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Left Atrial Appendage Closure
4 questions – Who? When? How? Results?

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Presenter Disclosure Information

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

"Left Atrial Appendage Closure
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The following relationships exist related to this presentation:

None

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Left Atrial Appendage Closure

- Who?
- When?
- How?
- Results

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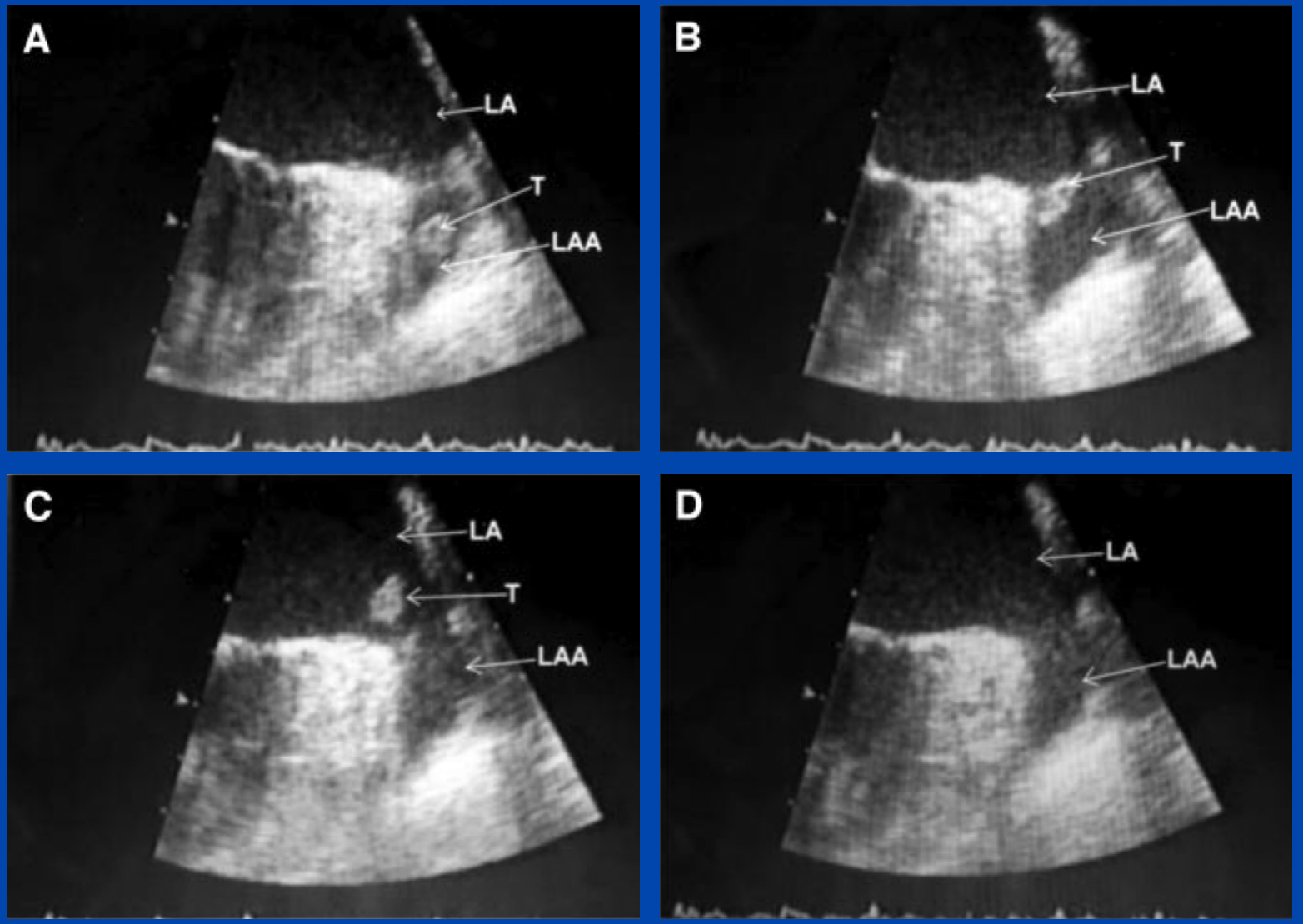
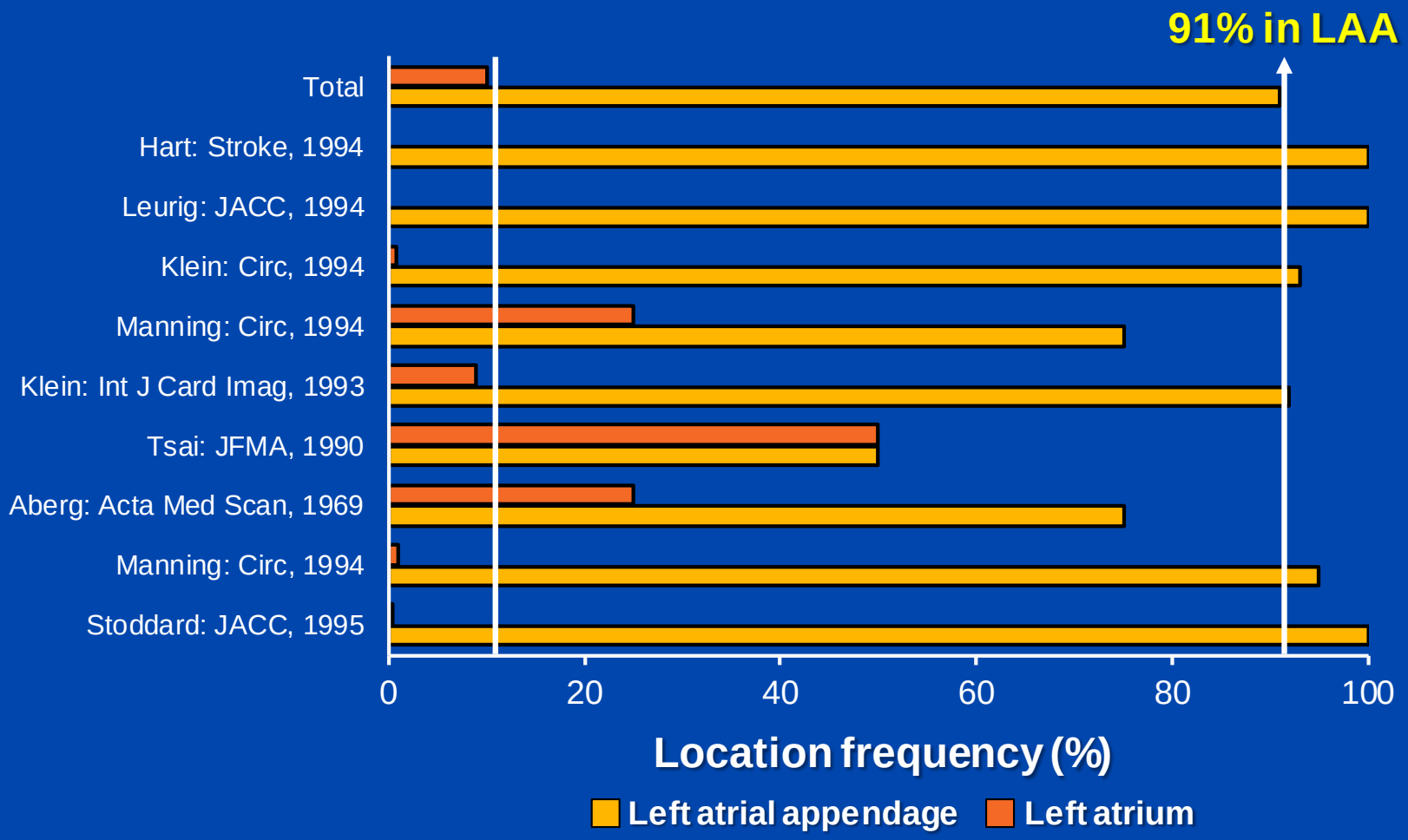
Disappearing LAA Thrombus Resulting in Stroke



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

Location of Thrombi in Left Atrium



Blackshear et al: Ann Thoracic Surg 61, 1996

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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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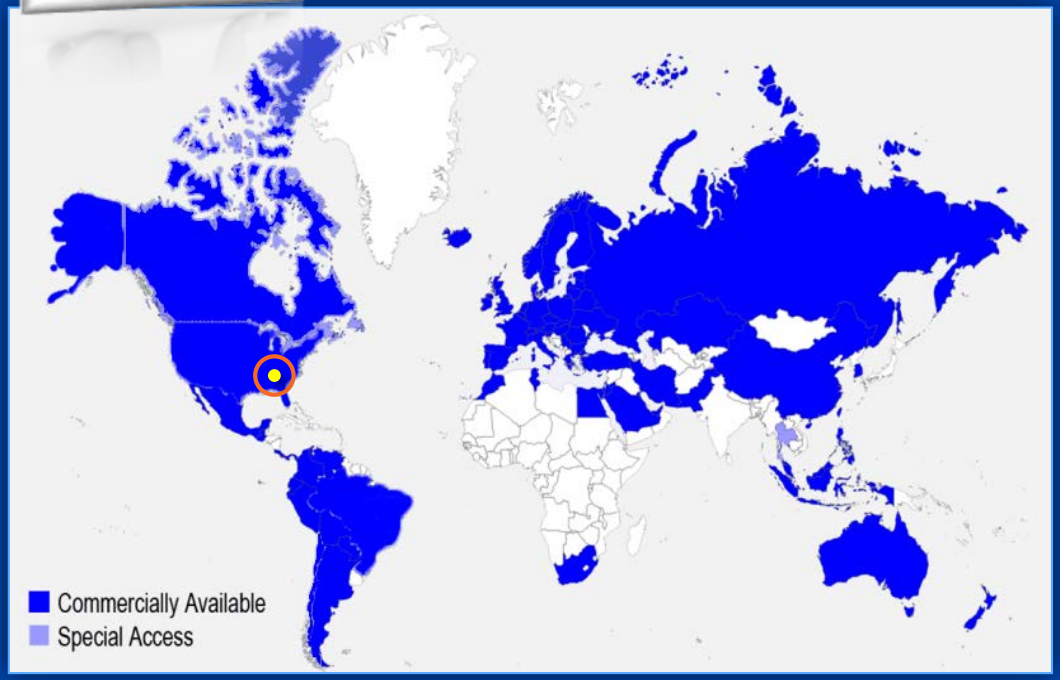
WATCHMAN Approved in >75 Countries



There are very few white spots

- **Central Africa**
- **Mongolia**
- **India**
- **Greenland and…**

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WATCHMAN™ Indications for Use

US Indication

- The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the LAA in patients with non-valvular AFib 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

International Indication

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

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WATCHMAN 2014 FDA Panel
A Safe & Effective Alternative Therapy

- NOT a broad first line replacement for oral anticoagulants
- IS an alternative for patients eligible for warfarin, with reasons to seek another long-term therapeutic option

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Gold Standards?

