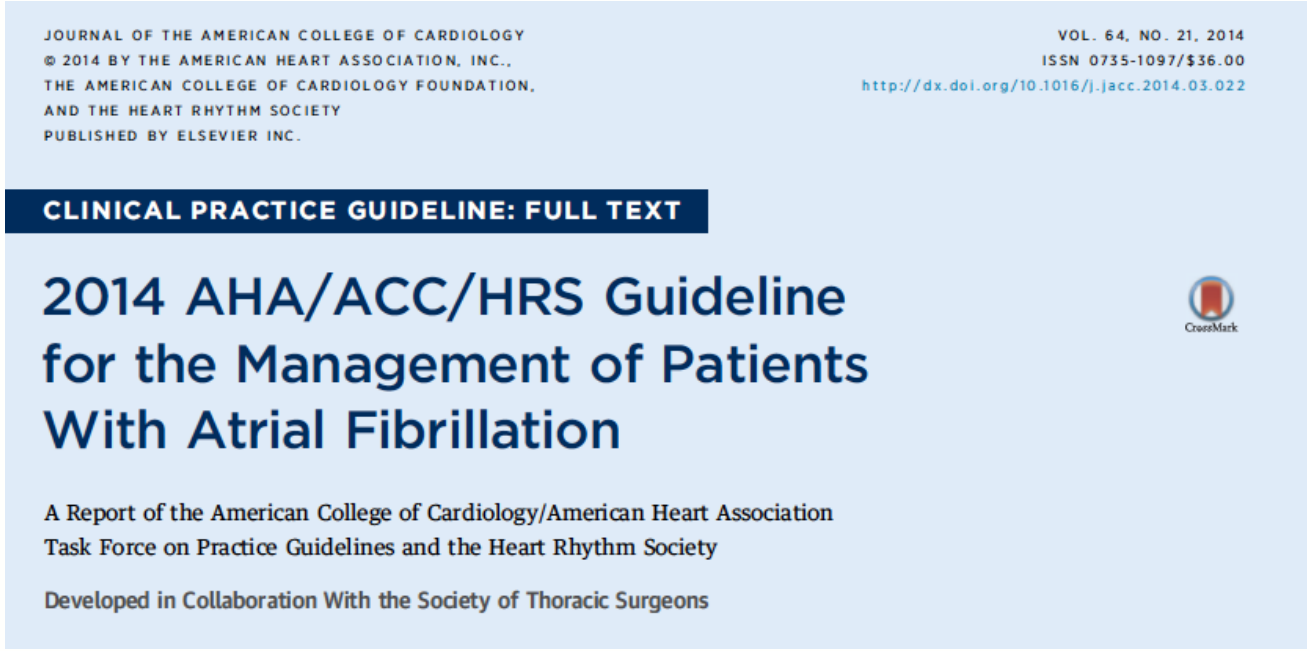
$CHADS_2$	
Congestive HF	1
Hypertension	1
Age ≥75 y	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	6

CHA_2DS_2-VASc	
Congestive HF	1
Hypertension	1
Age ≥75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65–74 y	1
Sex category (i.e., female sex)	1
Maximum score	9

J Am Coll Cardiol. 2014;64(21):2246-2280. doi:10.1016/j.jacc.2014.03.021

When to anticoagulate patients with AF

- Benefits of stroke risk reduction must outweigh risks of bleeding.
- CHADS2>1
- CHADS-VASc ≥1 for men and ≥2 for women



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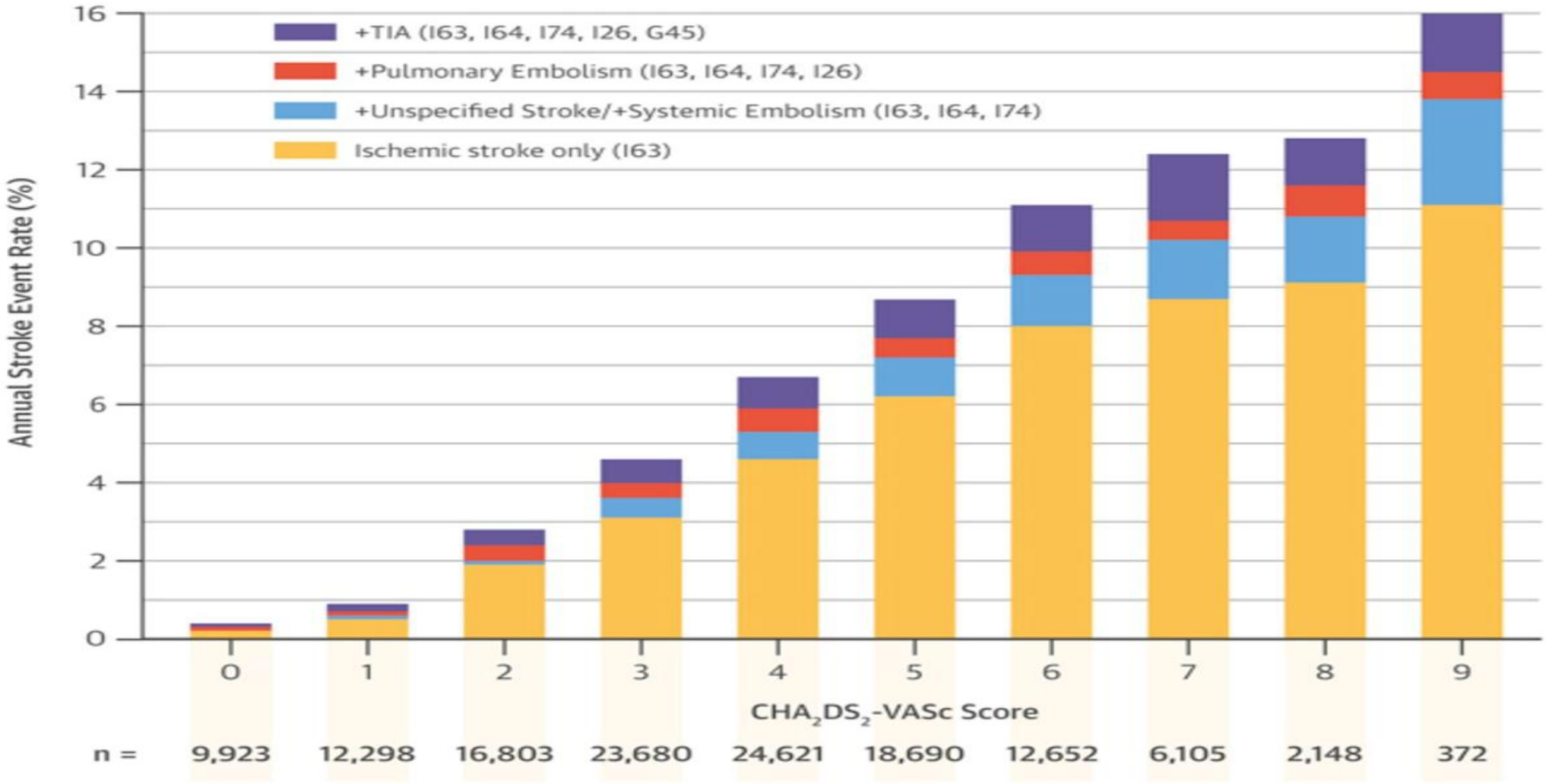
CLINICAL PRACTICE GUIDELINE: FULL TEXT

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

Validation of CHADS-VASc



Friberg, L. et al. J Am Coll Cardiol. 2015; 65(3):225-32.

Stroke prevention strategies

- Systemic anticoagulation
  - Warfarin
  - NOACs
- LAA closure
  - Watchman and other devices
  - Lariat
  - Atri-clip
- Selecting the right strategy requires individualization of risks/benefits!

