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Watchman: Data Synthesis and Ongoing Trials

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Presenter Disclosure Information

David R. Holmes, Jr., M.D.

"Watchman: Data Synthesis and Ongoing Trials"

The following relationships exist related to this presentation:

None

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Why do we need more data?

- Device landscape changes
  - New devices
    - Improved initial devices design
    - New designs
- Targets have changed
  - Patients not treated before
    - ICH, chronic kidney disease
  - New targets – Hybrid procedures
    - TAVR
    - MitraClip
    - PVI

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Why do we need more data?

- Alternative therapy changes
  - NOACs
- New information of ‘feet of clay’
  - Device associated thrombus
  - Residual leak
- Concepts change
  - Importance of LAA and homeostasis
  - Importance of LAA on atrial fibrillation
    - Induction vs maintenance

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Atrial Fibrillation
Patients

- Stroke is single most feared complication of CV disease
- Higher mortality and morbidity than non-embolic strokes
- Up to 15-20% AF strokes fatal
- High recurrence rates
- Cost of treatment
- Cost of prevention

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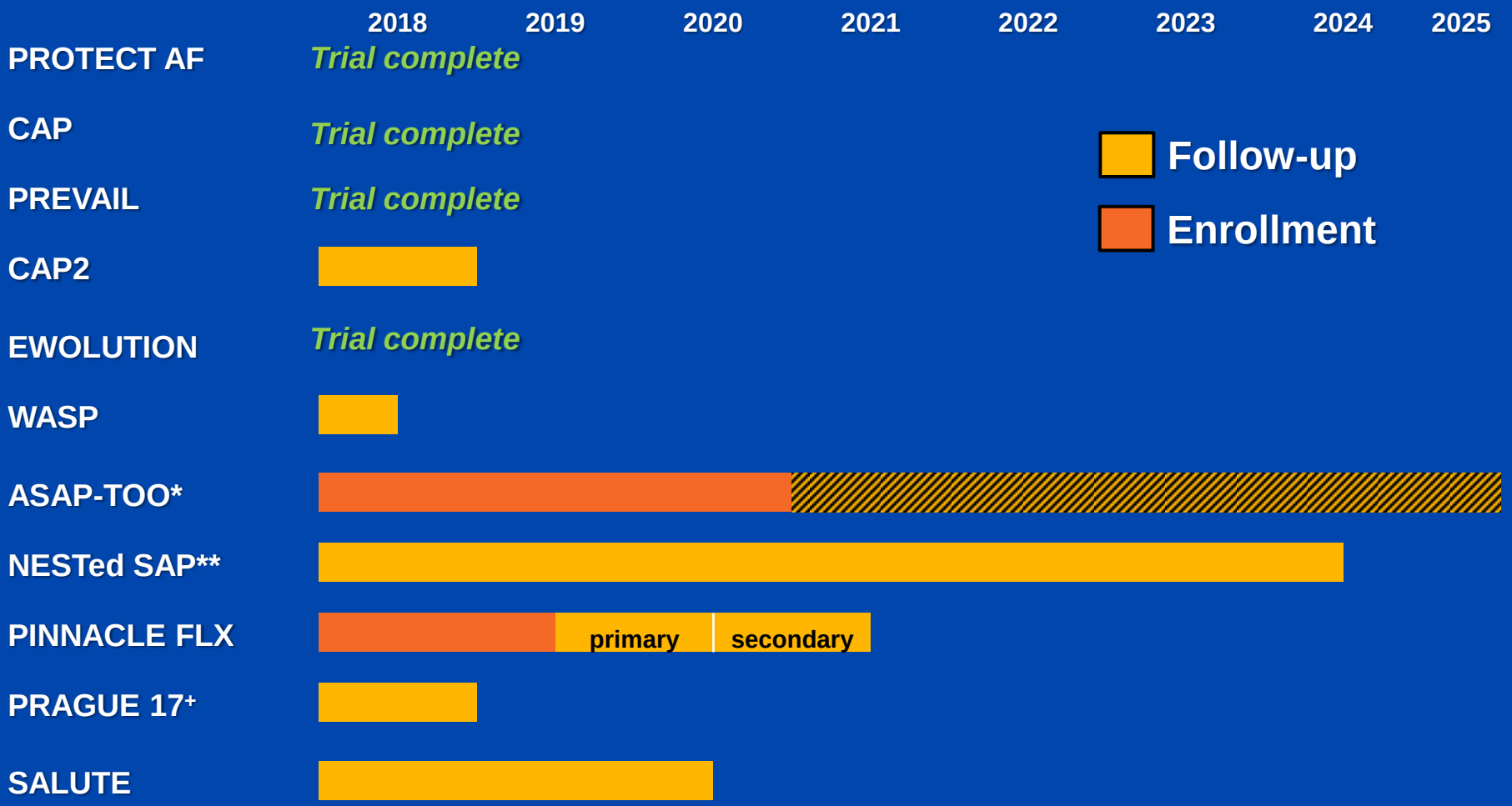
Clinical Trial Timelines



*ASAP TOO is event-driven, so follow-up timelines are variable
**Novel Evaluation of the WATCHMAN LAA Closure Therapy Surveillance Analysis Plan
+ Czech Ministry of Health sponsored study

