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Left Atrial Appendage Closure: Clinical Data & Future Perspective

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TCTAP 2014
Seoul, Korea
April 2014

Presenter Disclosure Information

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

"Left Atrial Appendage Closure: Clinical Data & Future Perspective"

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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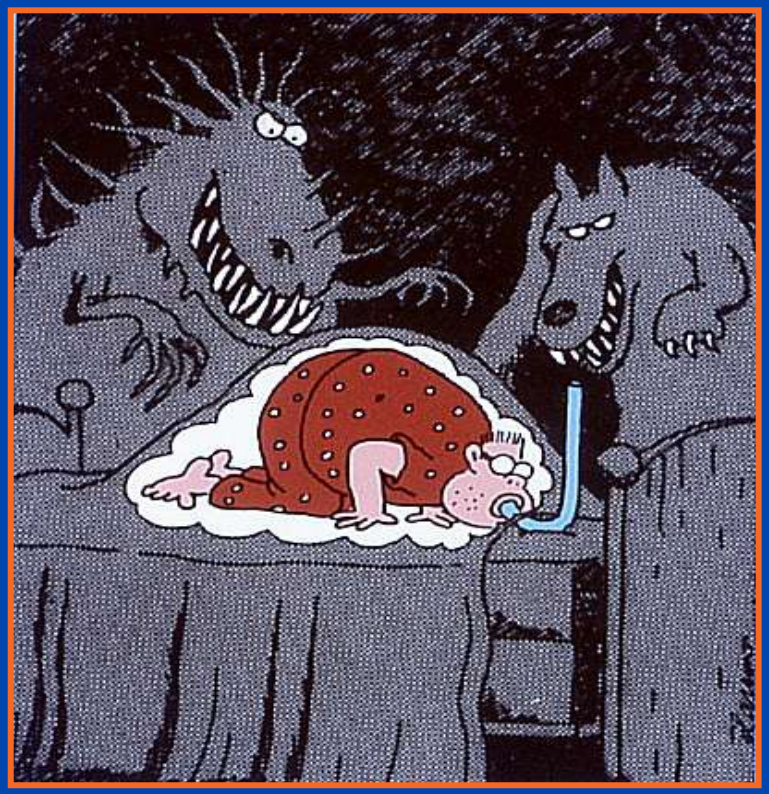
Monsters



The monster snorkel: Allows your child to breathe comfortably without exposing vulnerable parts to an attack

- Stroke
- Death
- MI
- Bleeding
- Procedural complications

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Stroke Risk

- Embolic stroke risk ≈5%/year (100,000 AF strokes/year)
- Large, debilitating strokes (31% fatal, 39% mod-severe neurologic deficit)
- Not homogeneous clinical models for risk stratification $CHADS_2$ (6) vs CHA_2DS_2VASc (9)

Recognizes importance of
1. Vascular risk factors
2. Greater sensitivity to age

- Significant limitations
  - Poor predictive value (c-statistic 0.6-0.7)
  - Changes over time: 12-year follow-up in patients with "lone" AF (c-statistic 0.5)
  - Anatomic factors not considered

Heart Disease Stroke Update: Circulation, 2009; Wolf: Stroke, 1991; Fisher: Geriatrics, 1979; Lip: Stroke, 2010

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ADVANCED FORMULA
BAIT PELLETS
Good Housekeeping
d-CON
KILLS
RATS
4
READY-TO-USE
BAIT FILLED TRAYS
CAN KILL IN ONE FEEDING*

Emergency Hospitalizations
Adverse Drug Events

- National Electronic Injury Surveillance System – Cooperative Adverse Drug Events Surveillance Project
- Estimated 99,628 emergency hospitalizations (95% CI 55,531 to 143,724) for adverse events each year from 2007-2009 for adults ≥65 years of age

Budnitz DS et al: N Engl J Med 365:2002-12, 2011

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National Estimates of Meds Commonly Implicated in Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007-2009

Medication	Annual National Estimate of Hospitalizations (N=99,628)		Proportion of ED Visits Resulting in Hospitalization
	#	% (95% CI)	%
Most commonly implicated medications			
Warfarin	33,171	33.3 (28.0-38.5)	46.2
Insulins	13,854	13.9 (9.8-18.0)	40.6
Oral antiplatelet agents	13,263	13.3 (7.5-19.1)	41.5

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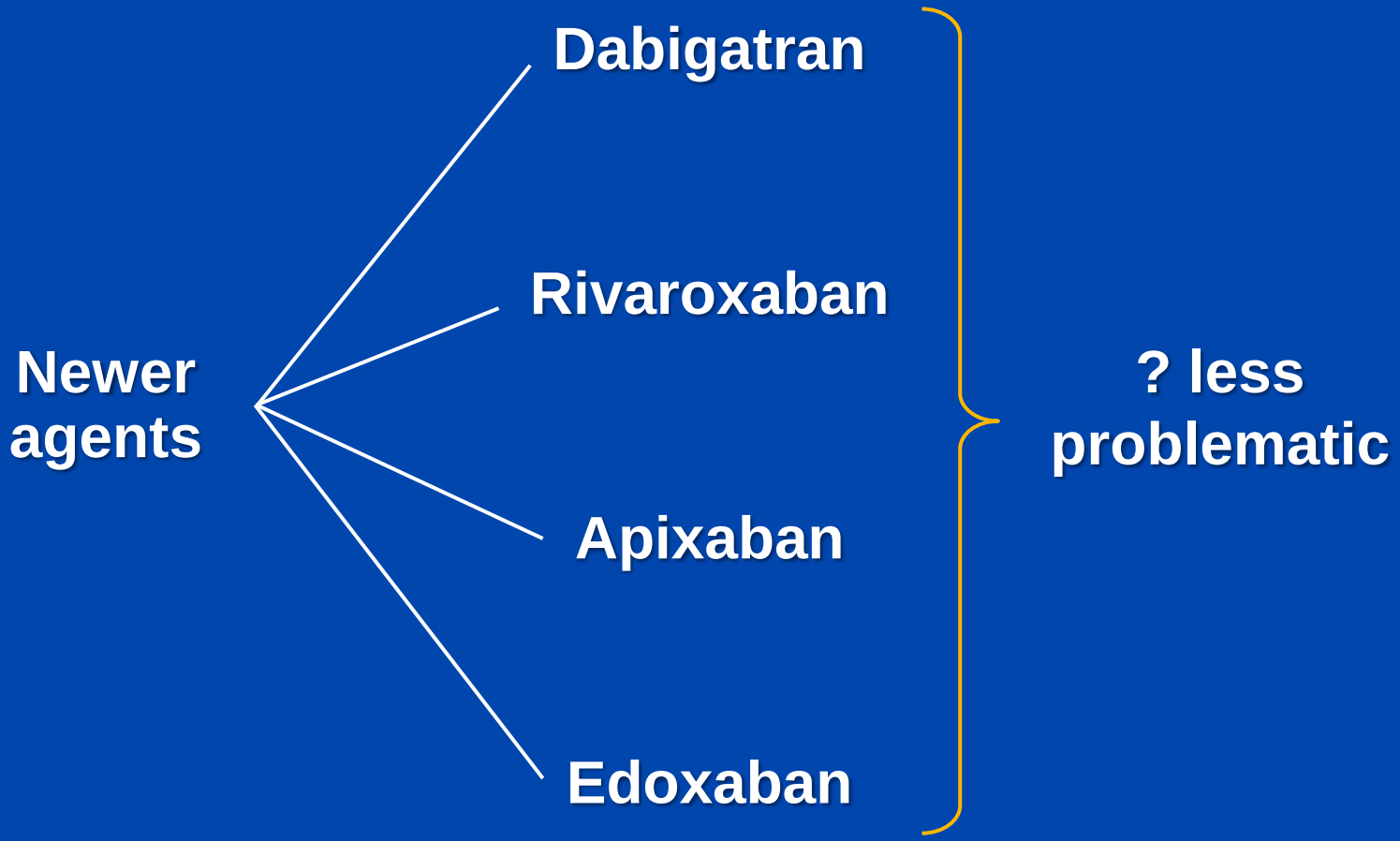
Warfarin Problematic



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NOACS versus Warfarin
Meta-Analysis

- Prespecified meta-analysis of 71,683 patients
  - RE-LY, ROCKET AF, ARISTOTLE, ENGAGE, AF-TIMI 48
- Main outcomes
  - Stroke and systemic embolism
  - Ischemic stroke, hemorrhagic stroke
  - All cause mortality, MI
  - Major bleeding, ICH, GI bleeding

Ruff et al: Lancet 383:955-62, 2014

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NOACS versus Warfarin

- NOACS:
  - Significant ↓ in all cause mortality
    - RR 0.90, 95% CI 0.85-0.95
  - Significant ↓ in ICH
    - RR 0.48, 95% CI 0.39-0.59
  - Significant ↑ in GI bleeding
    - RR 1.25, 95% CI 1.01-1.55