Preventing Strokes in AF patients
Individualizing Risk: 4 questions

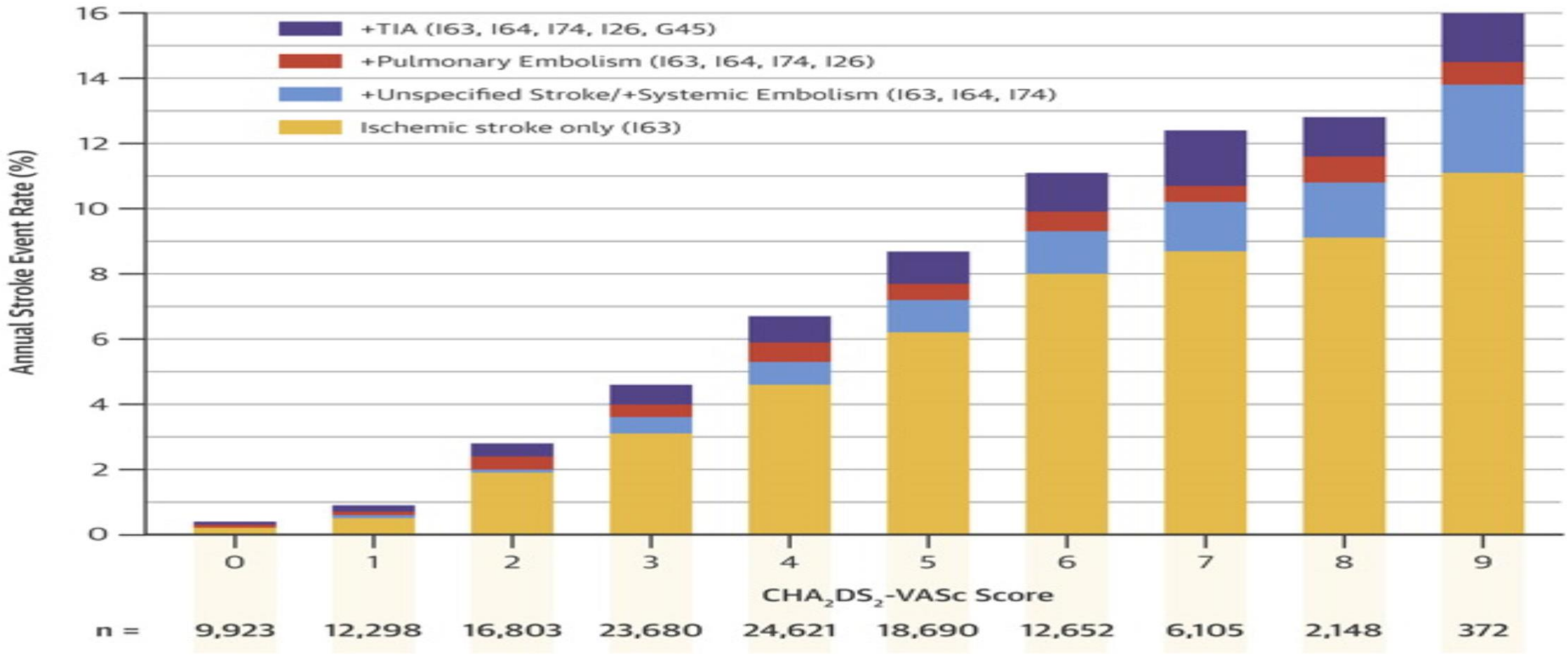
- **1. What are the causes of stroke risk in this patient?**
  - AF-related vs AF unrelated stroke
  - LAA-related vs LAA unrelated
- **2. What are the risks of stroke prevention strategies?**
  - Bleeding risk
  - Hemorrhagic stroke risk
  - Procedural risk
- **3. Are there benefits of anticoagulation besides preventing LAA thrombus in AF?**
- **4. What is the prior patient's experience on anticoagulation?**

1. Assessing Stroke Risk in AF

- A priori, the higher the risk of AF-related stroke, the greater the benefit of LAA exclusion…
- CHA_2DS_2-VASc score
  - History of congestive heart failure
  - Hypertension
  - Age >75 (2), >65 (1)
  - Prior stroke or TIA
  - Vascular disease
  - Sex (Female)

What is the role of the left atrial appendage in determining stroke risk?

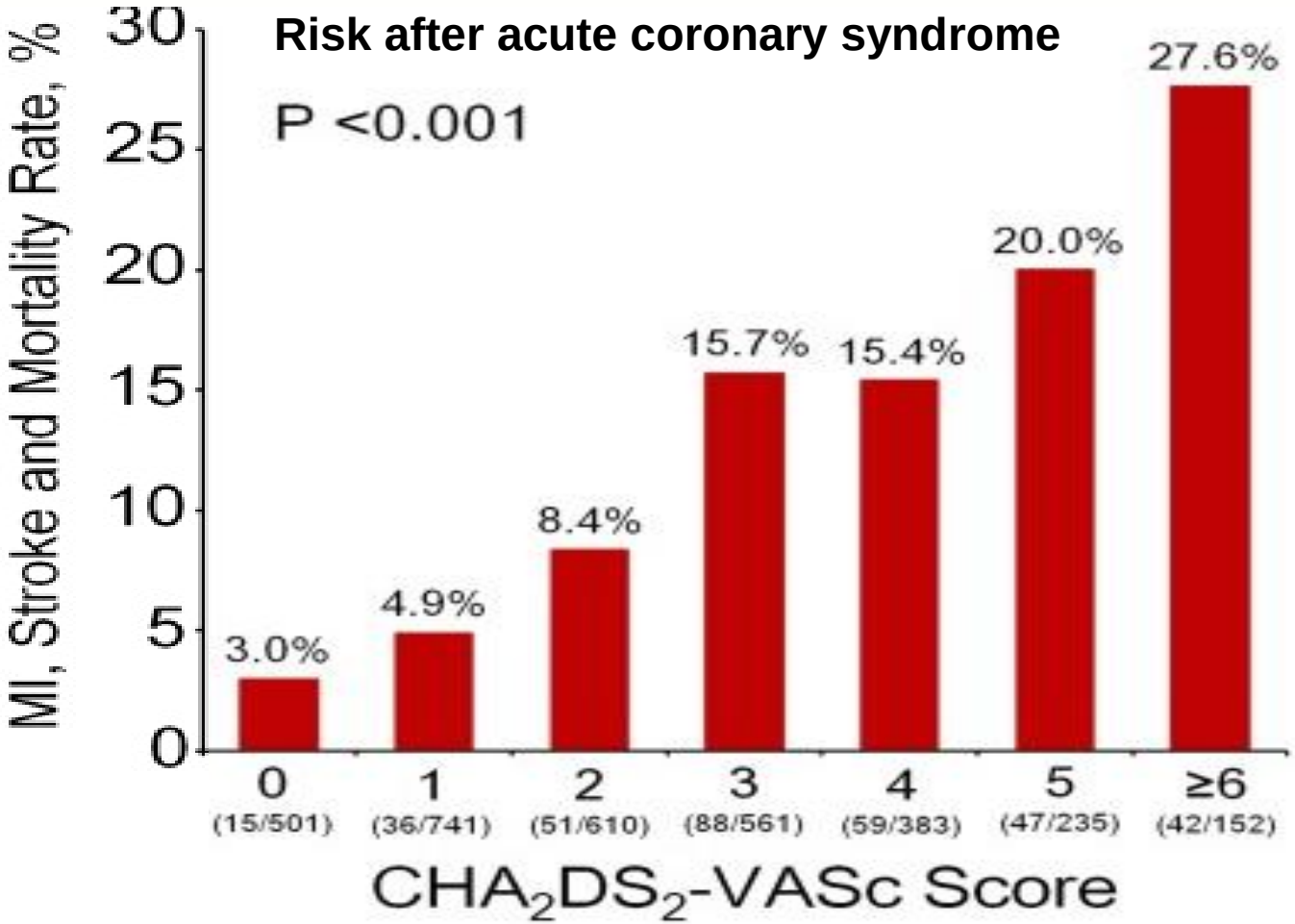
CHA_2DS_2-VASc Scores
Risk of Stroke in Atrial Fibrillation



Friberg, L. et al. J Am Coll Cardiol. 2015; 65(3):225-32.

1. Risk of LAA-related stroke
CHA_2DS_2-VASc Scores: Not specific

- CHA_2DS_2-VASc predicts risk of ischemic stroke in the ABSENCE of AF. (*Atherosclerosis*. 2014 Dec;237(2):504-13.)
- An assessment of LAA-related risk of stroke is necessary to decide on its closure.



PLoS One. 2014; 9(10): e111167.

Drug Discontinuation/Major Bleeding

Treatment	Study Drug Discontinuation Rate	Major Bleeding (rate/y)
Rivaroxaban[1]	24%	3.6%
Apixaban[2]	25%	2.1%
Dabigatran[3] (150 mg)	21%	3.3%
Edoxaban[4] (60 mg / 30 mg)	33% / 34%	2.8% / 1.6%
Warfarin [1-4]	17 - 28%	3.1% - 3.6%

There is an unmet need of stroke risk reduction for patients with AF who are seeking an alternative to long-term OACs

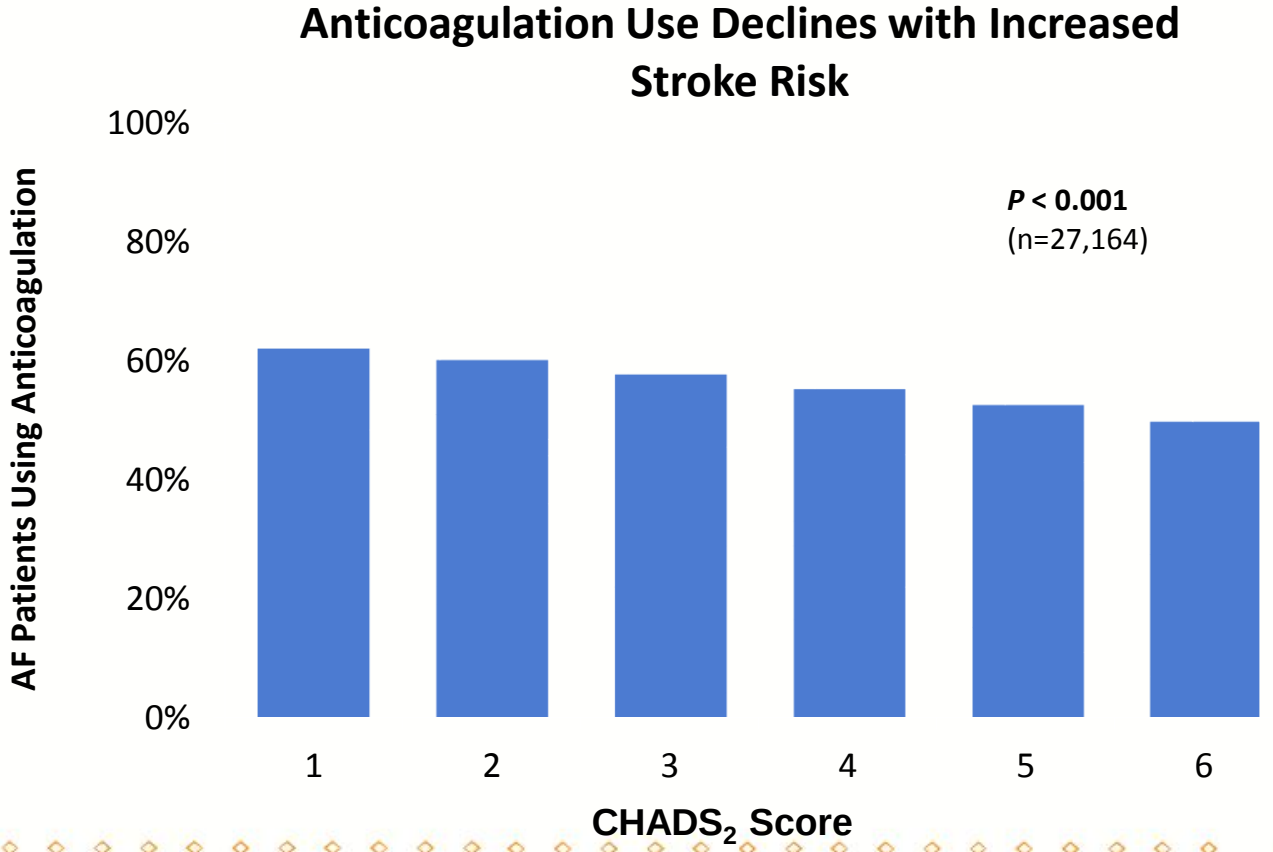
Although OACs May Be Indicated, They Are Under-utilized

