Novel Concepts in Left Atrial Appendage Closure Devices: Improving Safety and Efficacy

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Disclosures

- Consultant and/or Grant support:
  - Abbott, Acutus Medical*, Affera*, Apama Medical*, Aquqheart*, Atacor*, Autonomix*, Axon*, Backbeat*, Biosense-Webster, Biosig*, Biotronik, Boston Scientific, Cardiofocus, Cardionomics, CardioNXT/AFTx, Circa Scientific*, Corvia Medical*, East End Medical*, EBR, EPD*, EPIX*, EpiEP*, Eximo*, Farapulse*, Impulse Dynamics, Javelin*, Keystone*, LuxCath*, Manual Surgical Sciences*, Medlumics*, Medtronic, Middlepeak*, Newpace*, Nuvera*, Phillips, Stimda, Surecor*, Thermedical, Valcare*, VytronUS*

  * I have an equity stake in these companies

- I will be discussing devices that are not FDA-approved or have CE-Mark, and are investigational.

Outline

Novel Concepts in Left Atrial Appendage Closure Devices: Improving Safety and Efficacy

- Can't embolic strokes originate from outside the LAA?
- Issue of stroke severity
- Are there any new LAAC outcome data?
  - What is forthcoming?
- Post-Implant Follow-Up Strategy (TEE Strategy)
- Advances in Technology & Techniques

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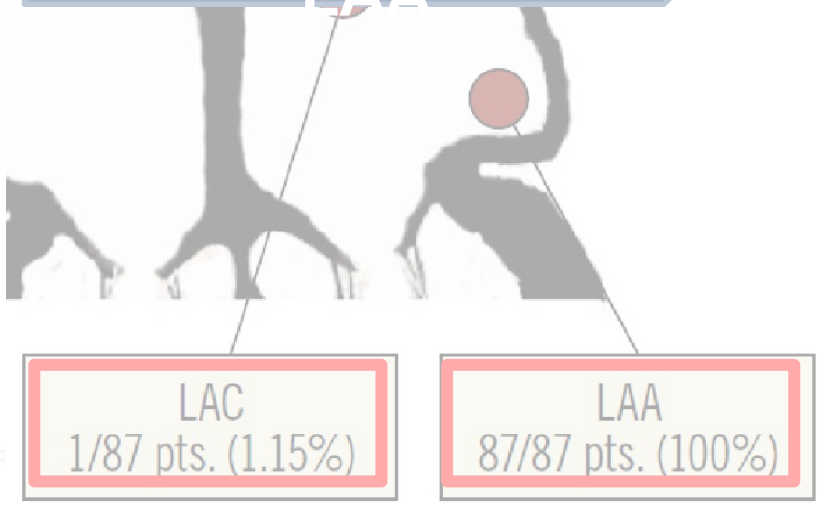
Conceptual Basis of LAA Closure

Does Site-Specific Therapy Make Sense?

TEE / CV Study

Non-valvular atrial fibrillation or flutter
n = 1,420
Atrial thrombosis = 87 patients (6.13%)

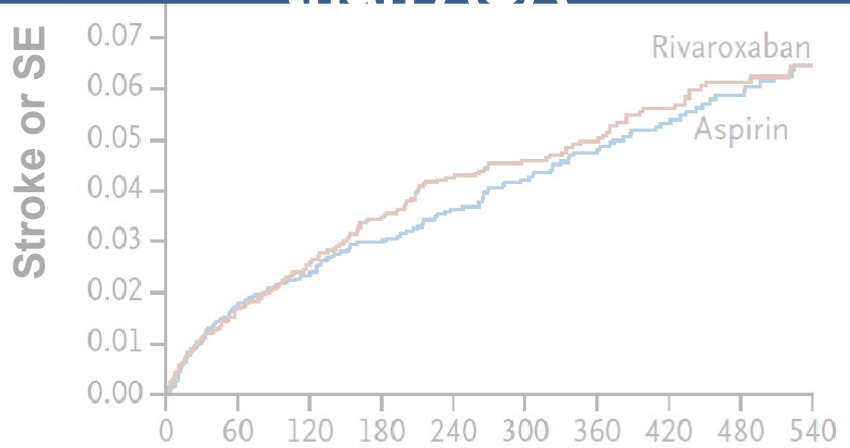
98% of left-sided thrombi are in the LAA



A.Cresti, MA.García-Fernández, H.Sievert, et al,
EuroIntervention 5:e225-e230 (2019)

- *WARSS / WASID* ASA ≈ Warfarin
- *NAVIGATE-ESUS* ASA ≈ $Riva_{15mg}$
- *RESPECT-ESUS* ASA ≈ Dabigatran
- *ATTICUS* (Compare Apixaban vs ASA)

Non-Cardioembolic Stroke: No evidence that (N)OACs provide any greater benefit than ASA



RG.Hart, M.Sharma, H.Mundl, et al, *NEJM*
doi. 10.1056/NEJMoa1802686 (2018)

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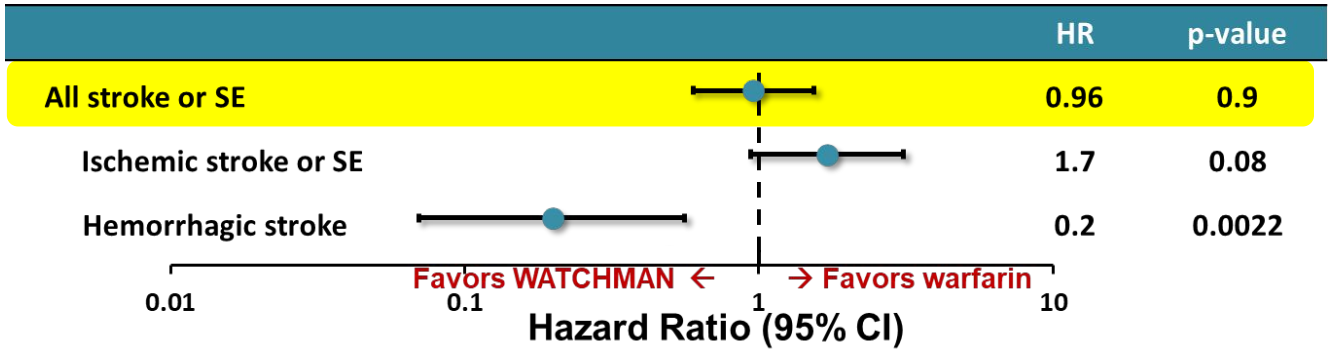
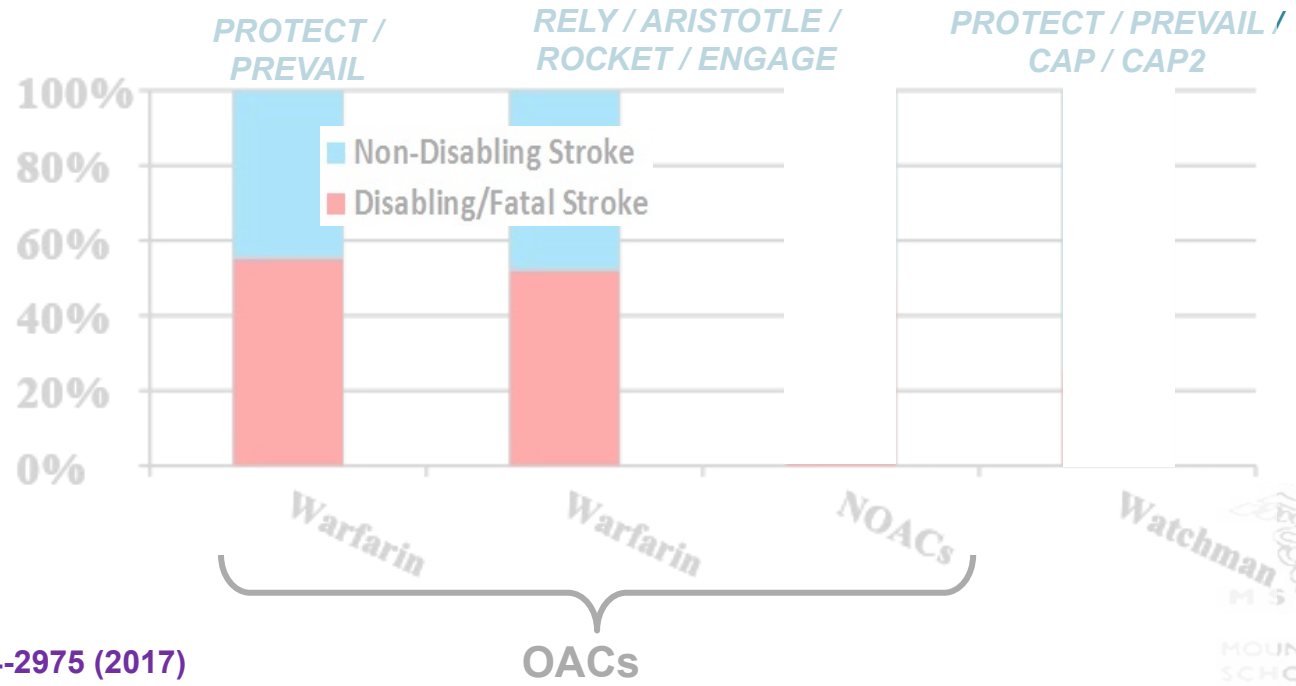
Stroke Severity in (N)OAC & LAAC Trials

Non-Disabling *vs* Disabling/Fatal

- **PROTECT-AF & PREVAIL:**
  - LAAC was non-inferior to VKAs for stroke



- **Stroke Severity**
  - Warfarin & NOACs: ~50% disabling/fatal
  - Post-LAAC strokes ~25% disabling/fatal