Ruff et al: Lancet 383:955-62, 2014

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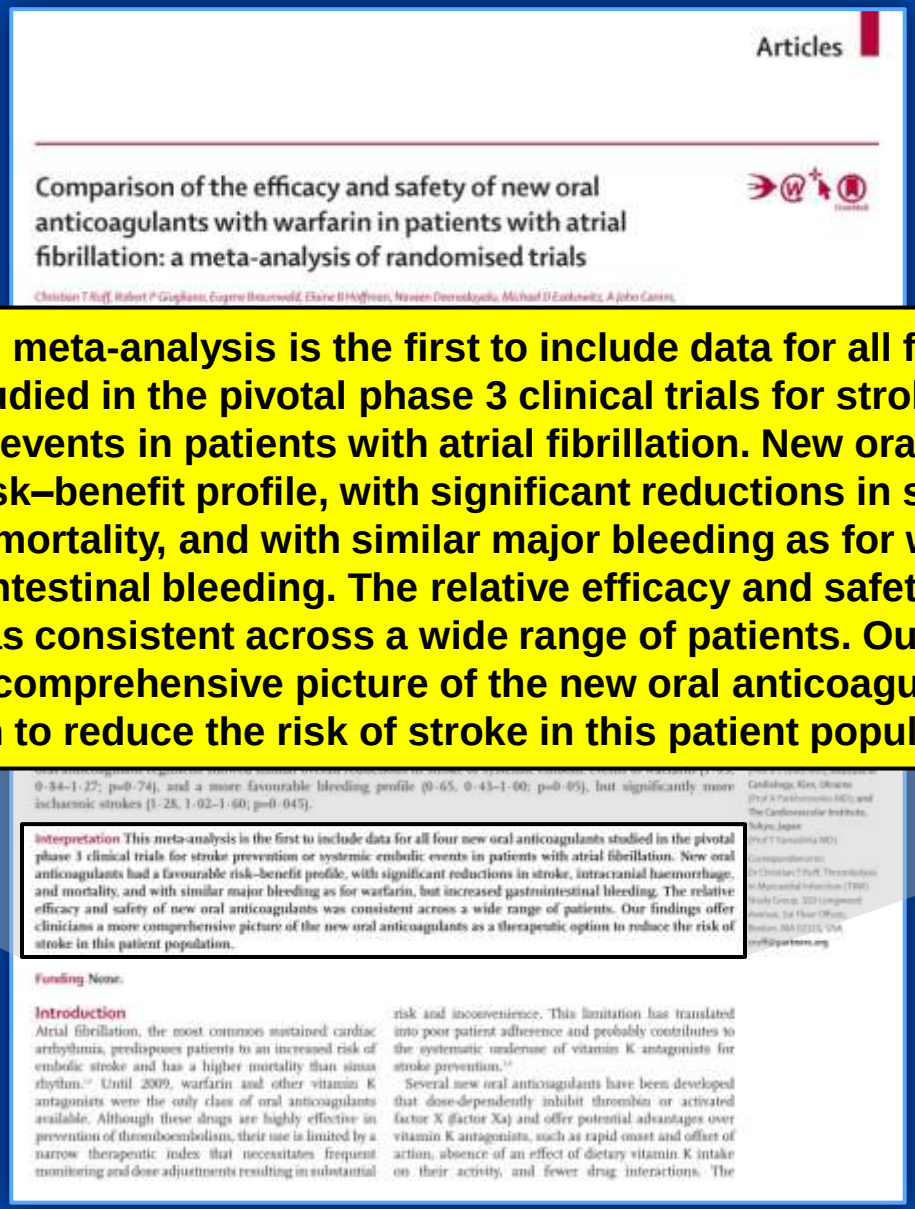

Articles

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Conclusions: This meta-analysis is the first to include data for all four new oral anticoagulants studied in the pivotal phase 3 clinical trials for stroke prevention or systemic embolic events in patients with atrial fibrillation. New oral anticoagulants had a favorable risk–benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients. Our findings offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in this patient population.

0·34–1·27; p=0·74), and a more favourable bleeding profile (0·65, 0·43–1·00; p=0·05), but significantly more ischaemic strokes (1·28, 1·02–1·60; p=0·045).

Interpretation This meta-analysis is the first to include data for all four new oral anticoagulants studied in the pivotal phase 3 clinical trials for stroke prevention or systemic embolic events in patients with atrial fibrillation. New oral anticoagulants had a favourable risk–benefit profile, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients. Our findings offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in this patient population.

Funding None.

Introduction

Atrial fibrillation, the most common sustained cardiac arrhythmia, predisposes patients to an increased risk of embolic stroke and has a higher mortality than sinus rhythm.[1,2] Until 2009, warfarin and other vitamin K antagonists were the only class of oral anticoagulants available. Although these drugs are highly effective in prevention of thromboembolism, their use is limited by a narrow therapeutic index that necessitates frequent monitoring and dose adjustments resulting in substantial risk and inconvenience. This limitation has translated into poor patient adherence and probably contributes to the systematic underuse of vitamin K antagonists for stroke prevention.[3,4]

Several new oral anticoagulants have been developed that dose-dependently inhibit thrombin or activated factor X (factor Xa) and offer potential advantages over vitamin K antagonists, such as rapid onset and offset of action, absence of an effect of dietary vitamin K intake on their activity, and fewer drug interactions. The

Ruff et al: Lancet 383:955, 2014

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Novel Oral Anticoagulants
Discontinuation and Bleeding Rates

Treatment	Discontinuation rate in study (%)	Major bleeding (rate/year) (%)
Dabigatran[1] (150 mg)	21	3.1
Rivaroxaban[2]	24	3.6
Apixaban[3]	22	2.1

1. Connolly SJ: N Engl J Med, 2009
2. Patel MR: N Engl J Med, 2011
3. Granger CB: N Engl J Med, 2011

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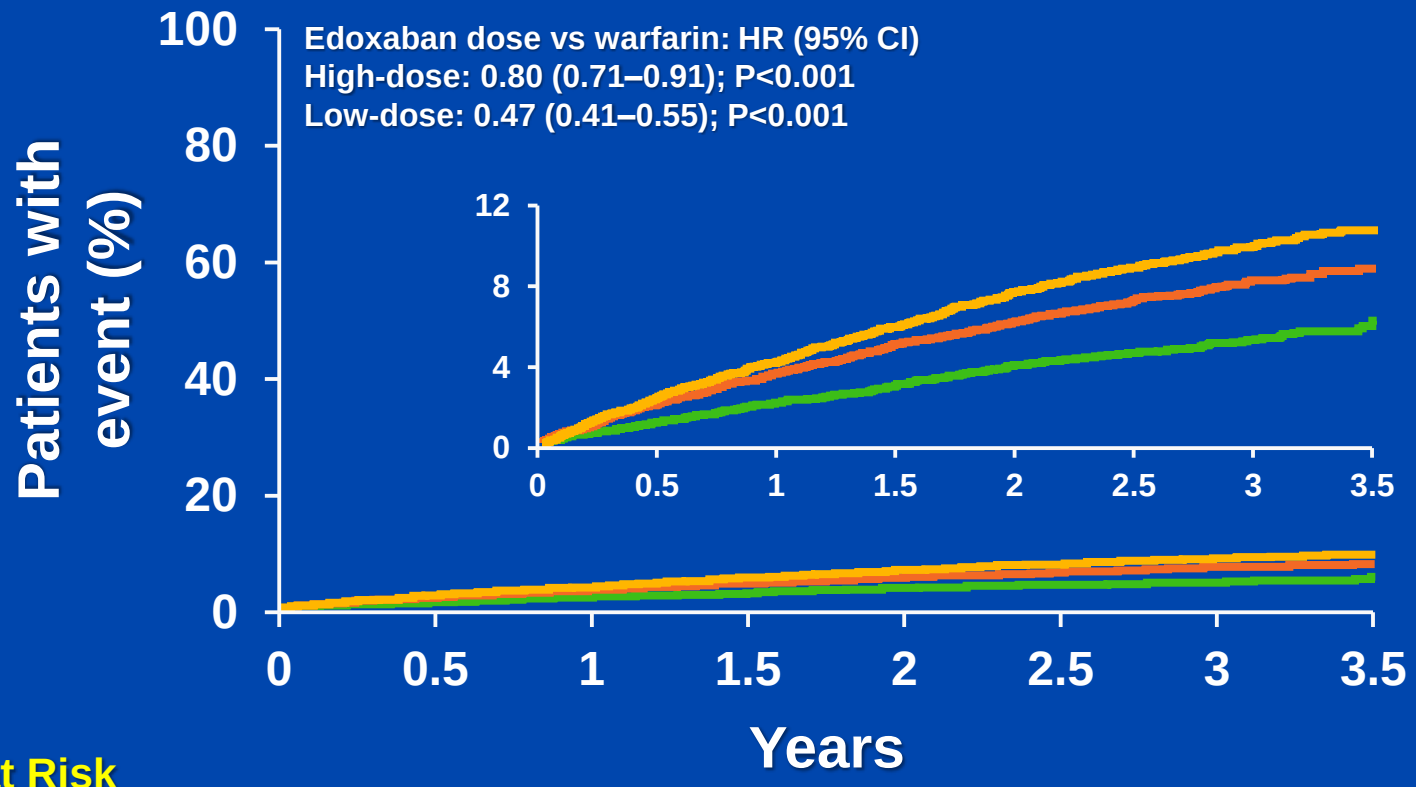
ENGAGE AF-TIMI 48
Major Bleeding



No. at Risk								
Warfarin	7,012	6,166	5,630	5,278	4,941	3,446	1,687	370
High-dose edoxaban	7,012	6,039	5,594	5,232	4,910	3,471	1,706	345
Low-dose edoxaban	7,002	6,218	5,791	5,437	5,110	3,365	1,793	386

Giugliano et al: NEJM 369(22):2093, 2013

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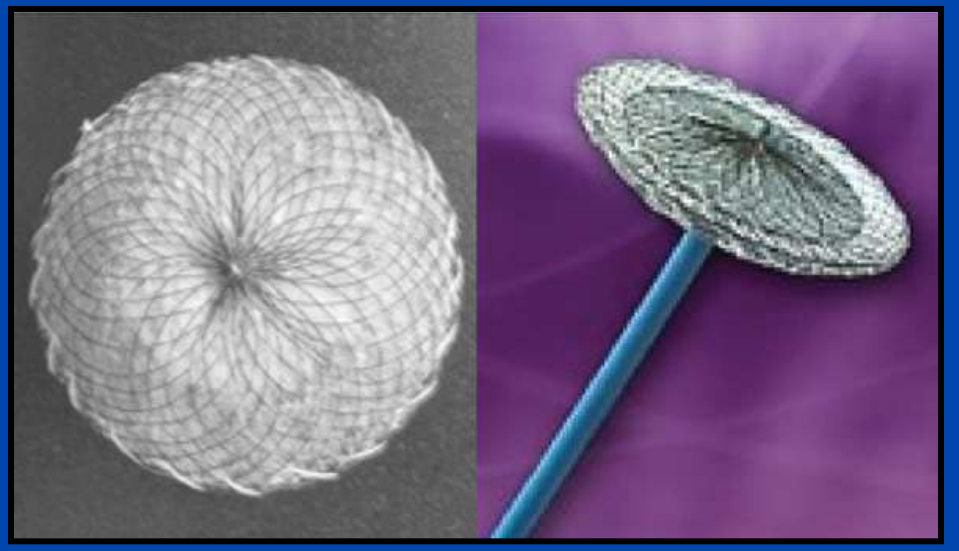

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Warfarin Cessation Rates High in WATCHMAN Patients

	PROTECT AF (n=408)		CAP (n=534)		PREVAIL (n=253)	
Visit	n/N	%	n/N	%	n/N	%
45-day	348/401	86.8	507/529	95.8	227/246	92.2
6-month	355/385	92.2	493/500	98.6	235/239	98.3
12-month	345/370	93.2	455/472	96.4	141/142	99.3