Warfarin

- Bleeding risk
- High non-adherence rates
- Regular INR monitoring
- Food and drug interaction issues
- Complicates surgical procedures

NOACs

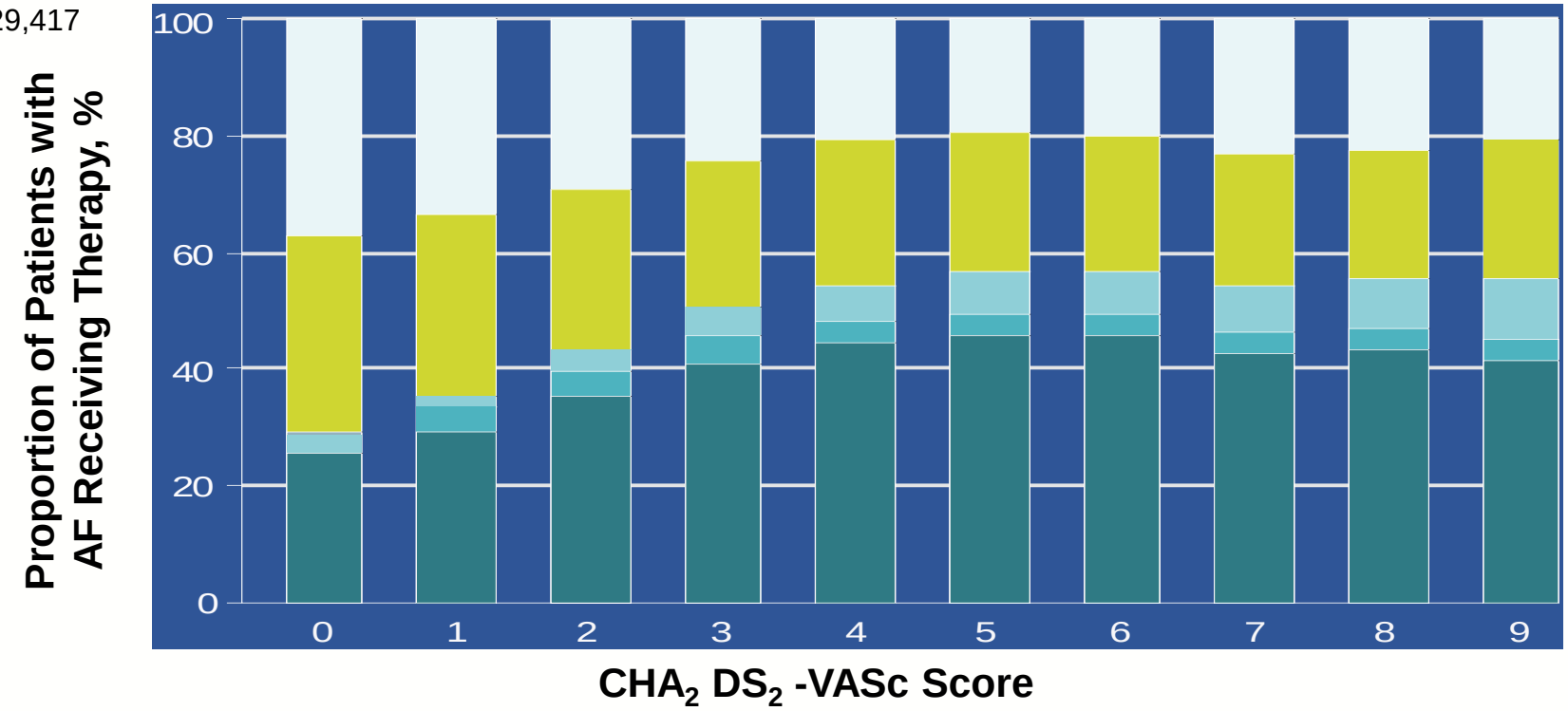
- Bleeding risk
- High non-adherence rates
- Complicates surgical procedures
- Lack of reversal agents
- High cost



Prevalence of Antithrombotic Therapies in AF Patients Across the Spectrum of Stroke Risk: Data from the NCDR-PINNACLE Registry

Prevalence of Treatment Strategies Across the Spectrum of CHA_2 DS_2-VASc Score

N=429,417



< 50% of high-risk patients get OACs

Hsu JC et al. *JAMA Cardiol*. 2016;1:55-62.

1. Risk of LAA-related stroke
CHA_2DS_2-VASc Scores: Not specific

CHA_2DS_2-VASc score 5

- Sixty-six year-old (1)
- Female (1)
- Diabetic (1)
- Hypertensive (1)
- Ca score of 450 (1)
- Persistent AF for 2 years
- TEE prior to cardioversion showing LAA thrombus, resolved 1 month later

CHA_2DS_2-VASc score 5

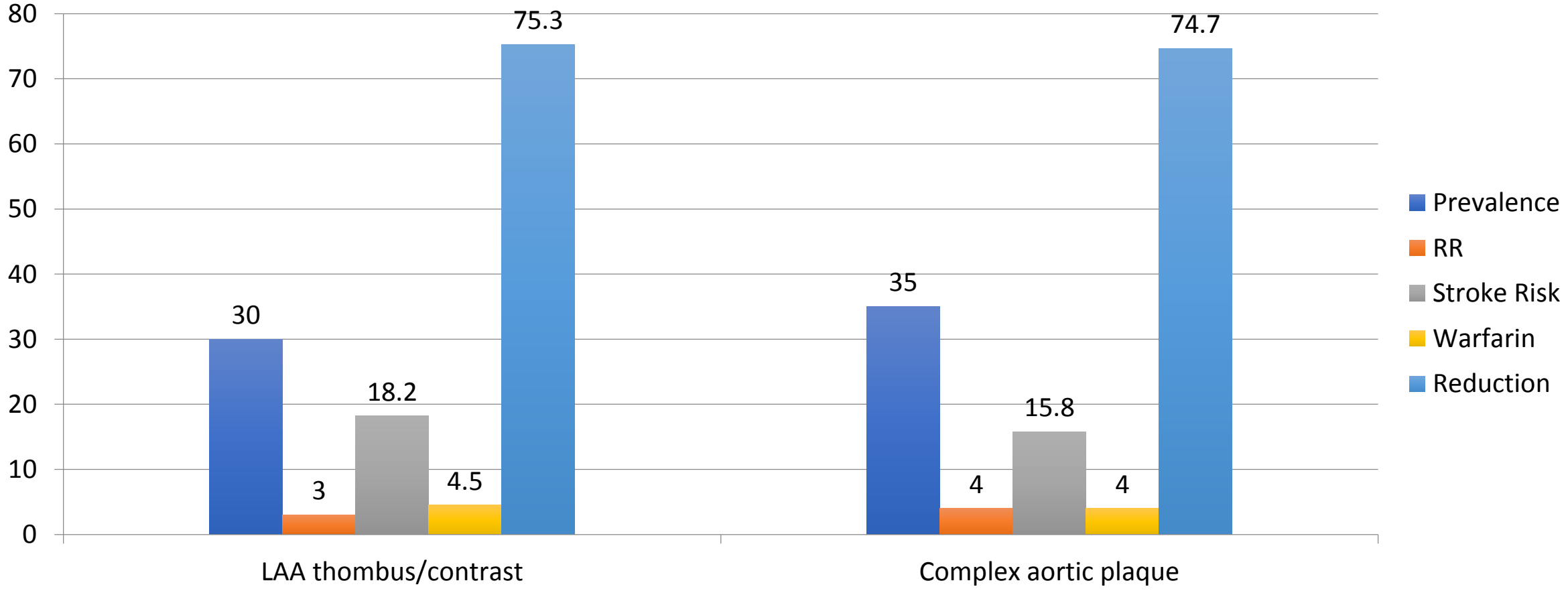
- Sixty-six year-old (1)
- Prior strokes (2)
- Ischemic cardiomyopathy with CHF (1)
- Extensive, mobile atheromatous plaque in the aortic arch (1)
- Persistent AF post CABG, cardioverted without recurrence