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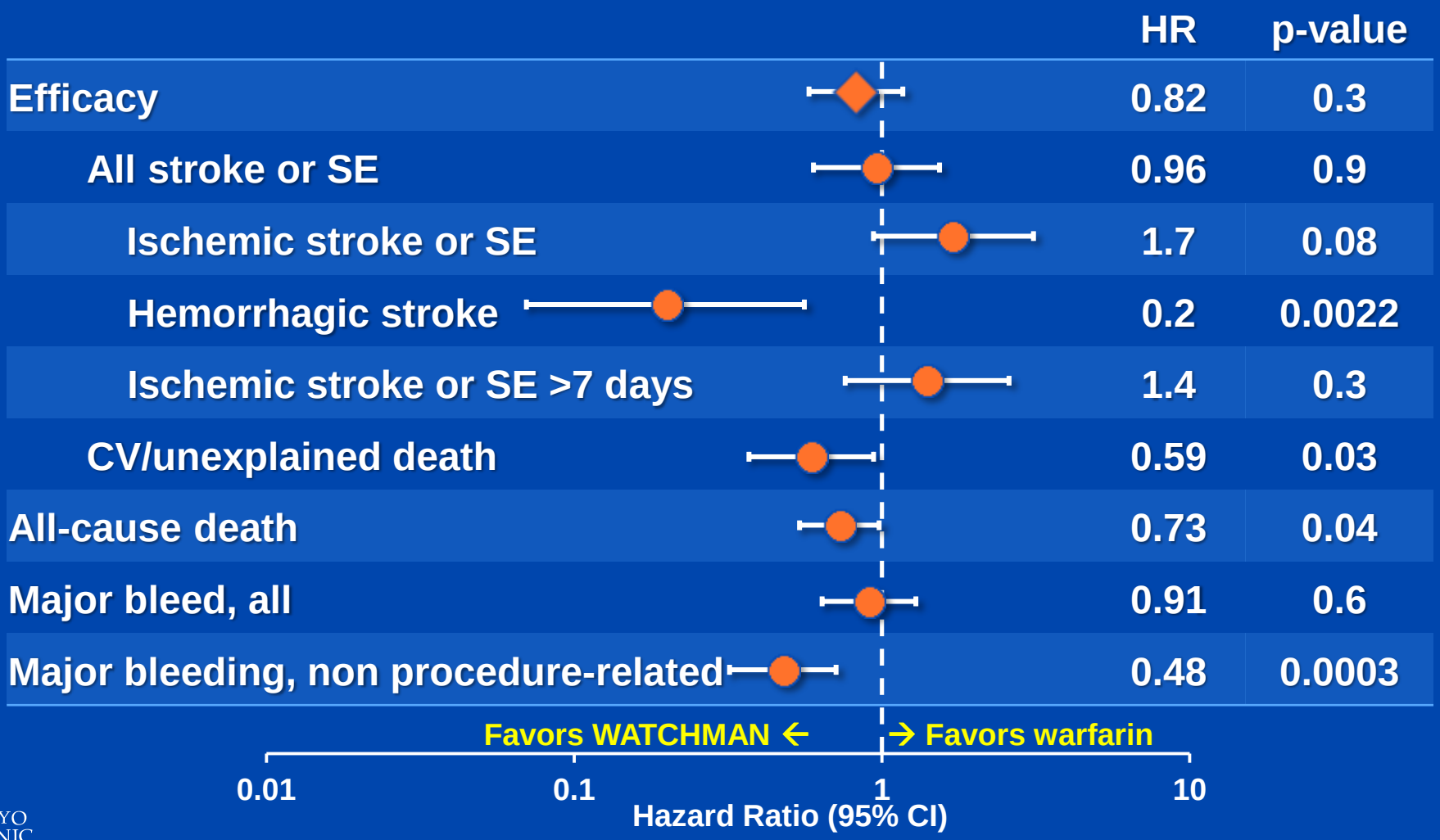
Patient-Level Meta-Analysis
PROTECT AF and PREVAIL 5 years



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Reddy VY, Holmes, DR et al. JACC 2017 in Press.

WATCHMAN NESTed SAP: Overview

Study Objective	**FDA mandated post-market surveillance analysis plan**
Study Design	**Prospective, newly implanted WATCHMAN device patients nested within the larger LAAO Registry (NCDR)**
Primary Endpoints	**<u>1st Effectiveness</u> All-stroke, CV/Unexplained death, and systemic embolism at 24 months <u>2nd Effectiveness</u> Ischemic stroke or systemic embolism (thrombolic events) at 24 months, excluding the 1st 7 days post implant <u>Safety Endpoint</u> Major safety events between the time of implant and within 7 days of the procedure or by hospital discharge, whichever is later**
Patient Population	**2000**
Enrollment	**On-going**
Follow-up	**45 days, 6, 12 and 24 months CMS linkage study patients during years 2-5**

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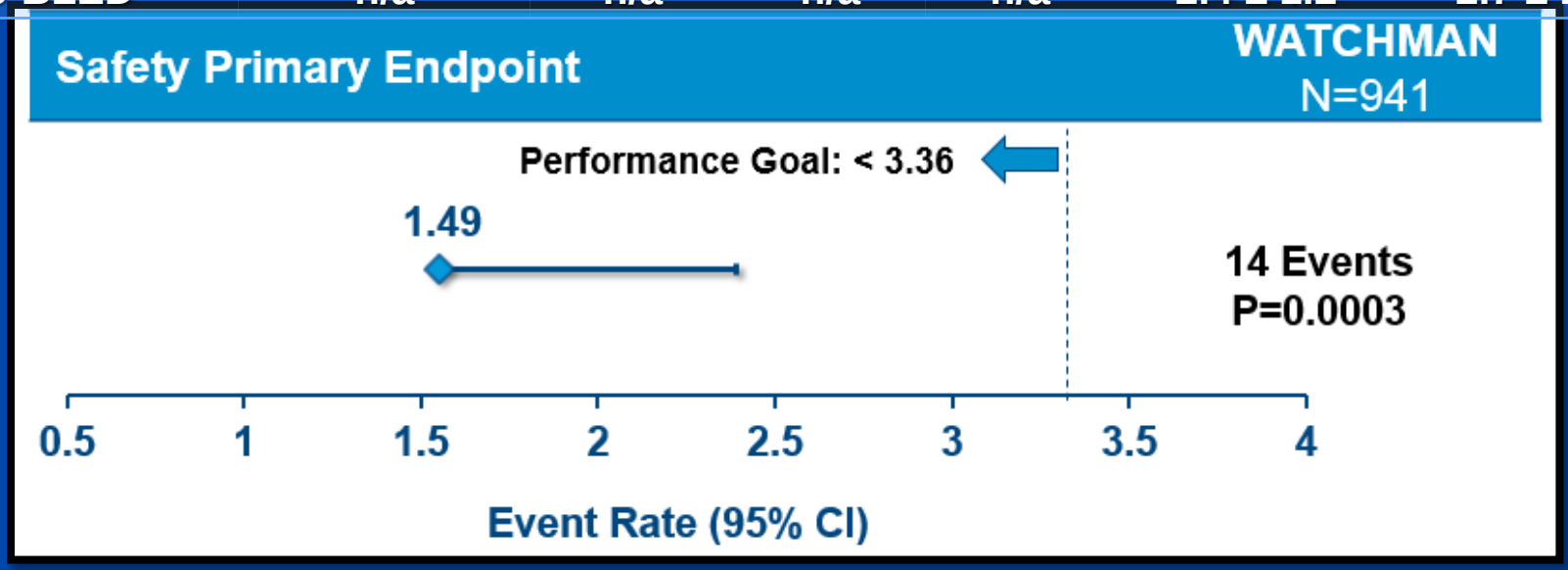
Reddy VY, Holmes, DR et al. JACC 2017 in Press.

Procedural Safety of WATCHMAN Implantation: NESTed SAP

	PROTECT AF N=707	PREVAIL N=407	CAP N=566	CAP2 N-579	EWOLUTION N=1014	NESTed PAS N=979
Age (yrs)	72±8.9	74.3±7.4	74.0±8.3	75.3±8.0	73±9	76.6±8.1
Male (%)	70.3	70	65.5	61.0	59.9	61.3
$CHADS_2$	2.2 ± 1.2	2.4 ± 1.2	2.6 ± 1.0	2.7 ± 1.1	2.8 ± 1.3	3.2 ± 1.3
CHA_2DS_2-VASc	3.4 ± 1.5	3.9 ± 1.5	4.0 ± 1.1	4.5 ± 1.3	4.5 ± 1.6	5.0 ± 1.4
HAS-BLED	n/a	n/a	n/a	n/a	2.4 ± 1.2	2.7 ± 1.0



Primary composite safety endpoint: death, ischemic stroke, systemic embolism, or device/procedure-related events necessitating cardiac surgery or major endovascular intervention within either 7-days post-implant or hospital discharge, whichever occurred later.

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Reddy VY, Holmes, DR et al. JACC 2017 in Press.