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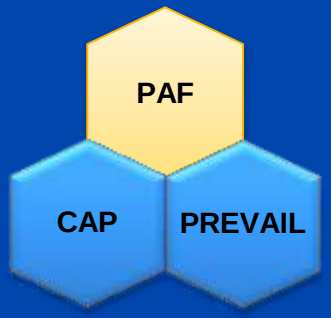
Long-term PROTECT AF Results

	Mean follow-up (years)	Event rate			Posterior probabilities	
		WATCHMAN	Control	Rate ratio	Non-inferiority	Superiority
900 pt-yr	1.3	3.4	5.0	0.68	0.998	0.837
1,588 pt-yr	2.3	3.0	4.3	0.71	>0.999	0.846
2,621 pt-yr	3.8	2.3	3.8	0.60	>0.999	0.960

Composite primary efficacy

- All stroke
- Cardiovascular / unexplained death
- Systemic embolism



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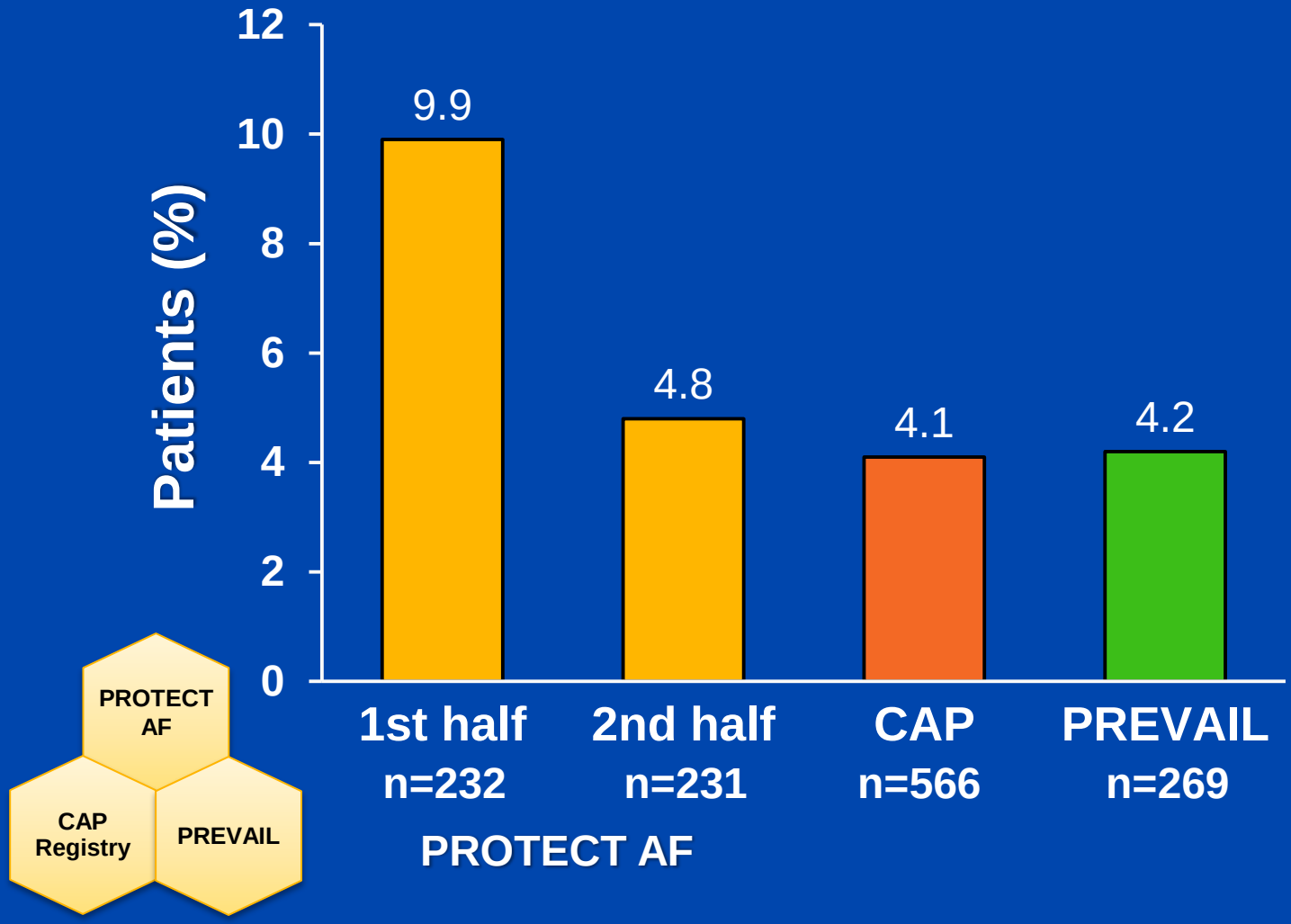
Safety Events: PROTECT AF, CAP, PREVAIL



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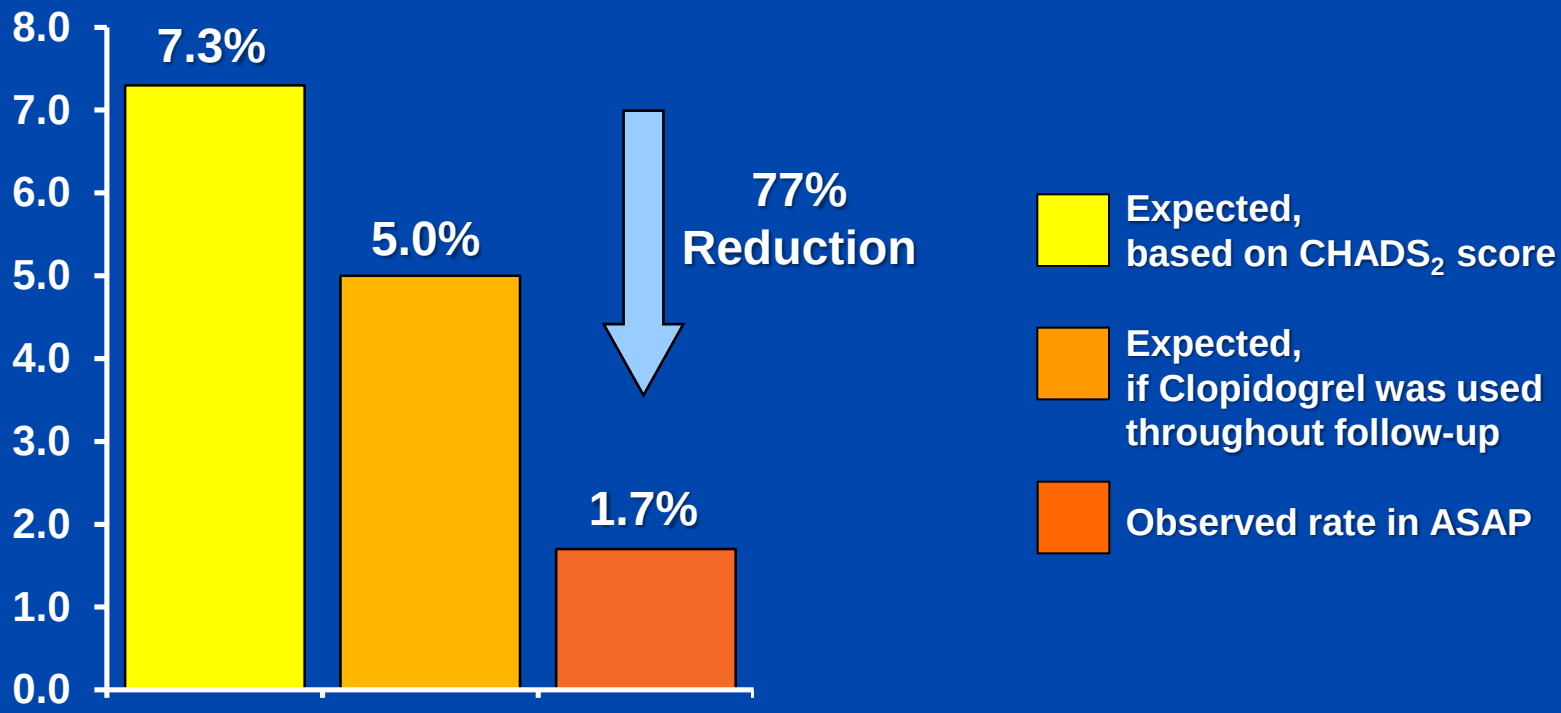
ASAP Trial
Anticoagulation Contraindicated

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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LAA Occlusion
It's not for everyone

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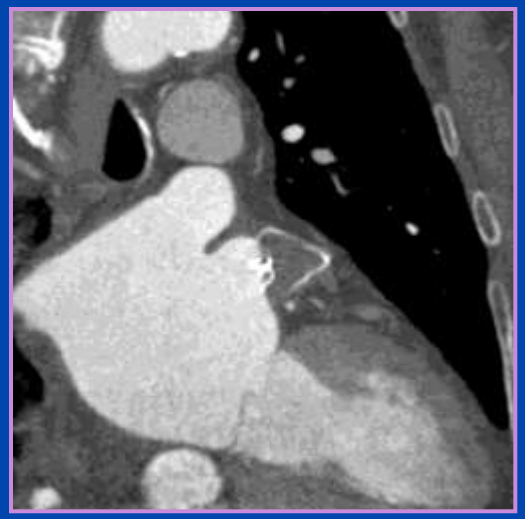
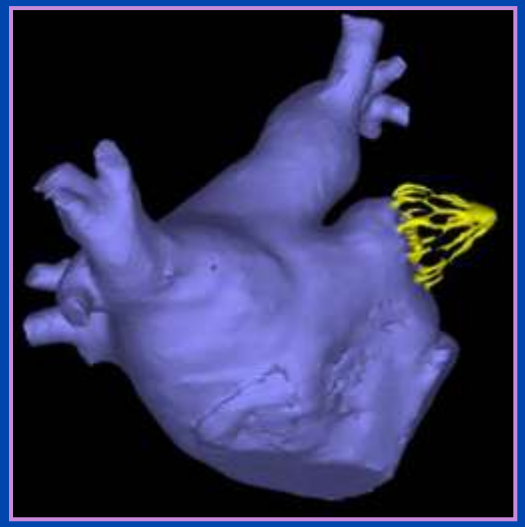
Stroke and Atrial Fibrillation
Alternative to Warfarin or NOACS





