Left Atrial Appendage Closure as an Alternative to Anticoagulants

Who? How? When? Results?

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Presenter Disclosure Information

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"Left Atrial Appendage Closure as an Alternative to Anticoagulants – Who? How? When? Results?"

The following relationships exist related to this presentation:

Both Mayo Clinic and I have a financial interest in technology related to this research. That technology has been licensed to Boston Scientific.

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Atrial Fibrillation

- The earliest record of AF seems to be in the Yellow Emperor's Classic of Internal Medicine in the 17th century
- William Harvey in 1628 was probably the first to describe "fibrillation of the auricles" in animals
- Edmé Félix Alfred Vulpian observed the irregular atrial electrical behavior that he termed "fremissement fibrillaire" in dog hearts
- Robert Adams reported in 1827 the association of irregular pulses with mitral stenosis by ausculation

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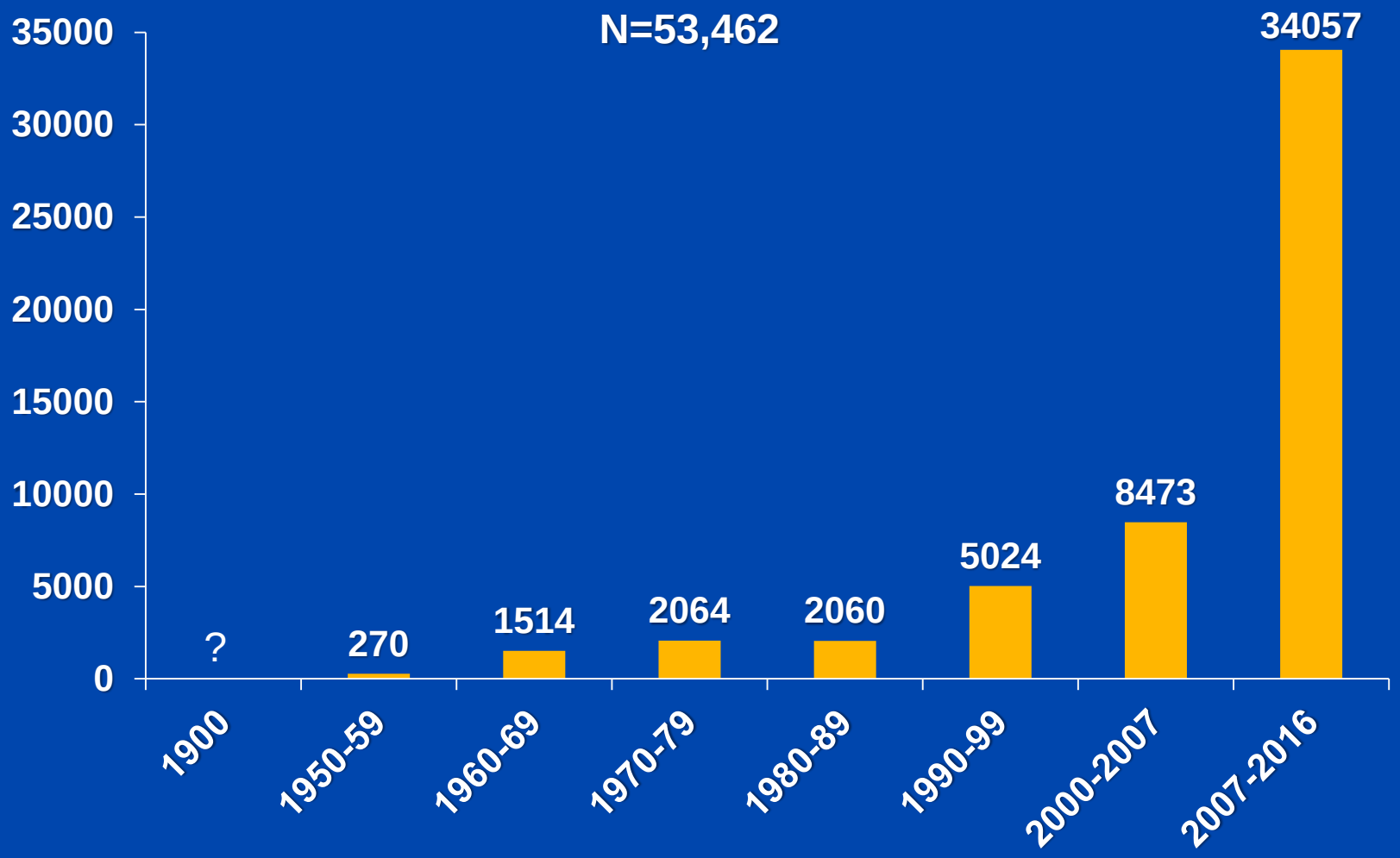
MedLine Search for Atrial/Auricular Fibrillation



Prystowsky EN: J Cardiovasc Electrophysiol 19:575-82, 2008

How Big is the Problem?

- AF is the most common arrhythmia
  - Affects more than 6 million individuals in the U.S.
  - Projected to increase to 16 million by 2050
- Lifetime risk in men and women >40 is 1 in 4
- Patients with AF have a 5-fold higher risk of stroke
  - Over 87% of strokes are thromboembolic
  - Cardioembolic strokes result in highest morbidity and mortality
  - Recurrence rates are high
  - Both AF and Stroke increase as we grow older

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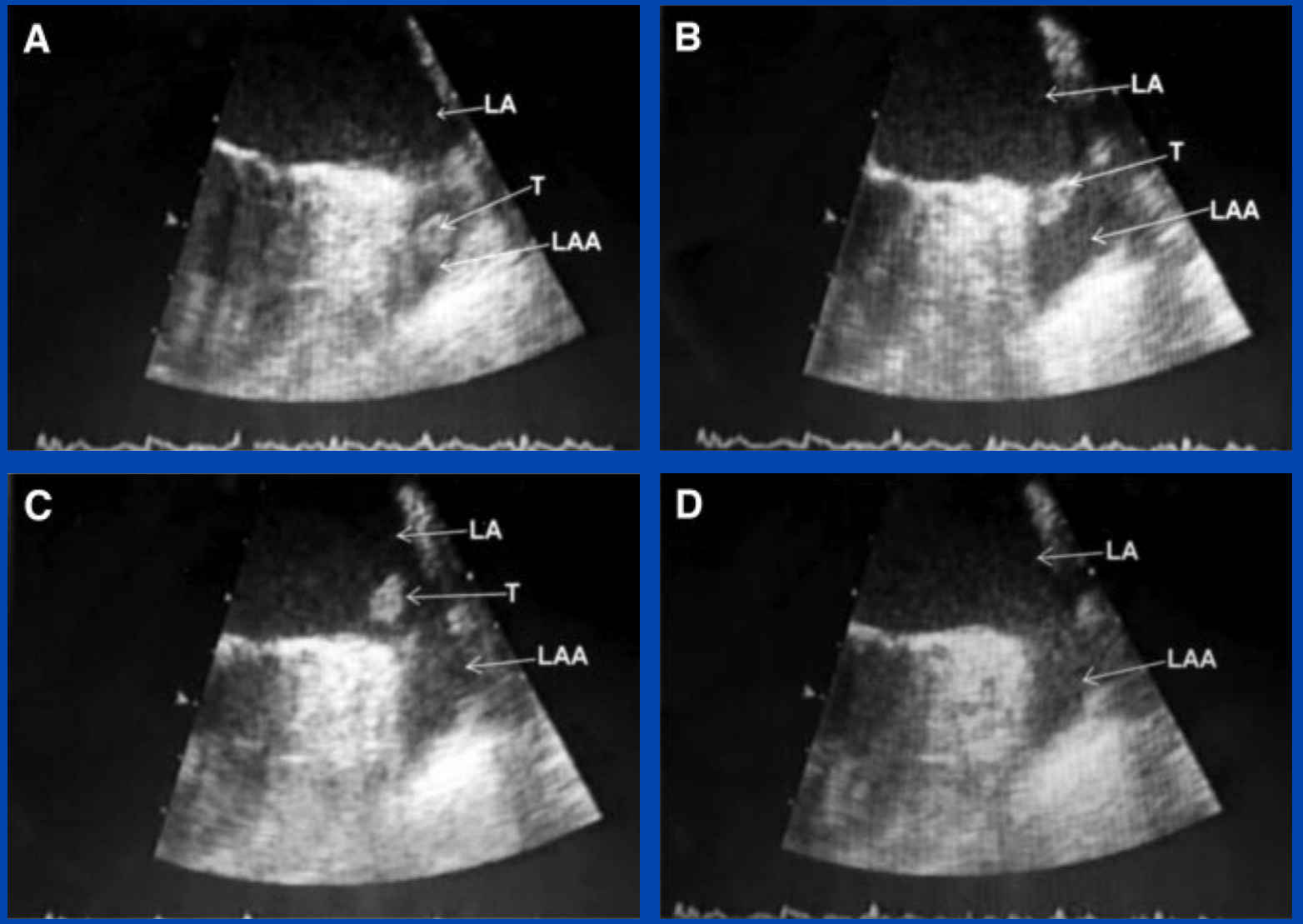
Disappearing LAA Thrombus Resulting in Stroke