ASAP-TOO (NCT02928497): Overview

Study Objective	**Evaluate LAA Closure with WATCHMAN in NVAF patients deemed not suitable for oral anti-coagulation therapy**
Study Design	**Prospective, multi-center** **Randomized 2:1 (Watchman vs Control)** **Considering Group Sequential Design**
Primary Endpoint	**<u>Effectiveness Endpoint</u>** **Time to first occurrence of ischemic stroke or systemic embolism** **<u>Safety Endpoint</u>** **7-day rate of all-cause death, ischemic stroke, systemic embolism, or device- or procedure- related events requiring open cardiac surgery or major endovascular intervention**
Patient Population	**888**
Number of Sites	**100 global sites**
Follow-up*	• **45 Day with TEE** • **6,18 month phone visit** • **12 month with TEE** • **Bi-annually for years 2-5**

*** Brain imaging required at baseline if prior stroke or TIA**

AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial

- **Target Population:** AF with CHADS2 score ≧2 or CHA2DS2-VASc ≧3, who are recommended for OAC therapy but have an appropriate rationale to seek a non-pharmacologic alternative to warfarin or other OACs
- **Sample Size/Sites:** 1600 patients (+ up to 300 roll in subjects) at 150 sites worldwide with at least 100 U.S sites. Enrolled 658 patients as of September 1st, expected to complete enrollment in Spring 2018.
- **Randomization:** 1:1 between Amulet LAAO device (treatment) and Watchman LAAO device (Control)

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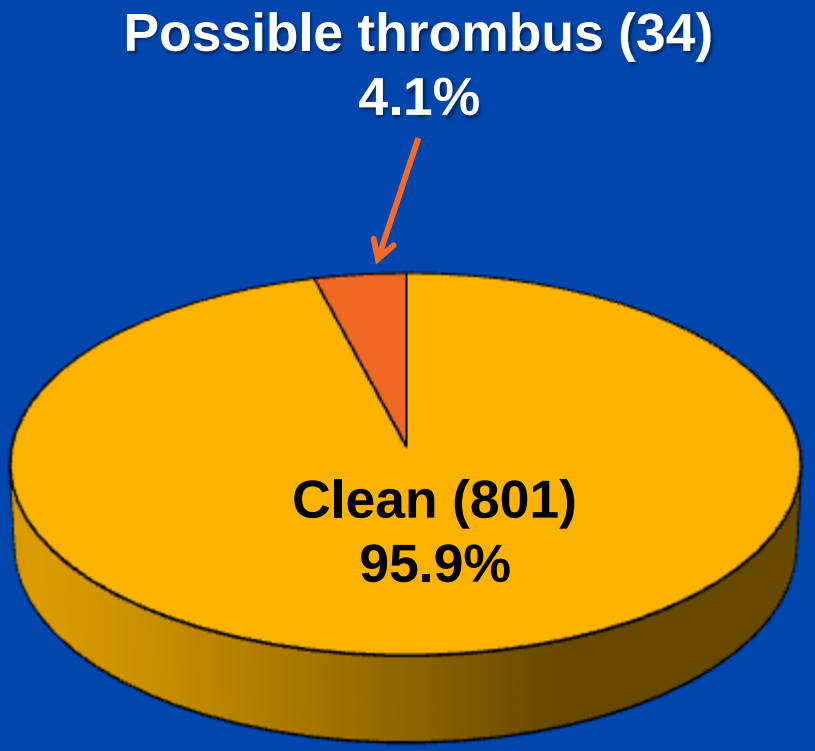
EWOLUTION – 2 year Follow-up
Device Thrombus

- 835 pts with LAA imaging
- 34 pts with a possible DRT
- 31/34 detected ≤90 d or at time of first TEE



- Pts with device thrombus with later stroke: 0/34
- Pts with stroke and device thrombus:1/22

Boersma LVA, et al. EHRA 2018

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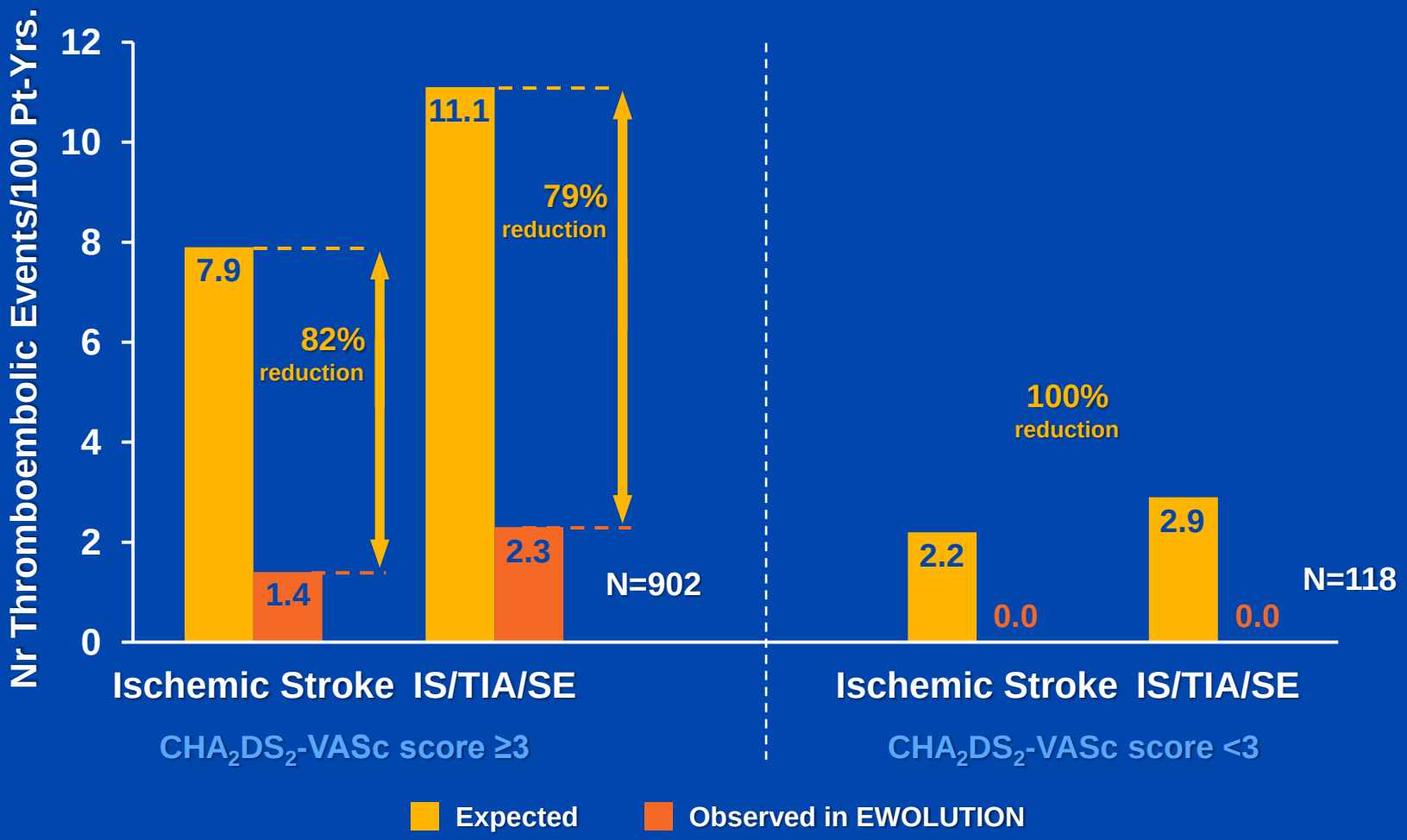
EWOLUTION – 2 Year Follow-up