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

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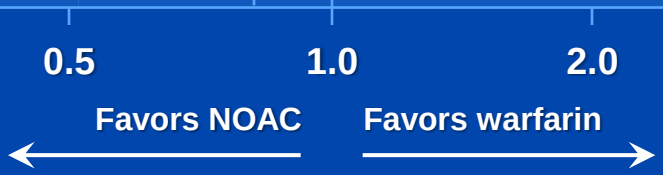
NOACS vs Warfarin
Stroke or Systemic Embolic Events

	NOAC events	Warfarin events	RR (95% CI)	P
RE-LY*	134 (6,076)	1,99 (6,022)	0.66 (0.53-0.82)	0.0001
ROCKET AF†	269 (7,081)	306 (7,090)	0.88 (0.75-1.03)	0.12
ARISTOTLE‡	212 (9,120)	265 (9,081)	0.80 (0.67-0.95)	0.012
ENGAGE AF-TIMI 48**	296 (7,035)	337 (7,036)	0.88 (0.75-1.02)	0.10
Combined (random)	911 (29,312)	1,107 (29,229)	0.81 (0.73-0.91)	<0.0001



*Dabigatran 150 mg twice daily; †Rivaroxaban 20 mg once daily; ‡Apixaban 5 mg twice daily
**Edoxaban 60 mg once daily; Ruff et al: Lancet 383:955, 2014

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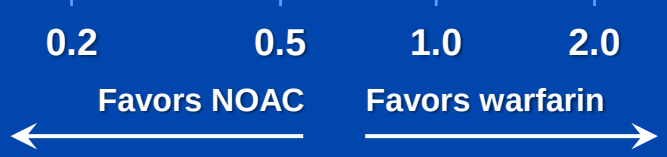
NOACS vs Warfarin

Secondary Efficacy and Safety Outcomes

	Pooled NOAC events	Pooled Warfarin events	RR (95% CI)	P
Efficacy				
Ischemic stroke	665 (29,292)	724 (29,221)	0.92 (0.83-1.02)	0.10
Hemorrhagic stroke	130 (29,292)	263 (29,221)	0.49 (0.38-0.64)	<0.0001
MI	413 (29,292)	432 (29,221)	0.97 (0.78-1.20)	0.77
All-cause mortality	2,022 (29,292)	2,245 (29,221)	0.90 (0.85-0.95)	0.0003
Safety				
Intracranial hemorrhage	204 (29,287)	425 (29,211)	0.48 (0.39-0.59)	<0.0001
GI bleeding	751 (29,287)	591 (29,211)	1.25 (1.01-1.55)	0.043



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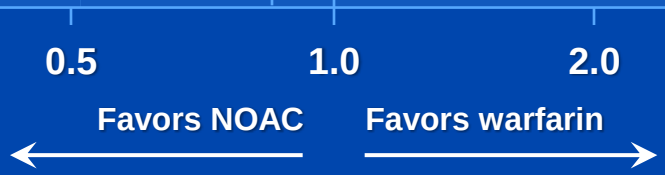
Ruff et al: Lancet 383:955, 2014

NOACS vs Warfarin
Major Bleeding

	NOAC events	Warfarin events	RR (95% CI)	P
RE-LY*	375 (6,076)	397 (6,022)	0.94 (0.82-1.07)	0.34
ROCKET AF†	395 (7,111)	386 (7,125)	1.03 (0.90-1.18)	0.72
ARISTOTLE‡	327 (9,088)	462 (9,052)	0.71 (0.61-0.81)	<0.0001
ENGAGE AF-TIMI 48**	444 (7,012)	557 (7,012)	0.80 (0.71-0.90)	0.0002
Combined (random)	1,541 (29,287)	1,802 (29,211)	0.86 (0.73-1.00)	0.06



*Dabigatran 150 mg twice daily; †Rivaroxaban 20 mg once daily; ‡Apixaban 5 mg twice daily
**Edoxaban 60 mg once daily; Ruff et al: Lancet 383:955, 2014

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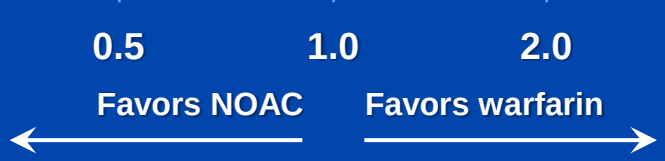
NOACS vs Warfarin

Stroke or Systemic Embolic Events Subgroups

	Pooled NOAC (events)	Pooled Warfarin (events)	RR (95% CI)	P
Age (years)				
<75	496 (8,073)	578 (18,004)	0.85 (0.73-0.99)	0.38
≥75	415 (11,188)	532 (11,095)	0.78 (0.68-0.88)	
Sex				
Female	382 (10,941)	478 (10,839)	0.78 (0.65-0.94)	0.52
Male	531 (18,371)	634 (18,390)	0.84 (0.75-0.94)	
Diabetes				
No	622 (20,216)	755 (20,238)	0.83 (0.74-0.93)	0.73
Yes	287 (9,096)	356 (8,990)	0.80 (0.69-0.93)	
Previous stroke or TIA				
No	483 (20,699)	615 (20,637)	0.78 (0·66-0.91)	0.30
Yes	428 (8,663)	495 (8,635)	0.86 (0·76-0.98)	
Creatinine clearance (mL/min)				
<50	249 (5,539)	311 (5,503)	0.79 (0.65-0.96)	0.12
50-80	405 (13,055)	546 (13,155)	0.75 (0.66-0.85)	
>80	256 (10,626)	255 (10,533)	0.98 (0.79-1.22)	
$CHADS_2$ score				
0-1	69 (5,058)	90 (4,942)	0.75 (0.54-1.04)	0.76
2	247 (9,563)	290 (9,757)	0.86 (0.70-1.05)	
3-6	596 (14,690)	733 (14,528)	0.80 (0.72-0.89)	
VKA status				
Naïve	386 (13,789)	513 (13,834)	0.75 (0.66-0.86)	0.31
Experienced	522 (15,514)	597 (15,395)	0.85 (0.70-1.03)	
Center-based TTR				
<66%	509 (16,219)	653 (16,297)	0.77 (0.65-0.92)	0.60
≥66%	313 (12,642)	392 (12,904)	0.82 (0.71-0.95)	



Ruff et al: Lancet 383:955, 2014

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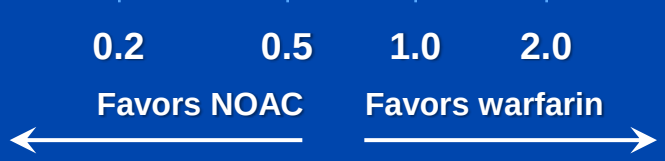
NOACS vs Warfarin
Major Bleeding Subgroups

	Pooled NOAC (events)	Pooled Warfarin (events)	RR (95% CI)	P
Age (years)				
<75	1,317 (18,460)	1,543 (18,396)	0.79 (0.67-0.94)	0.28
≥75	1,328 (10,771)	1,346 (10,686)	0.93 (0.74-1.17)	
Sex				
Female	751 (8,682)	920 (8,645)	0.75 (0.58-0.97)	0.29
Male	1,495 (14,530)	1,548 (14,544)	0.90 (0.72-1.12)	
Diabetes				
No	481 (11,278)	678 (11,294)	0.71 (0.54-0.93)	0.12
Yes	872 (7,691)	937 (7,583)	0.90 (0.78-1.04)	
Previous stroke or TIA				
No	1,070 (20,638)	1,280 (20,619)	0.85 (0.72-1.01)	0.70
Yes	495 (8,669)	553 (8,600)	0.89 (0.77-1.02)	
Creatinine clearance (mL/min)				
<50	514 (4,376)	620 (4,346)	0.74 (0.52-1.05)	0.57
50-80	1,104 (10,139)	1,174 (10,228)	0.91 (0.76-1.08)	
>80	625 (8,681)	672 (8,595)	0.85 (0.66-1.10)	
$CHADS_2$ score				
0-1	76 (3,090)	126 (3,078)	0.60 (0.45-0.80)	0.09
2	530 (7,403)	597 (7,498)	0.88 (0.65-1.20)	
3-6	1,640 (12,716)	1,745 (12,611)	0.86 (0.71-1.04)	
VKA status				
Naïve	656 (12,776)	786 (12,820)	0.84 (0.76-0.93)	0.78
Experienced	909 (16,446)	1,040 (16,265)	0.87 (0.70-1.08)	
Center-based TTR				
<66%	484 (10,972)	702 (11,021)	0.69 (0.59-0.81)	0.022
≥66%	668 (10,944)	736 (11,049)	0.93 (0.76-1.13)	



Ruff et al: Lancet 383:955, 2014

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Is LAA Occlusion Really an Alternative to Lifelong Anticoagulation?

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

Mayo Clinic, Rochester

ACC 2014
Washington, DC
March 2014

Presenter Disclosure Information

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

"Is LAA Occlusion Really an Alternative to Lifelong Anticoagulation?"