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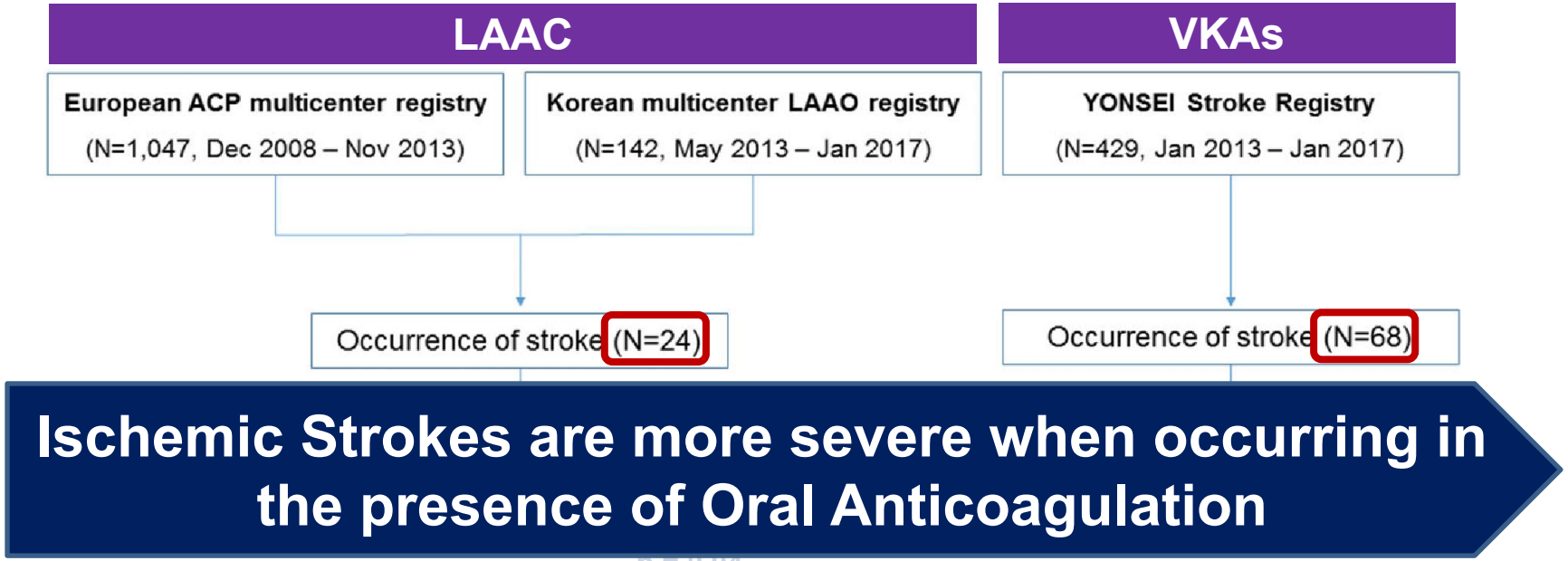
V.Reddy, SK.Doshi, S.Kar, et al, *JACC* 70(24):2964-2975 (2017)
W.Whang, DR.Holmes, NT.Gordon, et al, HRS-2019, (Abstract)

Ischemic Stroke Severity in LAAC *vs* OAC

Comparison of MRS Scores



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OH.Lee, YD.Kim, JS.Kim et al, *Catheter Cardiovasc Interv* 94:E23–E29 (2019)

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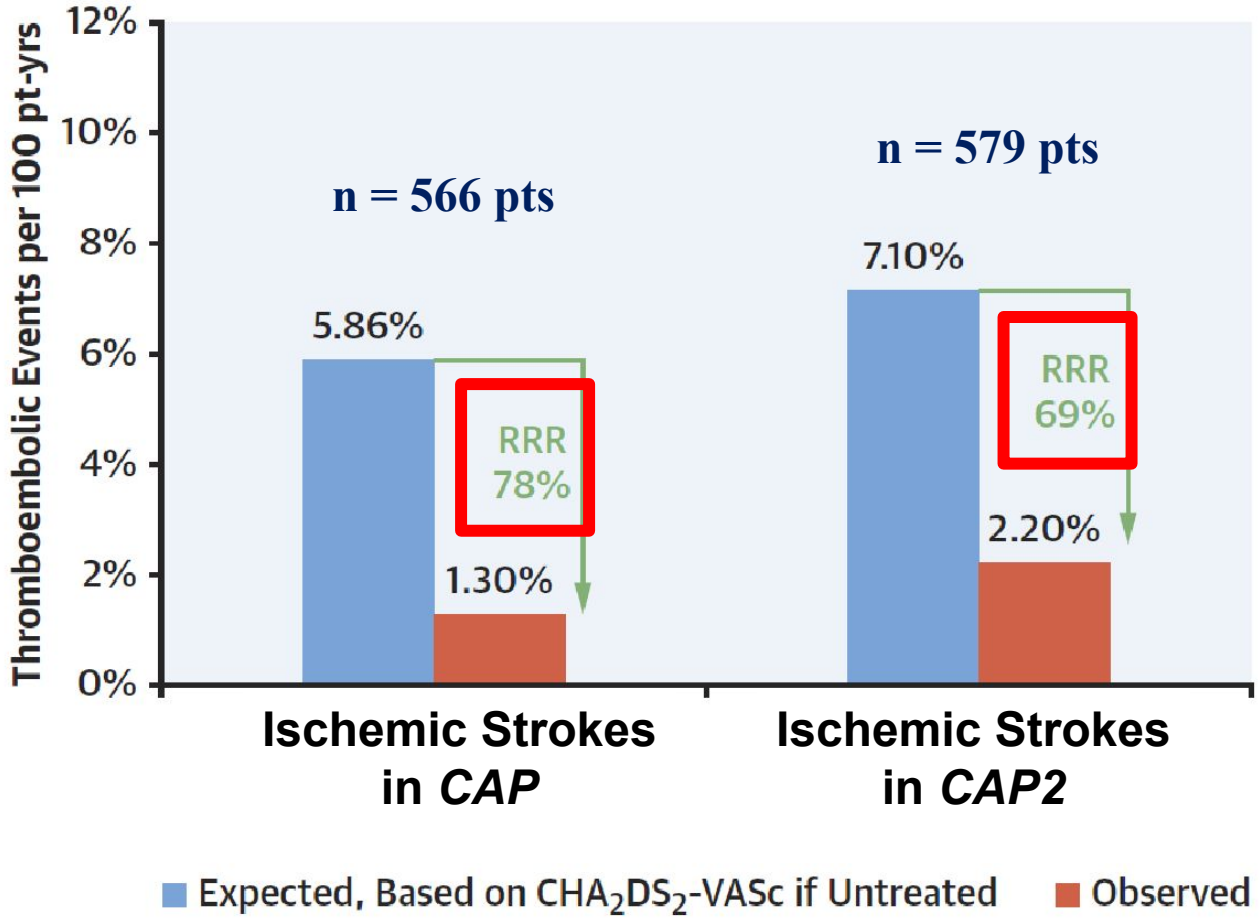
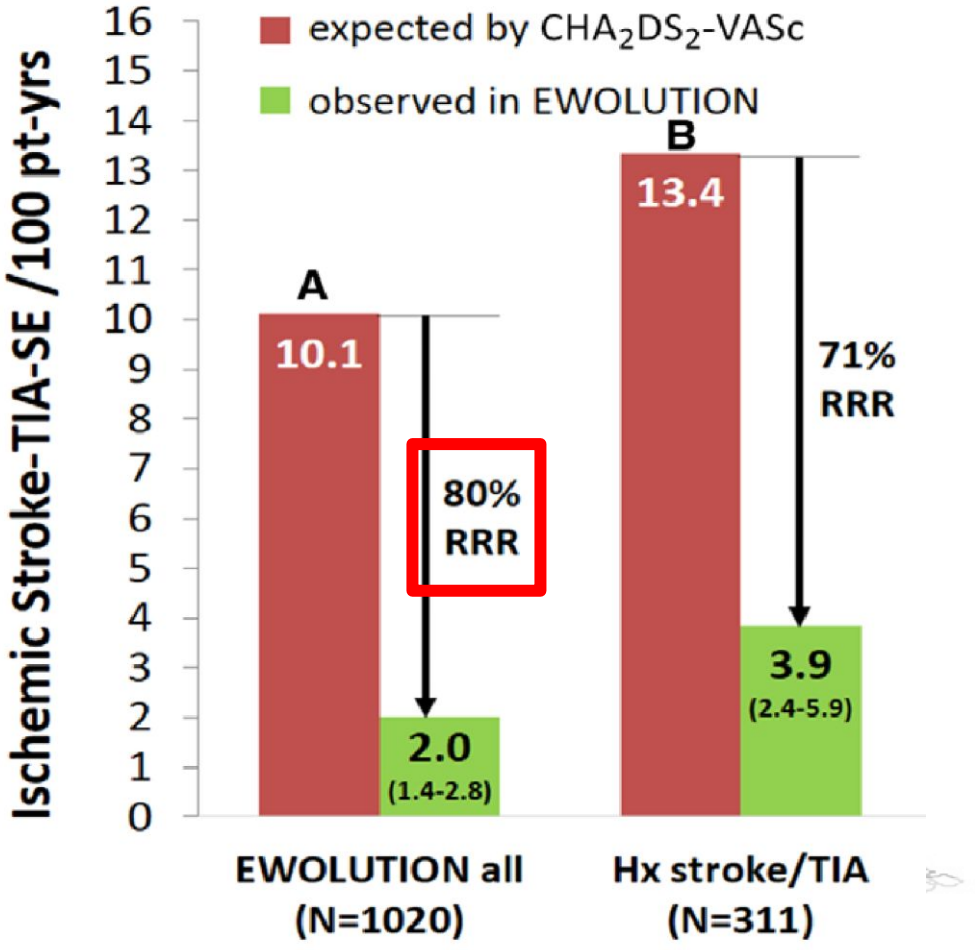
Efficacy of LAAC in Stroke Prevention