Only patients with high LAA-related risk of stroke would benefit from closure

1. Risk of LAA-related stroke
CHA_2DS_2-VASc Scores: LAA vs Aortic plaque

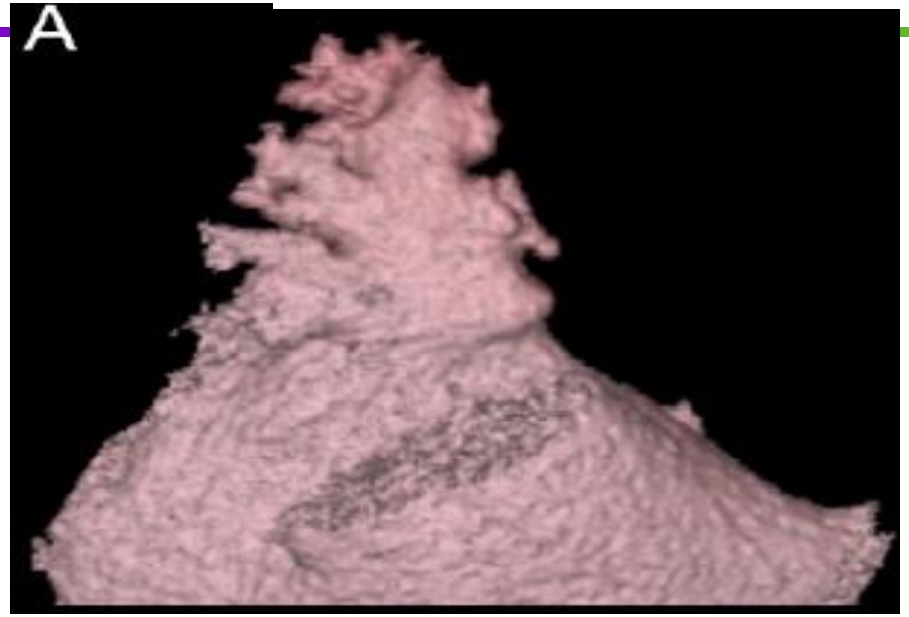
SPAF investigators. *Ann Intern Med*. 1998 Apr 15;128(8):639-47.

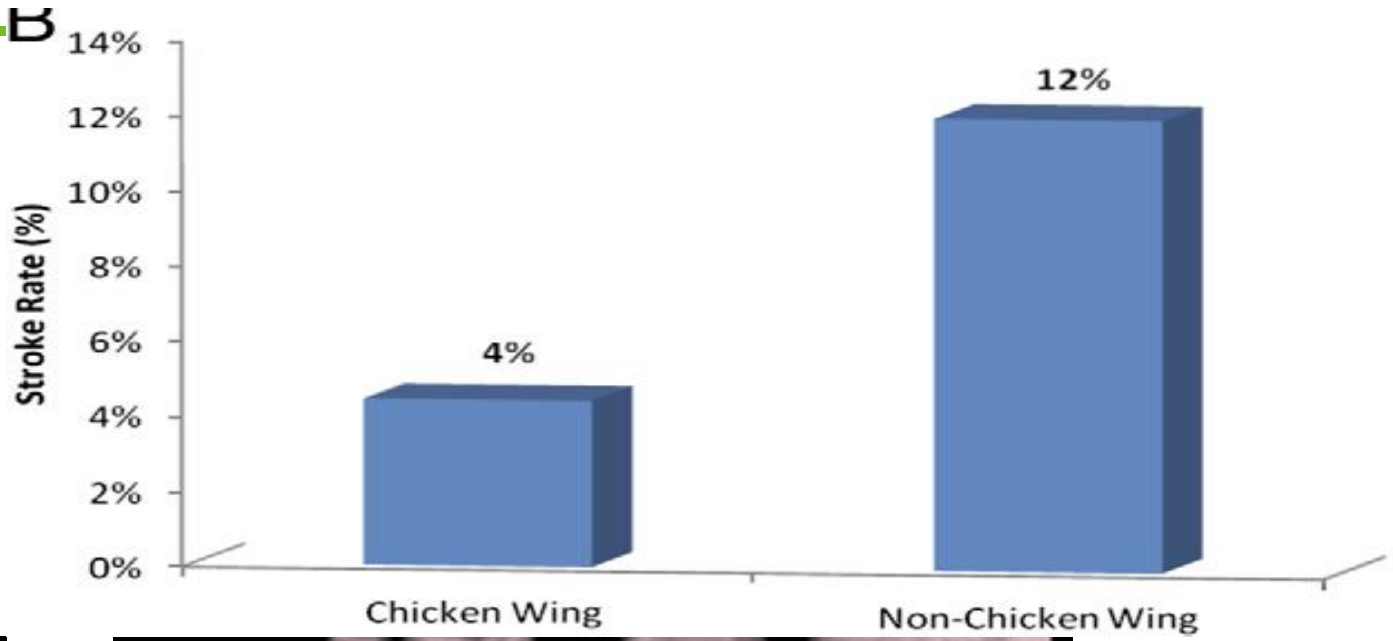
- SPAF-TEE study: Of 332 High-risk AF patients with CHF, prior stroke, female sex, Age >75. (One or more)

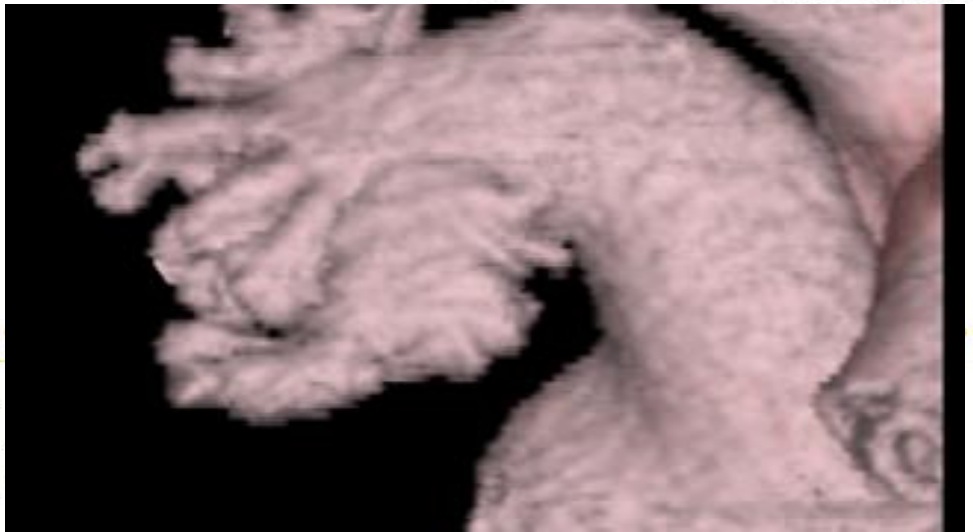


LAA-related stroke risk?

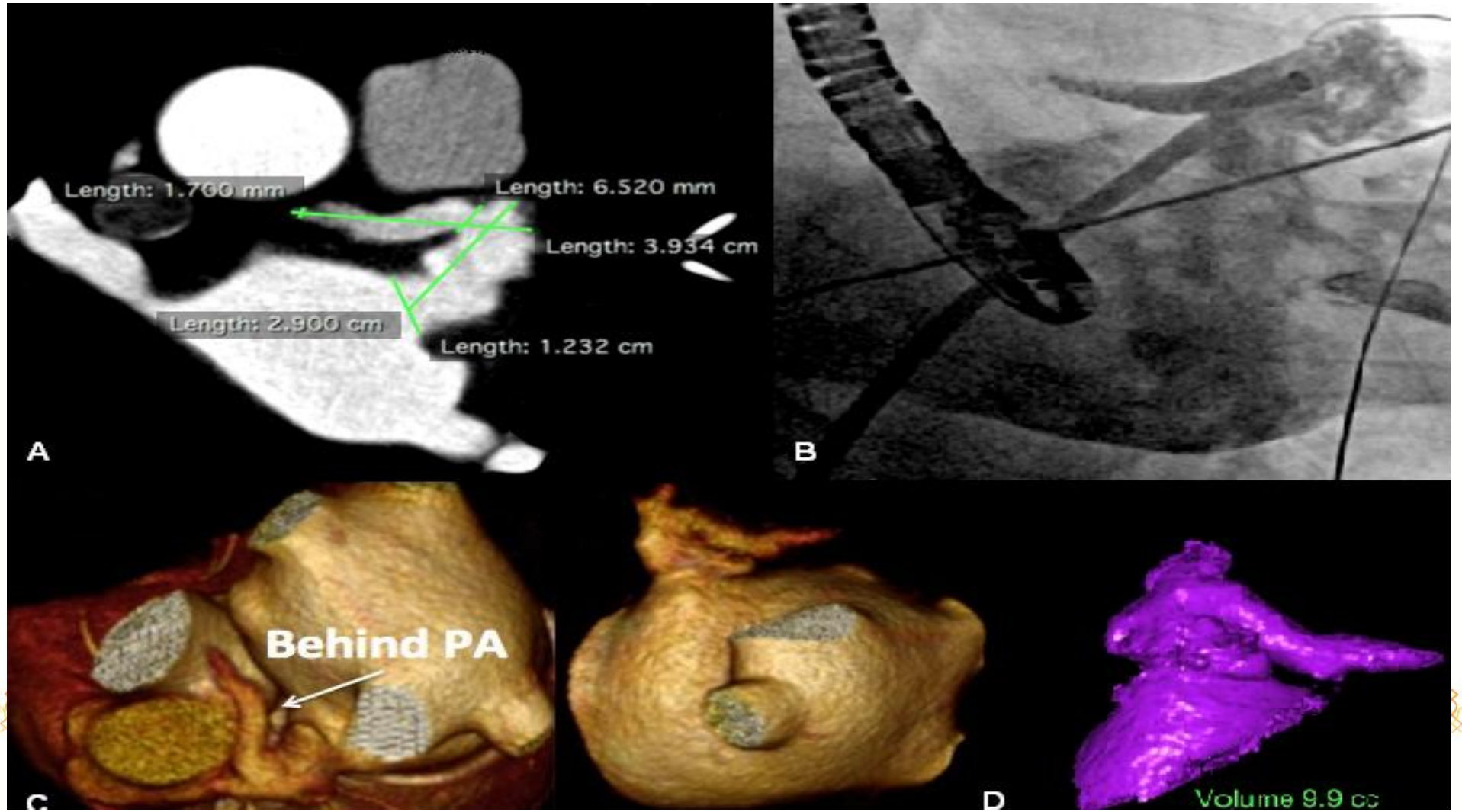
DiBiase *J Am Coll Cardiol.* 2012; 60(6):531-538. doi: 10.1016/j.jacc.2012.04.032