Parekh A, Ezekowitz M et al: Circ 114:e513, 2006

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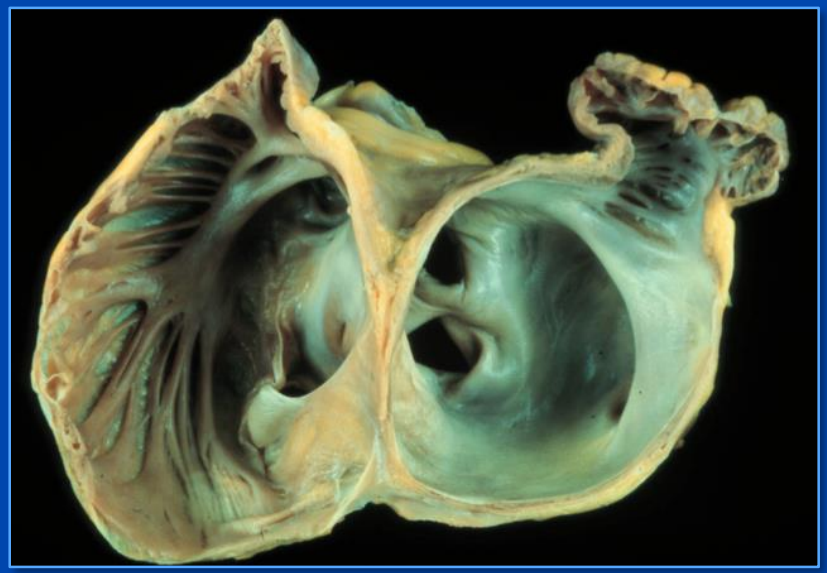
Anticoagulants – Tested in Trials With >60,000 Patients for Stroke Prevention

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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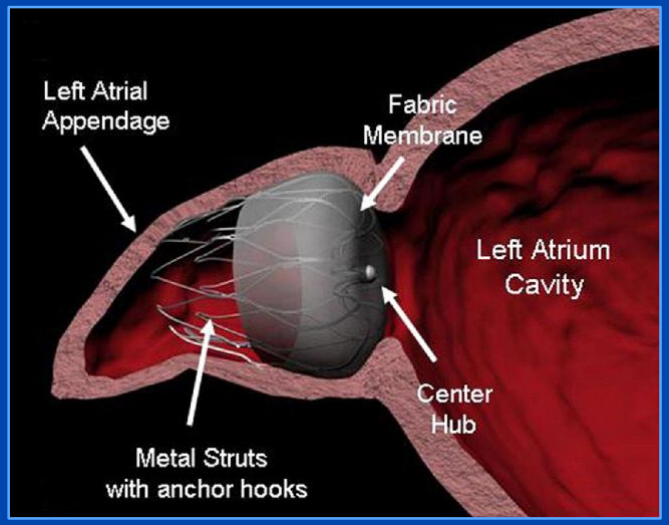
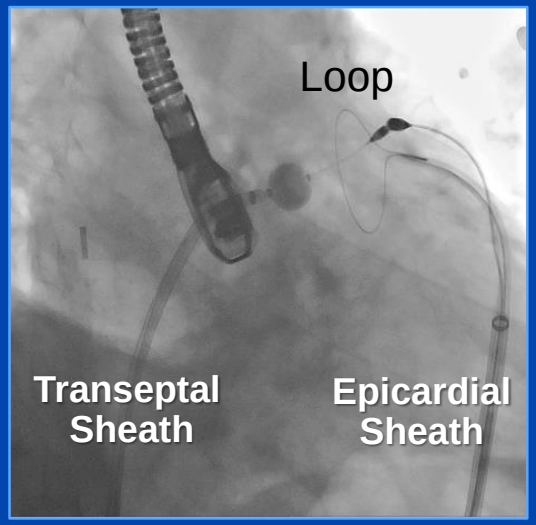
Types of Percutaneous Appendage Closure

Endocardial Plug



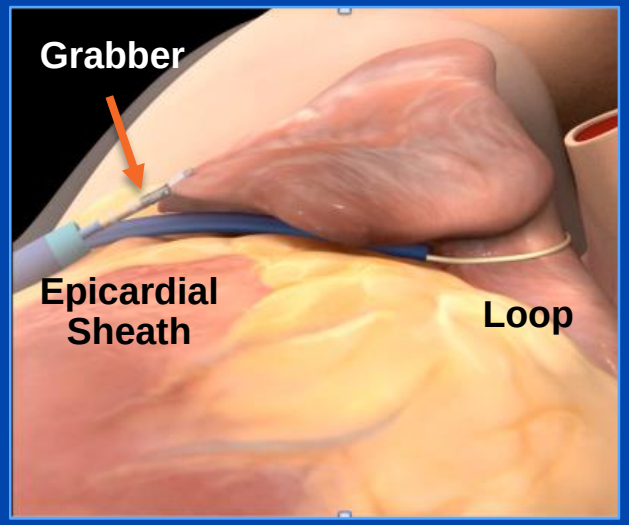
Watchman
Amplatzer - Amulet
WaveCrest

Hybrid Endo/Epi Loop



Lariat

Epicardial Loop



Aegis/Mayo

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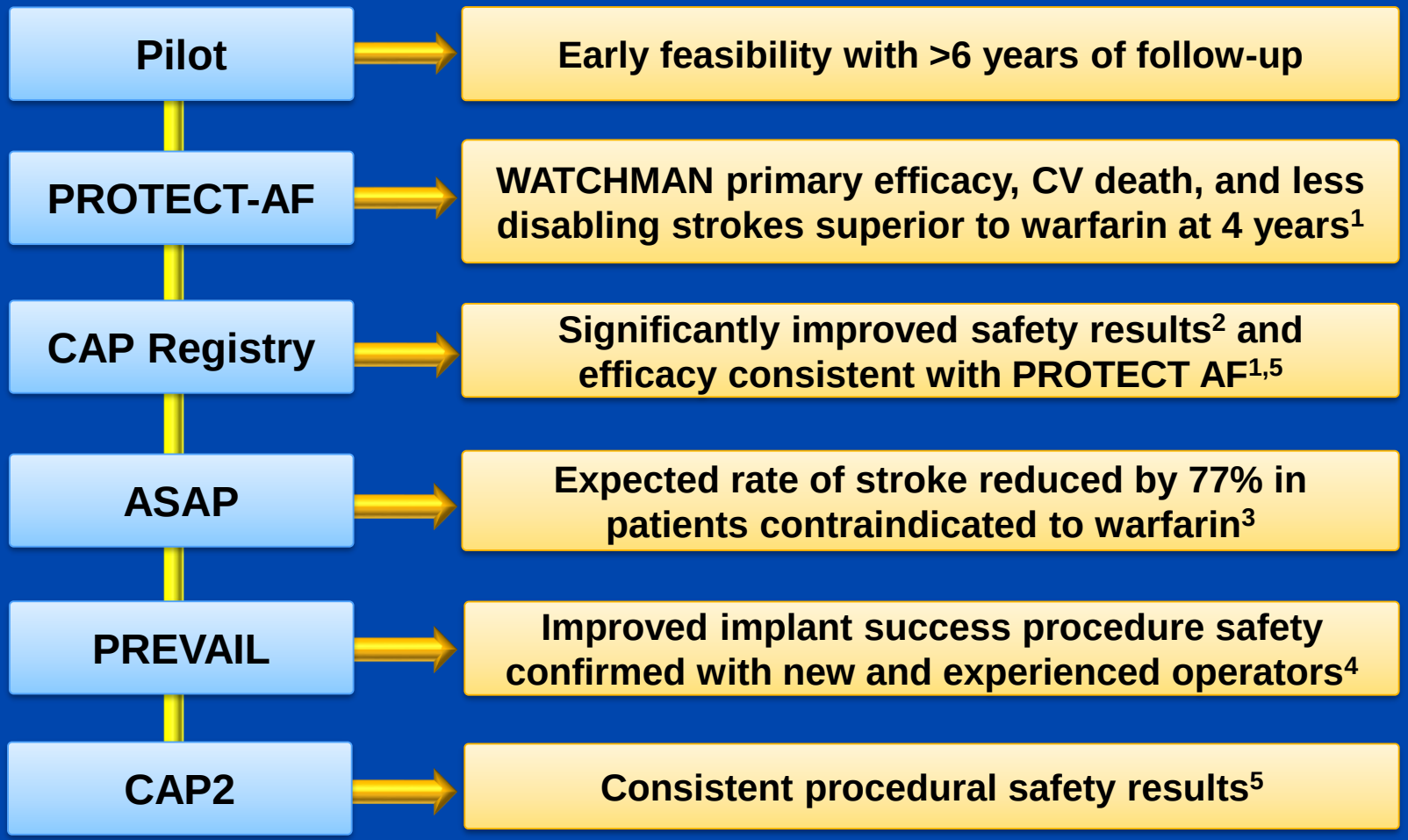
WATCHMAN™ Trials >2,500 Patients with >6,000 Patient Years Follow-Up