No Stroke/TE in Low-risk Patients



Phillips, K et al: APHS; 2017

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WASP (NCT03327350)

- Observational prospective study secondary prevention
- 400 Chinese patients S/P stroke/TIA >3 mo
- Primary endpoint
  - All stroke (ischemic & hemorrhagic)
  - Systemic embolism
  - CV death
  - Follow-up 3 yrs

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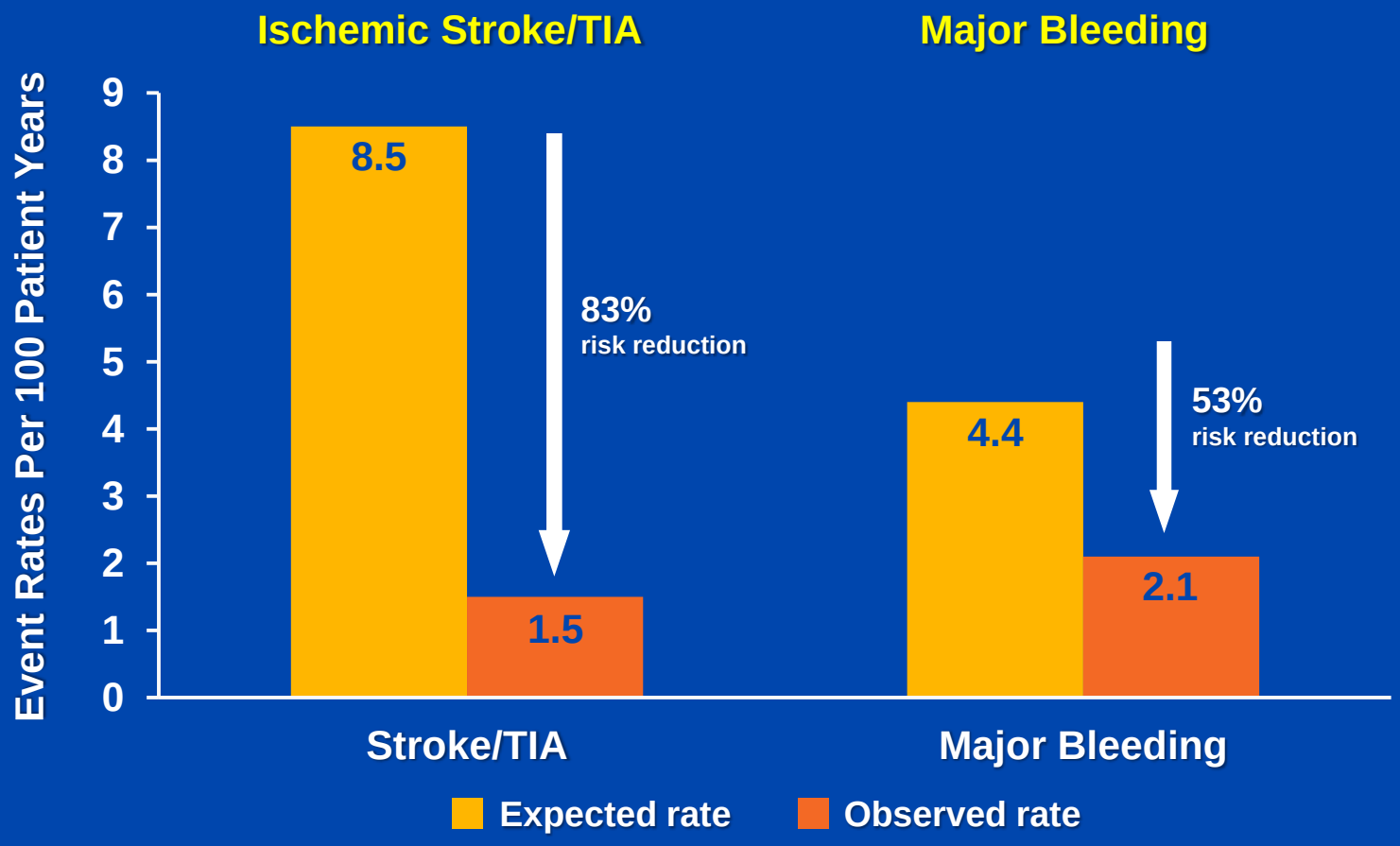
WASP
1 Year Follow-up – ALL PATIENTS



Based on CHA2DS2VASc & HASBLED scores

Phillips, K et al: APHS; 2017

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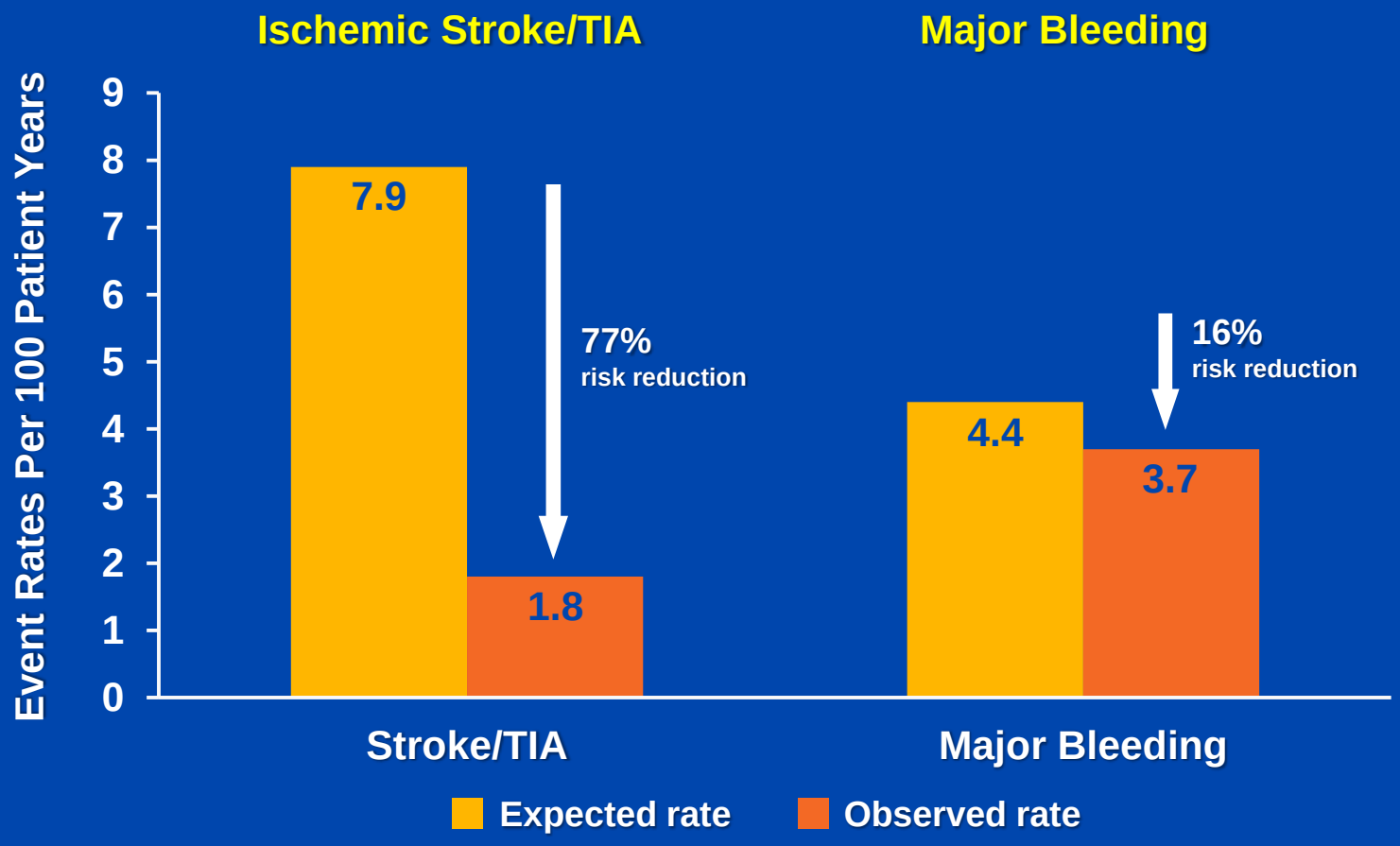
WASP
1 Year Follow-up – Non Asians