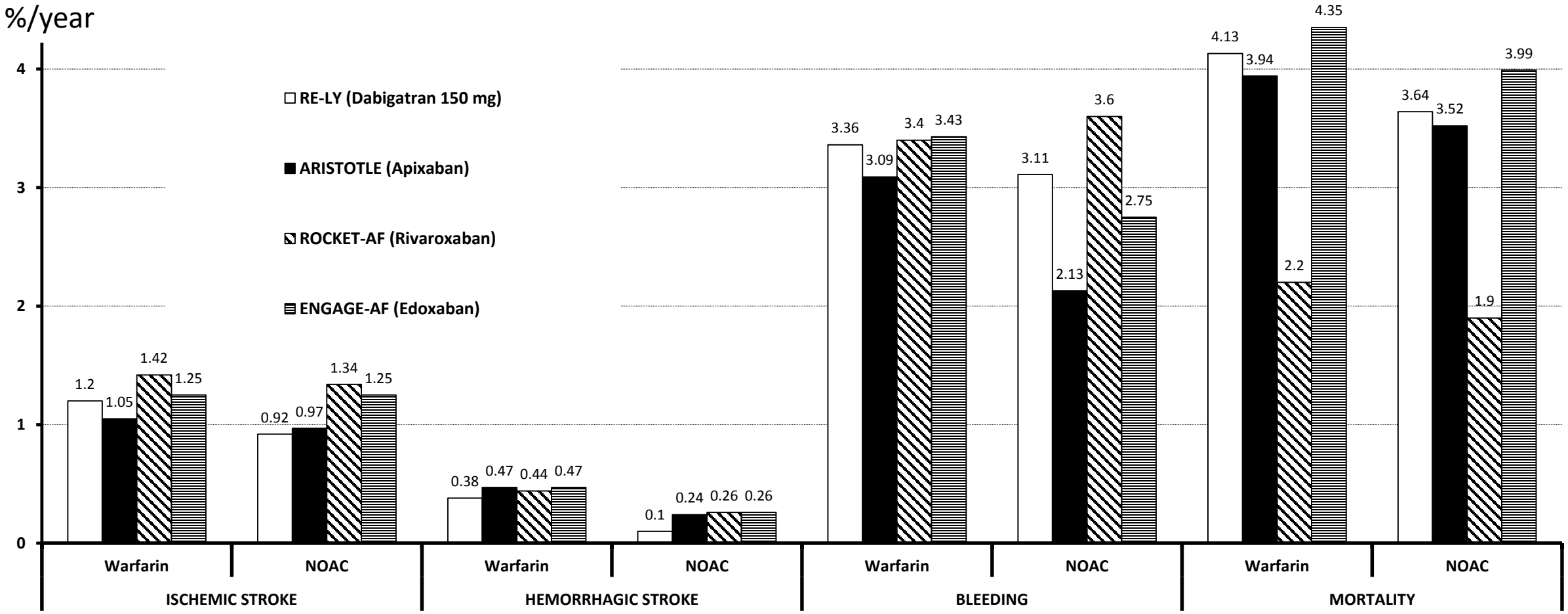


Extreme LAA Features



Kreideh B, Valderrábano M *HeartRhythm Case Rep*. 2015;1(6): 406-410

2. Risks of Stroke Prevention Warfarin vs NOACs



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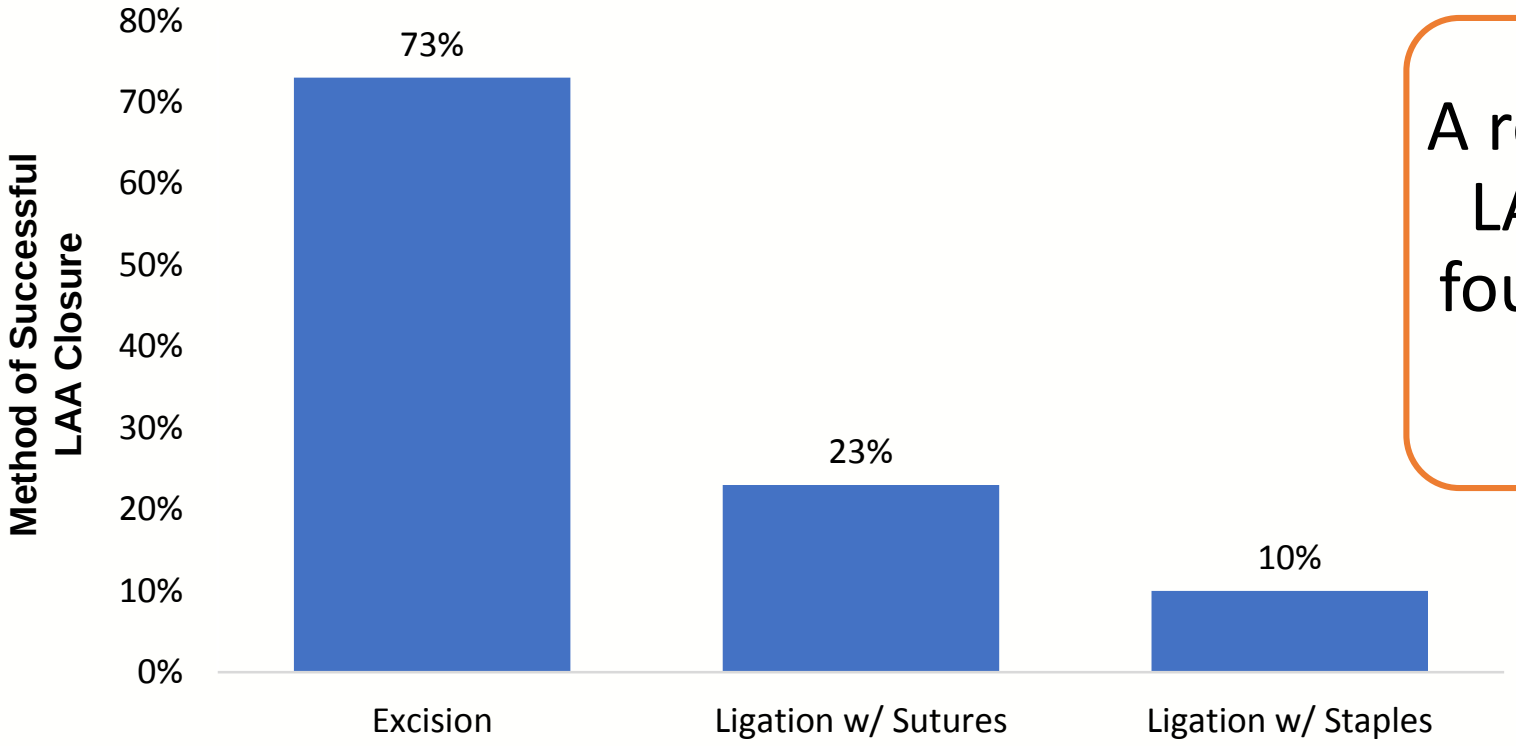
Price, Valderrábano. *Circulation* 2014;130:202-12

Surgical LAA Excision/Exclusion

- Surgical approaches to thromboembolic prophylaxis have been explored for more than 70 years
  - Surgical, invasive, open-heart procedure
- Often considered as an adjunct to other cardiac procedures, such as mitral valvotomy or cardiac bypass surgery
- Still unresolved issues
  - Lack of data on optimal patient selection
  - Risk of complications
  - Risk of leak and neurological sequelae?
  - Type and duration of anticoagulant treatment post-LAA excision?

Connolly SJ et al. *N Engl J Med*. 2009:361:1139-1151.
Bai Y et al. *Stroke*. 2017:Epub ahead of print.