[1] Reddy, VY et al: JAMA; 312(19):1988, 2014
[2] Reddy, VY et al: Circ.; 123:417, 2011
[3] Reddy, et al: JACC; 61(25):2551, 2013
[4] Holmes, DR et al: JACC; 64(1):1-12, 2014
[5] FDA Panel October, 2014

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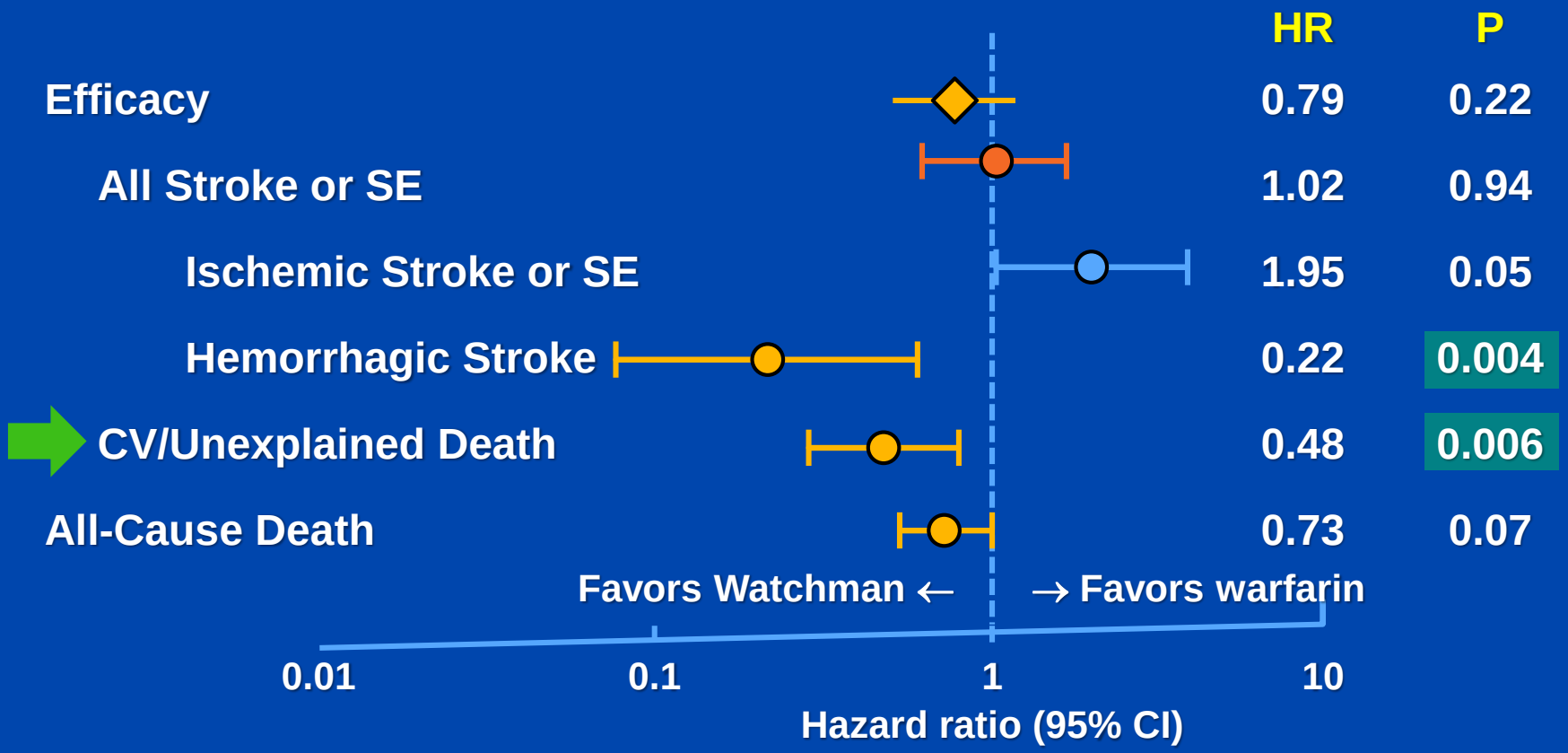
Left Atrial Appendage Closure vs Warfarin in AF

A Patient-Level Meta-Analysis



Combination of PROTECT AF and PREVAIL patients receiving the Watchman device, vs warfarin for overall stroke, ischemic stroke, and all-cause death.

J Am Coll Cardiol; 65:2614, 2015

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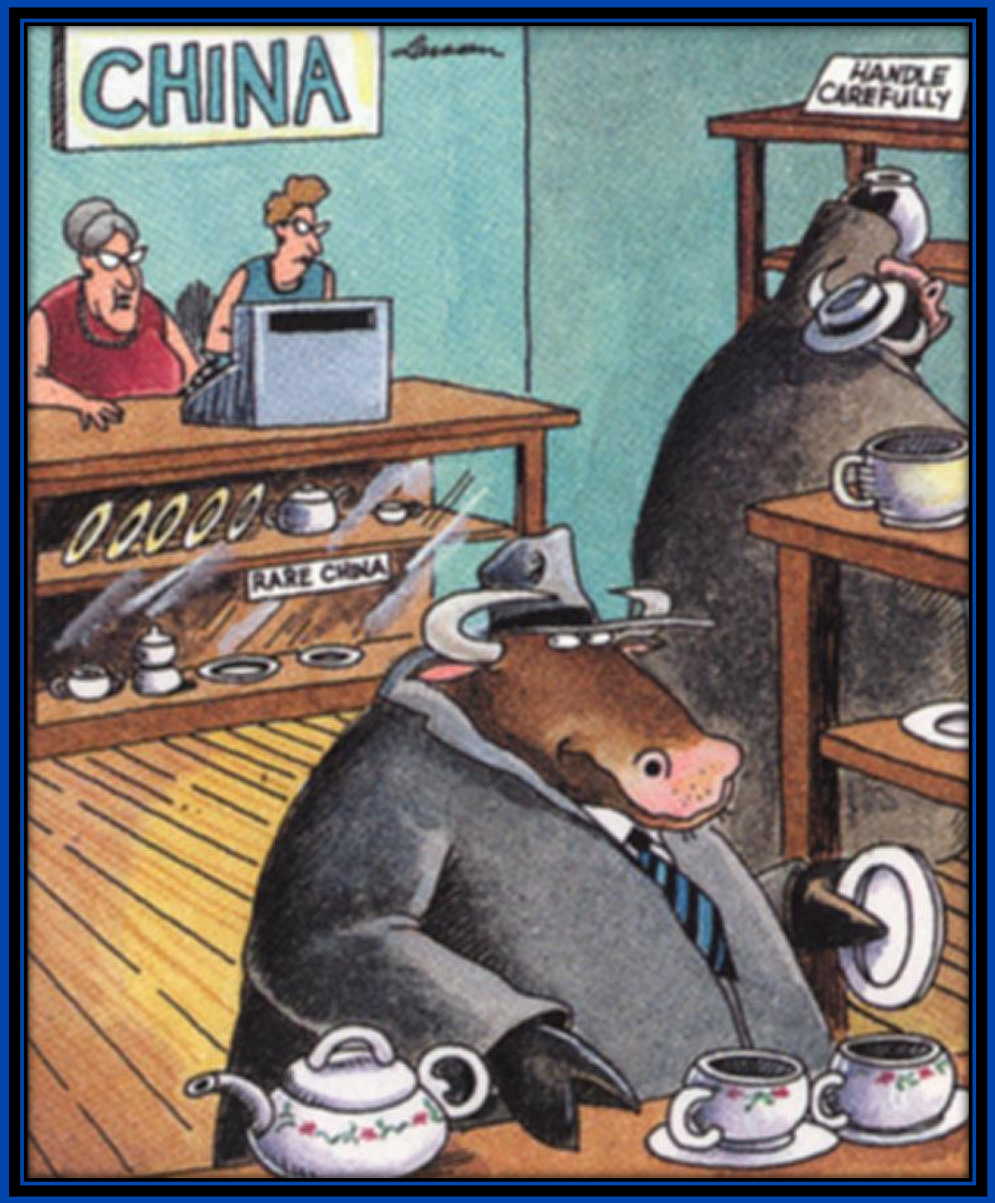

“I got a bad feeling about this, Harriet.”