- Dabigatran
- Apixaban
- Rivaroxaban
- Edoxaban

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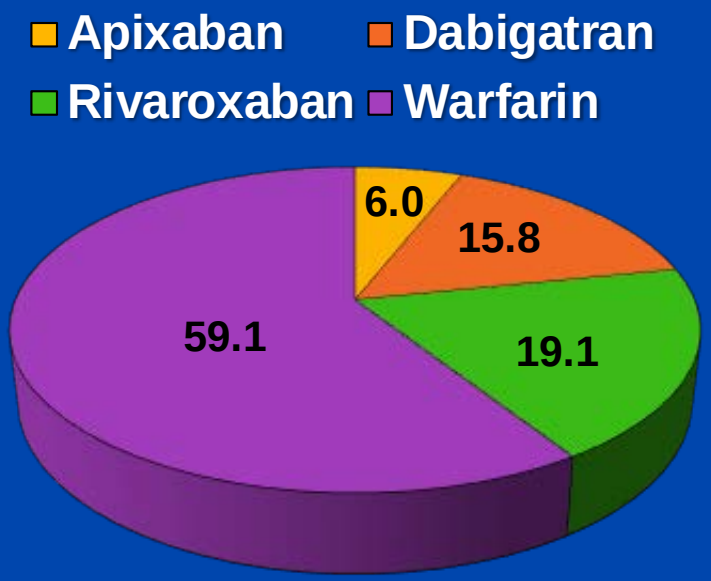
Adherence to OAC

- U.S. commercial insurance data base (administrative claims) 66,661 patients with atrial fibrillation treated between November 2010 and December 2014



CHA_2DS_2VASc score ≥2	~90%
HAS-BLED ≥3	~50%
Median F/U	1.1 yrs

Yao et al: J Am Heart Assoc doi:10.1161/JAHA.115.003074, 2006

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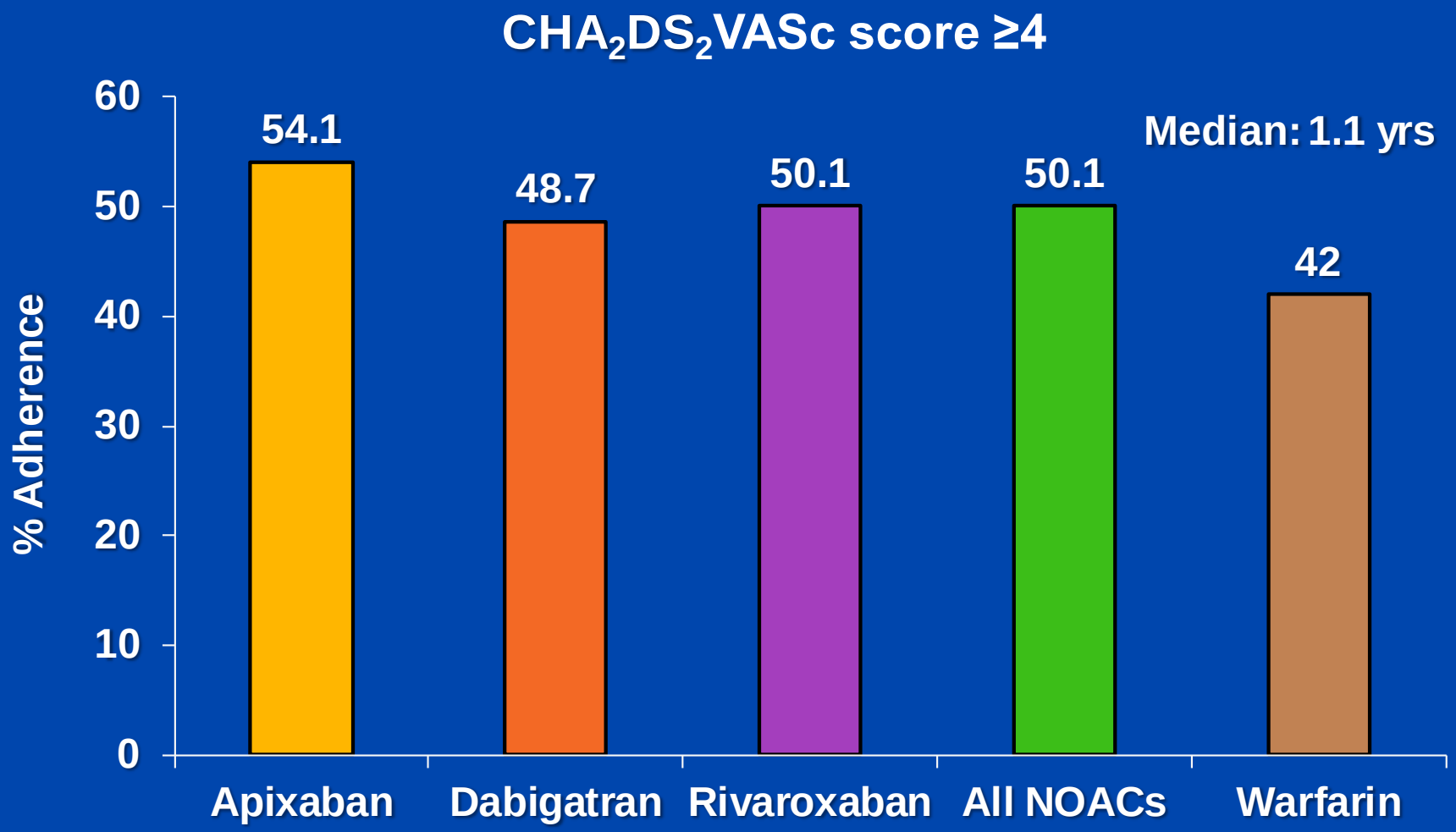
Adherence to OAC
Proportion of Days Covered



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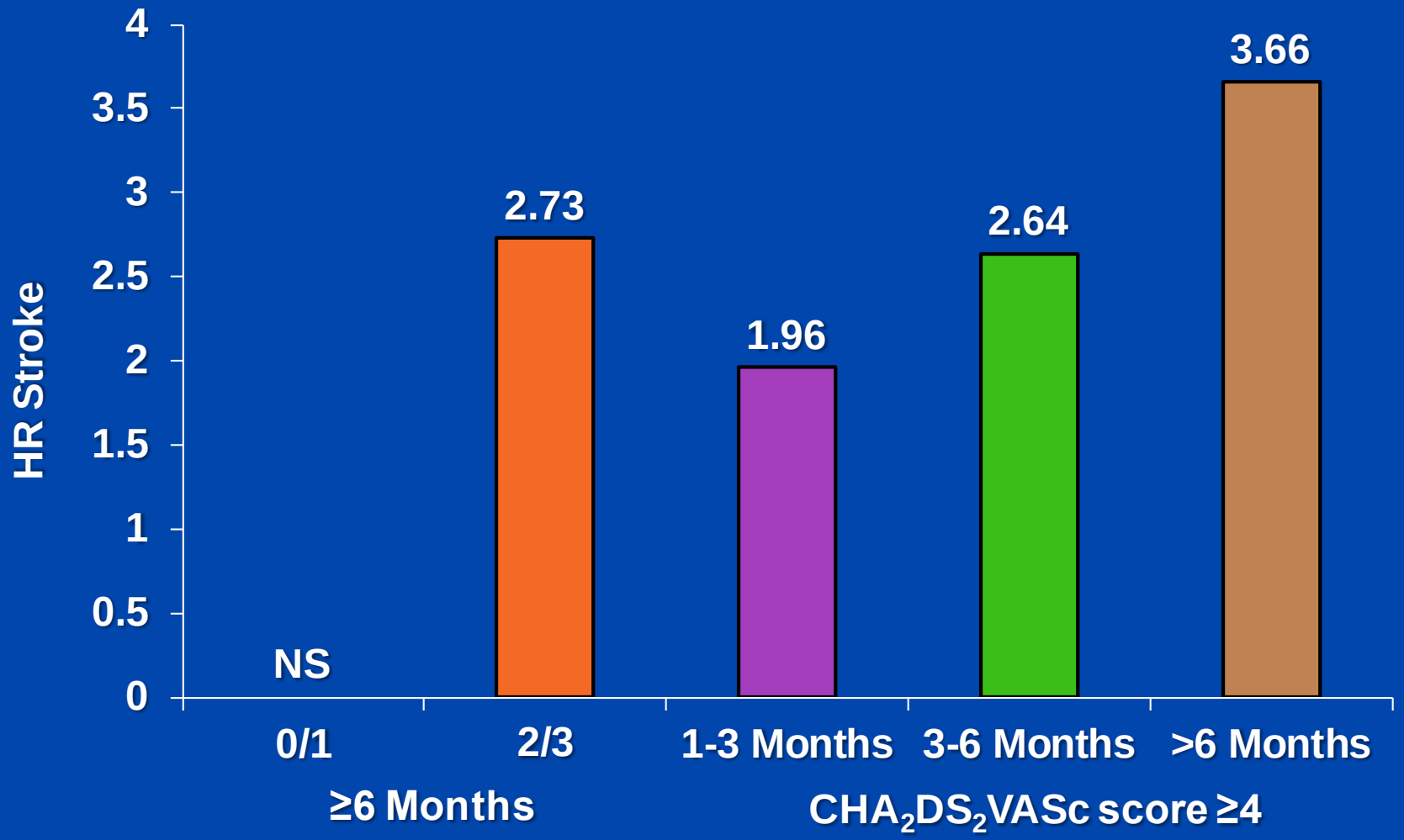
Yao et al: J Am Heart Assoc doi:10.1161/JAHA.115.003074, 2016

OAC
Non-Adherence on Stroke Risk



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Yao et al: J Am Heart Assoc doi:10.1161/JAHA.115.003074, 2016

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Adherence to OAC ≥6 Months
Findings

- No significant effect between non-adherence and risk of stroke with CHA_2DS_2VASc score 0/1
- In non-adherent patients risk of stroke with CHA_2DS_2VASc score 2/3; HR 2.73 (95% CI 1.76-4.23)
- In non-adherent patients risk of stroke with CHA_2DS_2VASc score ≥4 markedly elevated

Yao et al: J Am Heart Assoc doi:10.1161/JAHA.115.003074, 2016

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NOAC's and Renal Dysfunction

- Administrative data base
  - 14,865 patients with AF treated with Apixaban, dabigatran or rivaroxaban 2010-2015
- Evaluate
  - Use of SD in patients with a renal indication (potential overdosing)
  - Use of reduced dose when a renal indication was not present (underdosing)