Based on CHA2DS2VASc score 3.7 & HASBLED score 2.1

Phillips, K et al: APHS; 2017

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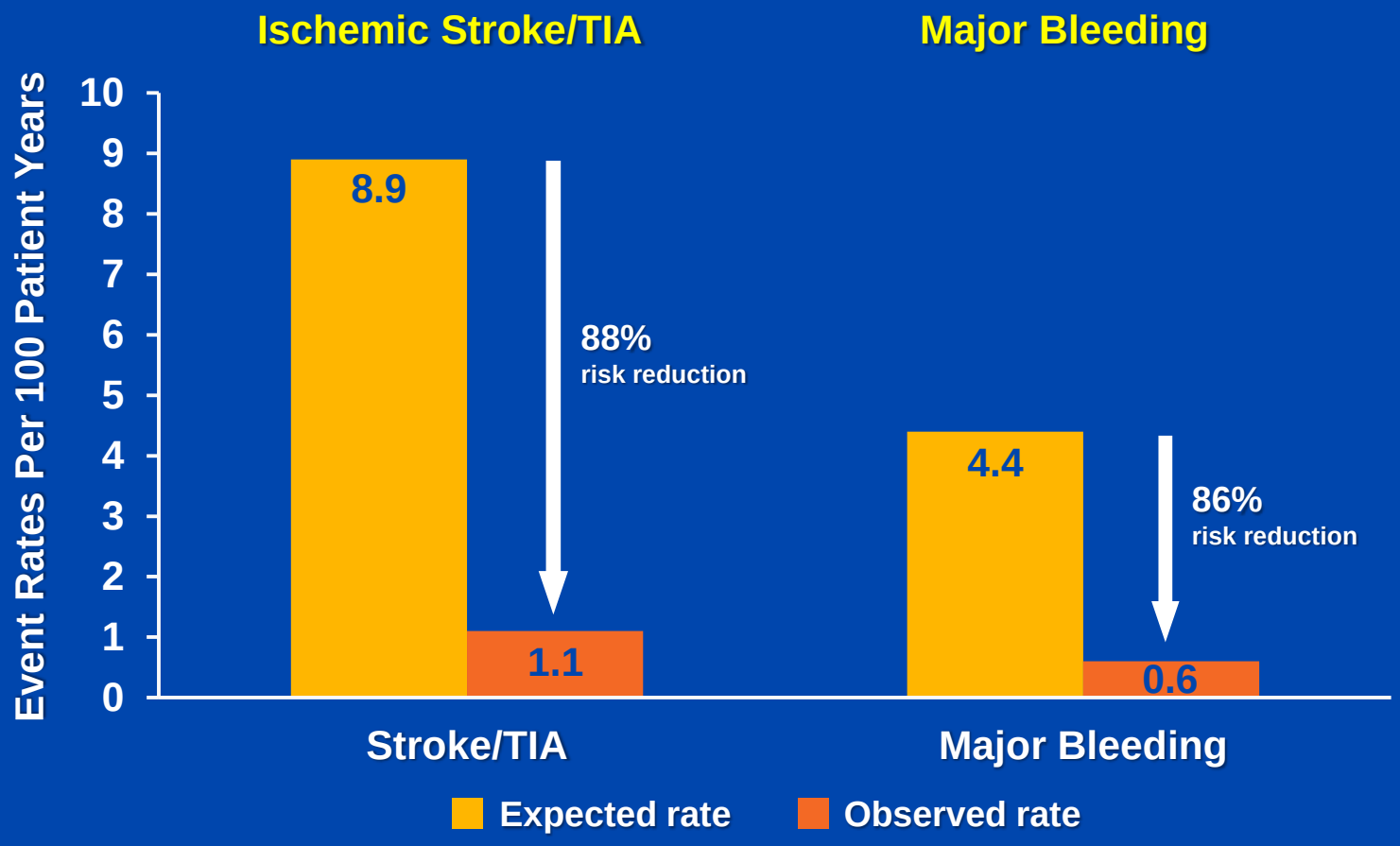
WASP
1 Year Follow-up – Asians