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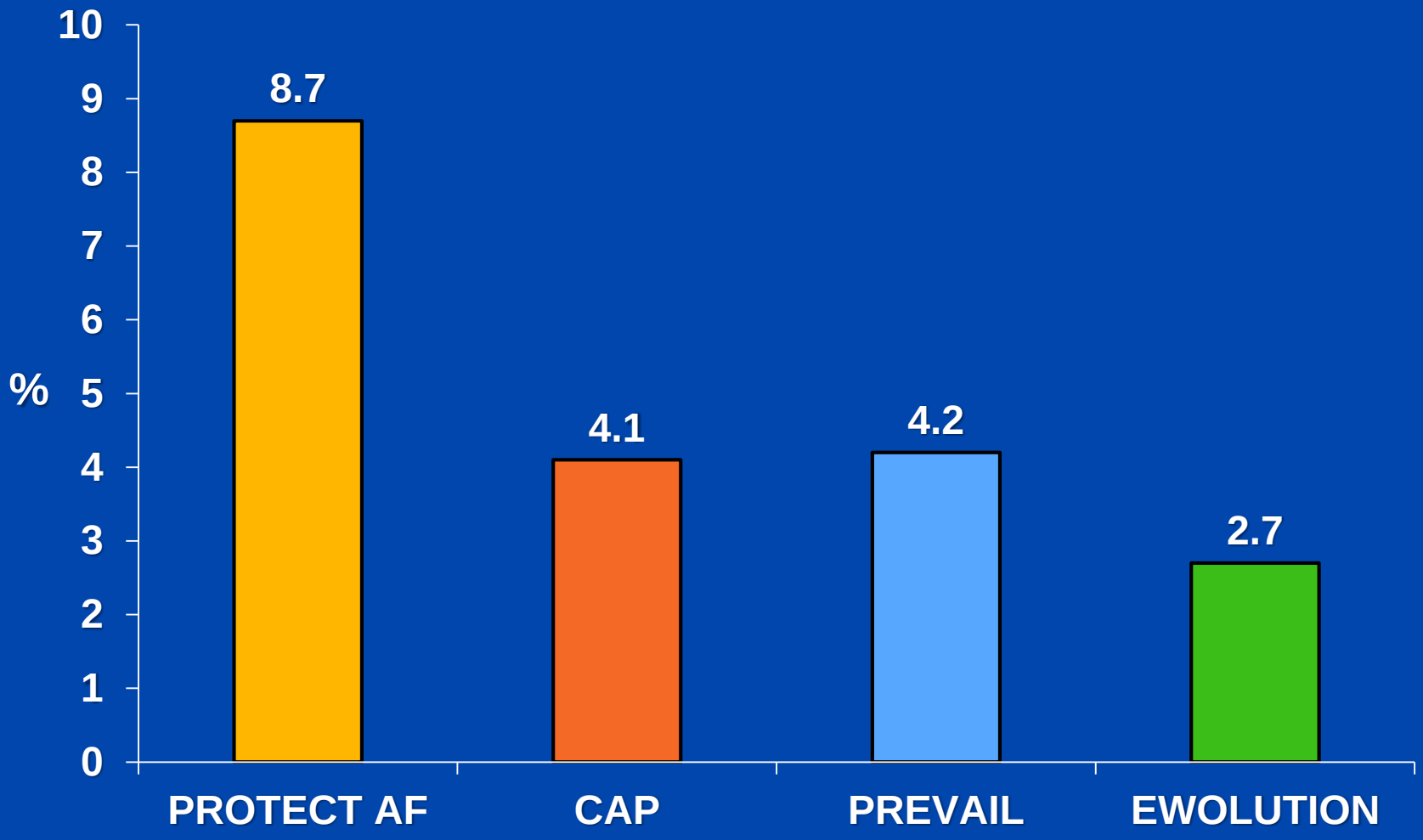
EWOLUTION

Serious Procedure-/Device-Related Events through 7 days



Boersma et al: Euro Heart J, doi:10.1083/eurheartj/ehv730

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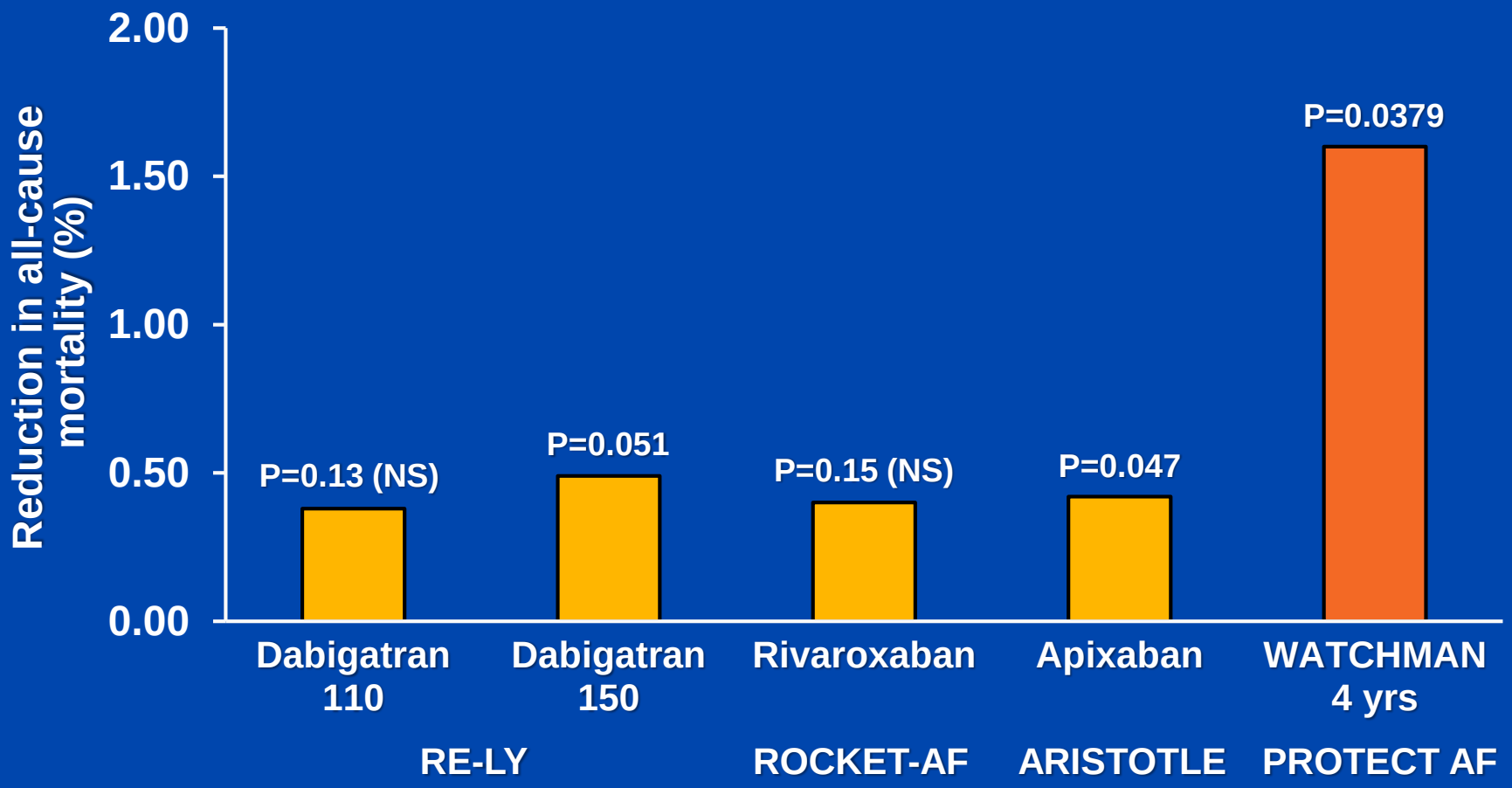
Mortality Reduction (vs warfarin)