Yao et al: J Am Coll Cardiol 69:2779-90, 2017

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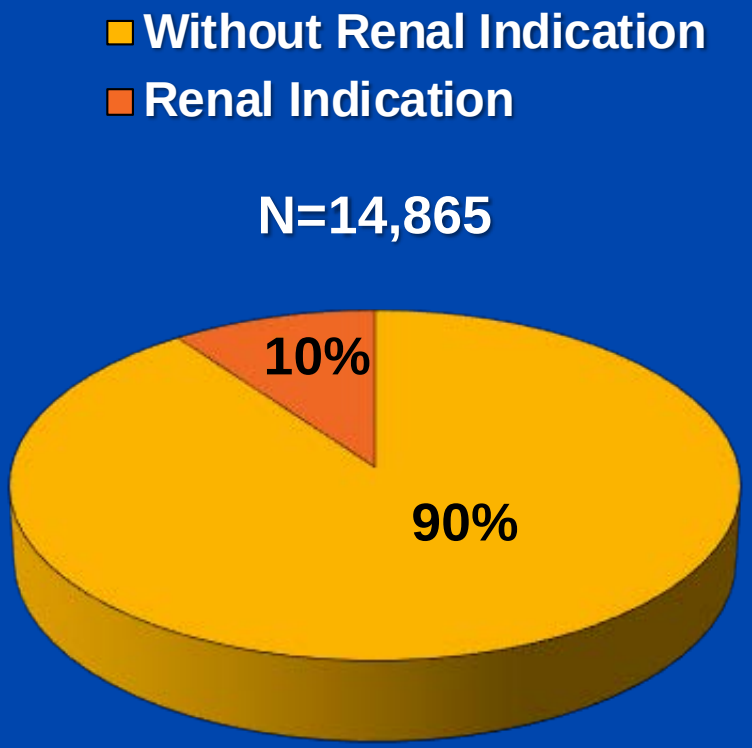
NOAC's and Renal Dysfunction



- Primary effective outcome
  - Ischemic stroke/SE
- Primary safety outcome
  - Major bleeding

Yao et al: J Am Coll Cardiol 69:2779-90, 2017

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NOAC's & Renal Dysfunction
Findings
N=1,473

- Potential overdosing seen in 43% of patients with renal indication associated with
  - Higher risk of major bleeding (HR 2.19, 95% CI 1.07, 4.46)
  - No significant difference in stroke
- In 13,392 with no renal indication for dose reduction 13.3% were potentially underdosed
  - Higher risk of stroke (HR 4.87, 95% CI 1.30, 18.26)
  - No significant difference in major bleeding

Yao et al: J Am Coll Cardiol 2017;69:2779–90

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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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Left Atrial Appendage Closure

- Who?
- When?
- How?
- Results

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- After shared decision making in patients with nonvalvular atrial fibrillation at risk for stroke/SE
- High risk for bleeding – CAA
- Prior bleeding
- Stroke/systemic embolism on AC
- Unable/unwilling to take AC
- Prior ICH
- Prior stroke

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Left Atrial Appendage Closure

- Who?
- When?
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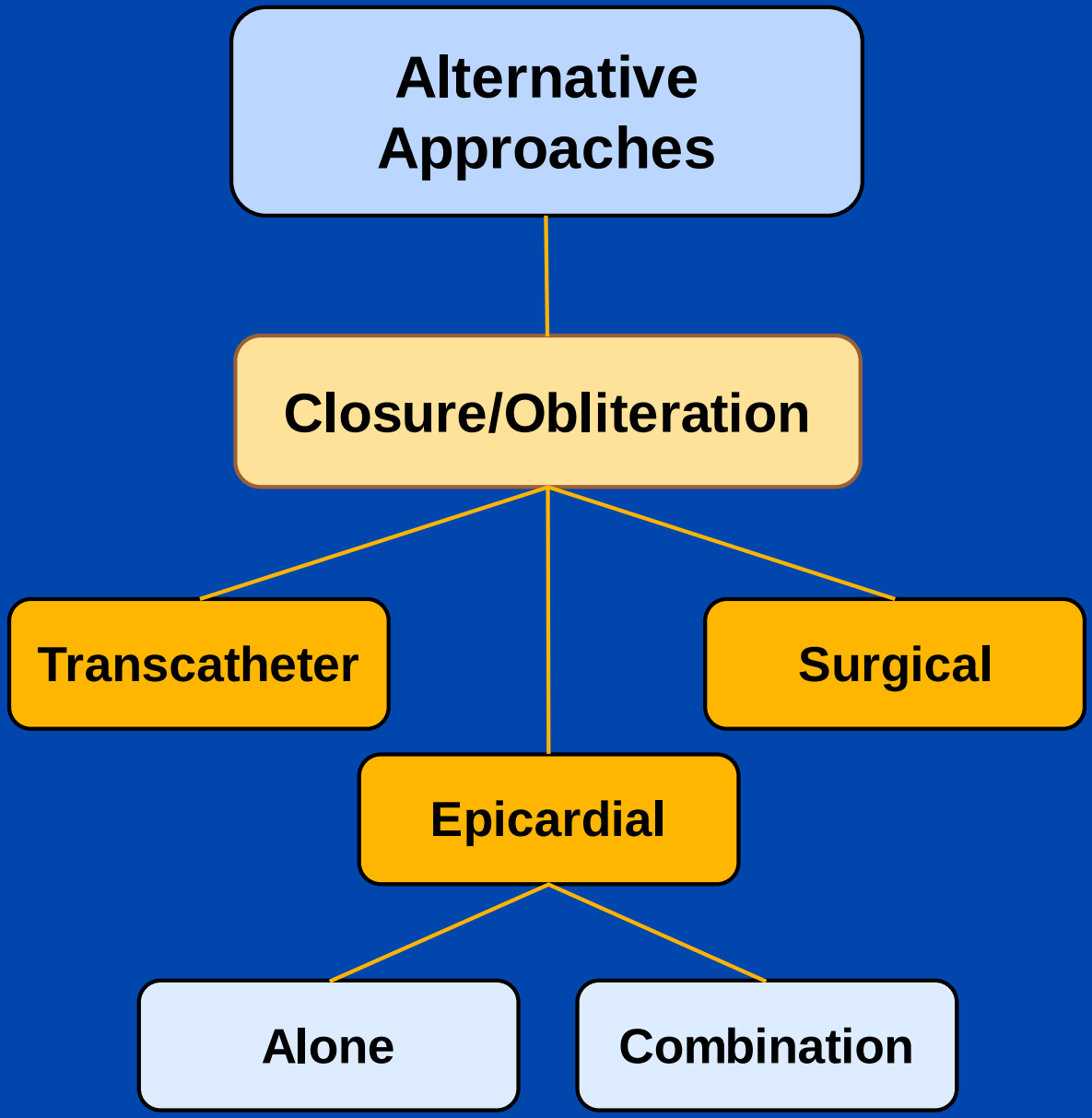
Alternative Approaches
Closure/Obliteration
Transcatheter
Surgical
Epicardial
Alone
Combination

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How?

- Other planned procedures
  - e.g. CABG, planned maze
- Devices available
- Commercial or clinical trial
- Physician expertise and experience
- Anatomy
  - Specifics of LAA morphology
  - Specifics of approach
    - Abnormalities of IAS
    - Thrombus in LAA
    - Prior pericardial procedures
- IFU constraints

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Left Atrial Appendage Closure

- Who?
- When?
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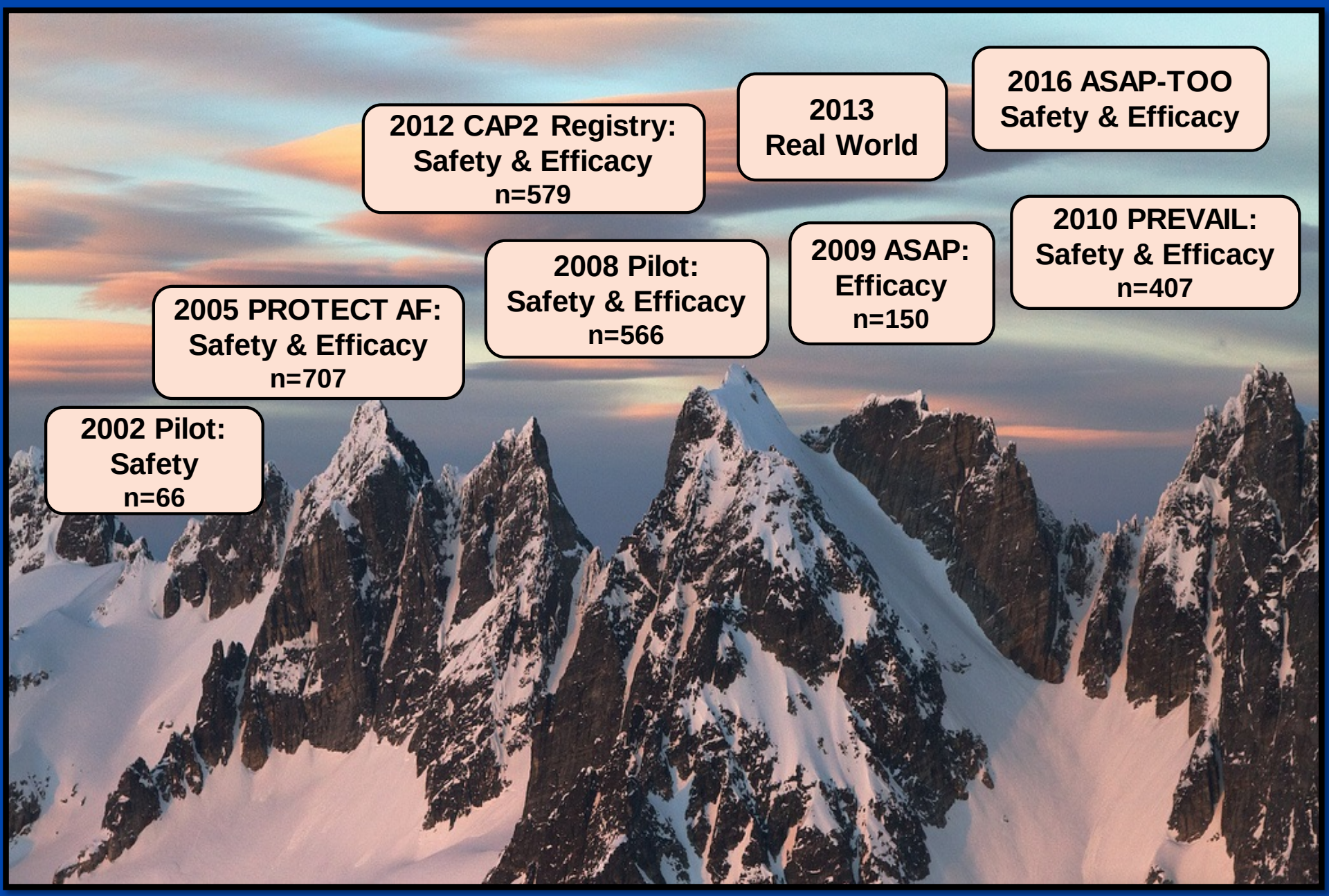
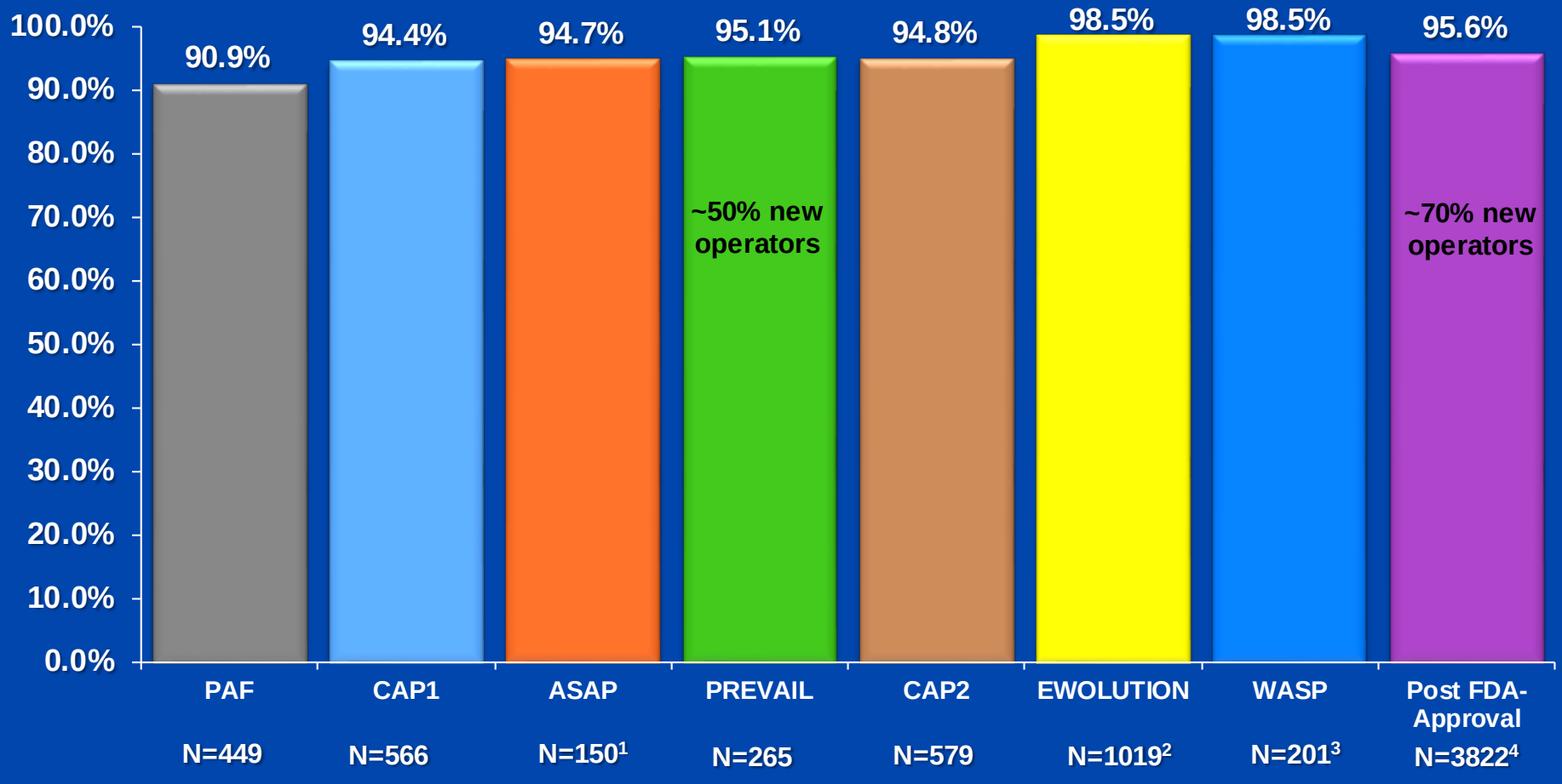