Recent Registry Data: *CAP* (5 yr) / *CAP2* (2 yr) & *EWOLUTION* (2 yr)



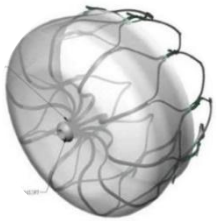
DR.Holmes, VY.Reddy, NT.Gordon et al, *J Am Coll Cardiol* 74(23):2878–89 (2019)

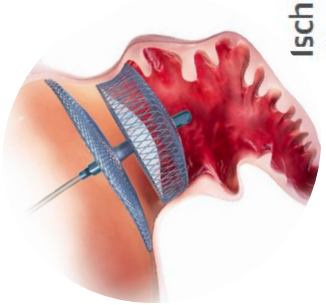


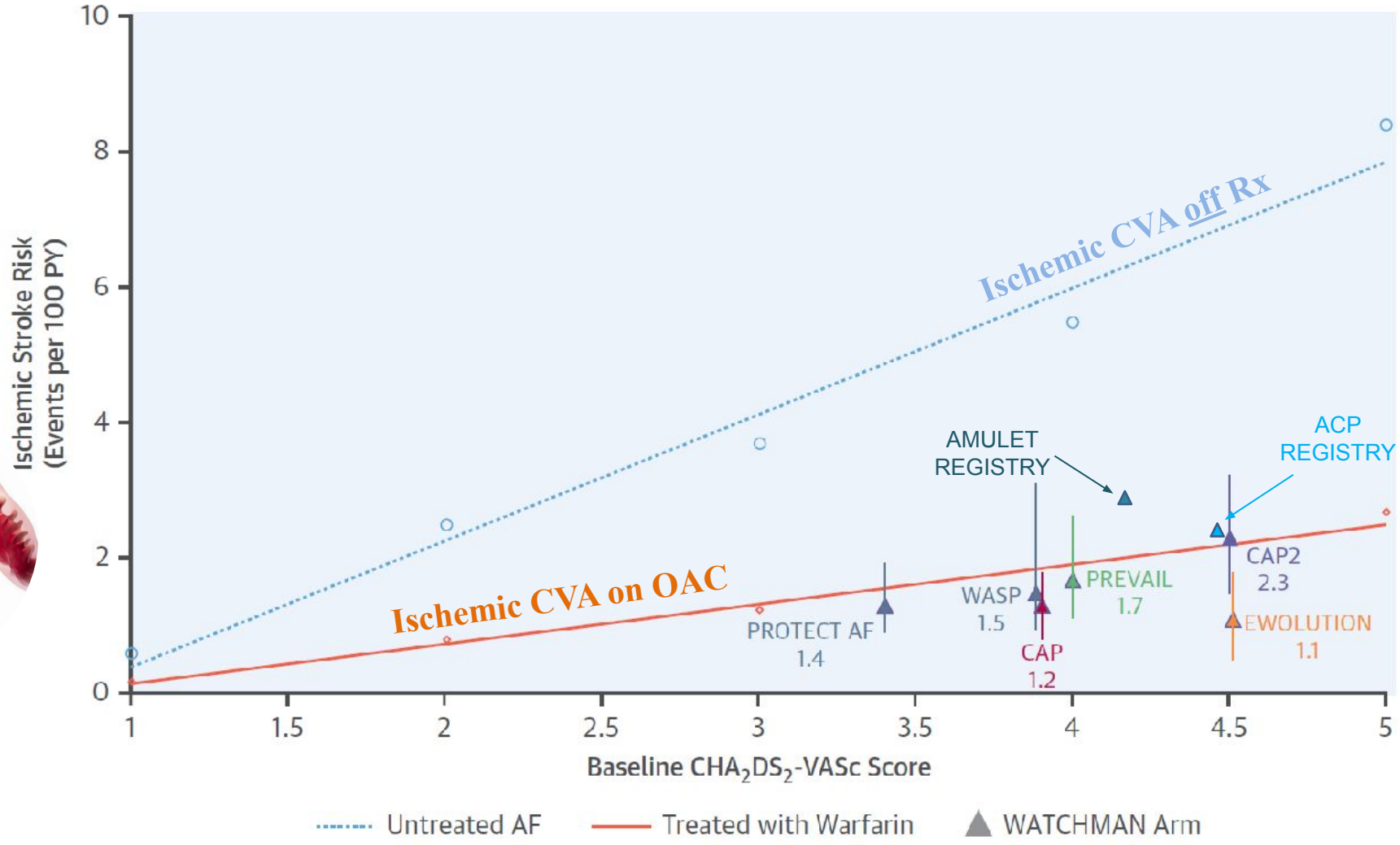
LV.Boersma, H.Ince, S.Kische et al, *Circ Arrhythm Electrophysiol. 2019;12:e006841* (2019)

Efficacy of LAAC in Stroke Prevention

LAAC FDA Studies & Large Multicenter Registries







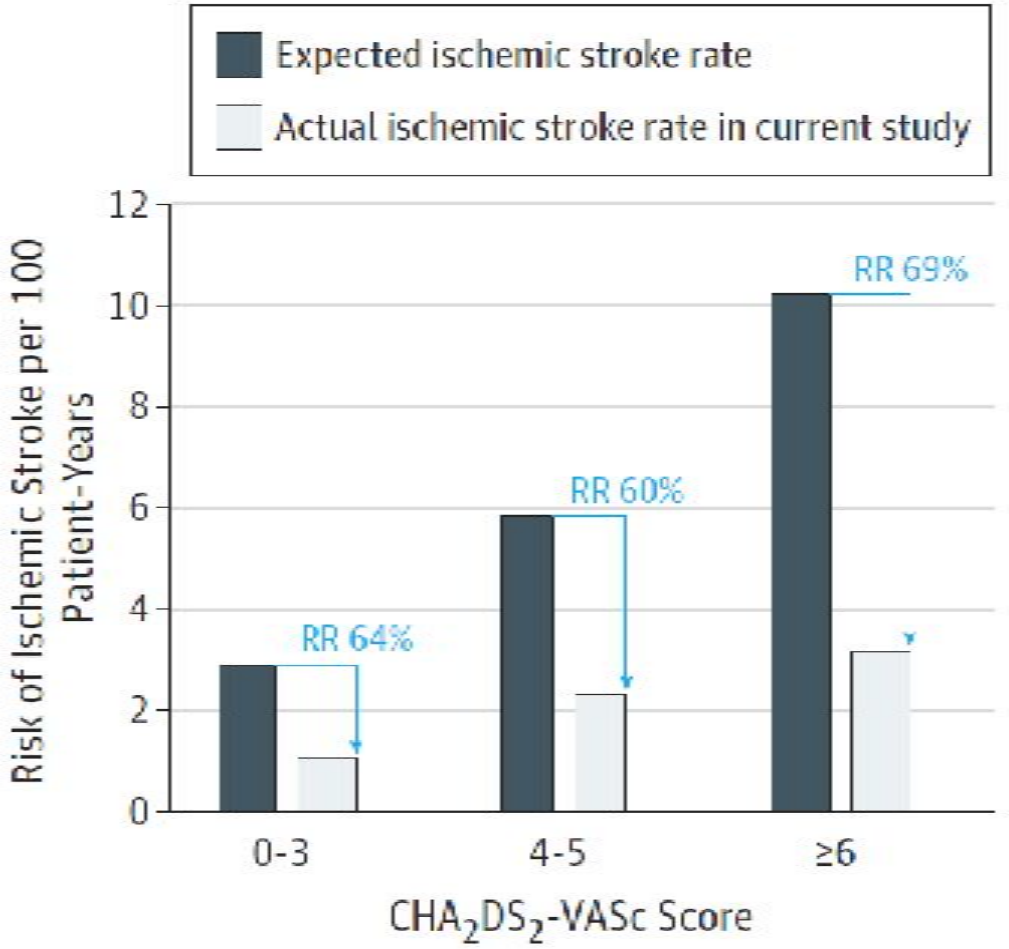
Graph adapted from data from: Friberg. *Eur Heart J (2012); NICE UK (2014)*

TOTAL ~ 4,500 pts

- *CAP*
  n=566; F/U = 5 yrs
- *CAP2*
  n=579; F/U = 2 yrs
- *EWOLUTION*
  n=1,021; F/U = 1 yr
- *WASP*
  n=201; F/U = 1 yr
- *ACP Registry*
  n=1,047; F/U = 1 yr
- *AMULET Registry*
  n=1,088; F/U =

Efficacy of LAAC in Stroke Prevention

CMS Claims Data (n=13,627)



R.Kabra, S.Girotra, MV.Sarrazin, *JAMA Network Open 2(10):e1914268* (2019)

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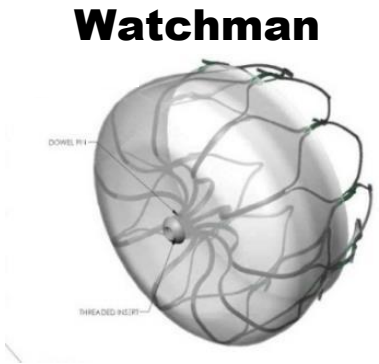
Efficacy of LAAC in Stroke Prevention