Results from different clinical trials:

[1]Connolly, S. NEJM 2009; 361:1139-1151 – 2 yrs f-up
[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
[4]Reddy, V. LBCT HRS 2013 – 4 yrs f-up

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Reduction in All-Cause Mortality vs Placebo/Control

Intervention	OR	95% CI
ASA	0.82	0.68-0.99
VKA	0.69	0.57-0.85
Apixaban	0.62	0.50-0.78
Dabigatran	0.62	0.50-0.78
Edoxaban	0.62	0.50-0.77
Rivaroxaban	0.58	0.44-0.77
Watchman	0.47	0.25-0.88

Tereshchenko et al: J Am Heart Assoc 2016;
doi: 10.1161/JAHA.116.003206

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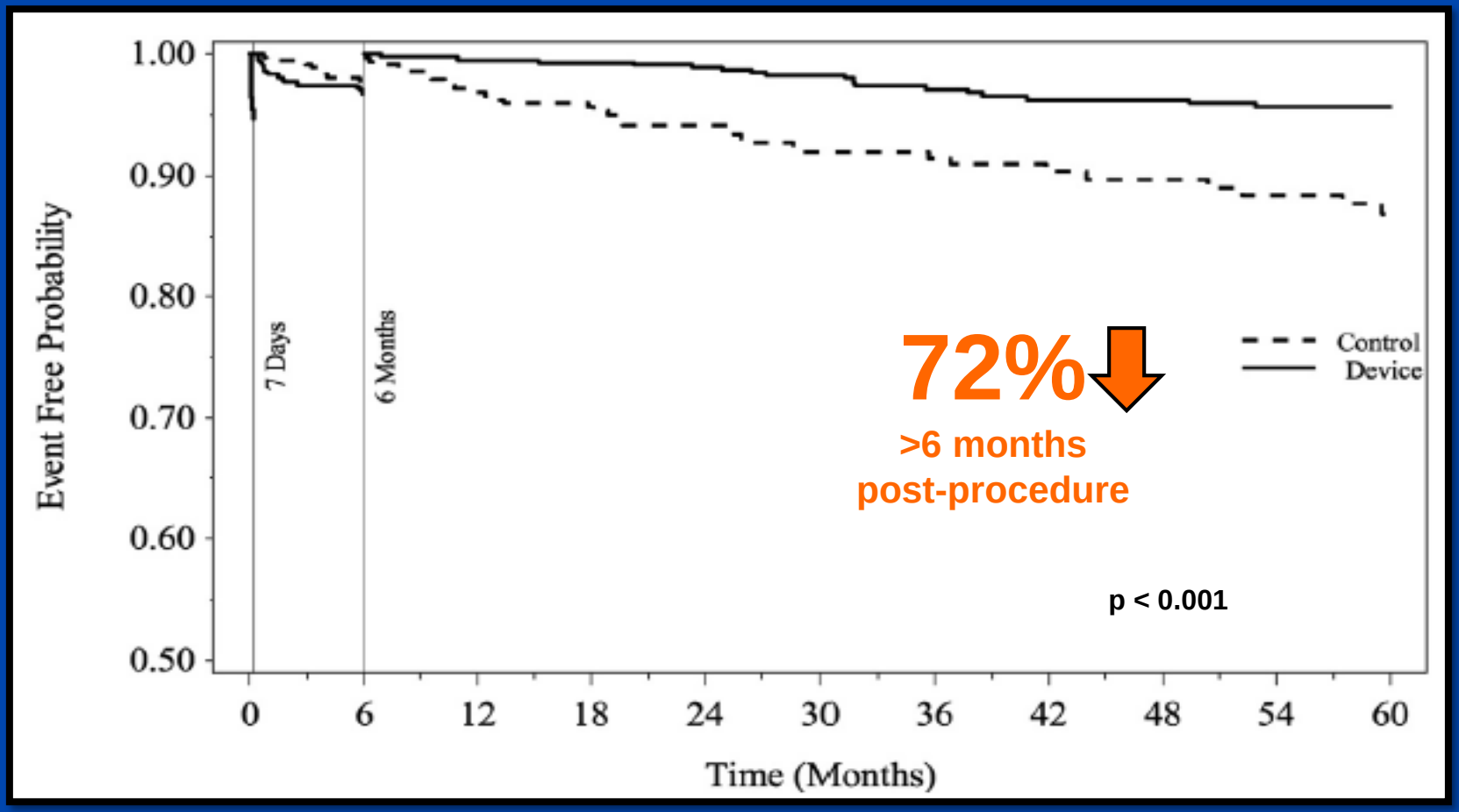
Bleeding Outcomes after Left Atrial Appendage Closure Compared with Long-term Warfarin

Freedom of Major Bleeding Over 3 Adjunctive Pharmacotherapy Intervals



Price, M. J., V. Y. Reddy, et al. JACC: CV Interv 2015; 8(15): 1925-1932

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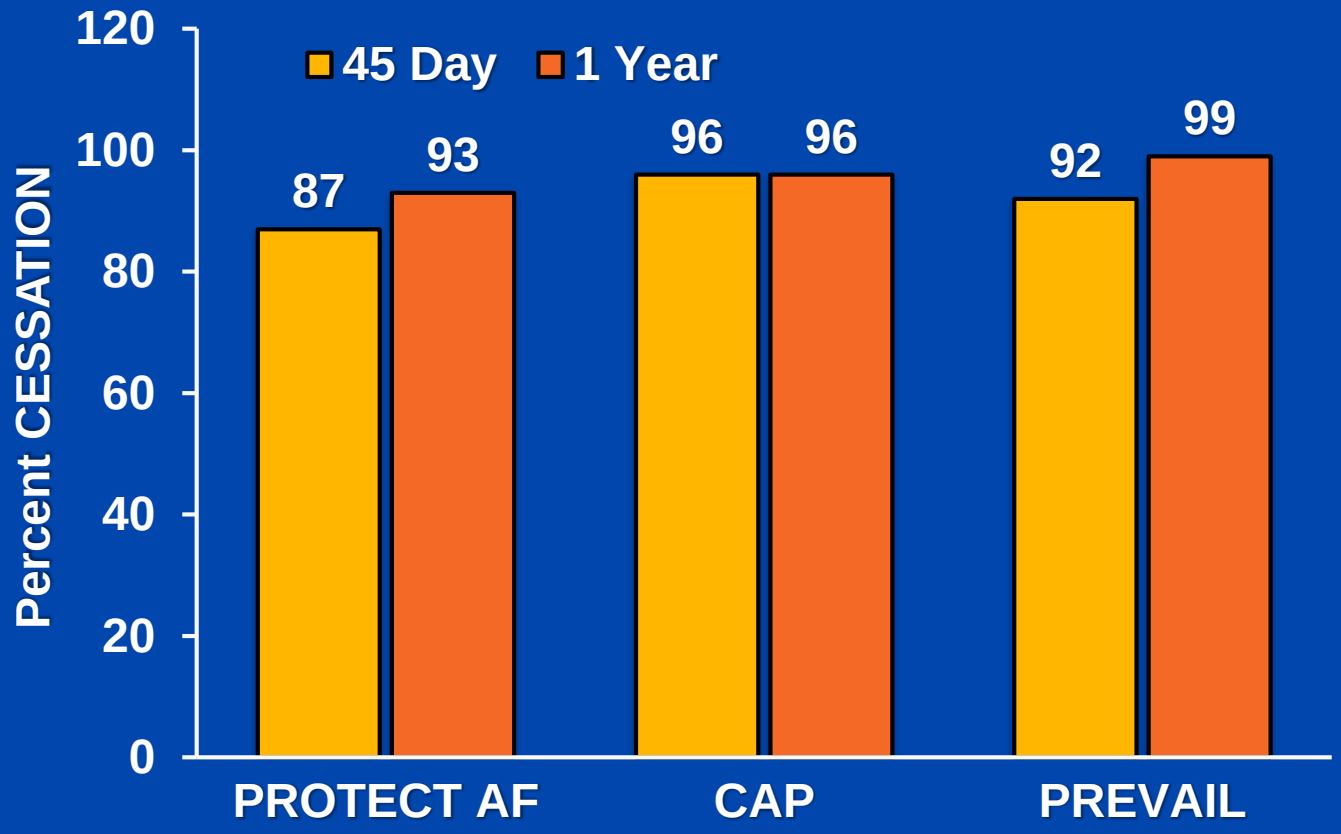
Warfarin Cessation after WATCHMAN