2002 Pilot:
Safety
n=66
2005 PROTECT AF:
Safety & Efficacy
n=707
2008 Pilot:
Safety & Efficacy
n=566
2009 ASAP:
Efficacy
n=150
2010 PREVAIL:
Safety & Efficacy
n=407
2012 CAP2 Registry:
Safety & Efficacy
n=579
2013
Real World
2016 ASAP-TOO
Safety & Efficacy

Consistent Procedural Success



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

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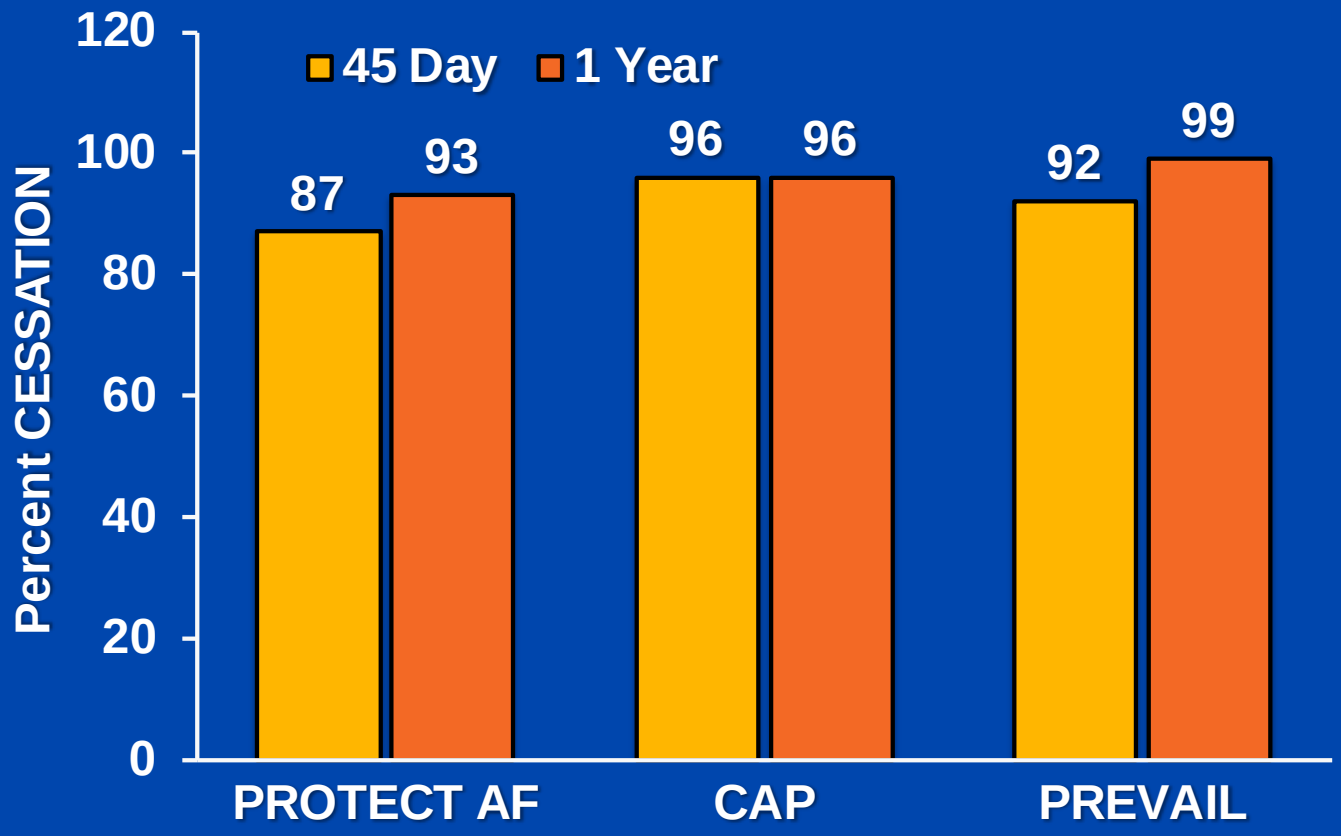
1 Reddy et al. JACC 2013; 61(25): 2551-6; 2 Boersma, L.et al. EHJ 37(31): 2465s; 3 Phillips et al. Journal of Arrhythmia; in press. 4 Reddy, VY., Gibson, DN, et al. *JACC* 2017; 69(3): 253-261.

Warfarin Cessation after WATCHMAN



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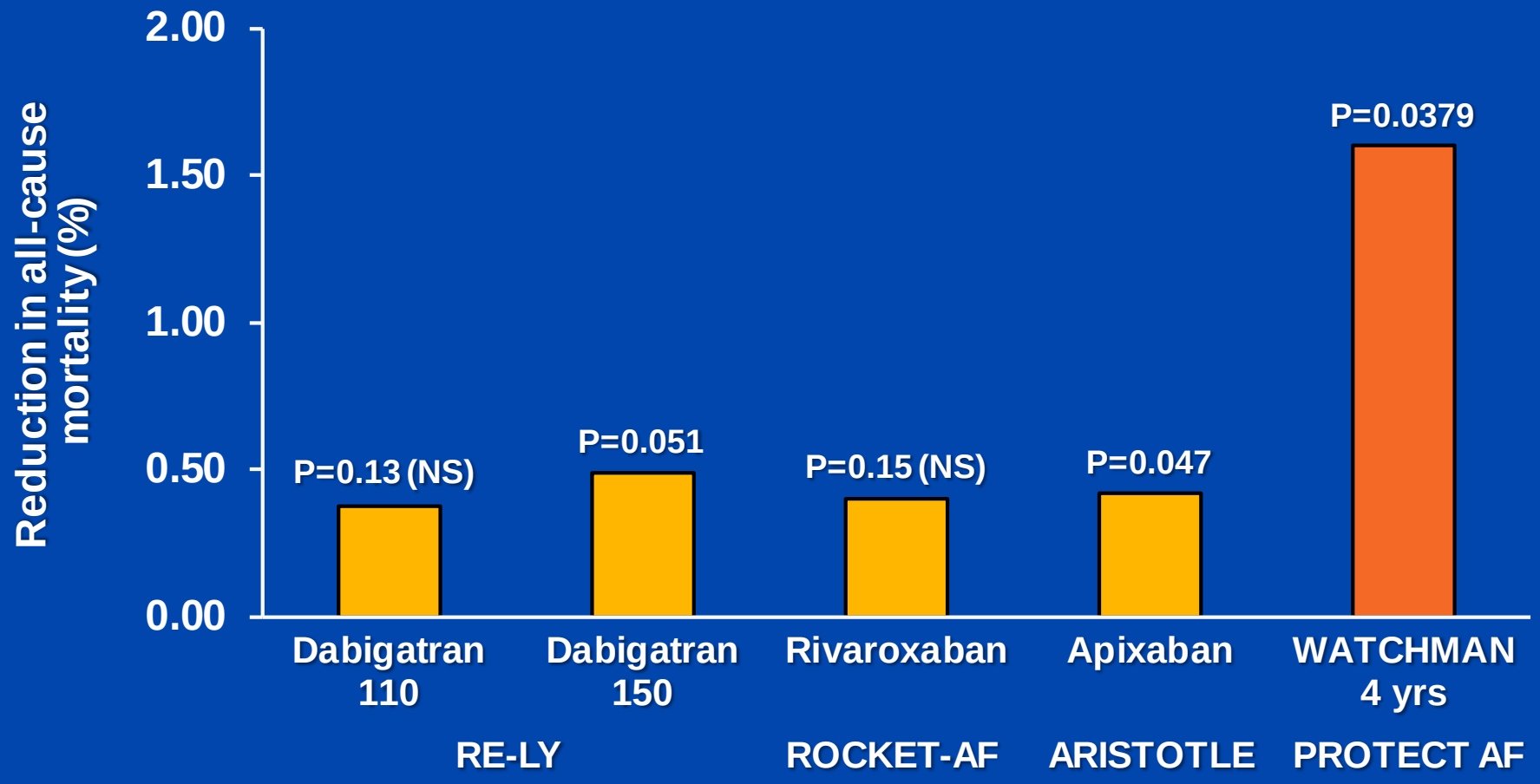
Mortality Reduction (vs warfarin)