LAA Excision and Exclusion: Successful Closure Varies By Approach



A review of the literature on LAA closure prior to 2010 found closure rates of 10%-73%[1]

A need exists for a less invasive approach that can consistently close the LAA

1. Dawson AG et al. *Interact Cardiovasc Thorac Surg*. 2010;10:306-311.
2. Kanderian AS et al. *J Am Coll Cardiol*. 2008;52:924-929.

Left Atrial Appendage Closure (LAAC)

- LAAC or occludder device is an alternative to oral anticoagulation
- Designed to reduce the risk of thromboembolism by closing off the LAA, which is believed to be the source of a majority of stroke-causing blood clots in people with nonvalvular AF
- Over time, patients may be able to

  stop taking OACs

LAA Clip

- AtriClip device
  - External clip closes the LAA effectively but it also interrupts the myocardial blood supply of the appendage itself, resulting in its gradual disappearance
  - In the multicenter FDA-approved EXCLUDE trial, the LAA was closed successfully with the AtriClip device in 98.4% of patients with no device-related mortality
  - FDA approved since 2009 for LAA closure **during open heart procedure**
  - Excellent reliability
  - No randomized clinical trial regarding stroke prevention

AtriCure Exclusion of the LAA in Patients Undergoing Concomitant Cardiac Surgery (EXCLUDE). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/study/NCT00779857. Published October 23, 2008. Updated May 31, 2013. Accessed April 15, 2017; Cox JL. *Ann Cardiothorac Surg*. 2014;3(91):80-88; Alqaqa A et al. *J Atr Fibrillation* 2016;9(1):1407; Ramlawi B et al. *Methodist Debakey Cardiovasc J*. 2015;11(2):100-103.

Transcatheter Ligation

- LARIAT device
  - Over-the-wire device
  - Currently does not have a specific indication for LAAC or stroke reduction
  - FDA approval for tissue approximation, but not LAA exclusion

  - Serious procedural safety concerns
  - High incomplete closure rates

Afzal MR et al. *Heart Rhythm*. 2015;12:52-59; Lakkireddy D. Safety and Efficacy of Left Atrial Appendage Occlusion Devices. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT01695564. Published July 5, 2012. Accessed April 15, 2017; Ramlawi B et al. *Methodist Debakey Cardiovasc J.* 2015;11:100-103.

Early Safety and Efficacy of Percutaneous Left Atrial Appendage Suture Ligation

Results From the U.S. Transcatheter LAA Ligation Consortium

Matthew J. Price, MD,* Douglas N. Gibson, MD,* Steven J. Yakubov, MD,† Jason C. Schultz, MD,* Luigi Di Biase, MD, PHD,‡ Andrea Natale, MD,‡ J. David Burkhardt, MD,‡ Ashish Pershad, MD,§ Timothy J. Byrne, DO,§ Brett Gidney, MD,|| Joseph R. Aragon, MD,¶ Jeffrey Goldstein, MD,# Kriegh Moulton, MD,# Taral Patel, MD,** Bradley Knight, MD,** Albert C. Lin, MD,** Miguel Valderrábano, MD††

Endpoint	N = 151
Procedural success (primary)[1]	131 (87%)
Safety	
Death, MI, CVA, pericardial effusion, or surgery at D/C	16 (10.6%)
Death, MI, CVA, pericardial effusion, major bleed, or surgery at D/C	18 (11.9%)

[1]Deployment of Lariat, < 5 mm residual shunt by post-procedure TEE, no major complication at hospital D/C.
CVA, cerebrovascular accident; D/C, discharge; MI, myocardial infarction.
Price MJ et al. *J Am Coll Cardiol*. 2014;64:565-572.

Bleeding Outcomes with Suture Ligation

Major Bleeding Events During Hospitalization in the Study Population (n = 154)*	
Major bleed	14 (9.1)
Any transfusion with overt bleeding	7 (4.5)
Overt bleed, hemoglobin drop 3 to < 5 g/dl	5 (3.2)
Overt bleed, hemoglobin drop ≥ 5g/dl	3 (1.9)
Cardiac tamponade	7 (4.5)
Bleeding requiring surgical control	2 (1.3)
Bleeding requiring vasoactive agents	4 (2.6)
Fatal bleeding	0

Values are n (%). Bleeding Academic Research Consortium type 3A or greater.
*More than 1 bleeding event may have occurred in a single patient.
Price MJ et al. *J Am Coll Cardiol*. 2014;64:565-572.

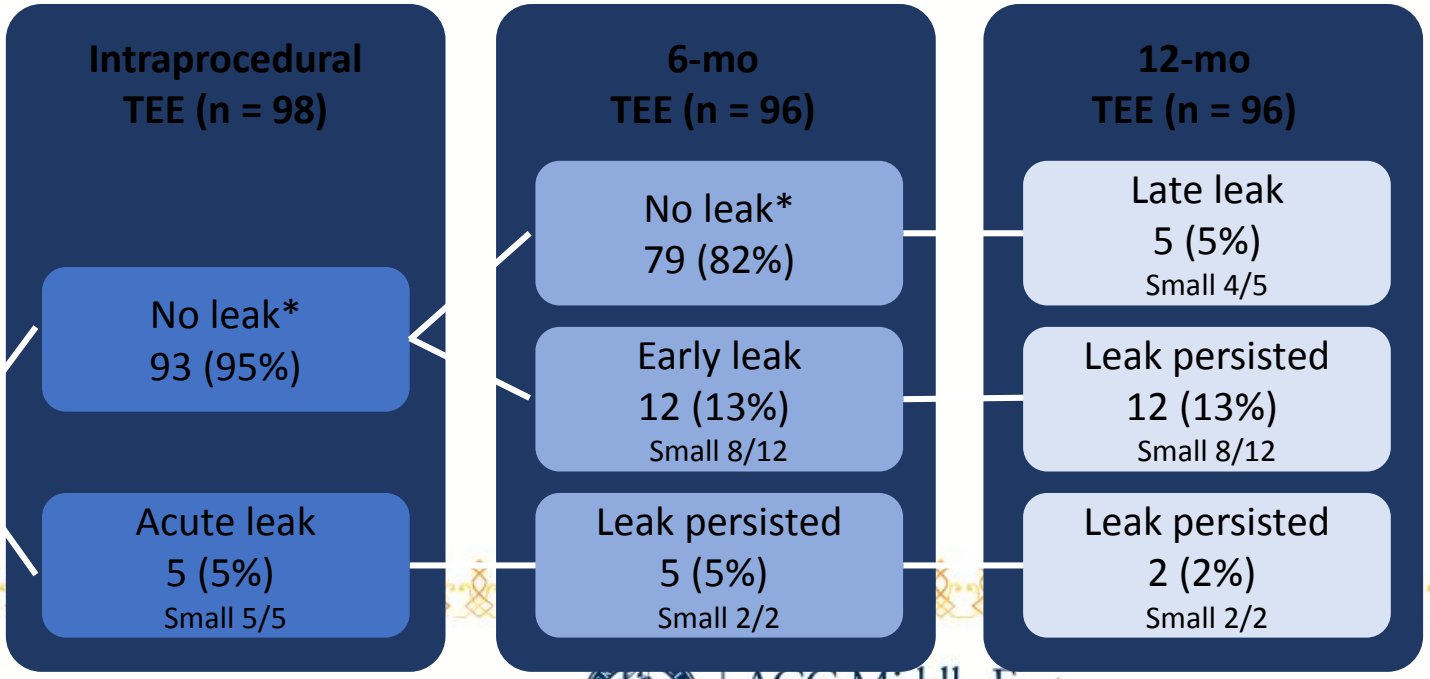
Reported Incidence of Post-Suture Ligation Leaks

Reported Incidence of Reopening after LAA Ligation with Suture Ligation					
First Author (y)	n*	Follow-up Imaging	Acute	Early (<6 mo)	Late (6-12 mo)
Bartus et al. (2013)	85, 81, 65	2D TEE	4%	5%	2%
Massumi et al. (2013)	20, 17, 17	2D TEE	0%	6%	6%
Stone et al. (2013)	25, 22	2D TEE	0%	0%	NA
Miller et al. (2014)	41, 41	2D TEE, CT	7%	24%	NA
Price et al. (2014)	145, 63	2D TEE	8%	20%	NA
Pillarisetti et al. (2015)	259, 259, 259	2D TEE	2%	13%	13%
Gianni et al. (2016)	98, 96, 96	2D TEE, 3D TEE	5%	15%	20%

*Number of patients with follow-up TEE across the 3 time points.
2D, 2-dimensional; 3D, 3-dimensional; CT, computed tomography; NA, not available; TEE, transesophageal echocardiography.
Gianni C et al. *JACC Cardiolvasc Interv*. 2016;9:1051-1057.