Based on CHA2DS2VASc score 4.1 & HASBLED score 2.2

Phillips, K et al: APHS; 2017

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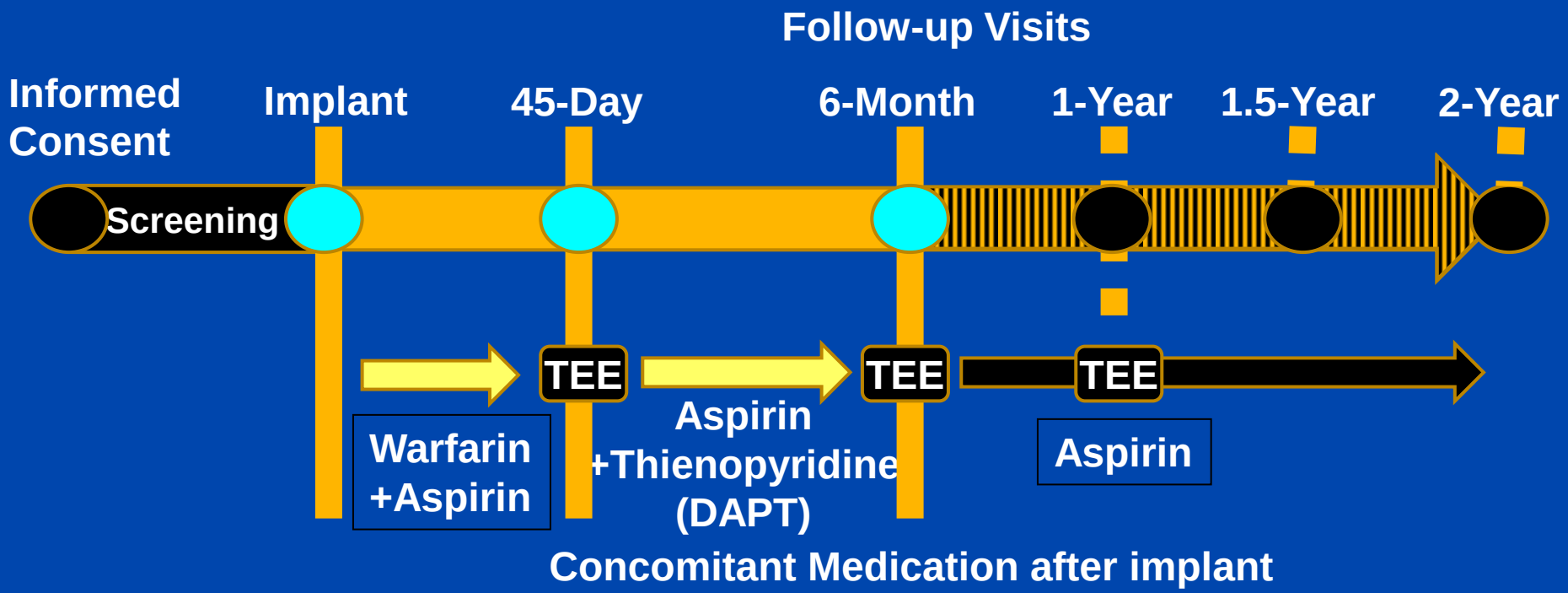
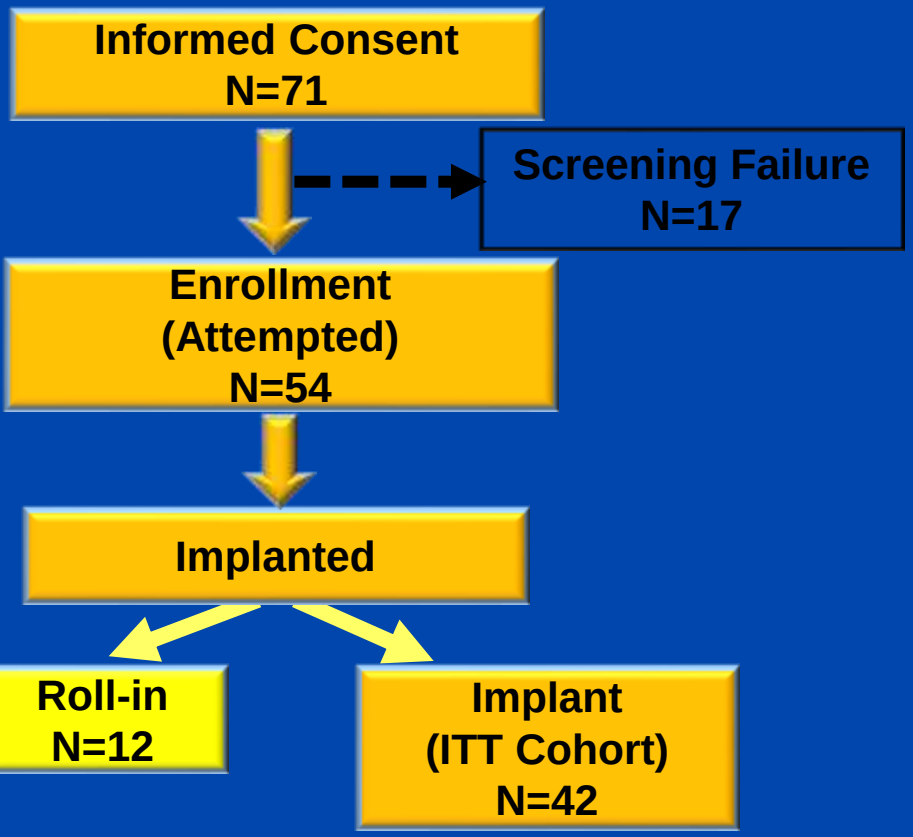
SALUTE Study Design and Follow-up Visits

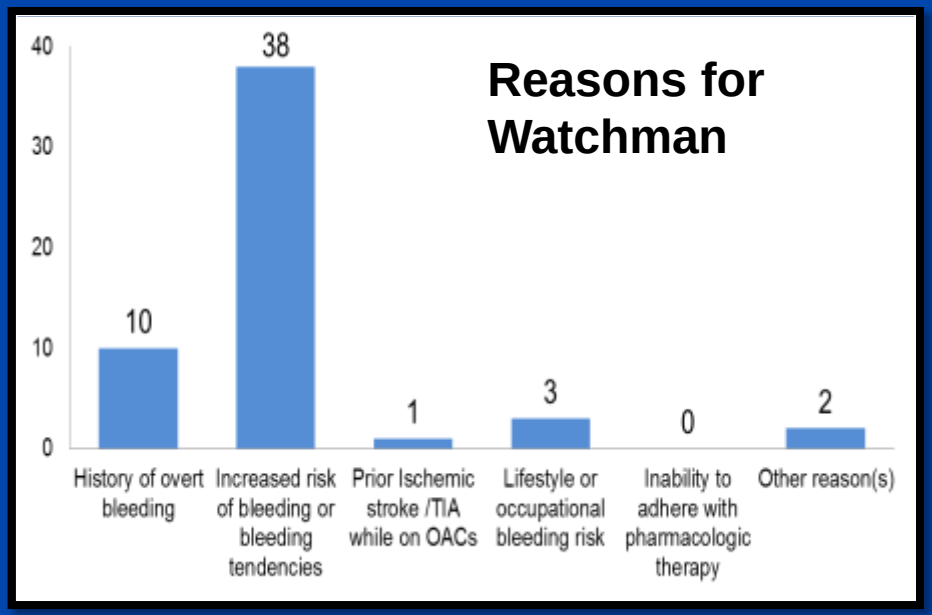
Multi-center, prospective, non-randomized, single-arm study for Japanese patients with NVAF: 54 subjects



Aonuma, K et al. JCS 2018 LBCT

SALUTE Subject Enrollment





Screening failure reasons (17): Cardiac Thrombus (6), Consent Withdrawn (5), LAA Anatomy(3) and Other reasons(3): Renal function (1), LVEF (1) and Safety concern (1).