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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What Will be the Role of Occlusion

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Non-Valvular AF Patients

- AF increases the risk of stroke 4 - 5 times[1]
  - Highest risk: older patients and those with prior stroke or TIA[2]
  - AF is responsible for 15 - 20% of all strokes, particularly in the elderly[3]
- Typically >70 years old[4]
- Taking multiple medications[5]

1. Wolf PA: Stroke, 1991
2. Gage BF: JAMA, 2001
3. Go AS: Am J Geriatr Cardiol, 2005
4. Lloyd-Jones D: Circulation, 2010
5. Hayes BD: Clin Geriatric Med, 2007

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Stroke in AF Patients

- Greater disability compared to non-AF related stroke
  - Larger infarcts[1]
  - More severe hemorrhagic transformation[2]
- High recurrence rate of stroke[3]
- Higher mortality[4]

1. Jorgensen HS: Stroke, 1996
2. Tu HT: Int J Stroke, 2013
3. Penado S: Am J Med, 2003
4. McGrath ER: Neurology, 2013

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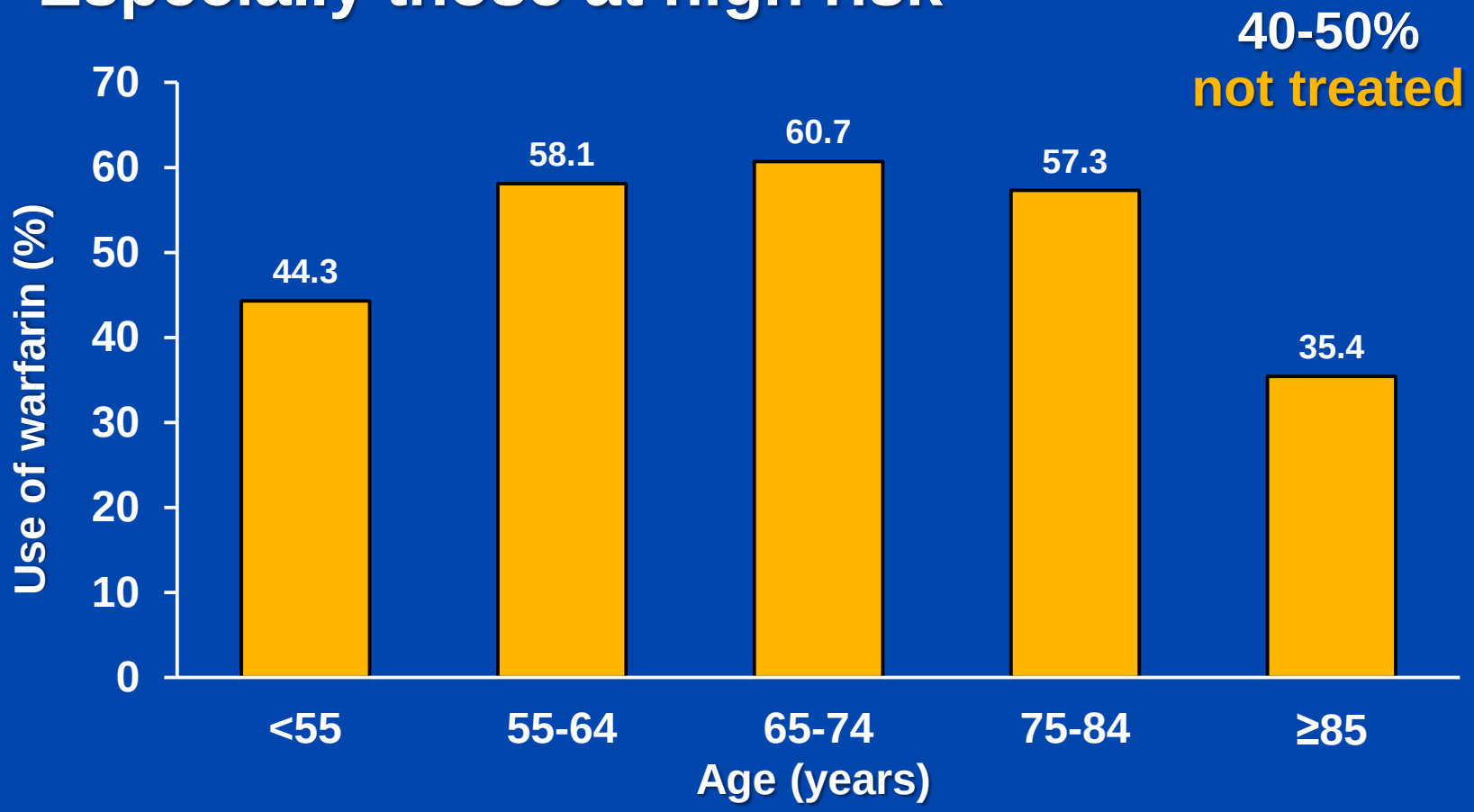
Significant Undertreatment

- Especially those at high risk



Levy: Circulation, 1999; Baker: J Man Care Pharm, 2009;
Samsa: Arch Int Med, 2000; Reynolds: Am J Cardiol, 2006

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Important Drug Warning
ELIQUIS (apixaban) tablets

- **Subject (Dec. 2013)**
  - **Discontinuing ELIQUIS without introducing an adequate alternative anticoagulant places nonvalvular atrial fibrillation patients at an increased risk of thrombotic events, including stroke**

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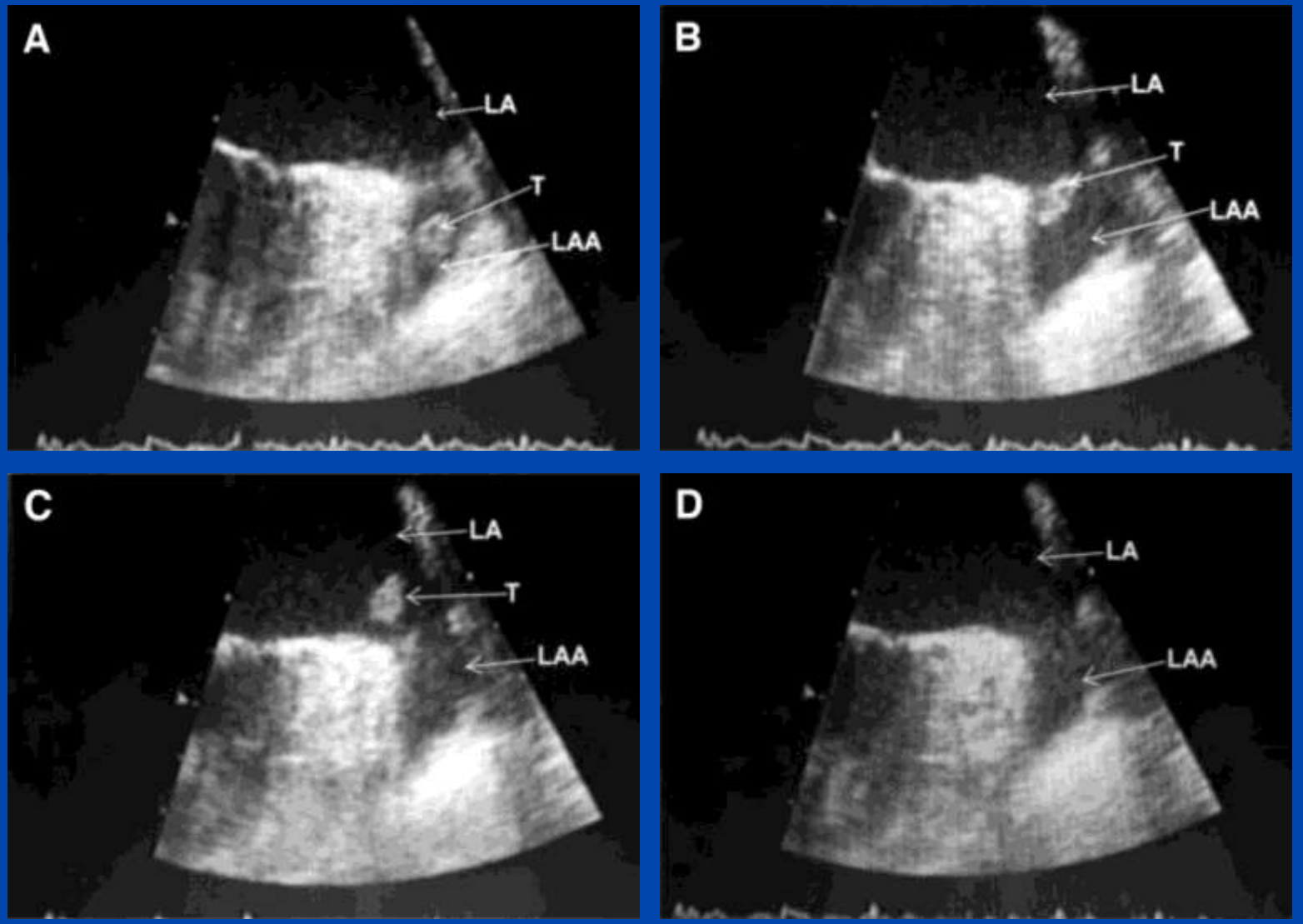
Disappearing LAA Thrombus Resulting in Stroke



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

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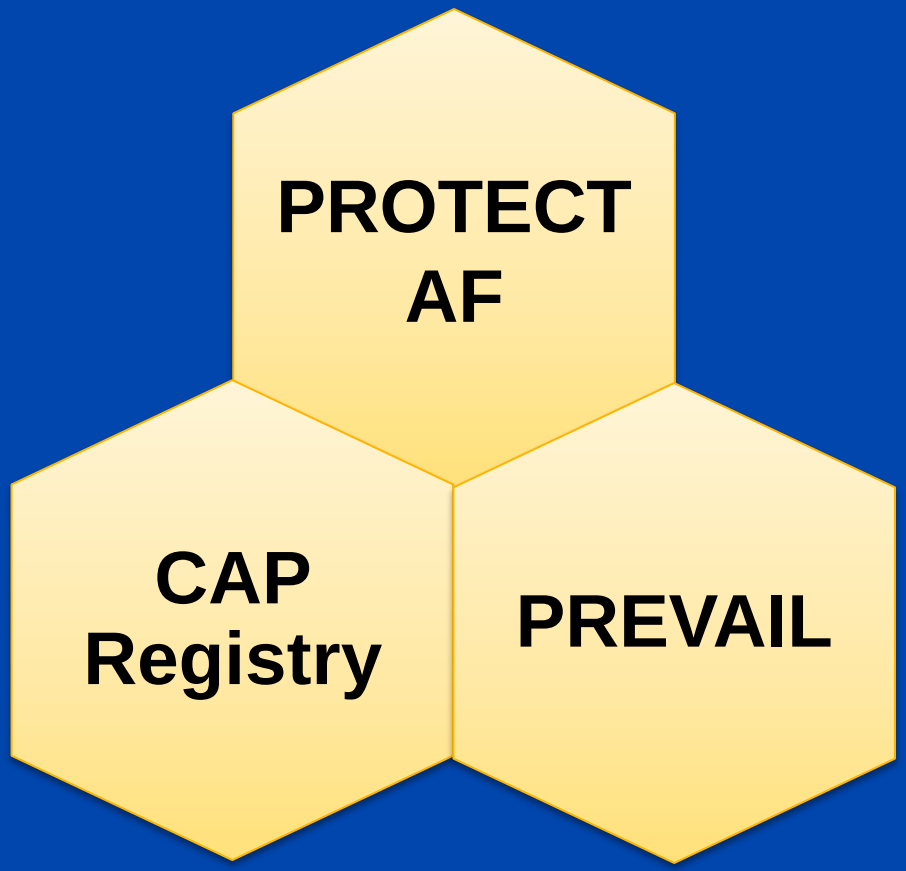
Totality of Data Support Safety and Efficacy of WATCHMAN



- ~2000 clinical patients
- ~4900 patient-years of follow-up
- Approved in 55 countries
- ~ 5,000 commercial implants