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March 2015
Instructions 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**

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US Reimbursement Status
CMS National Coverage Decision (2/8/16)

Criteria for coverage

- CHADS2 score ≥2 or CHA2DS2-VASc score ≥3
- A formal shared decision making interaction with an independent noninterventional physician using an evidence-based decision tool on oral anticoagulation in patients with NVAF
- Suitable for short-term warfarin but deemed unable to take long term oral anticoagulation

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Methods

- March 2015 – May 2016
  - 3,822 consecutive patients underwent LAAC with Watchman™ implantation by 382 physicians at 169 U.S. centers
  - 50% of procedures performed by newly trained operators
- Each implant was required to be performed with Watchman clinical specialist in attendance
- Details of each procedure recorded on standardized forms, and events reported to manufacturer per de-identified patient data

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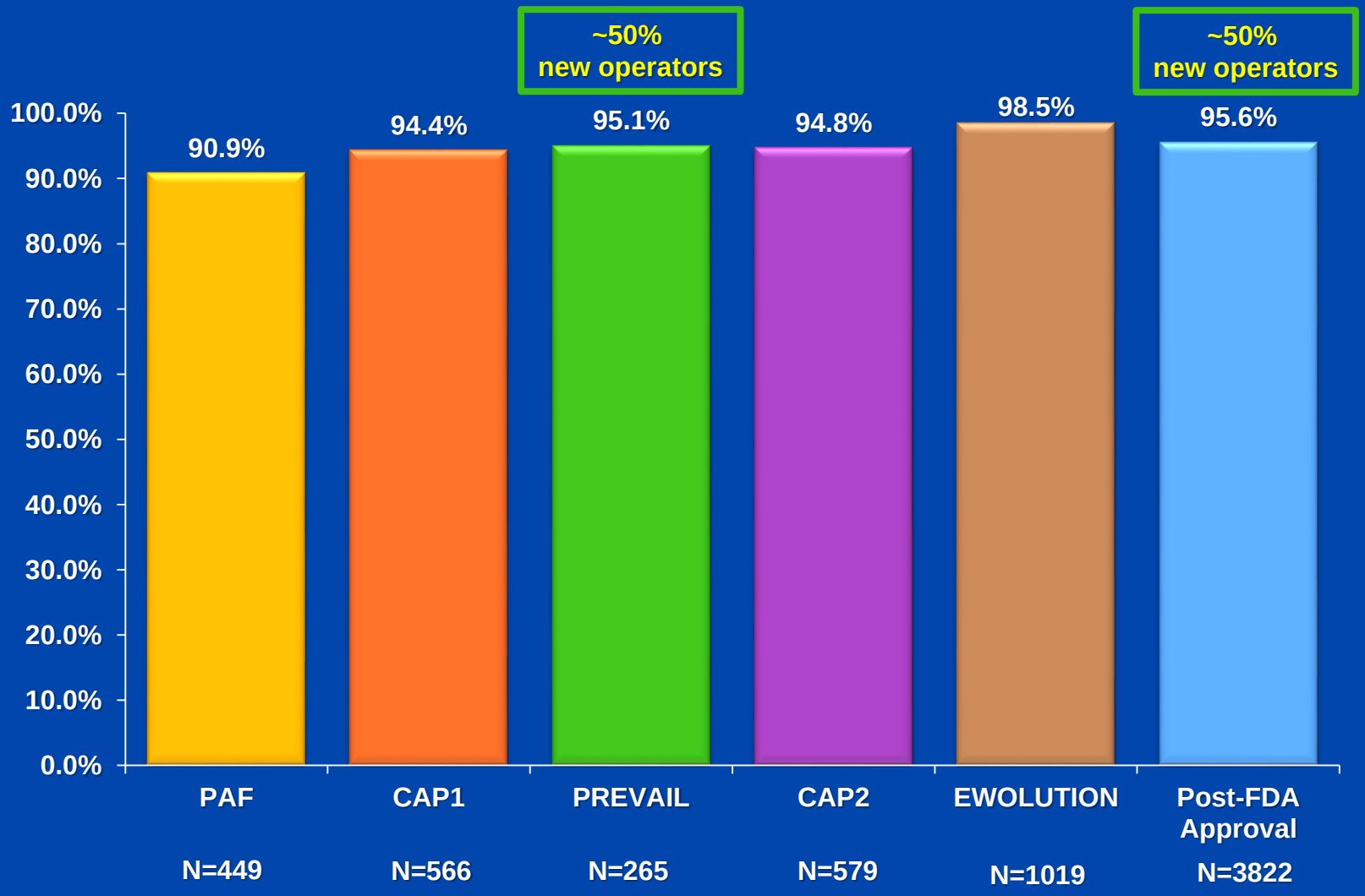
Procedural Success



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

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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%)

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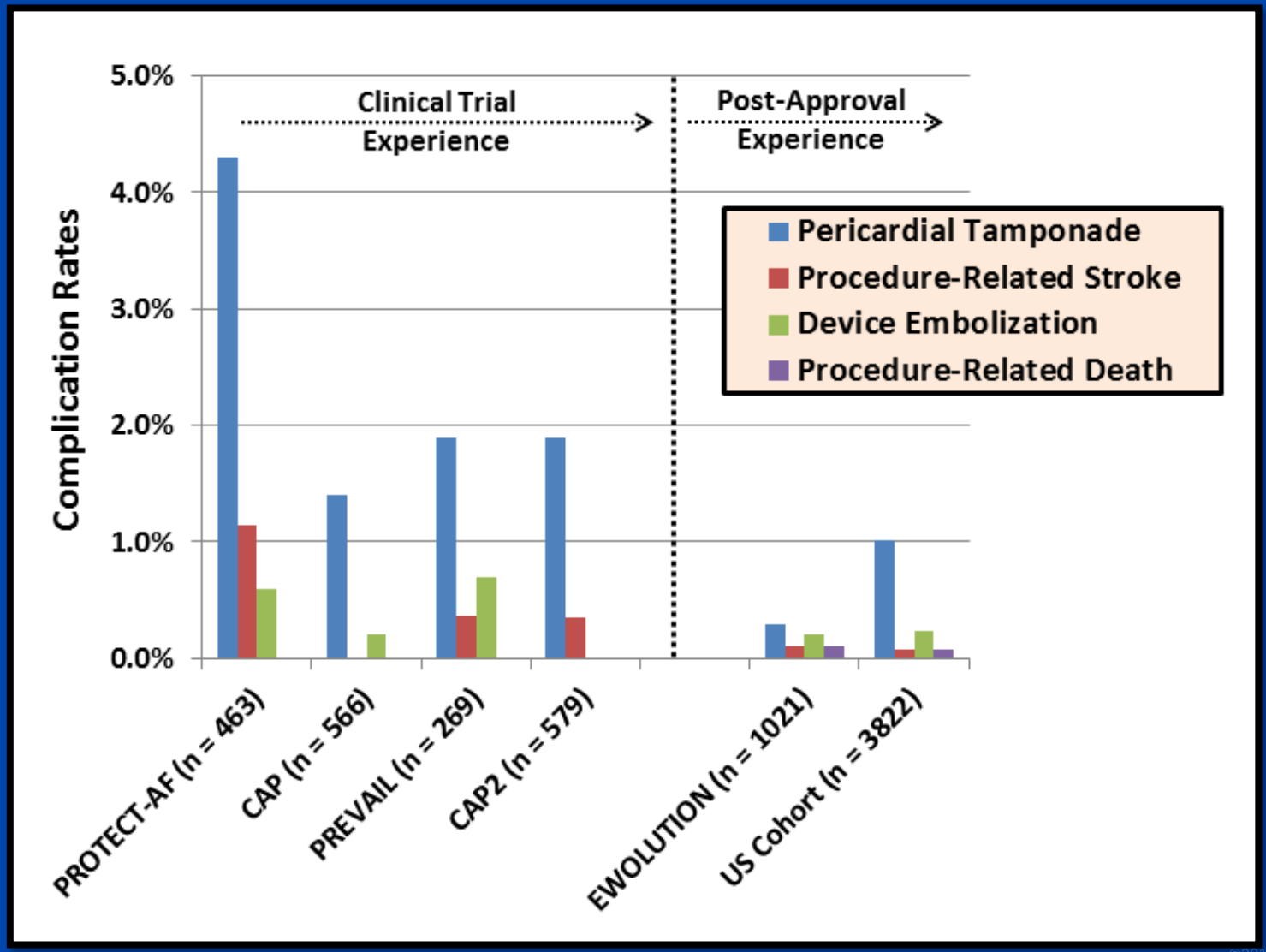
Comparison of Procedural Complications Across Watchman Studies