PRAGUE-17: RCT of LAAC *vs* NOACs

- *PRAGUE-17 (*NCT02426944) was an investigator-initiated, multicenter, open-label, **randomized non-inferiority trial**
  - Conducted in **10 Czech Cardiac Centers**
  - Funded by the Czech Ministry of Health



- RCT of NOACs vs LAAC

- Non-valvular AF + one of the following:
  I. History of **bleeding** requiring intervention or hospitalization, ***or***
  II. History of a **cardioembolic event** while taking anticoagulation, ***or***
  III. CHA_2DS_2-VASc ≥ 3 & HAS-BLED ≥ 2

- Primary Endpoint
  - Stroke / TIA, SE, CV Death, Major Bleed/CRNMB, Complications

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PRAGUE-17 Trial

Baseline Characteristics (n = 402 pts)

	NOAC (n = 201)	LAAC (n = 201)
Age (years)	73.2 ± 7.2	73.4 ± 6.7
Male gender (%)	130 (64.7%)	134 (66.7%)
AF type Paroxysmal (%)	67 (33.3%)	53 (26.4%)
Persistent (%)	46 (22.9%)	47 (23.4%)
LS persistent (%)	16 (8.0%)	18 (9.0%)
Permanent (%)	72 (35.8%)	83 (41.3%)
CHA_2DS_2-VASc	4.7 ± 1.5	4.7 ± 1.5
CHA_2DS_2-VASc $\geq$ 6 (%)	54 (26.9%)	56 (27.9%)
HAS-BLED	3.0 ± 0.9	3.1 ± 0.9
Heart failure (%)	90 (44.8%)	88 (43.8%)
Hypertension (%)	186 (92.5%)	186 (92.5%)
Diabetes mellitus (%)	90 (44.8%)	73 (36.3%)
History of cardioembolic event (%)	69 (34.3%)	73 (36.3%)
History of MI (%)	39 (19.4%)	30 (14.9%)
History of bleeding/bleeding predisposition	95 (47.3%)	109 (54.2%)

P.Osmancik / P.Neuzil / VY.Reddy, *ESC Congress* – LBCT (2019)

Treatment characteristics

LAAC & NOAC Arms

LAAC arm

- 14 (7.0%) did not undergo the procedure
- Procedure was **successful in 96.8%** (181/187) of procedure attempts
- Used: **Amulet-61%, Watchman-36%** or Watchman-Flex-3%
- Post-LAAC Antithrombotic regimen: **DAPT in 82%**
- Complications: in 9 pts (**4.8%**) including:
  - One procedure-related death (groin hematoma, vascular surgery, MI)
  - One device-related death (late pericardial tamponade)

[Operator experience: 40% = 0 cases & Only 1 operator > 100 cases]

NOAC arm

- **Apixaban** used in 192 patients (**95.5%**)

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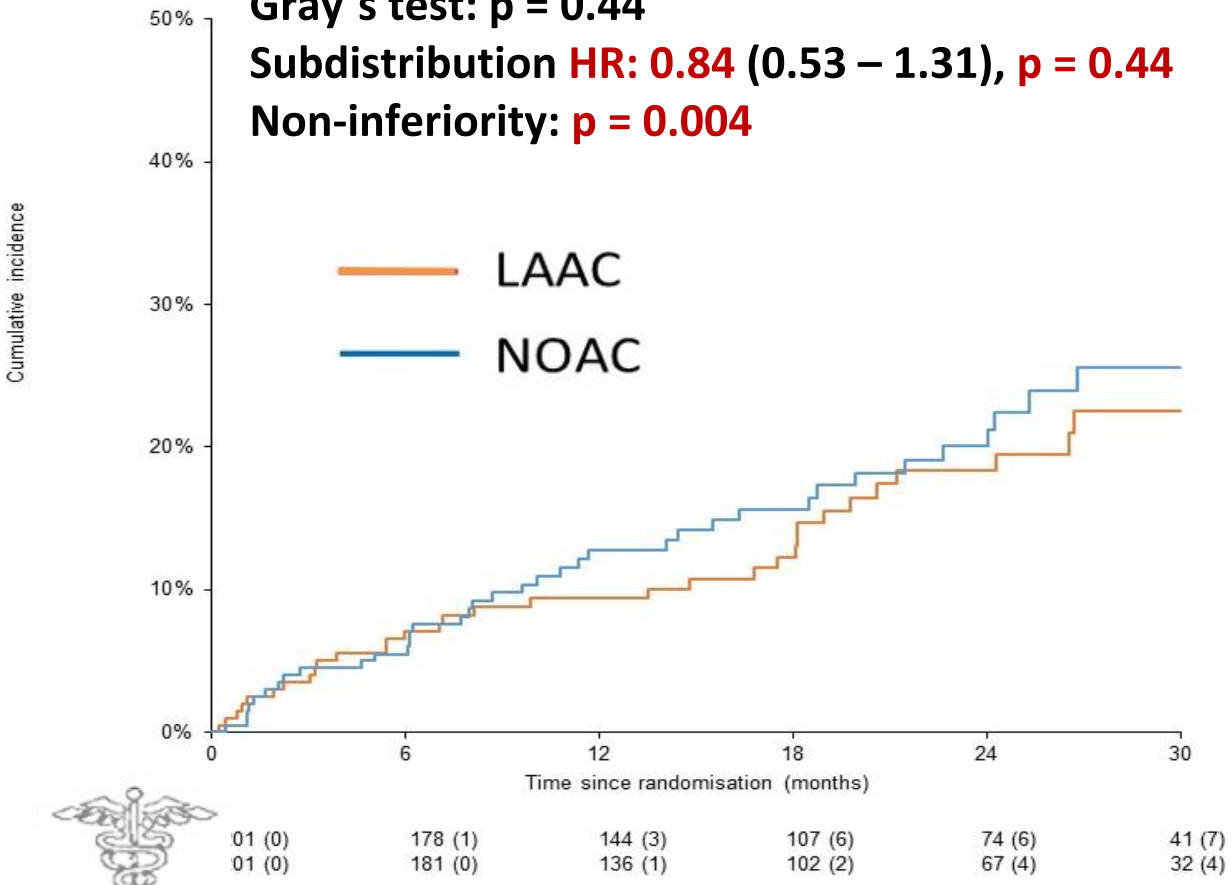
PRAGUE-17: Primary Endpoint

Cumulative Incidence Function (mITT Population)

Gray´s test: p = 0.44
Subdistribution HR: 0.84 (0.53 – 1.31), p = 0.44
Non-inferiority: p = 0.004



	sHR (95% CI)	p value
Primary Endpoint		
mITT	0.84 (0.53 – 1.31)	0.44
Per Protocol	0.82 (0.52 – 1.30)	0.40
On-Treatment	0.79 (0.49 – 1.25)	0.31
All-Stroke/TIA	0.99 (0.39 – 2.50)	0.99
CV Death	0.75 (0.34 – 1.62)	0.46
Bleeding*	0.81 (0.44 – 1.52)	0.51
Non-Procedure Bleeding*	0.53 (0.26 – 1.06)	0.07

Mean follow-up: 20.8 ± 10.8 mo (695 pt-yr)

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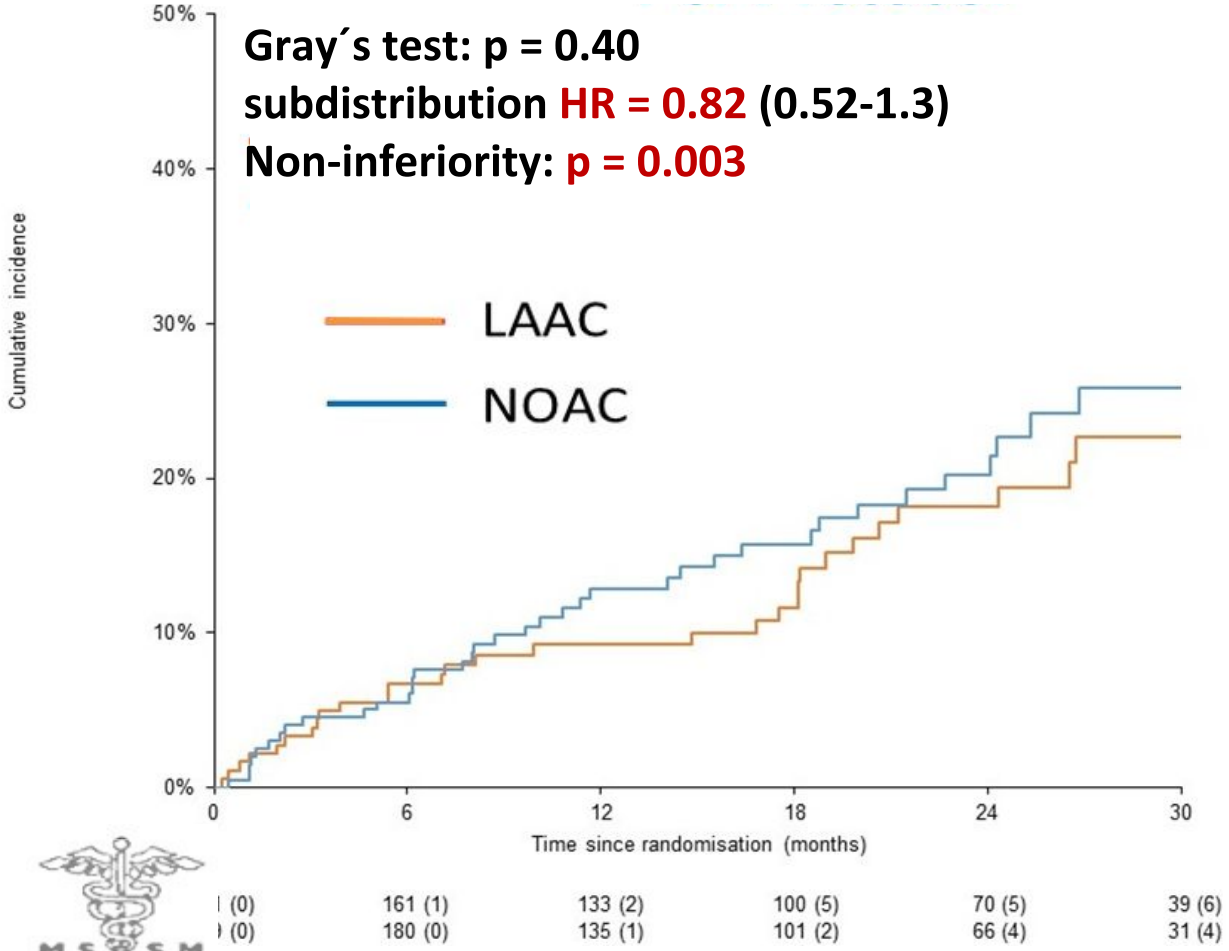
PRAGUE-17: Primary Endpoint