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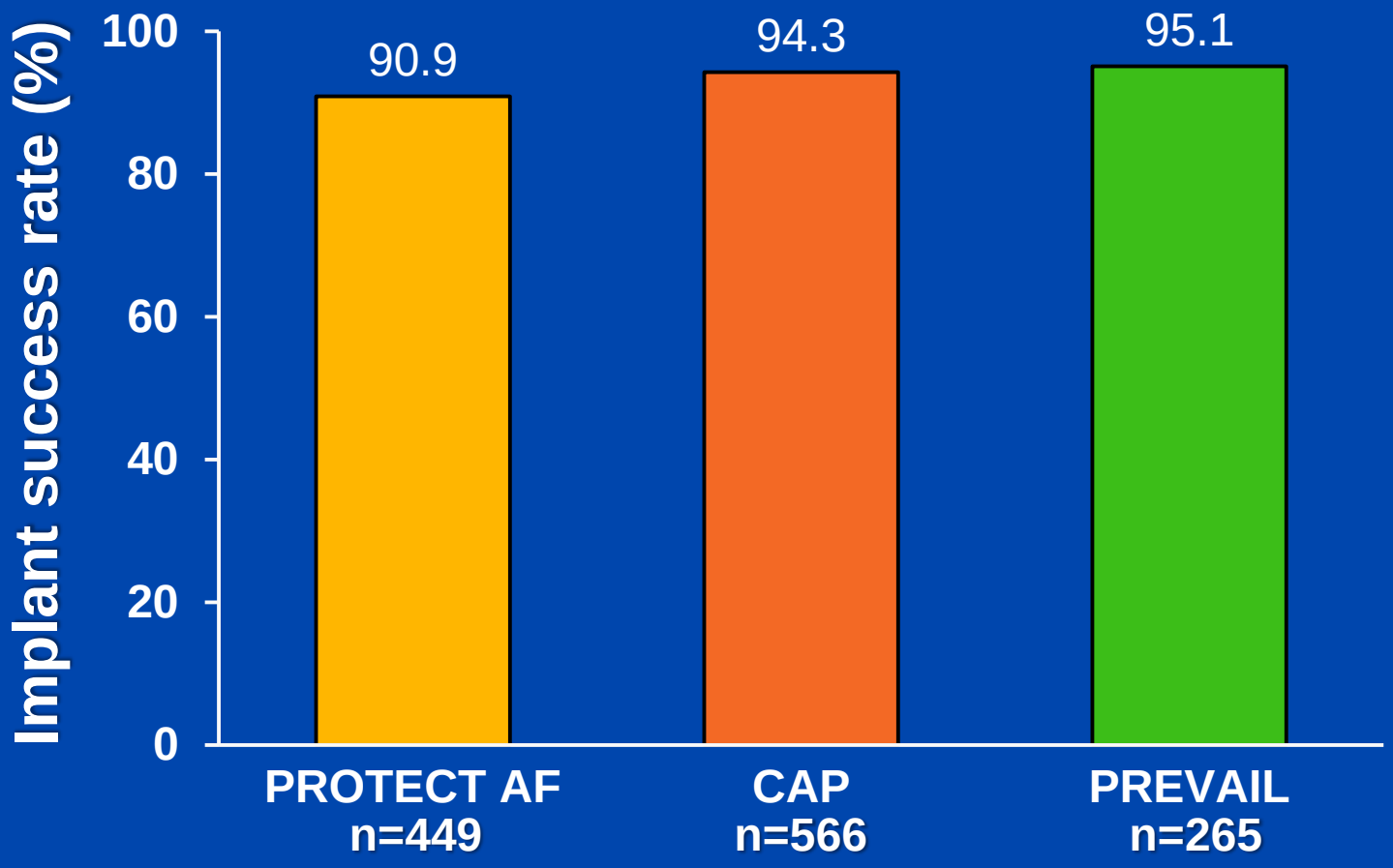
Implant Success Across Trials



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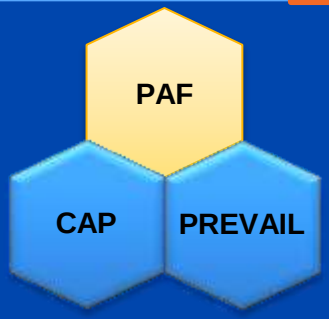
PROTECT AF: Long-Term Results (2,621 Patient-Years of Follow-Up)

	Event rate (per 100 pt-yr)			Posterior probabilities	
	WATCHMAN n=463	Control n=244	Rate ratio (95% CrI)	Non-inferiority	Superiority
Primary efficacy	2.3	3.8	0.60 (0.41, 1.05)	>0.999	0.960
Stroke (all)	1.5	2.2	0.68 (0.42, 1.37)	0.999	0.825
Ischemic	1.4	1.1	1.26 (0.72, 3.28)	0.779	0.147
Hemorrhagic	0.2	1.1	0.15 (0.03, 0.49)	0.999	0.999
Systemic Embolism	0.2	0.0	n/a	n/a	n/a
Death (CV & unexplained)	1.0	2.4	0.40 (0.23, 0.82)	>0.999	0.995



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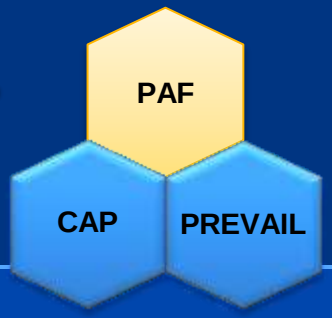
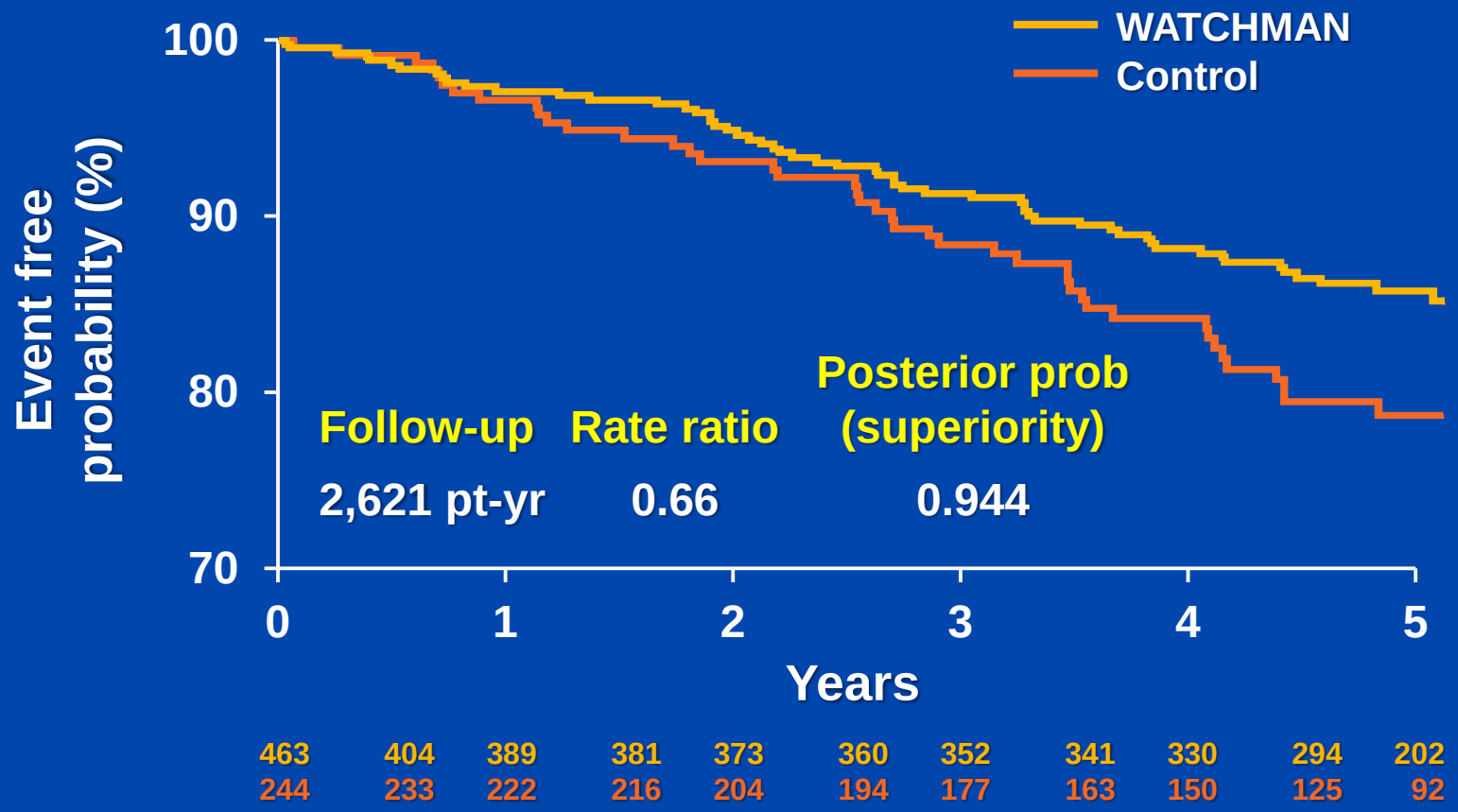
Long Term PROTECT AF All-Cause Mortality