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Comparison of Procedural Complications Across Watchman Studies

	PROTECT-AF	PREVAIL	CAP	CAP2	EWOLUTION	Post-FDA Approval	Aggregate Data
Pericardial Tamponade	20 (4.3%)	5 (1.9%)	8 (1.4%)	11 (1.9%)	3 (0.29%)	39 (1.02%)	86 (1.28%)
Treated with pericardiocentesis	13 (2.8%)	4 (1.5%)	7 (1.2%)	n/a	2 (0.20%)	24 (0.63%)	
Treated surgically	7 (1.5%)	1 (0.4%)	1 (0.2%)	n/a	1 (0.10%)	12 (0.31%)	
Resulted in death	0	0	0	0	0	3 (0.78%)	
Pericardial effusion – no intervention	4 (0.9%)	0	5 (0.9%)	3 (0.5%)	4 (0.39%)	11 (0.29%)	27 (0.40%)
Procedure-related stroke	5 (1.15%)	1 (0.37%)	0	2 (0.35%)	1 (0.10%)	3 (0.078%)	12 (0.18%)
Device embolization	3 (0.6%)	2 (0.7%)	1 (0.2%)	0	2 (0.20%)	9 (0.24%)	17 (0.25%)
Removed percutaneously	1	0	0	0	1	3	
Removed surgically	2	2	1	0	1	6	
Death							
Procedure-related mortality	0	0	0	0	1 (0.1%)	3 (0.078%)	4 (0.06%)
Additional mortality within 7 days	0	0	0	1 (0.17%)	3 (0.29%)	1 (0.026%)	5 (0.07%)

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Summary

- Following United States FDA approval, this dataset represents the first patients implanted with this novel therapy
- Device usage, procedure time, and implant success rates are consistent with clinical trial results
- Safety complications rates in the initial experience are consistent with clinical trial results
  - Cardiac tamponade and procedure-related mortality occurred in ~1% and <0.1% of patients, respectively

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WATCHMAN® Indications for Use

US Indication

- 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 CHADS2 or CHA2DS2-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

International Indication:

The WATCHMAN LAA Closure Technology is intended to prevent thrombus embolization from the left atrial appendage and reduce the risk of life-threatening bleeding events in patients with non-valvular atrial fibrillation who are eligible for anticoagulation therapy
or who have a contraindication to anticoagulation therapy.

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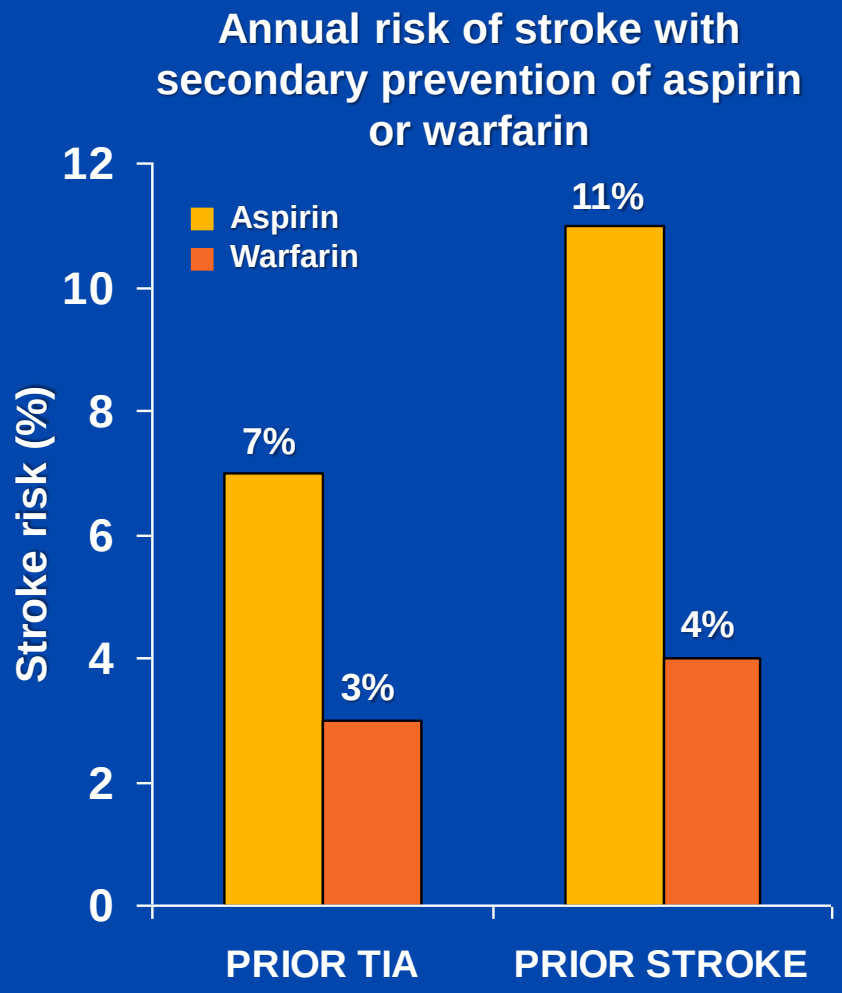
Aspirin and Plavix® Registry (ASAP)

The ASAP registry is a non-randomized feasibility study designed to evaluate if the WATCHMAN® Device is a safe and effective treatment for people unable to take warfarin

- AF patients who are contraindicated or intolerant of warfarin have few options for thromboembolic prophylaxis
- Patients may be treated with aspirin and/or clopidogrel; this treatment paradigm has a higher stroke risk than warfarin



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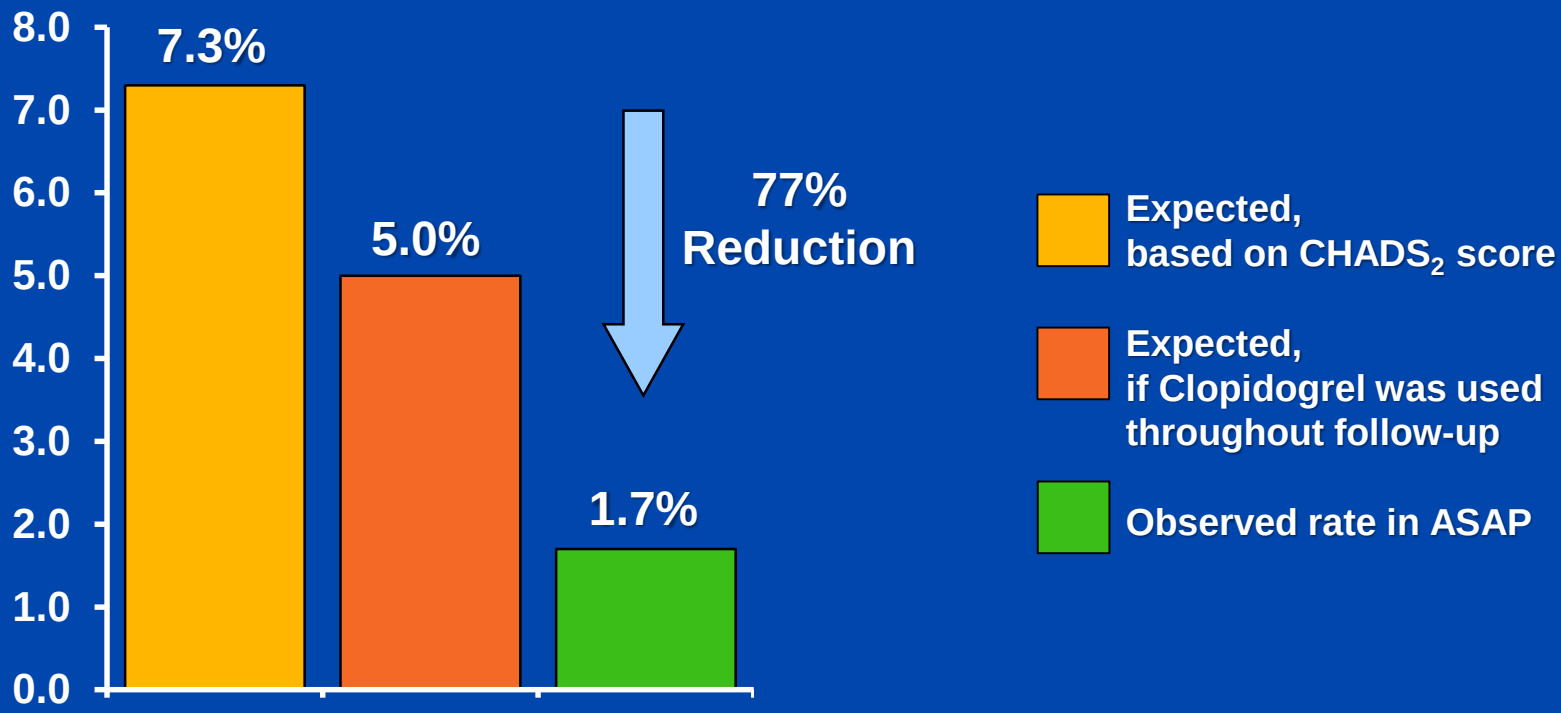
The WATCHMAN Device is not approved for patients contraindicated to OACs