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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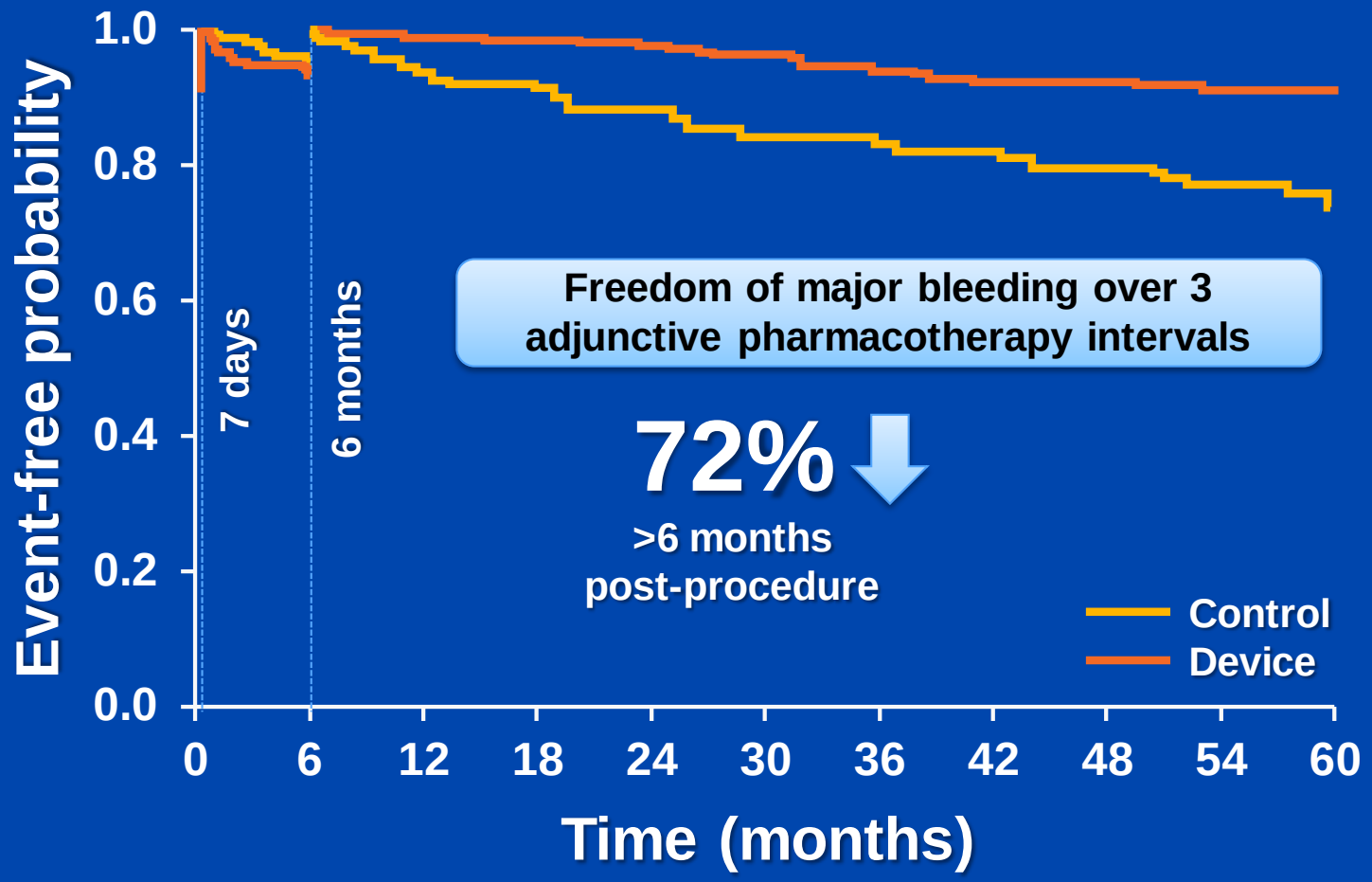
Bleeding Outcomes After LA Appendage Closure Compared with Long-term Warfarin



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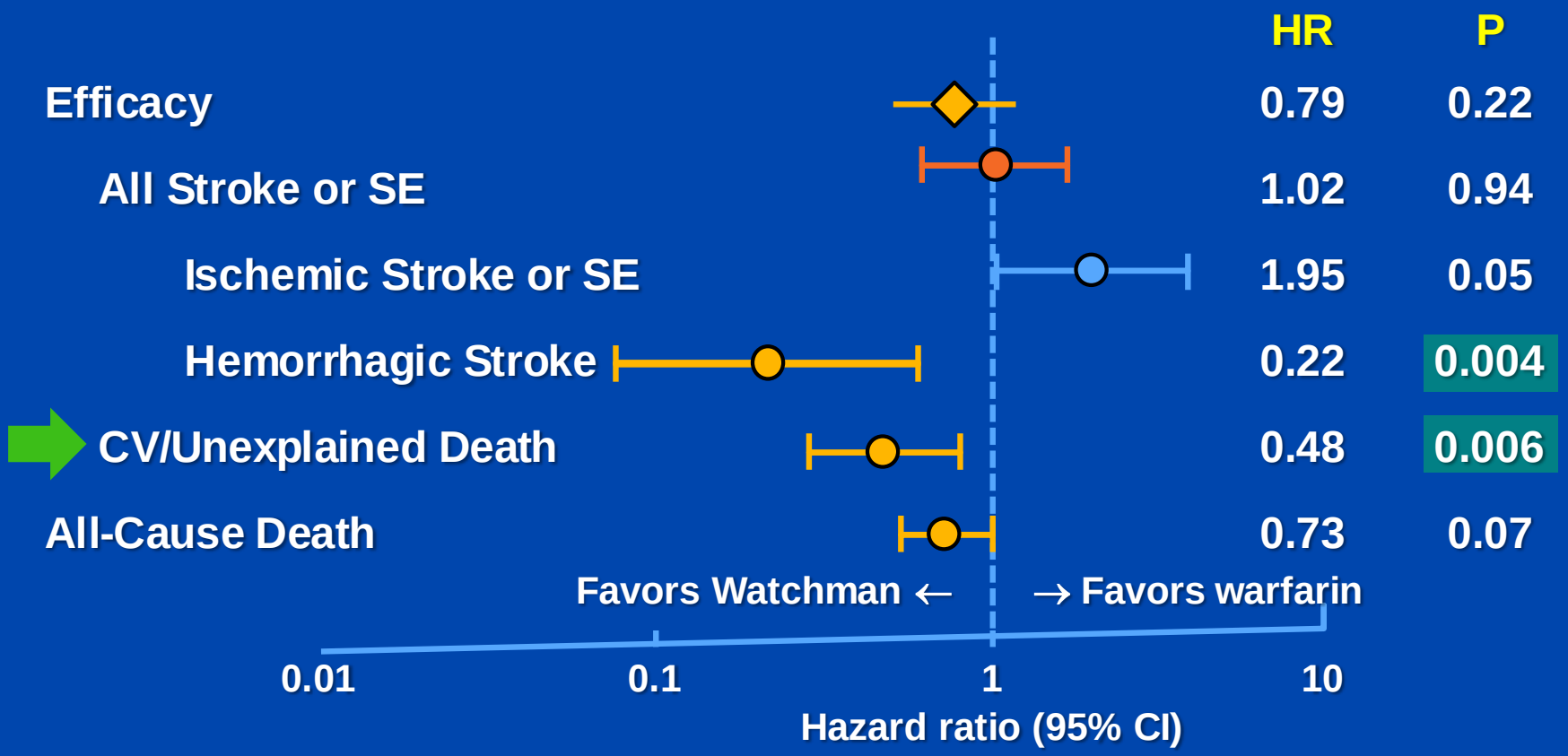
Left Atrial Appendage Closure vs Warfarin in AF

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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"Five-Year Outcomes of Left Atrial Appendage Closure: Final Results of the Continued Access to PROTECT AF (CAP) Registry" - Background

- PROTECT AF was the first randomized control trial to assess the safety and efficacy of LAAO with WATCHMAN when compared to warfarin for the reduction of stroke, systemic embolism, and CV mortality in NVAF patients
  - Long-term results show superiority of LAAO for efficacy
- Continued Access to PROTECT AF (CAP) Registry was initiated to allow a subset of investigators from the PROTECT AF study continued access to the WATCHMAN device in a non-randomized study where all enrolled patients underwent LAAO
  - N=566
  - Enrollment – Aug 2008 – Jun 2010
  - 26 centers (24 US, 2 Europe)
  - Full event adjudication
- All patients have completed 5 year follow-up

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Objective

- To demonstrate that the WATCHMAN LAA Closure Technology is effective in clinical practice for patients with non-valvular atrial fibrillation at increased risk for stroke/systemic embolism.

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Endpoints

Primary Efficacy

Composite of Stroke (ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism

Primary Safety

Occurrence of life threatening events* over the entire course of follow up, such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeding requiring transfusion and any bleeding related to the device or procedure that necessitated a surgical procedure

*As adjudicated by Clinical Events Committee

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Demographics
Device Patients

Characteristic	PROTECT AF N=463 % (n)	CAP N=566 % (n)
Age, years	71.7 ± 8.8 (46.0, 95.0)	74.0 ± 8.3 (44.0, 94.0)
Male	70.4% (326)	65.5% (371)
$CHADS_2$ Score (Continuous)	2.2 ± 1.2	2.5 ± 1.2
CHA_2DS_2 VASc Score (Continuous)	3.5 ± 1.6	3.9 ± 1.5
$CHADS_2$ Risk Factors		
CHF	26.8% (124)	19.1% (108)
Hypertension	89.6% (415)	88.9% (503)
Age ≥ 75	41.0% (190)	51.8% (293)
Diabetes	24.4% (113)	24.9% (141)
Stroke/TIA	17.7% (82)	30.4% (172)

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Visit Compliance and Study Follow-up

- Overall Visit Compliance = 98%
  - Attended vs Expected 5518/5643
- Average follow up = 50.1 ± 19.3 months
  - Patient-Years = 2293

Discontinuation Reason	Total N=566 % (n)
Patient successfully completed all study follow-up	67.8% (384)
Death	17.8% (101)
No Device Implanted	5.7% (32)
Lost to Follow-up	5.1% (29)
Subject Consent Withdrawn	2.3% (13)
Other	1.2% (7)

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Results in Context:
Efficacy Comparisons to PROTECT AF

	PROTECT AF Device N=463 (95% CI)	PROTECT AF Control N=244 (95% CI)	CAP N=566 (95% CI)
Primary Efficacy	2.24 (1.64, 3.05)	3.66 (2.61 , 5.12)	3.1 (2.4, 3.9)
All Stroke	1.45 (0.99, 2.14)	2.15 (1.39, 3.34)	1.5 (1.1, 2.1)
Ischemic Stroke	1.35 (0.90, 2.01)	1.07 (0.58, 1.99)	1.16 (0.78, 1.71)
Hemorrhagic Stroke	0.16 (0.05, 0.51)	1.06 (0.57, 1.97)	0.09 (0.02, 0.36)
Systemic Embolism	0.16 (0.0, 0.4)	0	0.05 (0.01, 0.32)
CV/Unexplained Death	1.03 (0.66, 1.62)	2.32 (1.53, 3.52)	1.7 (1.2, 2.3)