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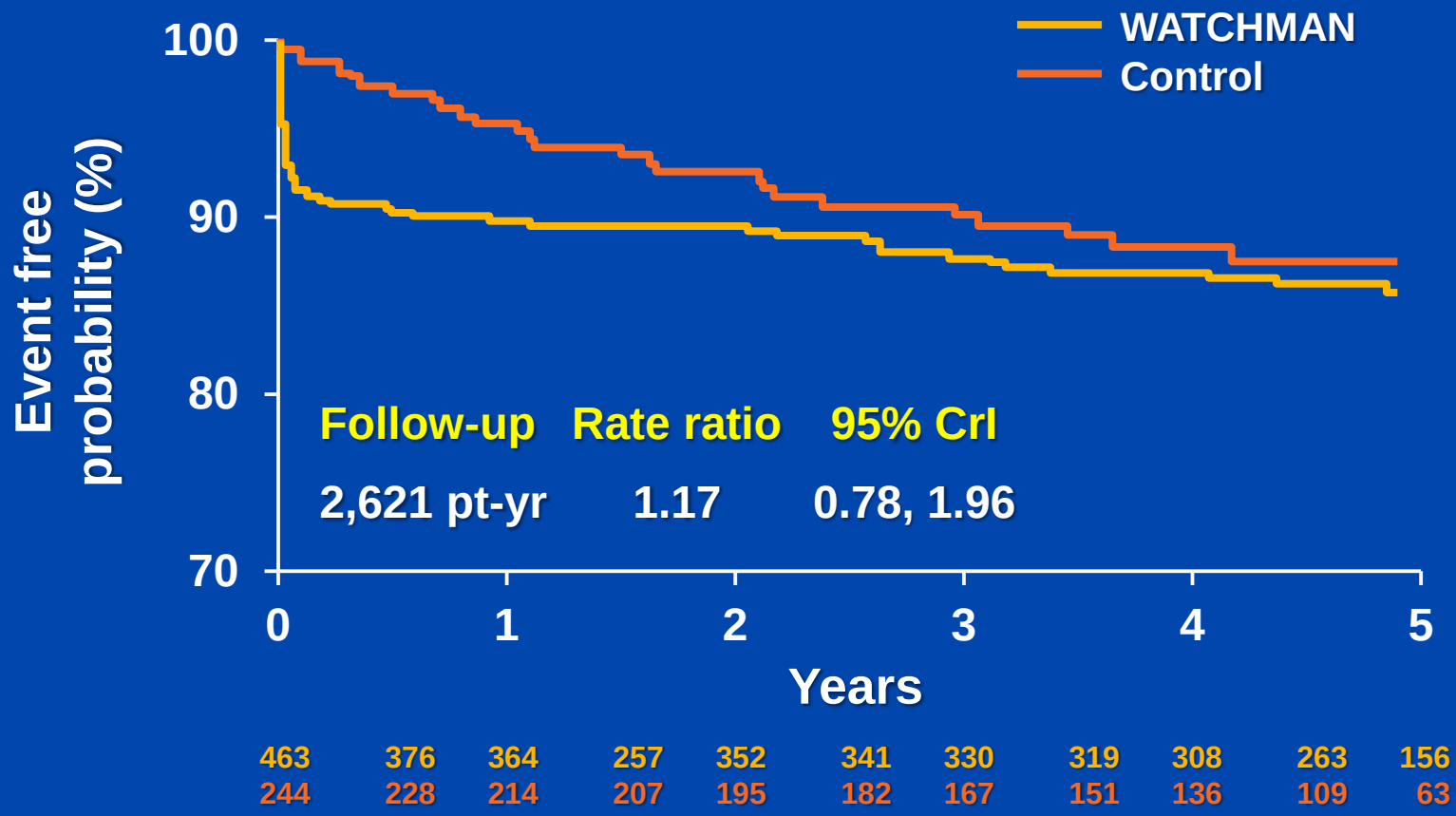
PROTECT AF:
Timing of Safety Events Differ by Arm



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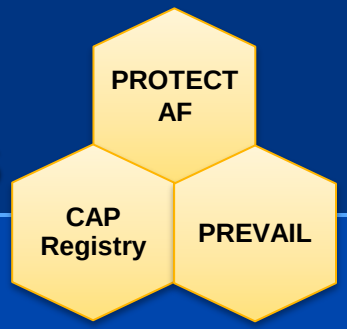
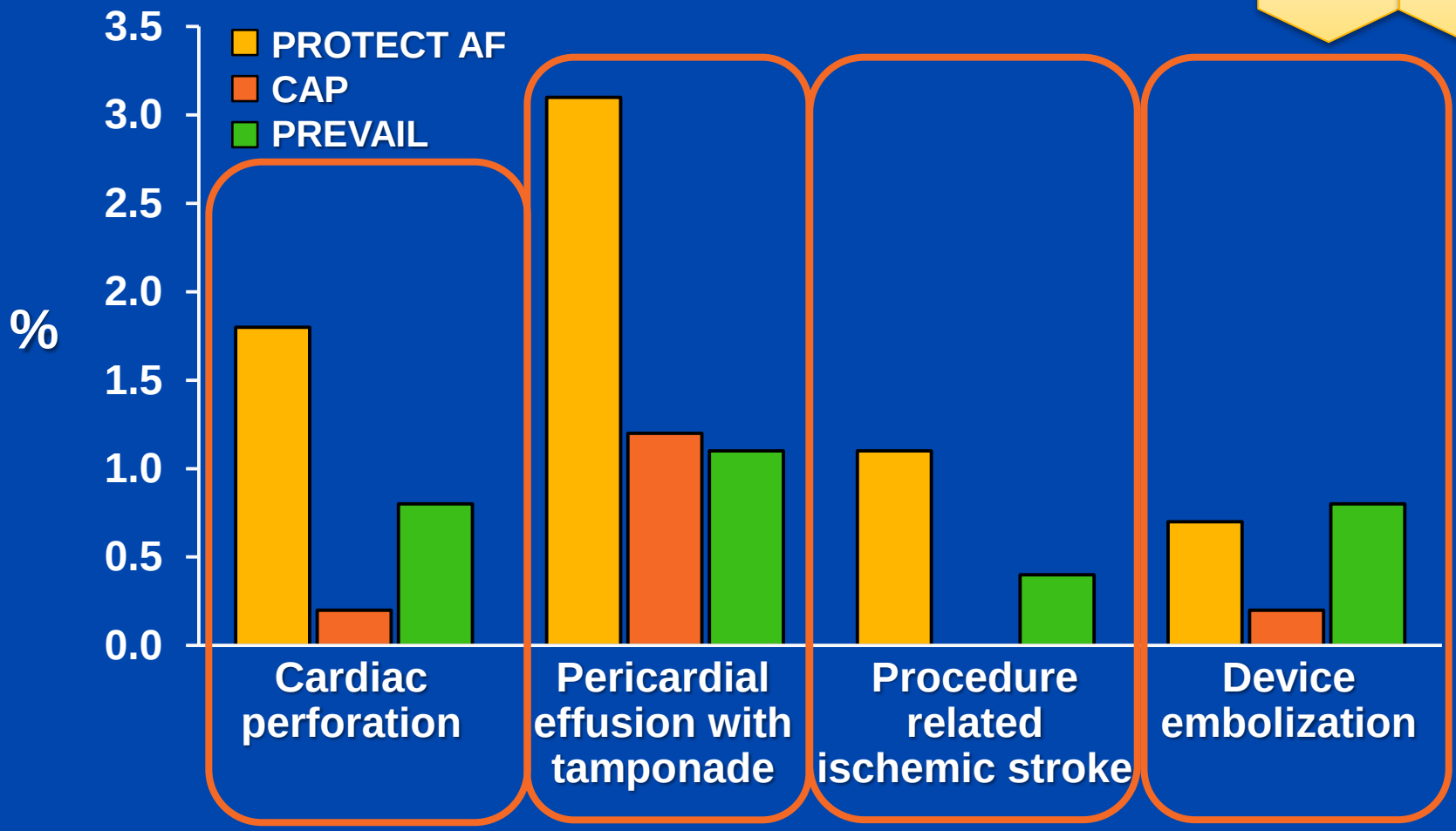
Trends in Key Procedural Safety Events Across Trials





* Overall embolization rate across studies is 0.5%

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“Nancy always had thick ankles, but no one really noticed.”

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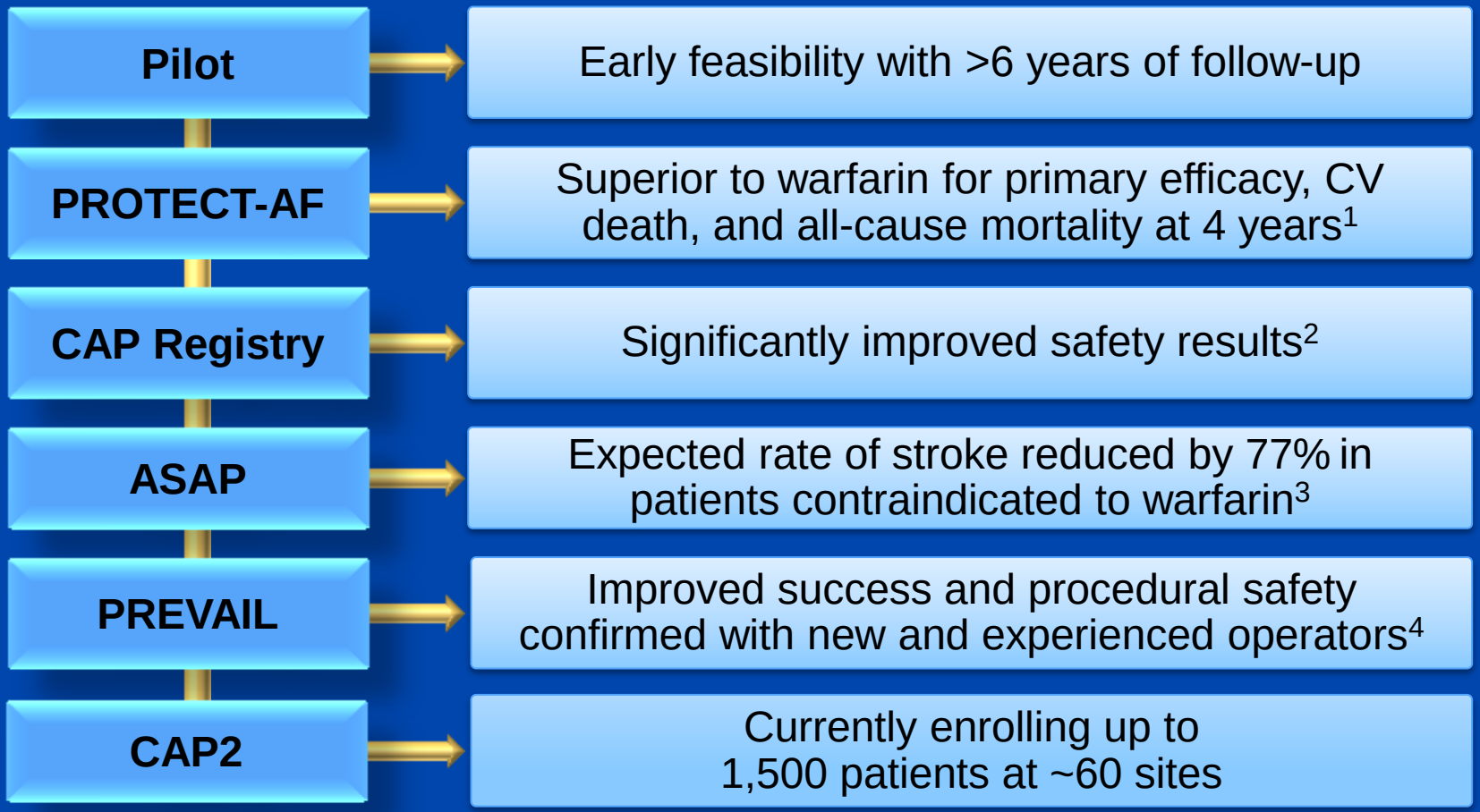
WATCHMAN Clinical History