Results

Expected and Observed Stroke Rates (per 100 patient-years)



Observed rate of ischemic stroke represents a 77% reduction from the expected event rate

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EWOLUTION

- Multicenter registry of 1,021 patients treated with Watchman LAAC – 2013-2015
  - 47 centers
  - 13 countries
- Objective: obtain clinical data on
  - Procedural success and 30-day outcomes
  - Long-term outcomes
    - Bleeding
    - Stroke/TIA

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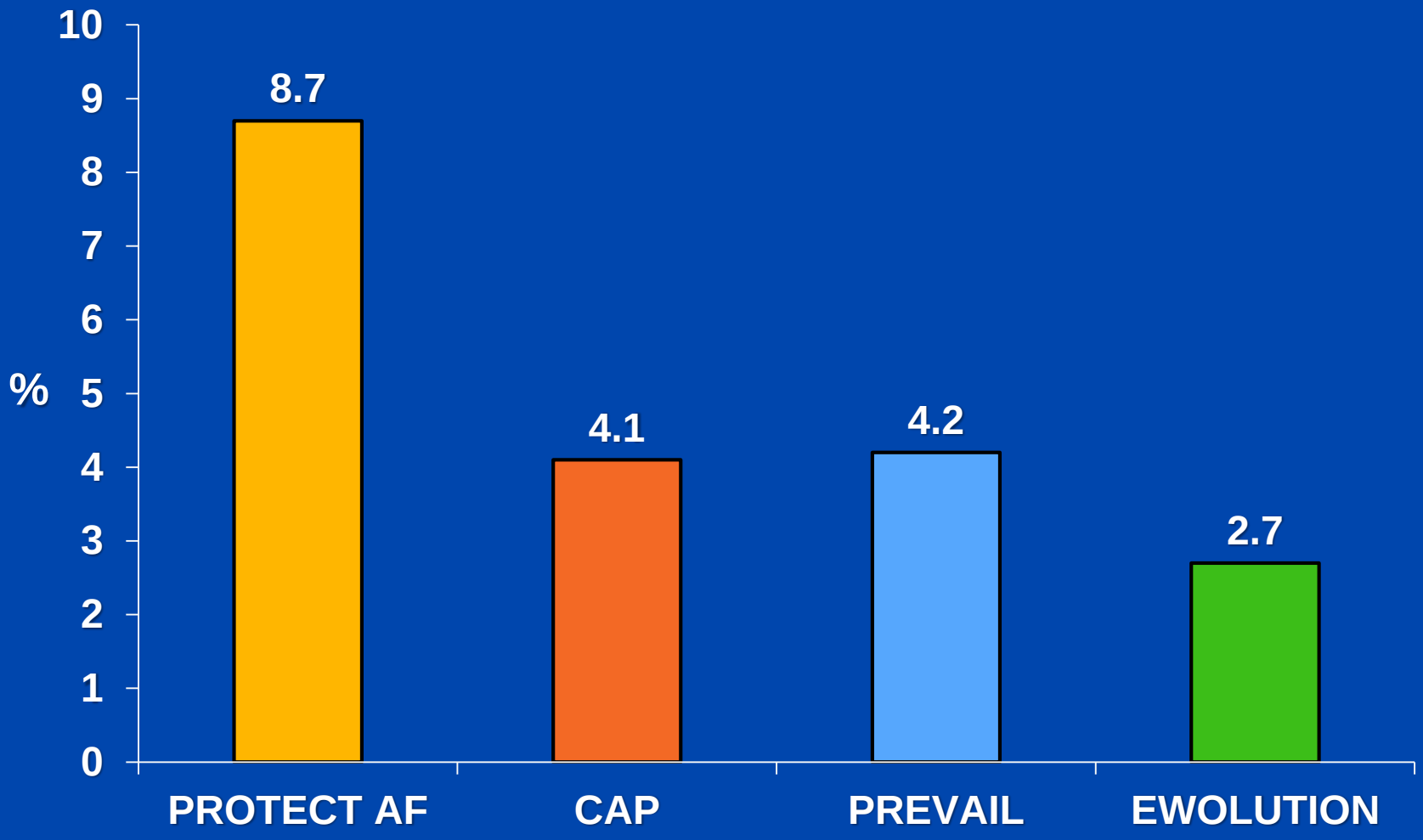
Boersma et al: Euro Heart J, doi:10.1083/eurheartj/ehv730

EWOLUTION

Serious Procedure-/Device-Related Events through 7 days



Boersma et al: Euro Heart J, doi:10.1083/eurheartj/ehv730

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ASAP-TOO Study Design

- Prospective, randomized, multi-center, global
- Patients with non-valvular atrial fibrillation deemed not suitable for oral anti-coagulation therapy to reduce the risk of stroke.
- Randomized 2:1 (Watchman vs Control)
- Considering Group Sequential Design
    - Allows early looks; potential to stop early for benefit
- 888 subjects at up to 100 global sites
- Follow-Up*
    - 45 Day with TEE
    - 6,18 month phone visit
    - 12 month with TEE
    - Years 2-5 bi-annually

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* Brain imaging required at baseline if prior stroke or TIA

AF Ablation and Watchman LAAC

- Single center study – 2010-2015
  - 98 patients with NVAF
  - Mean CHA_2DS_2VASc score 2.6±1.0
- Pulmonary vein isolation
  - Irrigated tip ablation catheter – RF
  - Antral ring electrical isolation
- Watchman implantation

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Phillips et al: J of Arrhythmia 32:119-126, 2016

AF Ablation and Watchman LAAC
Results

- Complete occlusion in
  - 94% - initially
  - 86% - 1 year
- Persistent late peri leaks more frequently
  - Associated with angulation/shoulder
  - Associated with lower compression
- No embolization
- 1 stroke 802 days

Phillips et al: J of Arrhythmia 32:119-126, 2016

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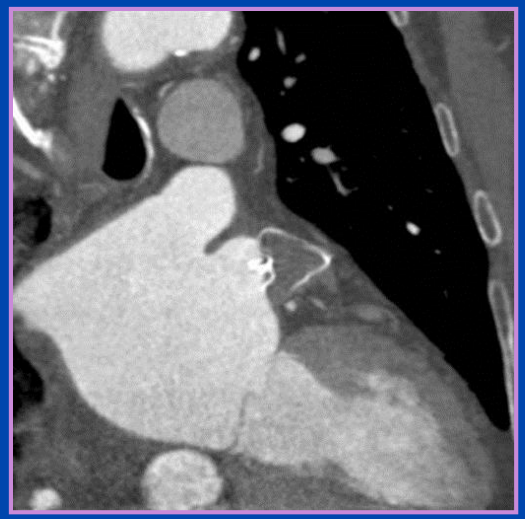
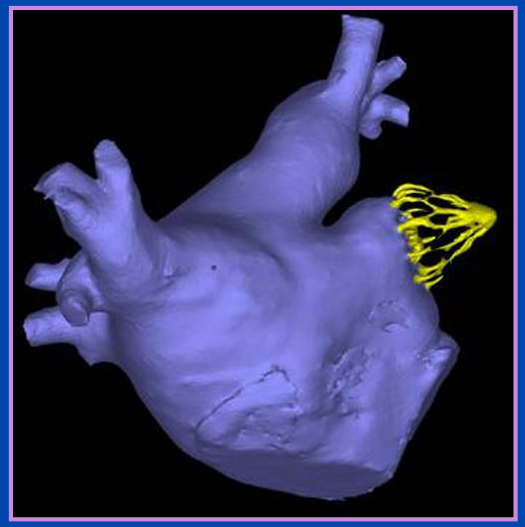
Stroke and Atrial Fibrillation
Alternative to Warfarin or NOACS





- Patients who could be treated with warfarin/NOACS
- Patients who choose not to be treated with warfarin/NOACS
- Contraindications to warfarin/NOACS
- In concert with ablation

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