Cumulative Incidence Function (Per Protocol Population)



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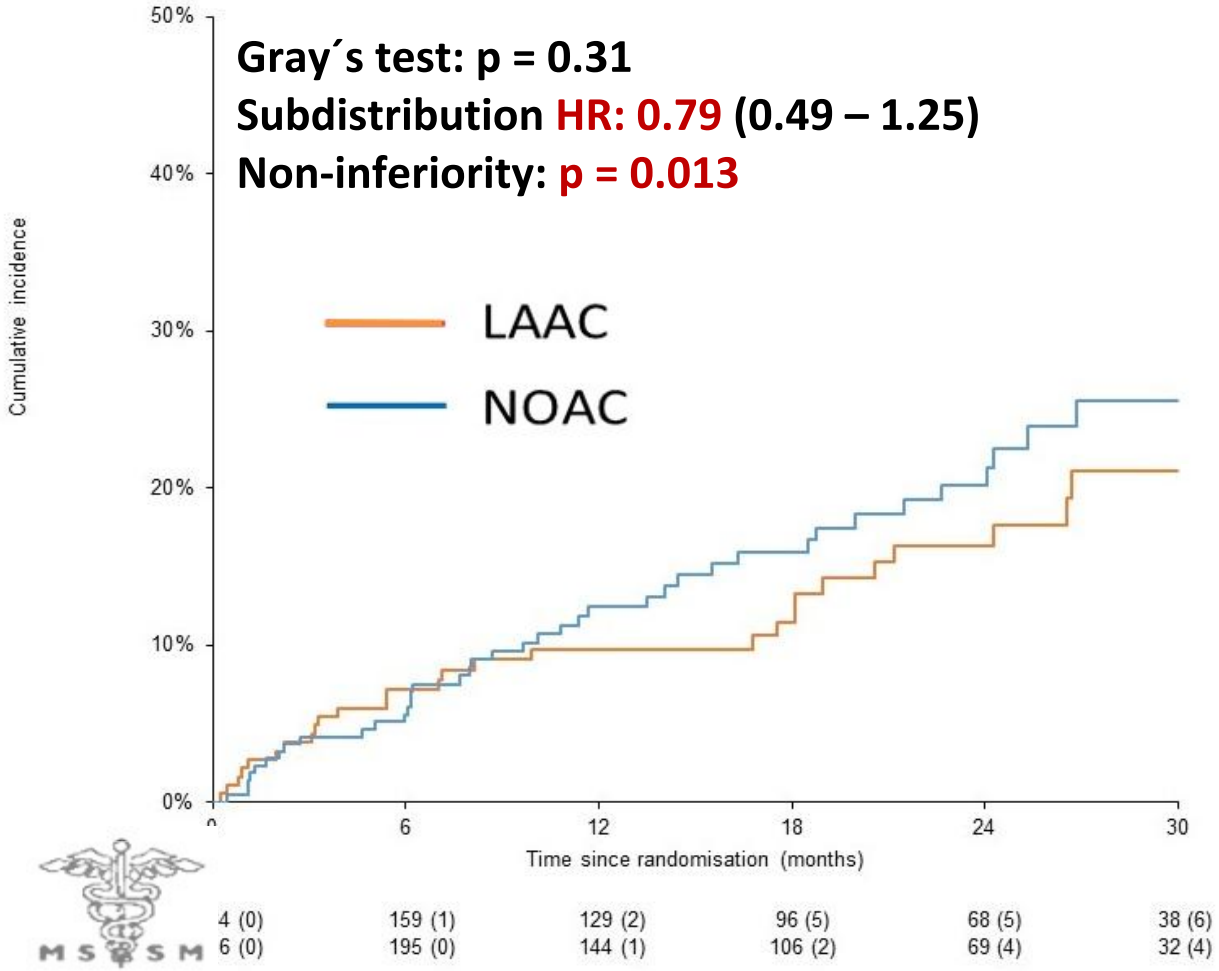
PRAGUE-17: Primary Endpoint

Cumulative Incidence Function (On-Treatment Population)



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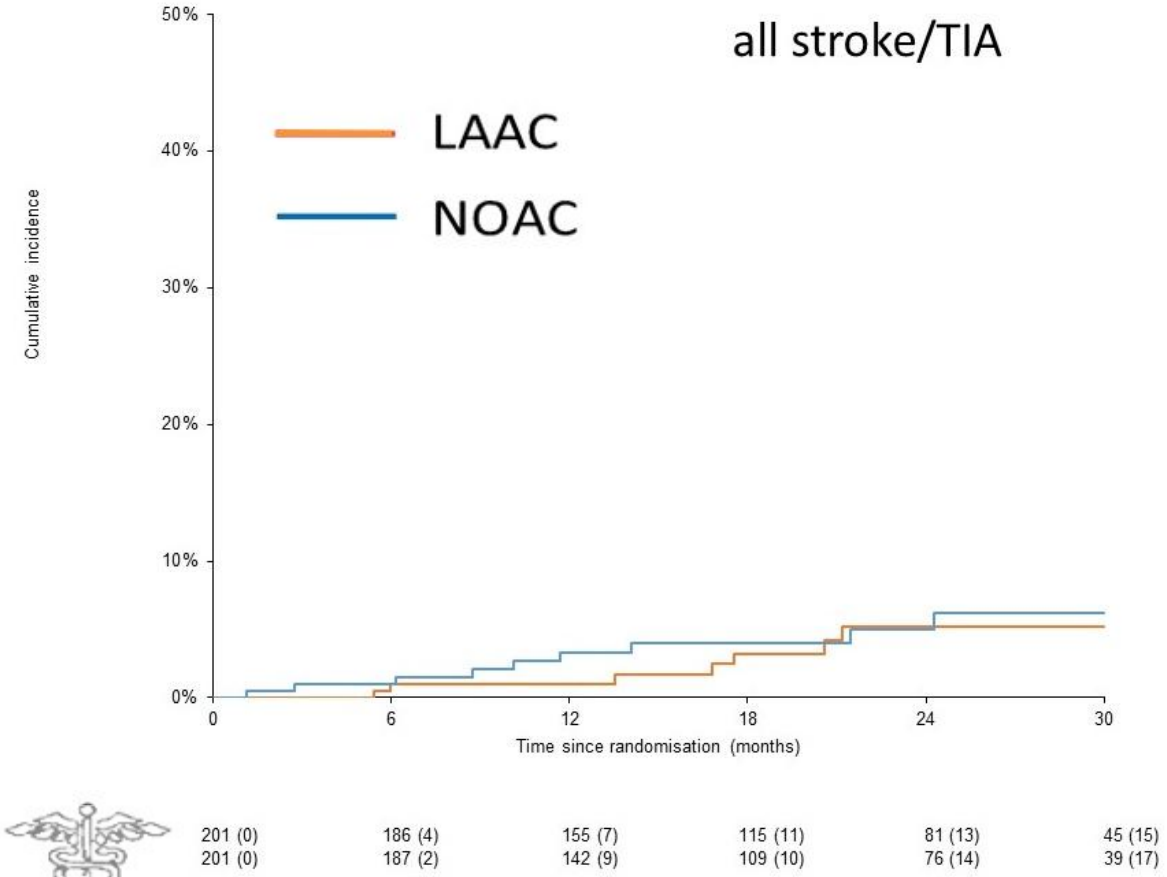
Secondary Endpoint: All Stroke/TIA

Cumulative Incidence Function (mITT Population)