- ✓ <u>Zero</u> Implant failures
- ✓ No Deaths till 6-month
- ✓ No Withdrawn till 6-month

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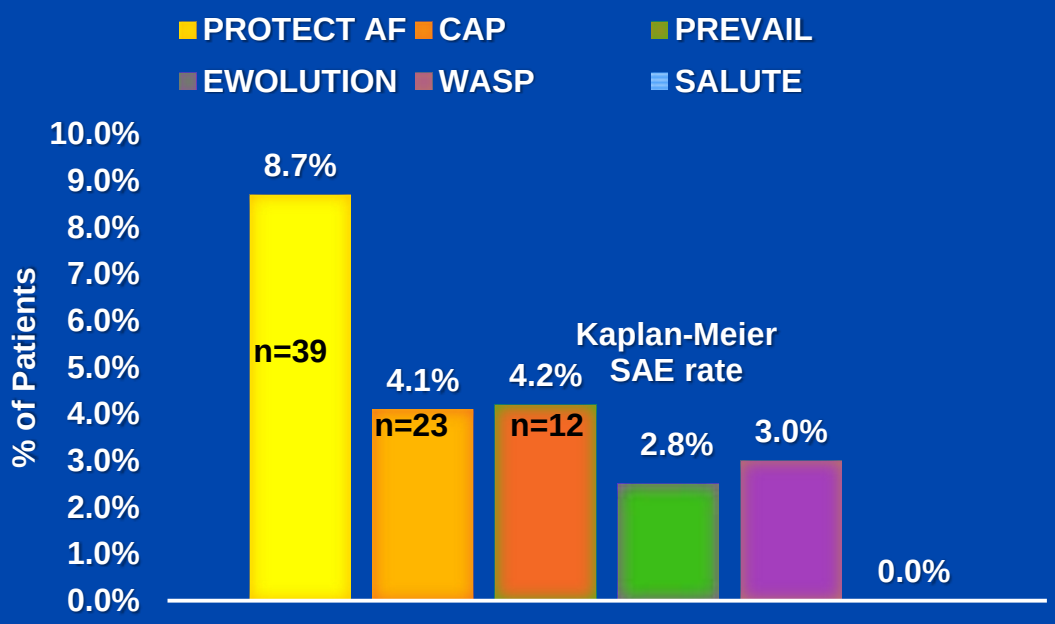
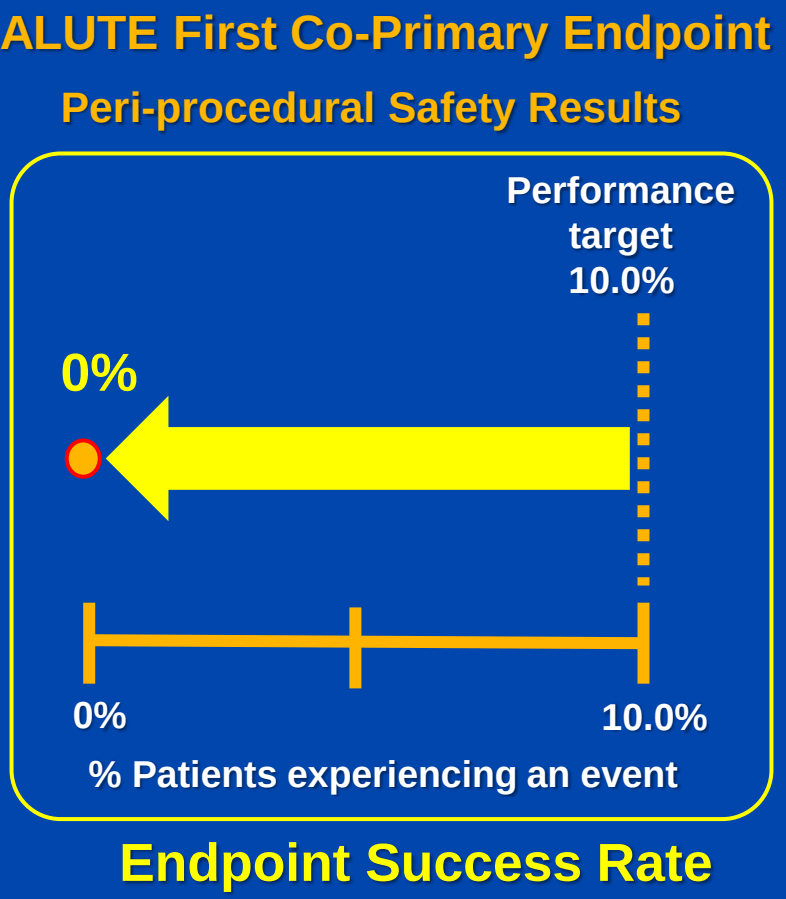
SALUTE
First Co-Primary Endpoint



Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications[1]



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SALUTE
Second Co-Primary Endpoint

Composite of Stroke, SE and CV death during 6-month follow-up

Event	% (n/N) [95%CI]
Second-Co Primary Endpoint	2.4% (1/42) [0.1, 12.6]
Composite Event Component	
Ischemic stroke	2.4% (1/42)
Hemorrhagic stroke	0.0% (0/42)
Systemic embolism (SE)	0.0% (0/42)
CV death/ Unexplained death	0.0% (0/42)

- One ischemic stroke occurred 118 days post implant.
  - No TEE evidence of device thrombus
  - Non-disabling stroke due to no change in the mRS
  - No admission for further observation/treatment

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Aonuma, K et al. JCS 2018 LBCT

Summary

- Multiple trials complete and results demonstrate safety and efficacy of the WATCHMAN device
  - Safe in the hands of new and experienced operators
  - No significant differences in ischemic stroke rates versus warfarin
  - Significant, superior reductions in disabling strokes, non-procedural bleeding, and mortality
- Two (2) trials in Asian sub-populations (WASP, SALUTE)
- Current trials evaluating post-implant medication regimens

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Other Trials

- Korean Multicenter Registry (NCT03108872)
  - Compare long-term effectiveness and safety in patients with AF treated with LAAO or NOACs
  - Case control prospective registry – 300 pts
- Chinese Multicenter RCT (NCT02549963)
  - Compare Watchman LAAO device with rivaroxaban in patients with NVAF
  - 200 patients
  - Combined endpoint: 2-year all stroke/systemic embolism, cardiac death

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Other Trials

- Royal Bromptom (NCT02028130)
  - Single center registry
  - Evaluate safety & feasibility of LAA electrical isolation and occlusion
  - 20 patients with persistent AF
- Swedish Trial (2022) (NCT02830152)
  - Multicenter prospective open label RCT
  - LAAO (amulet) vs medical therapy for 750 patients with ICH <6 months earlier
  - Endpoint: stroke (ischemic/hemorrhagic) systemic embolism, major bleeding, all-cause mortality – 2 yrs
- Maastricht Registry Trial (NCT02471131)
  - Assess safety & efficacy of Watchman LAAC implantation during hybrid AF ablation
  - 10 patients