Clinical Implications of Leaks Following Left Atrial Appendage Ligation With the Lariat Device

Carola Gianni, MD,[a,b] Luigi Di Biase, MD, PHD,[a,c,d,e] Chintan Trivedi, MD, MPH,[a] Sanghamitra Mohanty, MD, MS,[a] Yalçın Gökoğlan, MD,[a] Mahmut F. Güneş, MD,[a] Rong Bai, MD,[a] Amin Al-Ahmad, MD, CCDS,[a] J. David Burkhardt, MD,[a] Rodney P. Horton, MD,[a,d] Andrew K. Krumerman, MD,[c] Eugen C. Palma, MD, CCDS,[c] Miguel Valderrábano, MD,[f] Douglas Gibson, MD,[g] Matthew J. Price, MD,[g] Andrea Natale, MD[a,c,d,g,h,i,j,k]

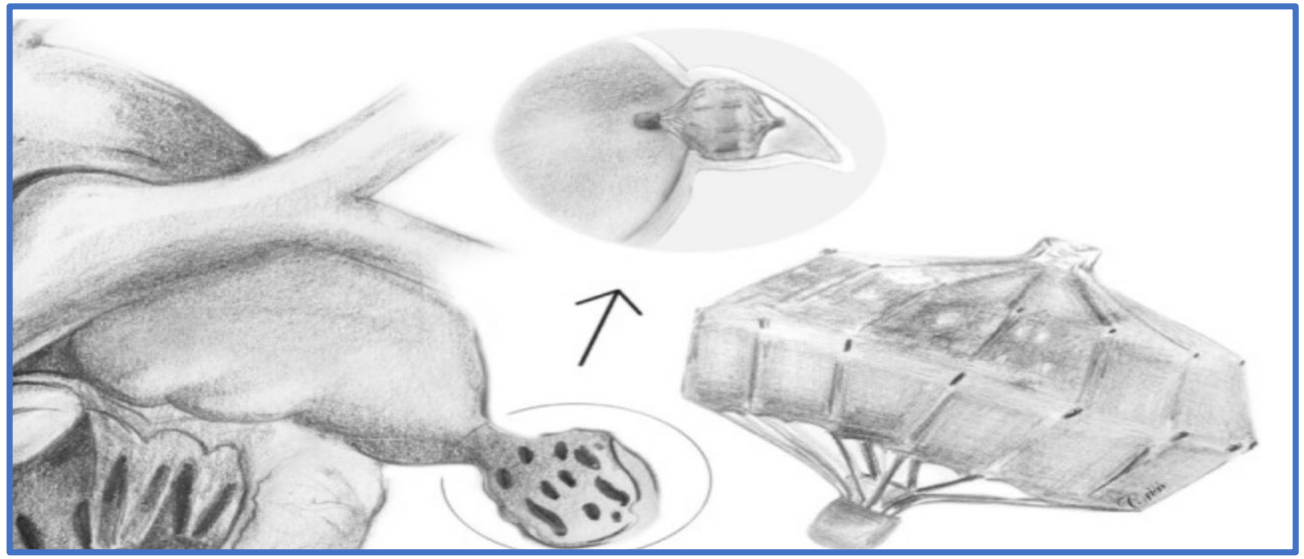


- 3 strokes occurred > 6 mo
- All associated with leak < 5 mm

Gianni C et al. *JACC Cardiolvasc Interv*. 2016;9:1051-1057.

PLAATO

- First device approved for LAAC
- Self-expanding nitinol cage covered with polytetrafluoroethylene
- Three rows of anchors along the maximum circumference secured the cage within the LAA ostium
- Positive 5-year study results, but discontinued in 2007 for commercial reasons



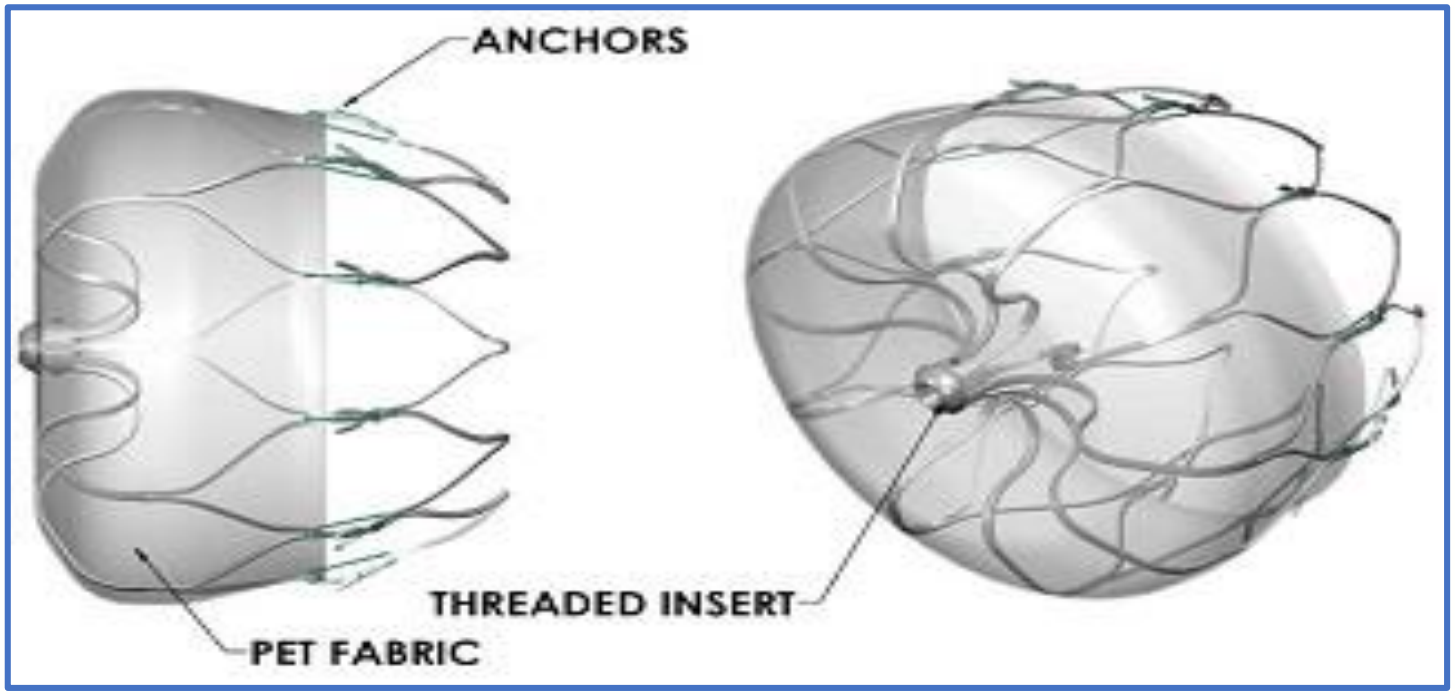
Romero J et al. *Clin Med Insights Cardiol*. 2014;8:45-52.

WATCHMAN Device

- Only LAAC device with two randomized controlled trials
- FDA approved with specific indication to reduce the risk of thromboembolism

WATCHMAN

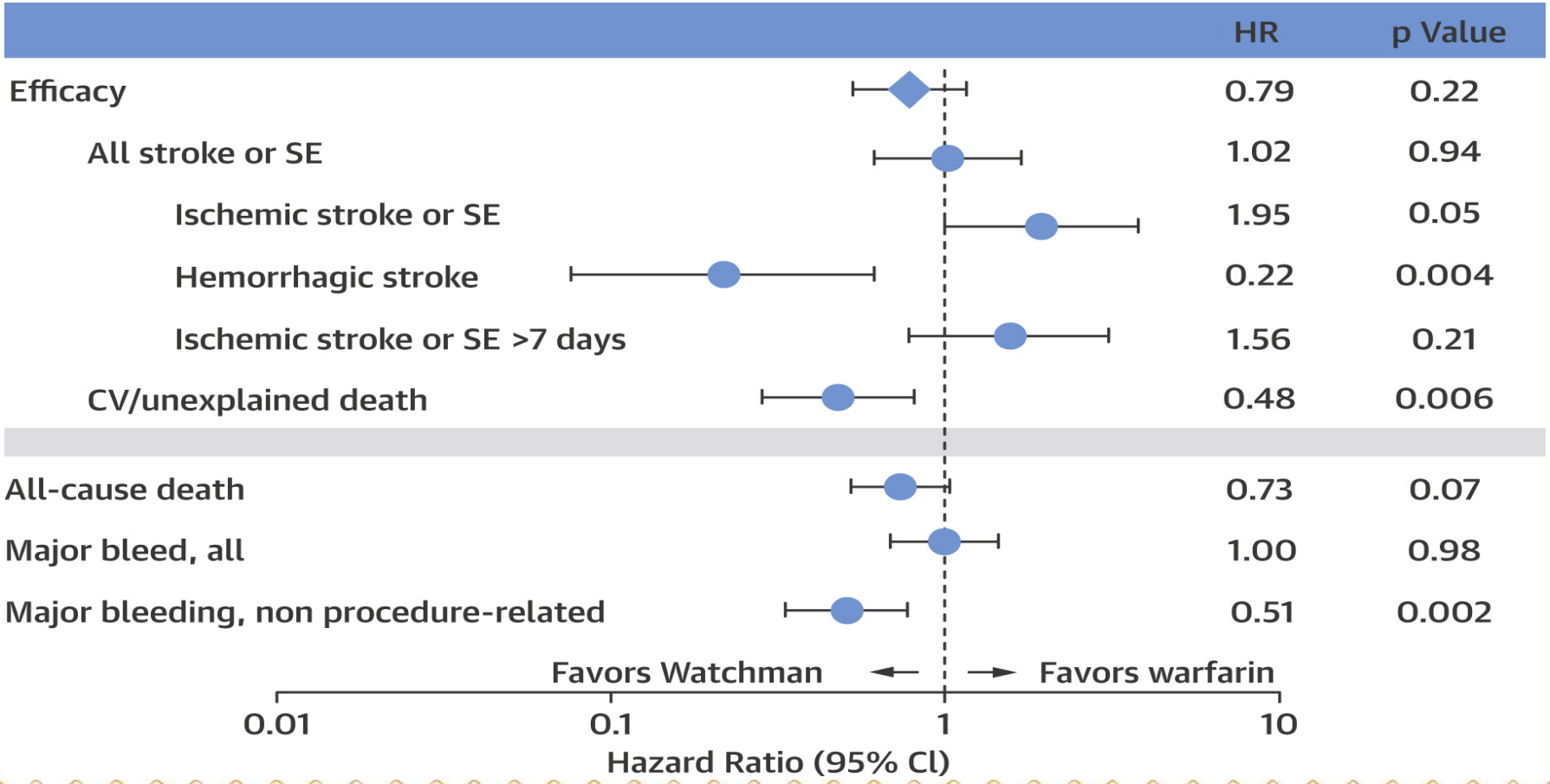
- The WATCHMAN device is designed specifically for the left atrial appendage; featuring an intra-LAA design to avoid contact with the left atrial wall, it is engineered to (1) conform to the unique anatomy of the LAA to reduce embolization risk and (2) minimize the surface area facing the left atrium to reduce the risk of post-implant thrombus formation