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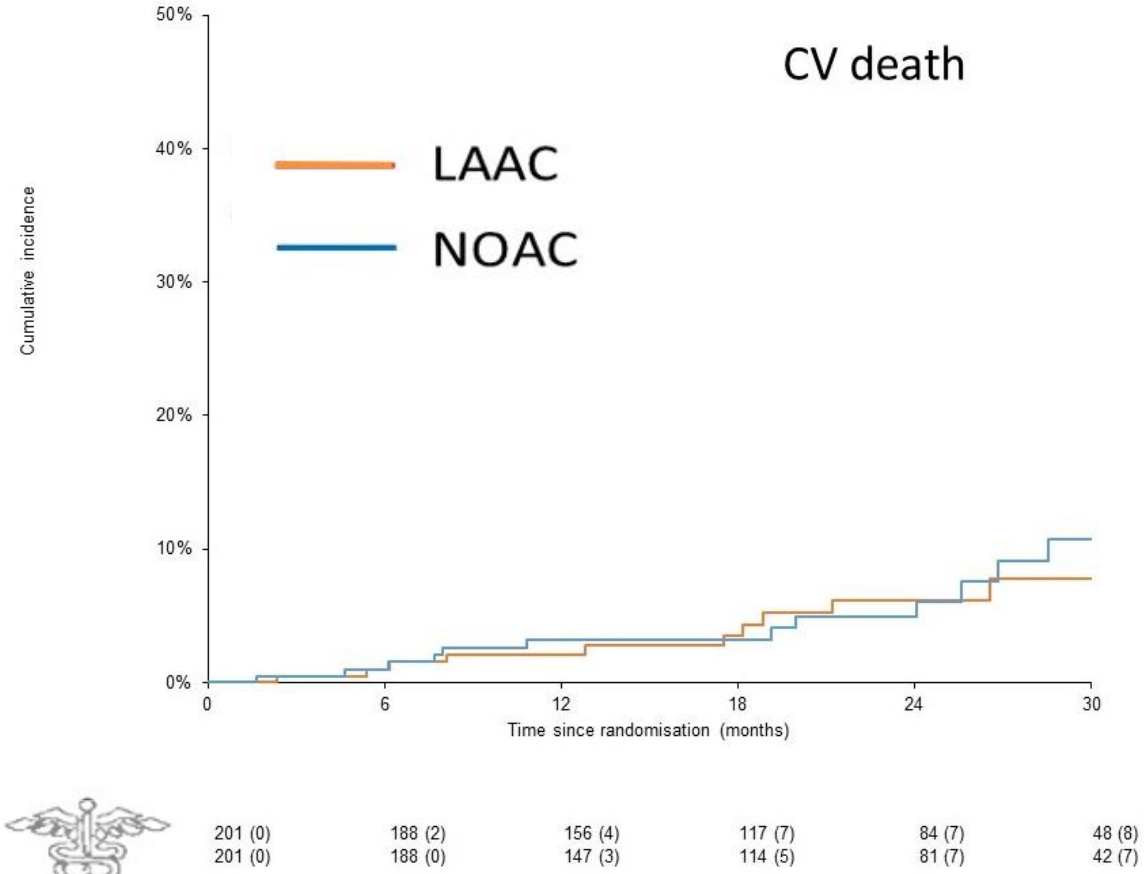
Secondary Endpoint: Cardiovascular Death

Cumulative Incidence Function (mITT Population)



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*** Incorporates the 2 LAAC deaths**

Mean follow-up: 20.8 ± 10.8 mo (695 pt-yr)

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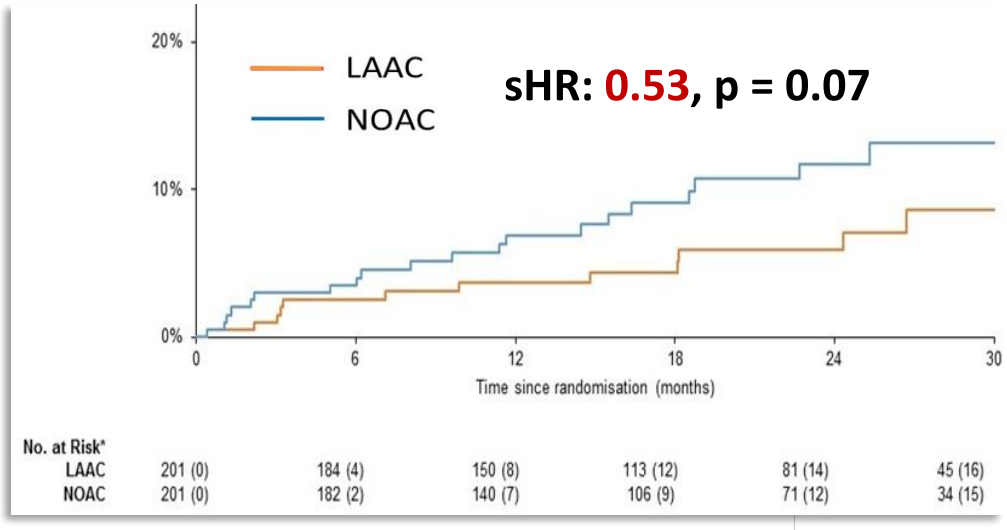
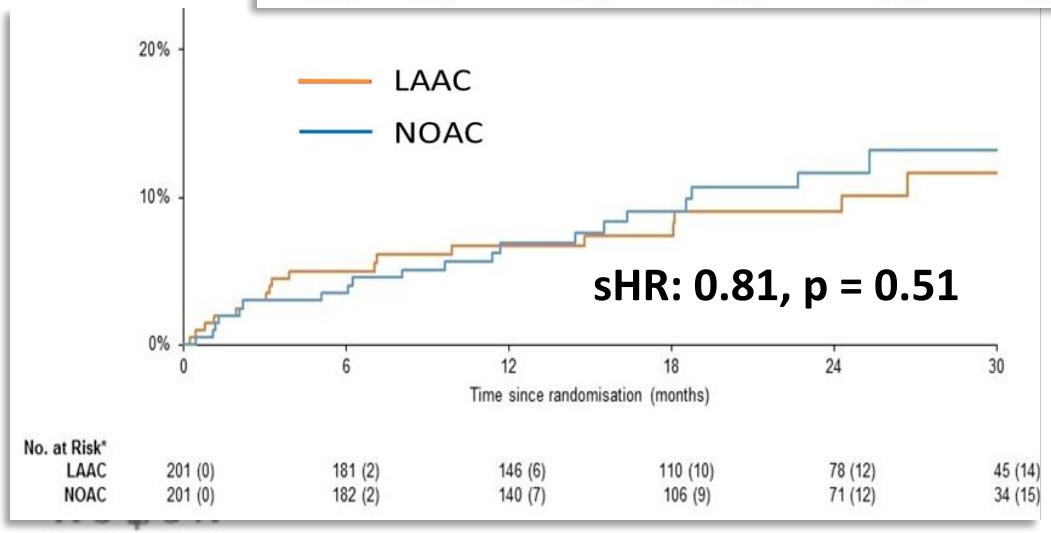
Secondary Endpoint: Bleeding

Cumulative Incidence Function (mITT Population)





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* Major + CRNM Bleeding

Mean follow-up: 20.8 ± 10.8 mo (695 pt-yr)

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PRAGUE-17

Conclusions

- Among high-risk AF patients, LAAC was noninferior to NOACs in preventing major cardiovascular or neurological events
- Safety issues remain with LAAC, warranting further refinements in operator technique and device technology
- **Limitation**: *PRAGUE-17* was insufficiently powered to separately evaluate differences in the "safety" and "efficacy" components of the primary endpoint (eg: stroke/death, bleeding)

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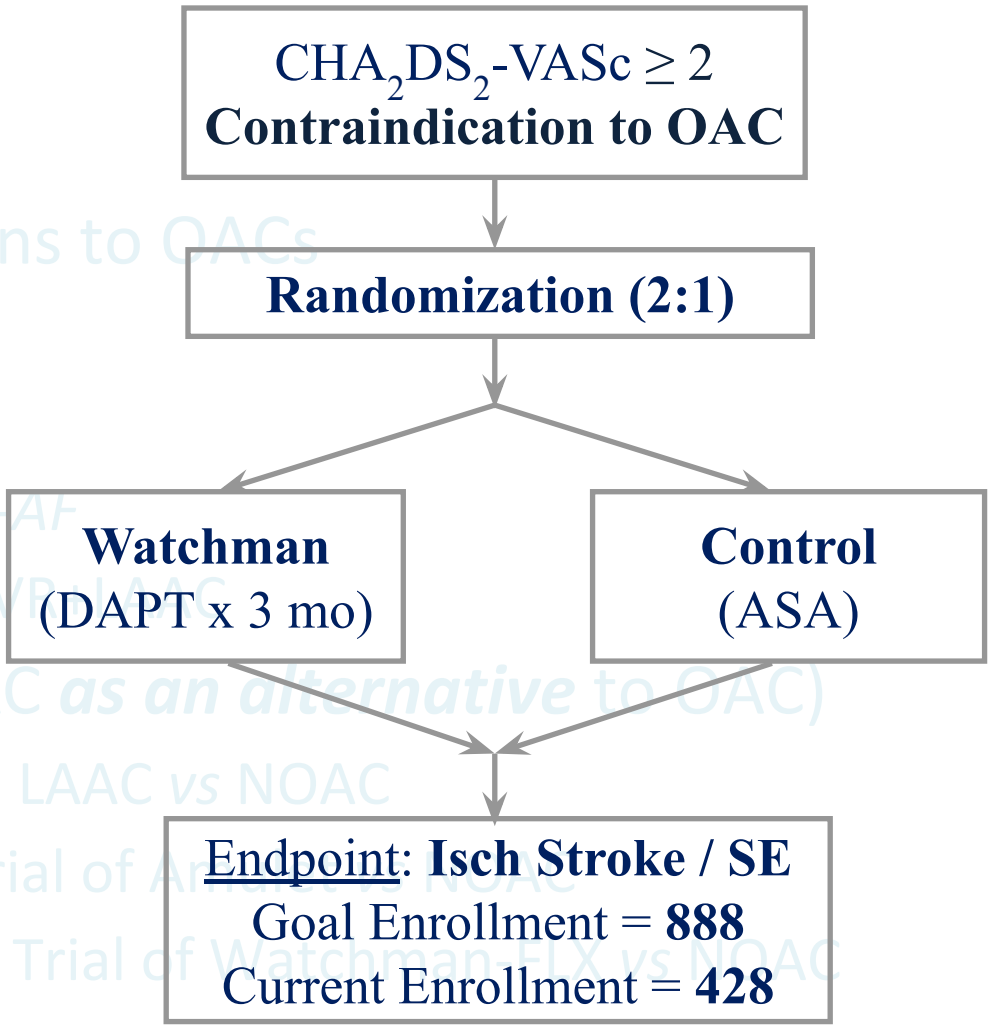
LAA Closure
Randomized Clinical Trials