CI = Confidence interval
CV = Cardiovascular

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Results in Context:
All Stroke Consistent with Device

	PROTECT AF Device N=463 (95% CI)	PROTECT AF Control N=244 (95% CI)	CAP N=566 (95% CI)
Primary Efficacy	2.24 (1.64, 3.05)	3.66 (2.61 , 5.12)	3.1 (2.4, 3.9)
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CV = Cardiovascular

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Results in Context:
Ischemic Stroke Comparable to Warfarin

	PROTECT AF Device N=463 (95% CI)	PROTECT AF Control N=244 (95% CI)	CAP N=566 (95% CI)
Primary Efficacy	2.24 (1.64, 3.05)	3.66 (2.61 , 5.12)	3.1 (2.4, 3.9)
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CV = Cardiovascular

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Results in Context: Hemorrhagic Stroke Consistent with Device

	PROTECT AF Device N=463 (95% CI)	PROTECT AF Control N=244 (95% CI)	CAP N=566 (95% CI)
Primary Efficacy	2.24 (1.64, 3.05)	3.66 (2.61 , 5.12)	3.1 (2.4, 3.9)
All Stroke	1.45 (0.99, 2.14)	2.15 (1.39, 3.34)	1.5 (1.1, 2.1)
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CI = Confidence interval
CV = Cardiovascular

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Results in Context:
CV Death Consistent with Device

	PROTECT AF Device N=463 (95% CI)	PROTECT AF Control N=244 (95% CI)	CAP N=566 (95% CI)
Primary Efficacy	2.24 (1.64, 3.05)	3.66 (2.61 , 5.12)	3.1 (2.4, 3.9)
All Stroke	1.45 (0.99, 2.14)	2.15 (1.39, 3.34)	1.5 (1.1, 2.1)
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CI = Confidence interval
CV = Cardiovascular

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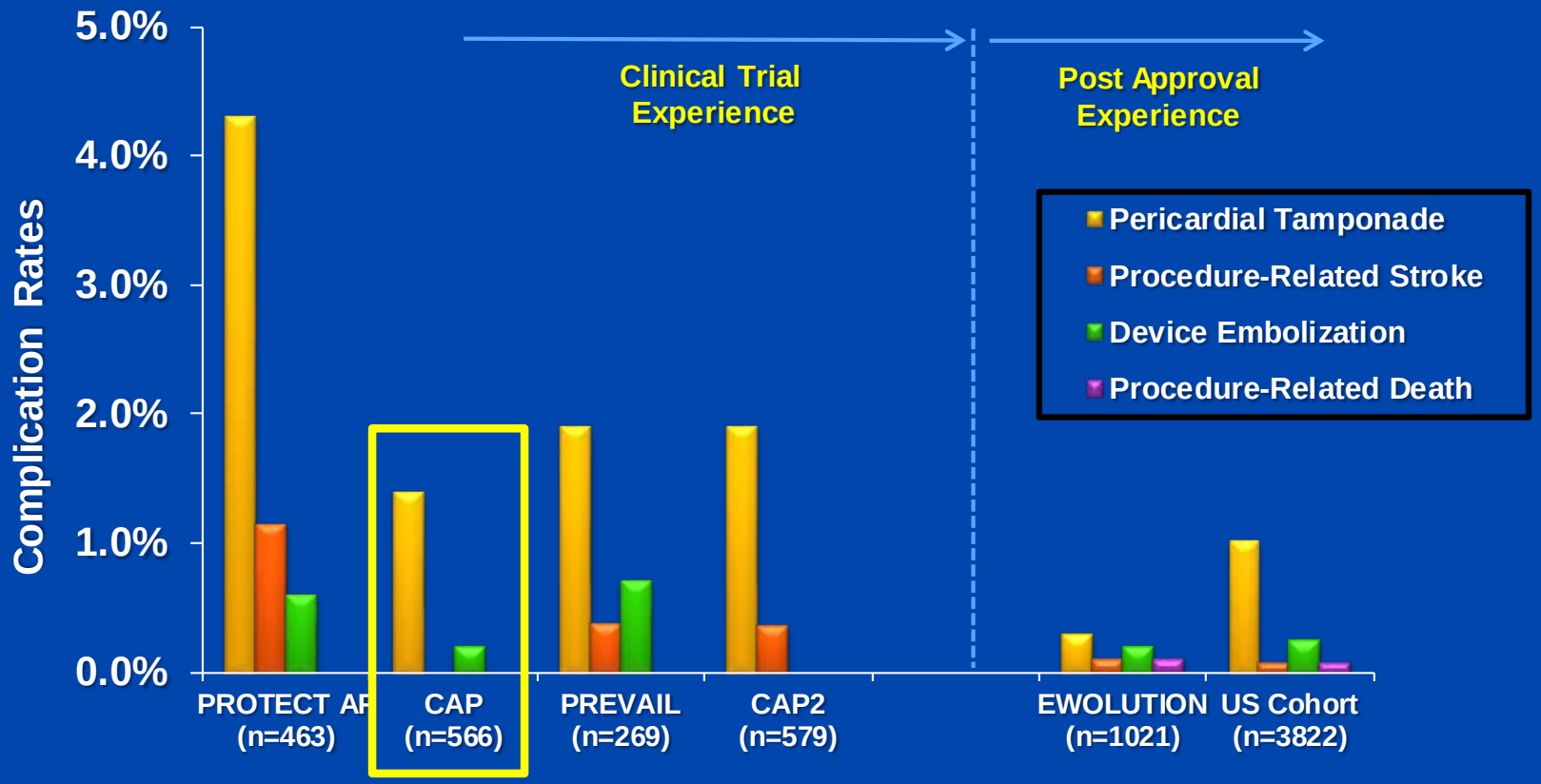
Results in Context:
Procedural Events in CAP Lower Than US Trials



No procedure-related stroke or death

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LAA – What is Ideal?
The Wish List

- A predictable, safe and effective device for reducing ischemic and hemorrhagic strokes
- Is minimally invasive and can be used during hybrid procedures
- Does not require adjunctive AC/APT therapy
- Can be delivered by IC, EP and CV surgery
- Can be used to treat a variety of LAA sizes and shapes
- Is stable, heals fully and completely without residual leaks

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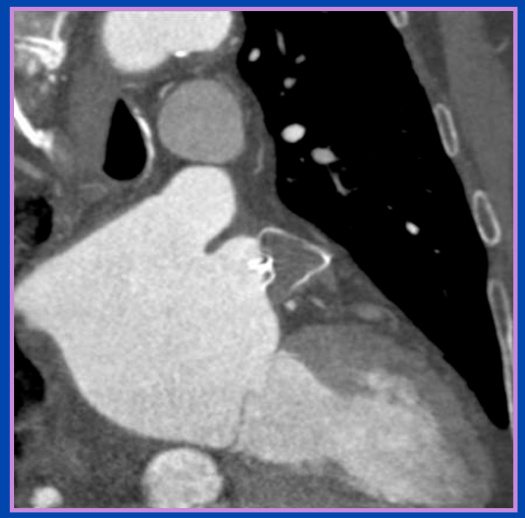
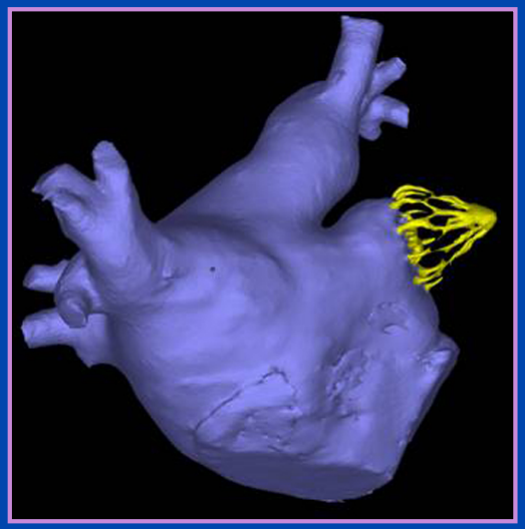
Stroke and Atrial Fibrillation
Alternative to Warfarin or NOACS





- 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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NOAC's and Renal Dysfunction
Background

- Dosage varies depending on specific NOAC and specific renal function
- Renal indication for dose reduction
  - Dabigatran eGFR <30ml/min/1.73m^2
  - Rivaroxaban eGFR <50ml/min/1.73m^2
  - Apixaban
    - SCr ≥1.5mg/dl
    - Age ≥80 years
    - Weights ≤60kg

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Yao et al: J Am Coll Cardiol 69:2779-90, 2017

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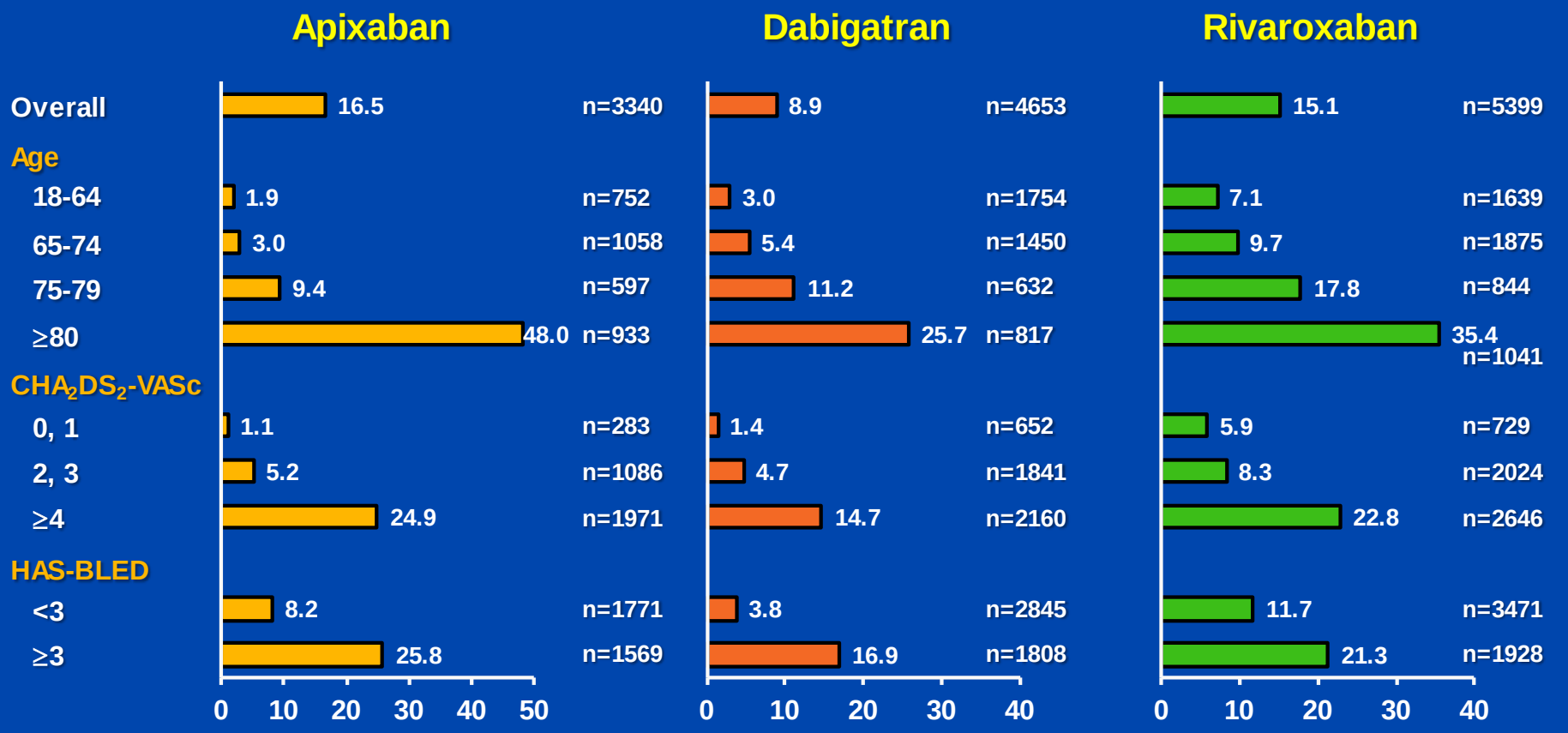
NOAC's & Renal Dysfunction