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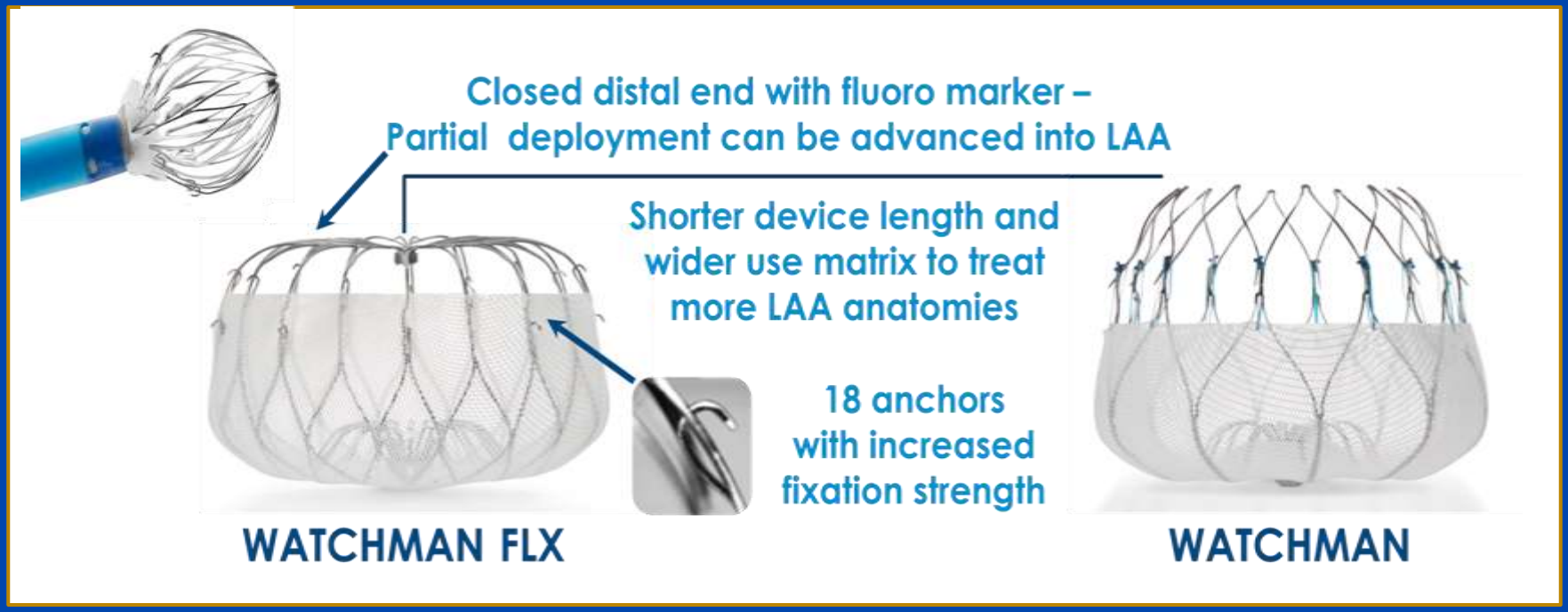
WATCHMAN FLX™: Designed to Broaden Treatment Matrix and Improve Ease of Use



- Designed for greatly enhanced stability and ease-of-use
- Designed for greater apposition to appendage wall
  - New anchor design, additional anchors and reduced main body taper
- Anticipate starting EU and U.S. clinical trials mid-year 2018

PINNACLE FLX CLINICAL TRIAL

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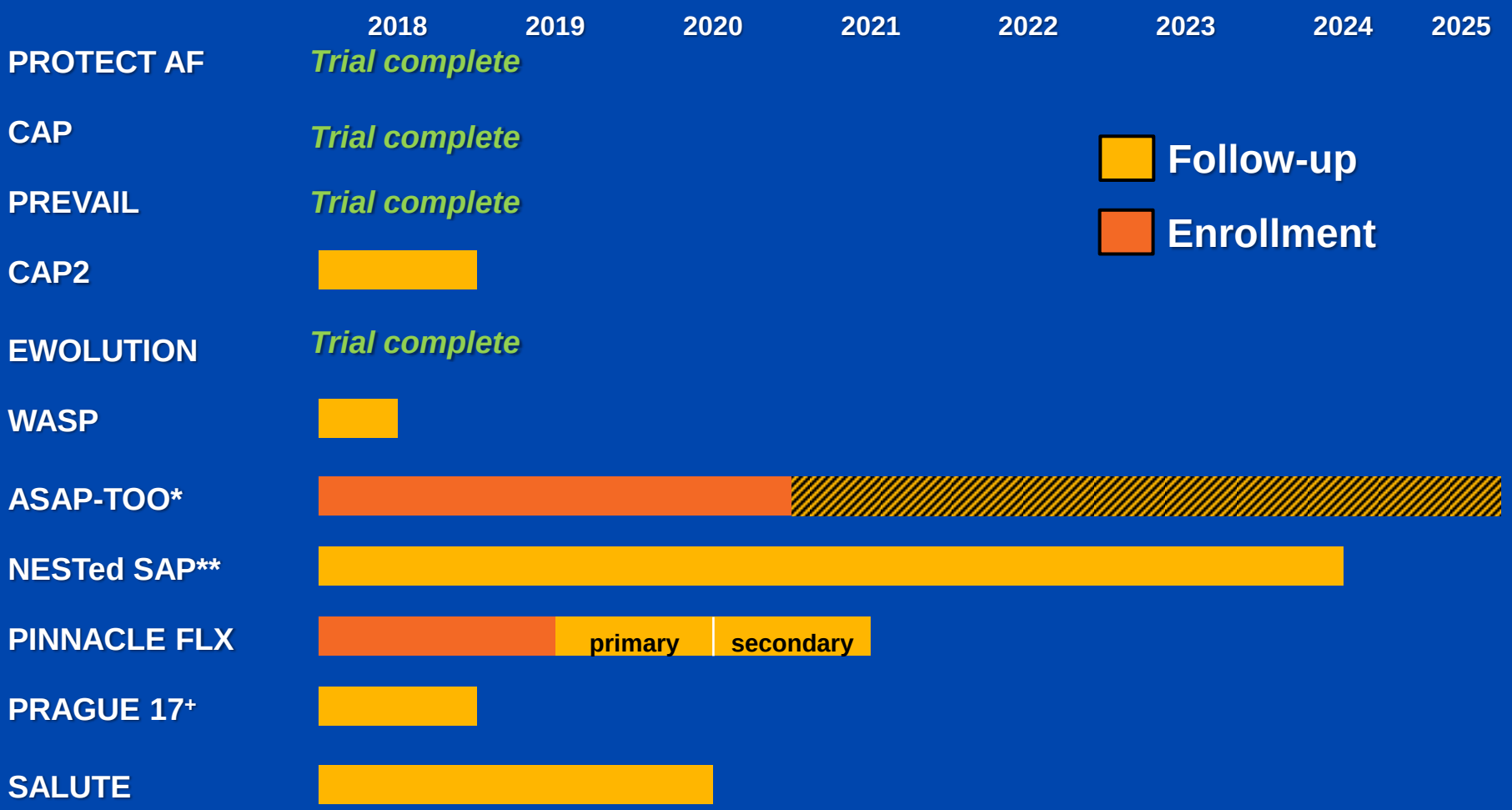
Caution: WATCHMAN FLX is an Investigational Device. Limited by Federal (or US) law to investigational use only. Not available for sale.

Clinical Trial Timelines



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**Novel Evaluation of the WATCHMAN LAA Closure Therapy Surveillance Analysis Plan
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Issues with Trial Design

- Definition of endpoints
  - Is stroke both a safety and efficacy endpoint?
- Primary stroke endpoint
  - All-cause stroke, ischemic stroke, hemorrhagic stroke
- Definition of relative vs absolute contraindication
- Should residual leak count in a composite endpoint?
- What should the comparator be?
- Can we use registries instead of RCT's?

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