- "Absolute" Contraindications to OACs
  - *ASAP-TOO*: FDA Trial
  - *STROKECLOSE*
- "Relative" Contraindications to OACs
  - ✔ *PROTECT-AF / PREVAIL*
  - ✔ *PRAGUE-17*
  - *CLOSURE-AF / OCCLUSION-AF*
  - *WATCH-TAVR*: TAVR *vs* TAVR+LAAC
- No Contraindications (LAAC ***as an alternative*** to OAC)
  - *OPTION*: After AF ablation, LAAC *vs* NOAC
  - *CATALYST* (Abbott): FDA Trial of Amulet vs NOAC
  - *CHAMPION-AF* (BSCI): FDA Trial of Watchman-FLX vs NOAC



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LAAC *vs* NOAC

CATALYST: FDA Randomized Clinical Trial

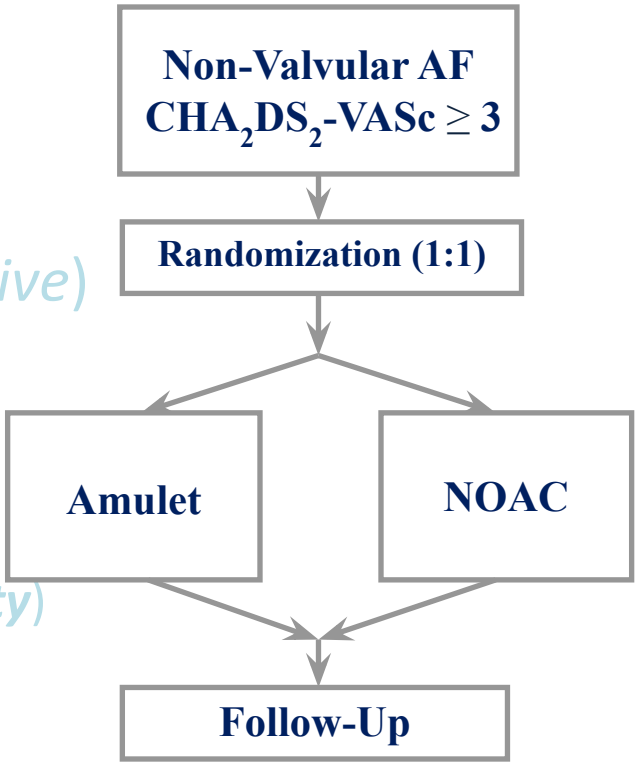
Amulet

vs

- Multicenter, multinational RCT
- Randomization, 1:1 Amulet *vs* NOACs
- Key Inclusion Criterion
  - CHA_2DS_2-VASc ≥ 3 (*tentative*)
- Total sample size **~2650 patients** (*tentative*)
- Enrollment at ~150 centers

- Primary Endpoints (*tentative*):
  - Isch Stroke / SE / CV Mortality (***non-inferiority***)
  - Major Bleed / CRNMB (***non-superiority***)
  - Non-procedure MB / CRNMB (***superiority***)

- Trial enrollment expected in ~2 months



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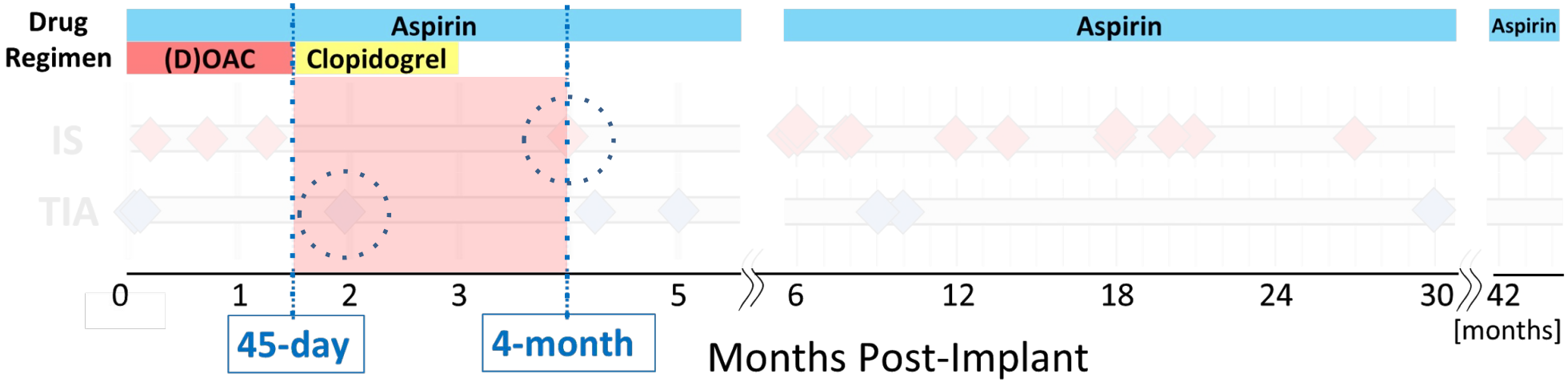
What is the Optimal Time for the Follow-Up TEE?

Results of a Two-Center Analysis

- What is the purpose of the TEE?
  - Assess for closure to determine whether to continue OAC
  - Assess for device-related thrombus (DRT)
- 2-Center retrospective study: Strategy of TEE at 4 months
  - 521 Patients: Warfarin – 26%, NOACs – 55%, DAPT – 19%
  - Median f/u = 12mo 17 ischemic strokes / 6 TIAs



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K.Kuroki, SK.Doshi, CB.Ducharme, et al, *HRS-2019,* Abstract

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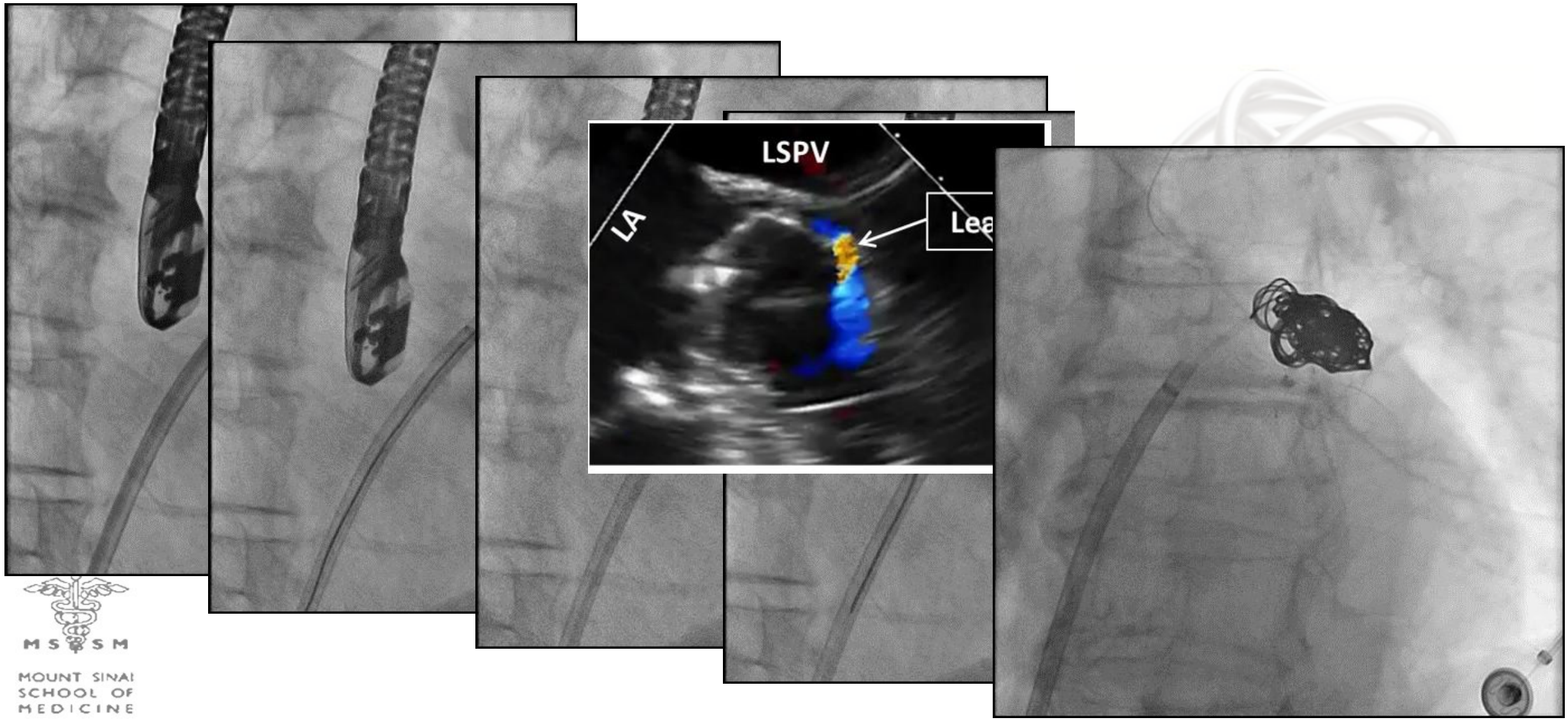
Peri-Device Leaks After LAAC

Obliteration with Coils In whom should this be employed?