- Its nitinol frame radially expands to maintain position in the LAA; the nitinol frame is covered by a polyethylene terephthalate (PET) cap designed to block emboli from exiting the LAA; over time, tissue grows over the face of the PET cap

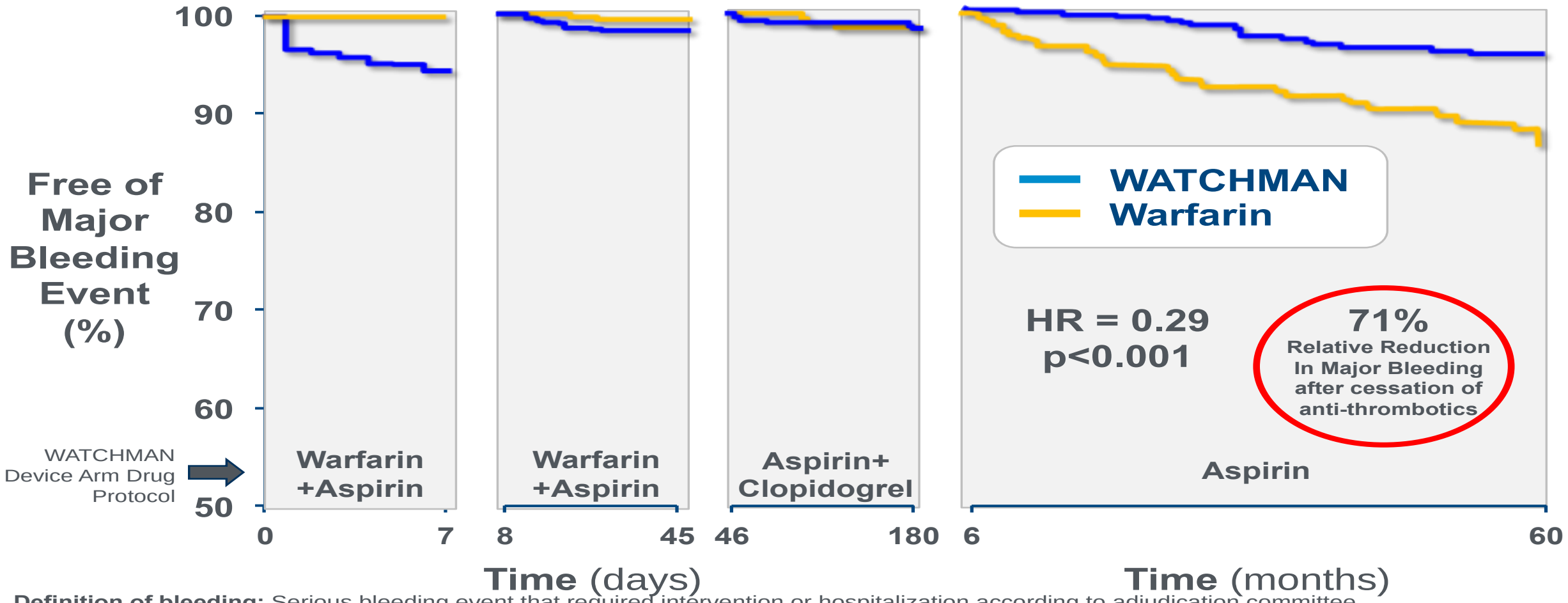
Source: FDA website
Alipour A et al. *Vasc Health Risk Manag*. 2017;13:81-90.

2. Risks of Stroke Prevention
Warfarin vs Watchman



Reddy et al *JAMA.* 2014;312(19):1988-1998.
Holmes et al. *J Am Coll Cardiol*. 2015;65(24):2614-2623.

2. Risks of Stroke Prevention
Bleeding on Warfarin vs Watchman



Definition of bleeding: Serious bleeding event that required intervention or hospitalization according to adjudication committee

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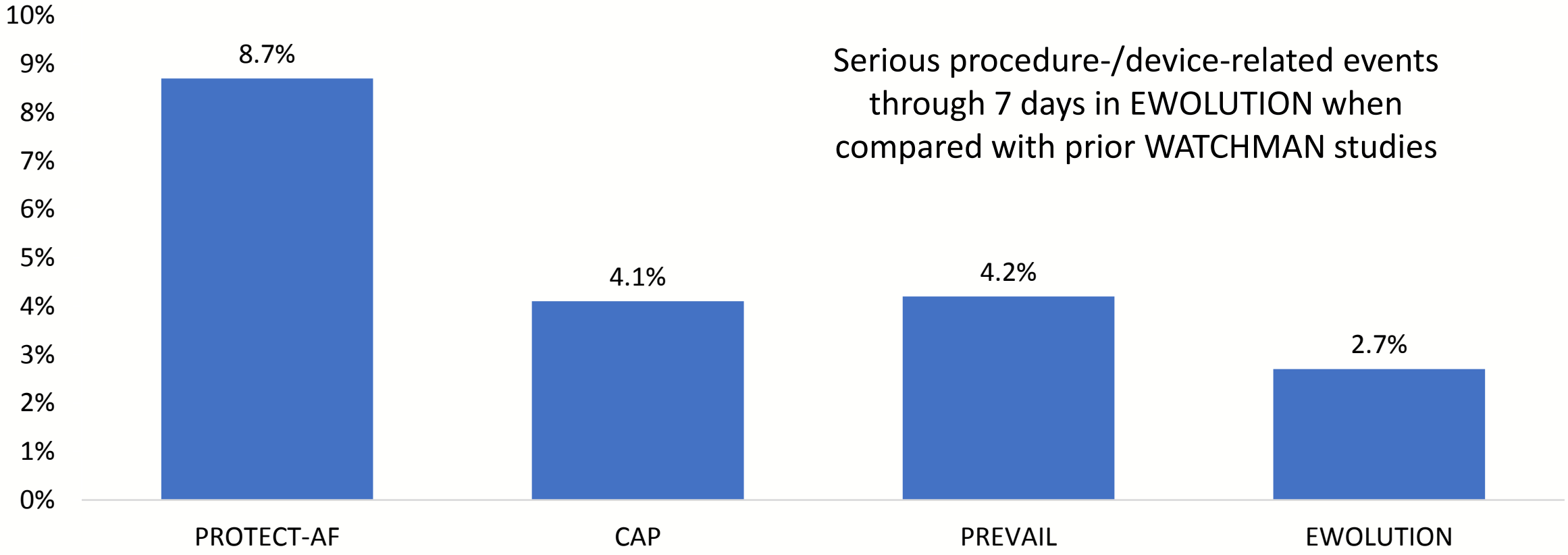
Price et al. *JACC Cardiovasc Interv.* 2015 Dec 28;8(15):1925-32

2. Risks of Stroke Prevention
Watchman Procedural Risks



Serious procedure-/device-related events through 7 days in EWOLUTION when compared with prior WATCHMAN studies

Holmes et al. *J Am Coll Cardiol*. 2015;65(24):2614-2623.

Boersma LV et al. *Eur Heart J*. 2016;37:2465-2474.

Boersma LV et al. *Catheter Cardiovasc Interv*. 2016;88:460-465.

3. Are there benefits of anticoagulation beyond the LAA?

- SPAF study (*Neurology*. 1993; 43: 32–6) :
  - 65 % of strokes in atrial fibrillation classified as cardioembolic.
  - Up to 25% of strokes can be related to intrinsic cerebrovascular disease
- AF associations “procoagulant systemic state”:
  - Myocardial infarction. Internal and Emergency Medicine. April 2010, Volume 5, Issue 2, pp 91-94
  - Complex aortic atherosclerotic plaque. Ann Intern Med. 1998 Apr 15;128(8):639-47.
  - Abnormal carotid IMT in patients with AF. Atherosclerosis. 2015 Feb;238(2):350-5.
  - AF in patients with carotid atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2013 Nov;33(11):2660-5.
- 4. Are there other diagnoses: DVT, PE?

Making decisions

- Extreme risk: LAA thrombus, other diagnoses requiring anticoagulation

- First choice

- Financial constrains
- Stable INRs
- No bleeding
- Good tolerance

- Bleeding
- Stroke on anticoagulation
- Poor tolerance
- Hemorrhagic stroke
- Procedural candidacy
- High LAA-risk

NOACs Warfarin Watchman