Percentage of Patients Underdosed



Yao et al: J Am Coll Cardiol 2017;69:2779–90

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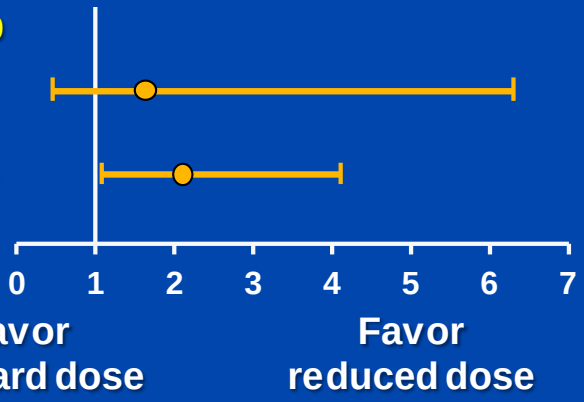
NOAC's & Renal Dysfunction
Outcomes Associated with Overdosing

	Event rate per 100 person-years		Hazard ratio (95% CI)	P value
	Reduced dose	Standard dose	Standard dose vs reduced dose	
	n=410	n=410		
S/SE	1.85	2.32	1.66 (0.40-6.88)	0.48
Major bleeding	5.06	11.29	2.19 (1.07-4.46)	0.03



Yao et al: J Am Coll Cardiol 2017;69:2779–90

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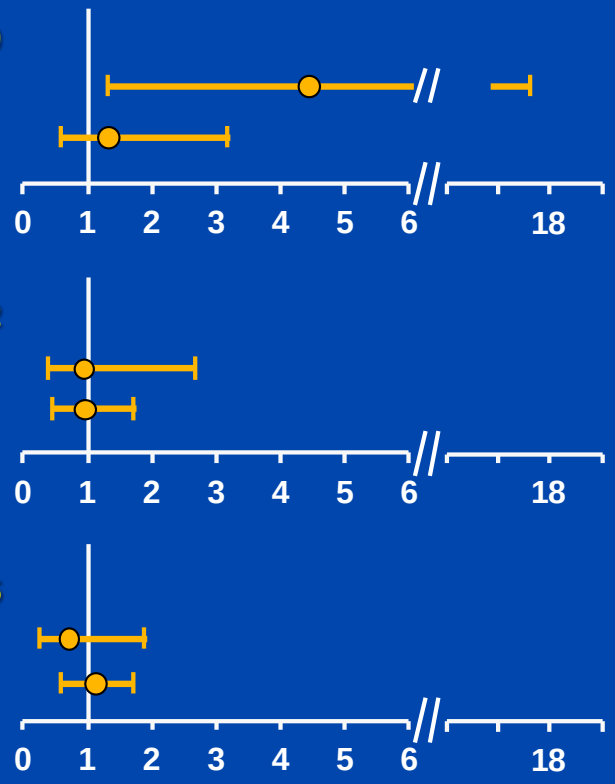
NOAC's & Renal Dysfunction

Outcomes Associated with Underdosing

	Event rate per 100 person-years			Hazard ratio (95% CI)	P value
	Reduced dose	Standard dose		Reduced dose vs standard dose	
Apixaban	n=550	n=550			
S/SE	2.57	0.54		4.87 (1.30-18.26)	0.02
Major bleeding	6.01	4.64		1.29 (0.48-3.42)	0.61
Dabigatran	n=412	n=412			
S/SE	1.64	1.75		0.92 (0.30-2.87)	0.89
Major bleeding	4.99	5.54		0.91 (0.45-1.85)	0.80
Rivaroxaban	n=815	n=815			
S/SE	1.23	1.65		0.71 (0.24-2.09)	0.54
Major bleeding	5.42	4.90		1.09 (0.63-1.87)	0.76



Yao et al: J Am Coll Cardiol 2017;69:2779–90

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Five-Year Outcomes of Left Atrial Appendage Closure: Final Results of the Continued Access to PROTECT AF (CAP) Registry

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

Mayo Clinic, Rochester

On behalf of the CAP Investigators and Study Participants

TCT 2017

Denver, CO

October 2017

Methods

- Descriptive statistics were used to present results, as there was no active control
- **Continuous variables:** mean, standard deviation, median, range and 95% confidence intervals are reported
- **Proportions:** 95% confidence intervals were reported
- **Time-to-event analyses:** all subjects not having an event or lost to follow-up were censored at the time of last documented follow-up visit

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Summary

- CAP is a prospective registry, with the longest follow-up for the WATCHMAN device
- Low procedural safety events
- High rates of successful closure and warfarin discontinuation
- Lowest rates of ischemic stroke for device group of all US approval trials
  - ≥ 75% reduction in ischemic events versus no therapy

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Conclusion

- Long term 5-year outcomes of the CAP registry demonstrate low rates of stroke and mortality, adding to the body of evidence in support of LAAO with WATCHMAN as a viable alternative to long-term oral anticoagulation in carefully selected patients

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Background

- PROTECT AF and PREVAIL were RCTs comparing left atrial appendage closure (LAAC) with WATCHMAN to warfarin
- PROTECT-AF demonstrated similar stroke reduction to warfarin (at a mean of 3.8 years follow up)
  - *JAMA* 312:1988-98 (2014)
- PREVAIL produced inconclusive findings due to a warfarin cohort with an implausibly low ischemic stroke rate, relatively few patients and relatively short follow up (~10 months)
  - *JACC* 64:1-12 (2014)
- Both protocols specified 5 years of follow-up for all patients
  - 5 year follow up completed in 2013 (final)
  - 5 year follow up completed in 2017 (final)

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

Objectives

- To report the final, 5 year results of PREVAIL, both alone and as part of a patient-level meta-analysis with PROTECT-AF final 5 year data

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

Methods
PREVAIL

PREVAIL efficacy endpoints were never designed to be analyzed without the informative prior from PROTECT AF.

- **1st Primary efficacy:** Comparison of rate ratios of 18-month event rates for composite of stroke, SE, and CV/Unexplained death; Upper CrI 1.75 for NI
- **2nd primary efficacy:** 1-tailed test, either the ratio or the difference between rates of ischemic stroke or SE >7 days post implant in the two arms satisfied the non-inferiority criteria, using 95% upper credible intervals (CrI) <2.0 and <0.0275, respectively, and posterior probability for non-inferiority ≥ 97.5%
- All analyses ITT; rates are events per 100 patient-years (indicated for simplicity by %).

All PREVAIL analysis were pre-specified to use an informative prior that included a portion of PROTECT AF

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Methods
Patient-Level Meta-Analysis

- **ITT:** censoring data from patients without events at the time of the last known status
- **Disabling Strokes:** increase in the Modified Rankin Score (MRS) by at least 2 points
- **Comparison of Event Rates:** Cox proportional hazards model with confidence intervals (CIs)
  - Stratified by study to account for differences in risk profiles
  - Kaplan-Meier curves used for graphical assessment of time-dependent events
  - Frequentist statistics and 2-sided p-values nominally significant at $p < 0.05$, without adjustment for multiple comparisons

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Follow-up

Trial	Number of Patients		Total	Mean Follow-up (months)	Total Patient Years
	Device	Control			
PROTECT AF	463	244	707	47.6 ± 21.3	2,717
PREVAIL-only*	269	138	407	47.9 ± 19.4	1,626
Total	**732**	**382**	**1114**		**4,343**

* Does not include PROTECT AF informative prior from Bayesian model

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Results
PROTECT AF and PREVAIL Event Rates

	PROTECT-AF Subjects					PREVAIL Subjects				
	Device (n=463)		Control (n=244)			Device (n=269)		Control (n=138)		
	No. of Events	Rate *	No. of Events	Rate *	p-value	No. of Events	Rate *	No. of Events	Rate *	p-value
2:1 Randomization										
Primary Efficacy: Stroke/SE/CV Death	40 / 1787.7	2.24	34 / 929.4	3.66	0.04	37 / 1038.3	3.65	15 / 530.4	2.94	0.47
All Stroke	26 / 1781.7	1.46	20 / 929.4	2.15	0.23	19 / 1042.4	1.97	7 / 530.4	1.29	0.32
Ischemic Stroke	24 / 1781.7	1.35	10 / 932.8	1.07	0.49	17 / 1043.1	1.68	4 / 533.3	0.73	0.13
Hemorrhagic Stroke	3 / 1837.7	0.16	10 / 945.6	1.06	0.005	2 / 1084.6	0.18	3 / 538.0	0.54	0.23
Systemic Embolism	3 / 1837.1	0.16	0	n/a	n/a	1 / 1080.6	0.09	0 / 540.9	n/a	n/a
CV/Unexplained Death	19 / 1843.2	1.03	22 / 948.9	2.32	0.009	18 / 1084.7	1.79	10 / 540.9	1.98	0.76

* Events are per 100 patient-years

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2:1 randomization
Control Group continues to over perform
Rate = 0.7%