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Novel LAAC Devices for Stroke Prevention

Status in the United States

Watchman-FLX

Amulet

Wavecrest

Conformal

- *PINNACE-FLX* (Watchman-FLX): Data to be presented soon (? HRS)
- *E* (Amulet vs Watchman): In follow-up
- IDE (W st vs W Recruiting
- EF

18 strut frame (*vs* 10)

Watchman

Watchman-FLX

Recessed metal screw on proximal face

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Novel LAAC Devices for Stroke Prevention

Status in the United States

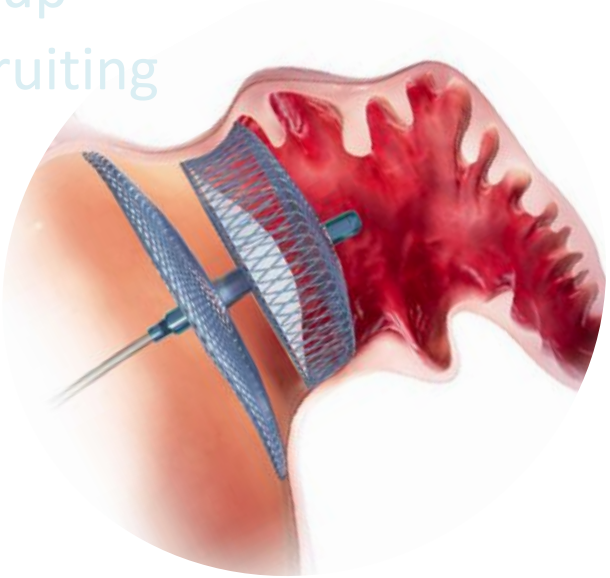
Watchman-FLX

Amulet

Wavecrest

Conformal

- *PINNACE-FLX* (Watchman-FLX): Data to be presented soon (? HRS)
- *AMULET IDE* (Amulet vs Watchman): In follow-up
- Wavecrest IDE (Wavecrest vs Watchman): Recruiting
- Conformal: EFS IDE Ongoing



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Novel LAAC Devices for Stroke Prevention

Status in the United States

Watchman-FLX

Amulet

Wavecrest

Conformal

- *PINNACE-FLX* (Watchman-FLX): Data to be presented soon (? HRS)
- *AMULET IDE* (Amulet vs Watchman): In follow-up
- Wavecrest IDE (Wavecrest vs Watchman): Recruiting
- Conformal: EFS IDE Ongoing

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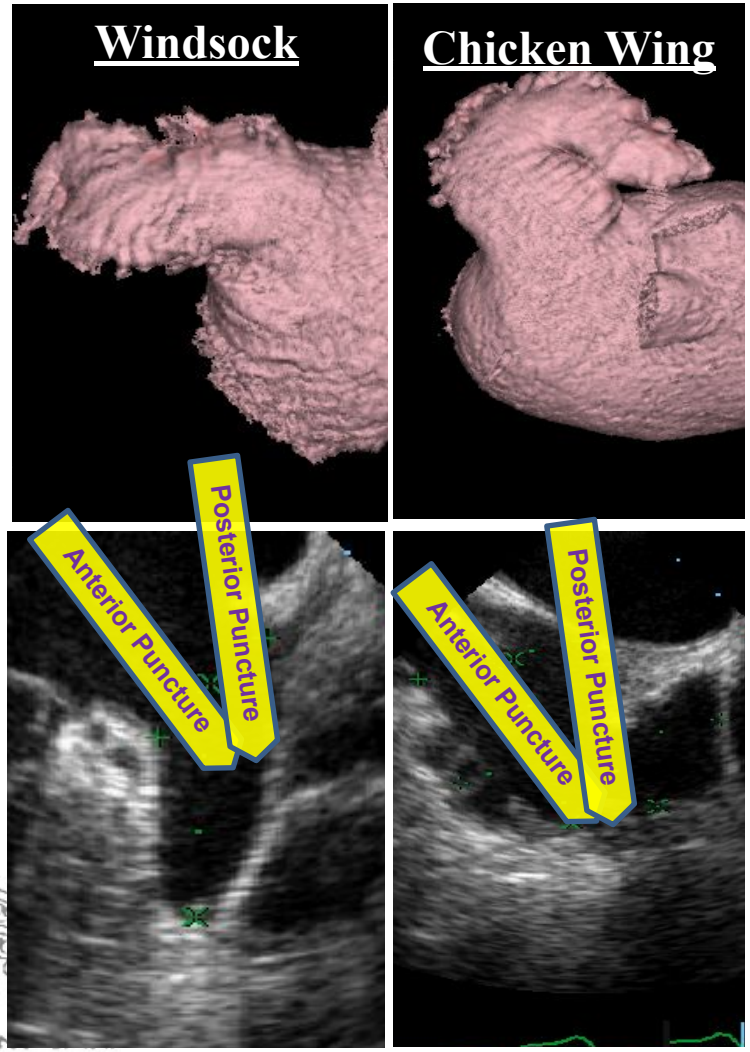
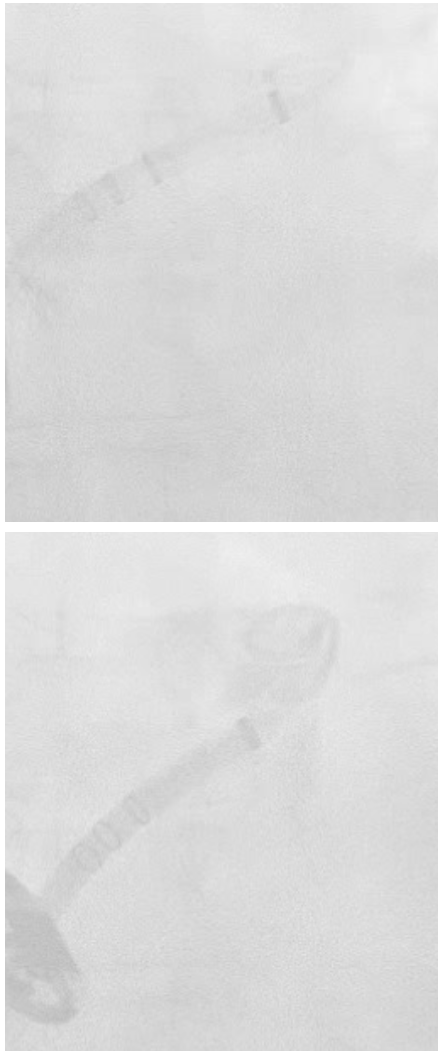
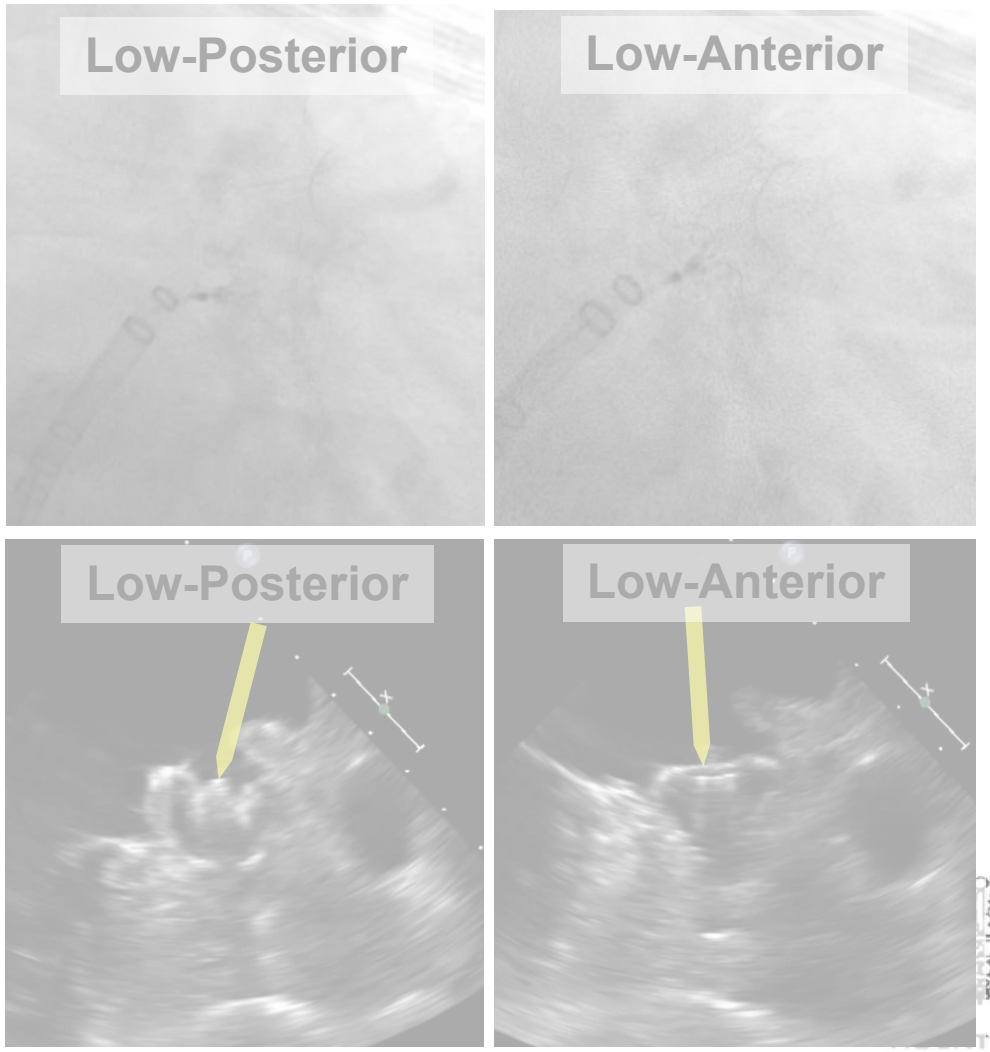
The Transeptal Puncture

Making the Difficult Case Easy … or *Vice Versa*







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