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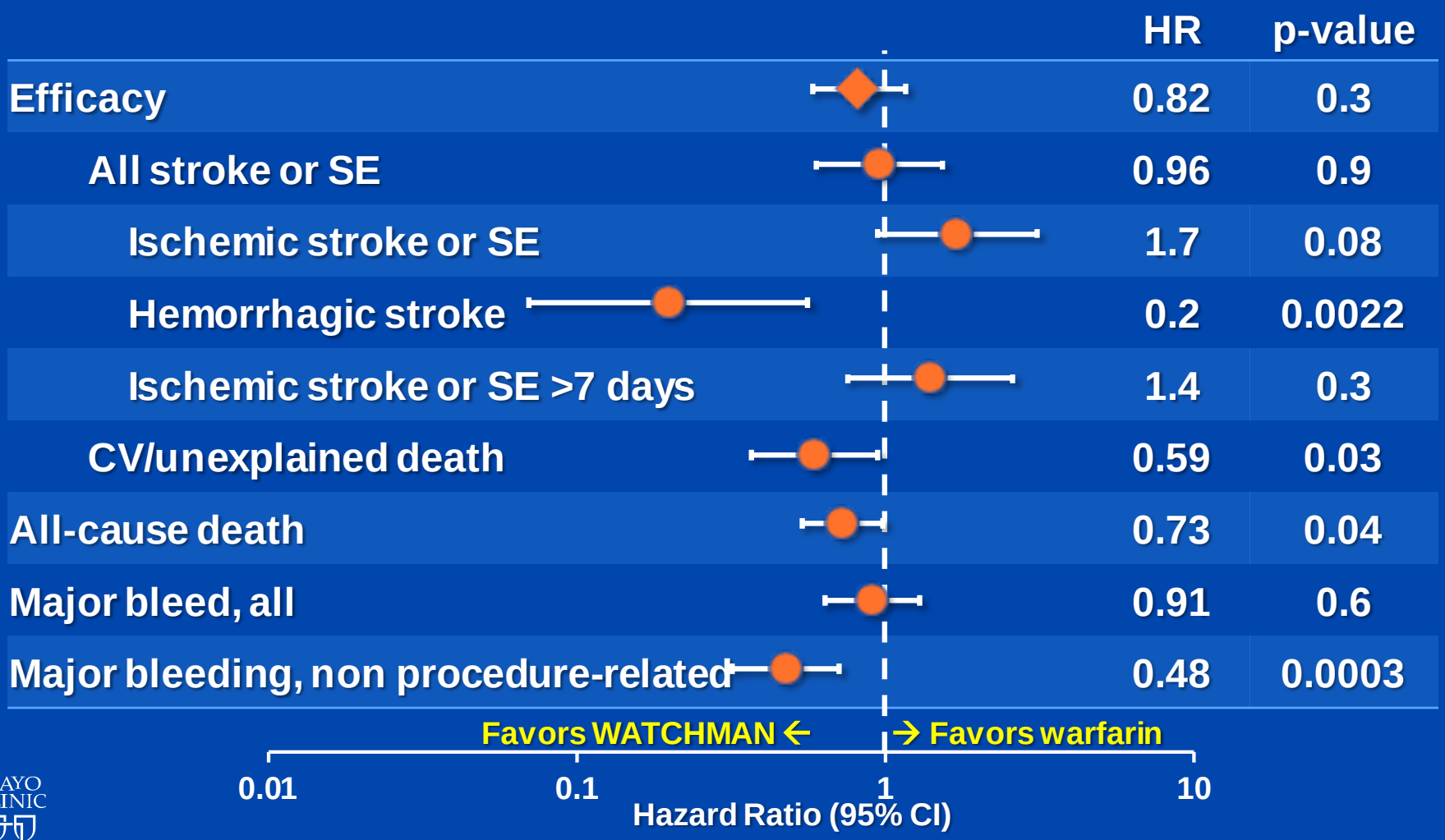
Patient-Level Meta-Analysis
PROTECT AF and PREVAIL 5 years



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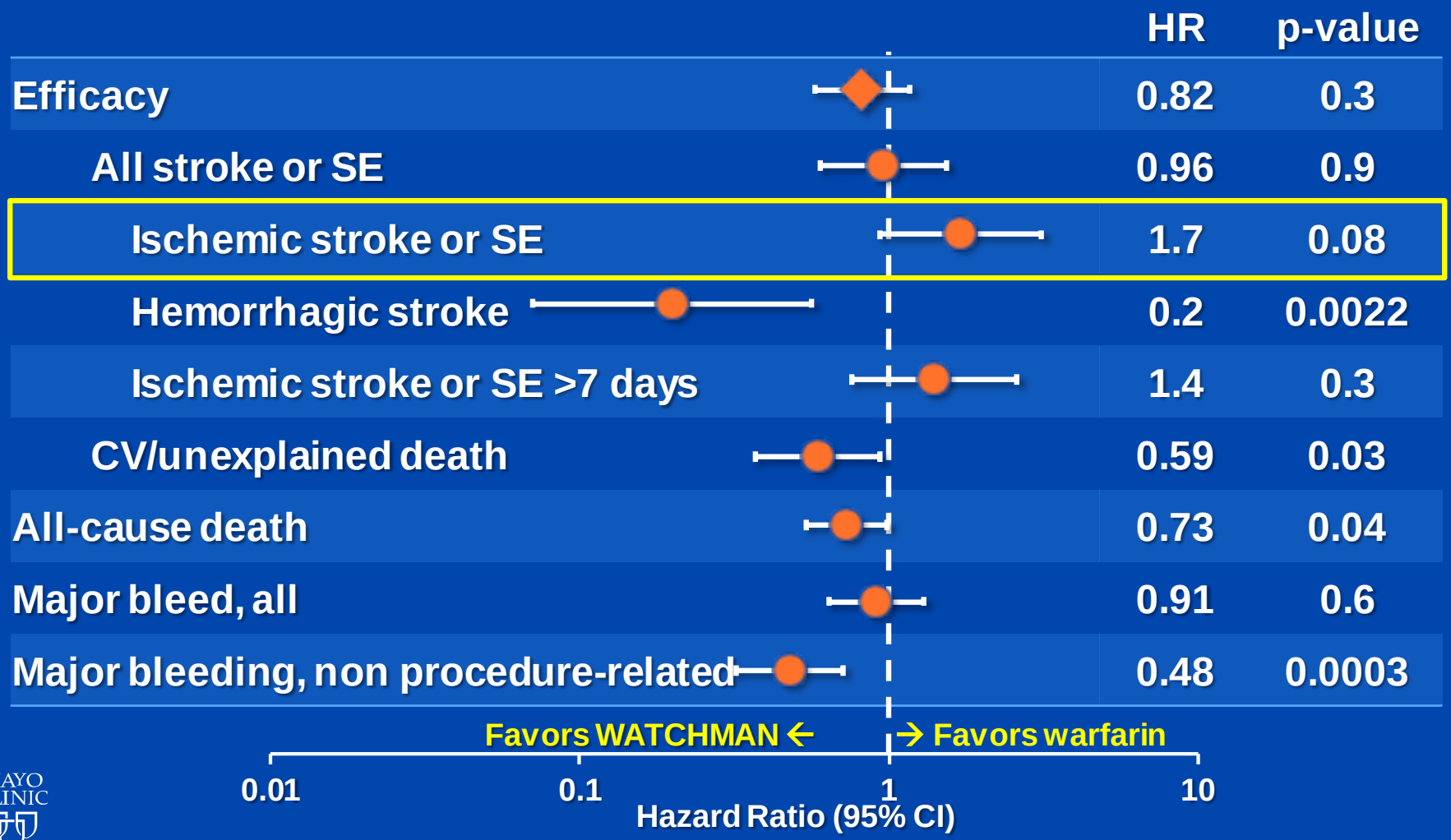
Patient-Level Meta-Analysis
PROTECT AF and PREVAIL 5 years



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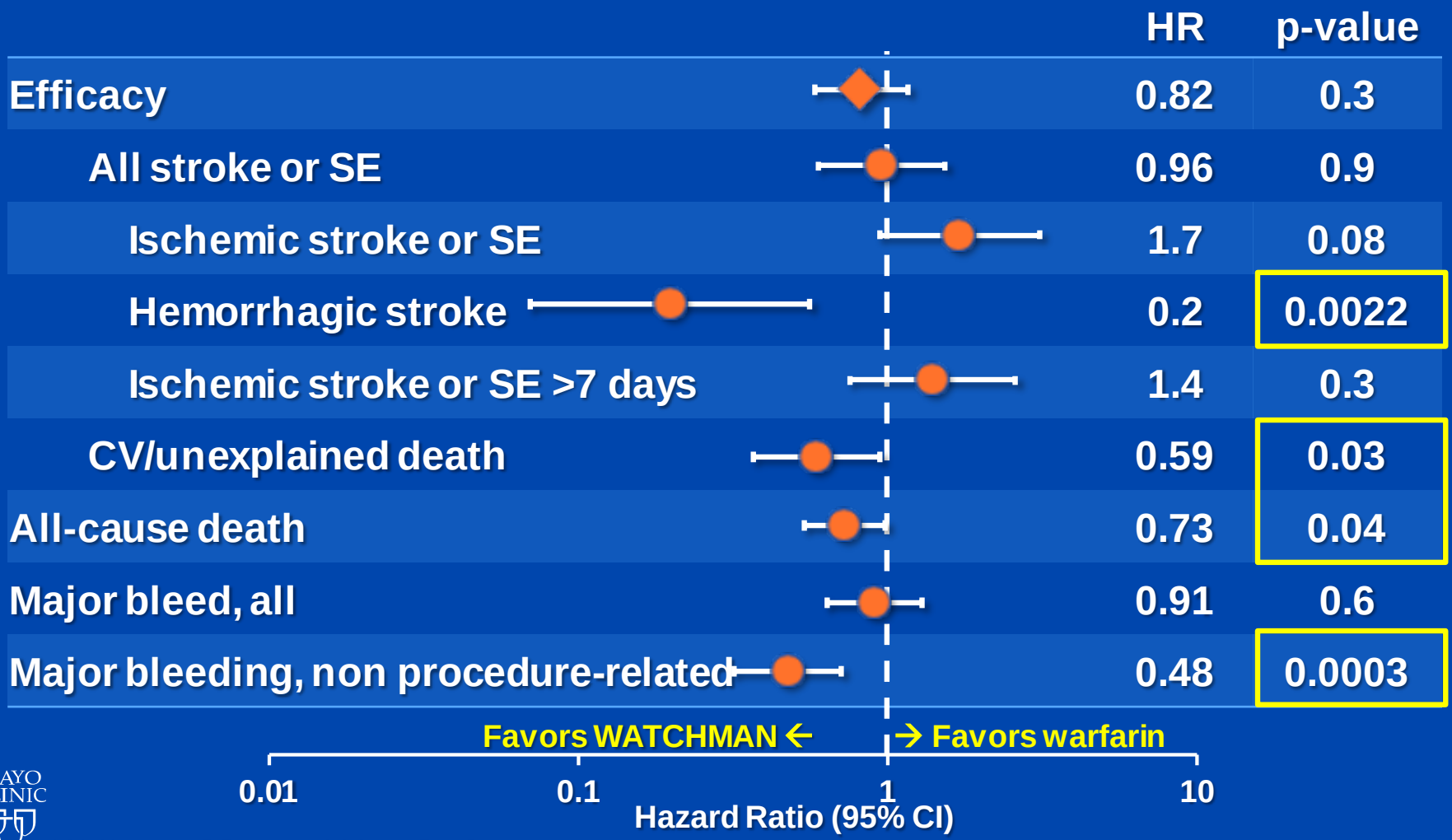
Patient-Level Meta-Analysis
PROTECT AF and PREVAIL 5 years



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