Over 2,000 Patients With 4,800 Patient Years Follow-Up



[1]Reddy et al: HRS 2013; [2]Reddy et al: Circulation 123:417, 2011; [3]Reddy et al: JACC. 2013; In Press; [4]Holmes et al: CIT 2013; in the U.S., WATCHMAN is an investigational device, limited by applicable law to investigational use only and not available for sale; CE Mark 2005

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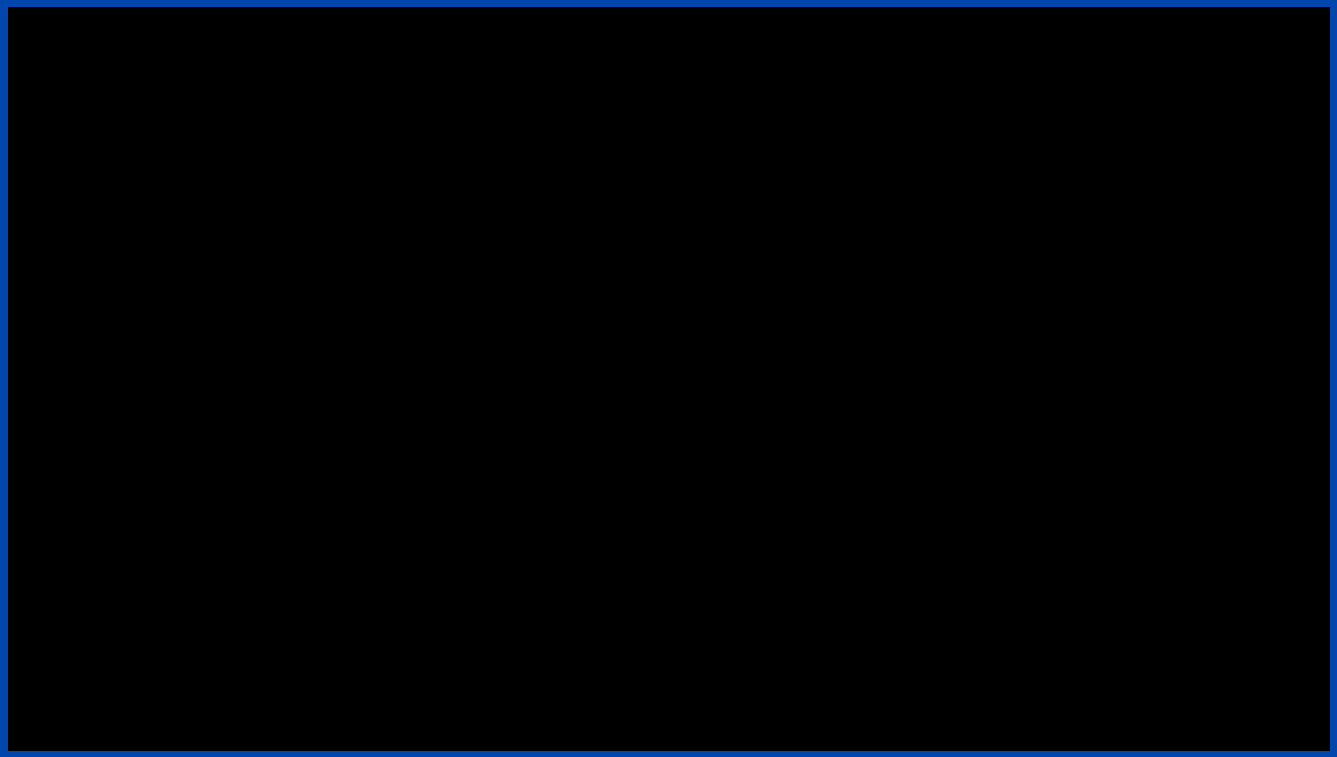

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LAA Occlusion
It's not for everyone

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One Size Does NOT Fit All

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Net Benefit
Risk/Reward

- **Unclear balance even with best clinical trials available/heterogeneous/difficult to apply to specific patient**

CHA_2DS_2VASc		Stroke (%)
Low	0	0.0
Mod	1	1.3
High	2	2.2
	3	3.2
	4	4.0
	5	6.7

?
?
?

Bleed (%)	HAS-BLED	
0.9	0	Low
3.4	1	Mod
4.1	2	
5.8	3	High
8.9	4	
9.1	5	

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Stroke Prophylaxis

- Cornerstone of therapy: OAC with warfarin
  - 60-70% risk reduction vs placebo
  - 30-40% risk reduction vs antiplatelet Rx/ASA
- Antiplatelet therapy: 22% risk reduction vs placebo
- ACTIVE W: Warfarin vs DAPT; 42% RRR
- ASA only: 19% risk reduction vs placebo (P=NS)
- Older patients (>65): Absolute benefit of OAC increases while effect of ASA declines

Warfarin "preferred therapy"

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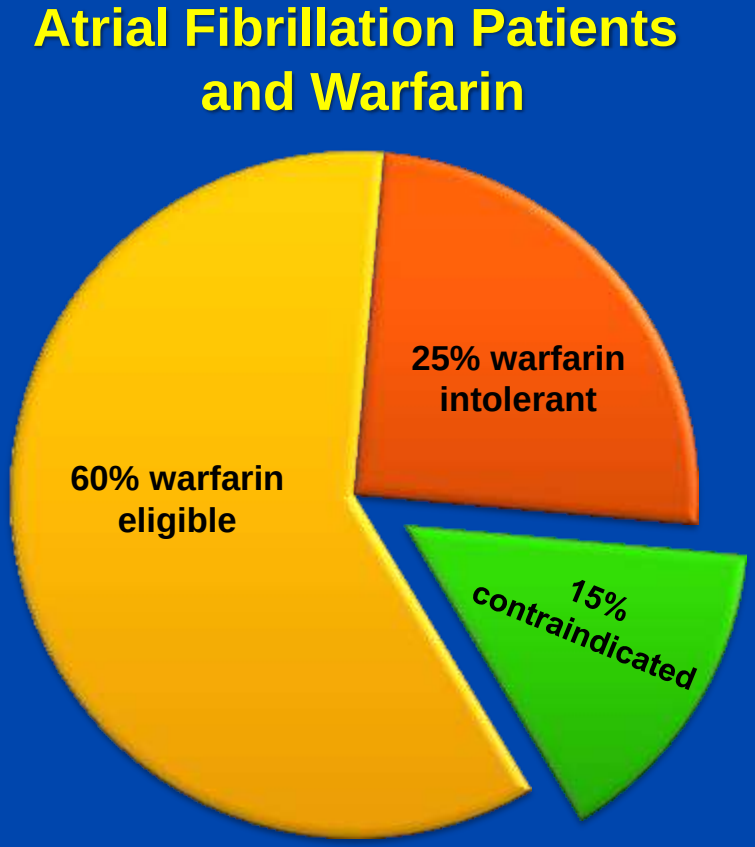
Hart: Ann Int Med, 2007
Connoly: Lancet, 2006

Warfarin Remains Standard of Care for Stroke Prevention in AF

- 50% of patients indicated for warfarin do not receive it[1]
- Reasons for not receiving warfarin range from patient preference to history of hemorrhage
- As many as 40% of AF patients have relative or absolute contraindications to warfarin therapy[2]
- Contraindicated patients are often treated with aspirin which has a lower risk of bleeding but also lower efficacy in preventing stroke



1.Patel, et al. Left atrial appendage exclusion for stroke prevention in atrial fibrillation. Cardiol Res Pract. 2012;2012:610827.
2.Brass LM, et al. Warfarin use among patients with atrial fibrillation. Stroke. 1997;28:2382-9.

Patient/Family Perspective on Bleeding

- "Major bleed": Death, 2 unit Tx, >20 g/dL ↓ HCT or bleeding involving a critical extracranial anatomical site (ICH = stroke, not bleed)
  - Sure, but what about "meaningful bleeds"
    - Clinically relevant, nonmajor bleeding
    - "minor bleeding"
- 60% of patients at "moderate risk" (>3%) of "major bleed"
  - Sure, but what is risk over 10 or 20 years?
- 26% of patients ≥80 stop at 1 year
  - 81% because of perceived safety issues; not major bleeding

Reynolds: Am J Cardio, 2006; Hylek: Circulation, 2007

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Other Warfarin Issues

- Drug-drug interactions
  - Challenging in elderly patient with frequent changes in concomitant medications (antibiotics/antiarrhythmics)
- Pharmacokinetic challenges (slow onset/offset)
  - Periprocedural challenges (Vit K, FFP)
  - Lovenox/heparin bridging for interruptions in therapy
- QOL
  - Frequent INR checks
  - Food-drug interactions
- Genetic variability

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Risk of Triple Therapy

- AF linked to increased likelihood of vascular disease → ACS
- 82,000 patients follow-up 2.6 years
  - 3.7-fold increased risk triple therapy vs warfarin
  - 11.4% fatal or nonfatal major bleeds
  - OAC + DAPT 15.7%/patient-year
  - OAC + clopidogrel only 13.9%/patient-year

Sorensen: Lancet, 2009; Hansen: Arch Int Med, 2010

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Antithrombotics vs Warfarin in Nonvalvular Atrial Fibrillation

	RELY	ROCKET AF	ARISTOTLE	ACTIVE W
Intervention	Dab 110 mg bid or 150 mg bid	Rivar 20 mg once/day	Apix 5 mg bid	Plavix 75 mg/day + aspirin 75-100 mg/day
# Pts.	18,113	14,264	18,201	6.706
Primary outcome	CVA/Emb	CVA/Emb	CVA/Emb	CVA, Emb, MI or CVD
F/U (yrs, median)	2.0	1.9	1.8	1.3
Age (yrs, median)	71.5	73	70	70
$CHADS_2$ score (mean)	2.1	3.5	2.1	2.0

MAYO CLINIC

Danelich et al: Pharmacotherapy 33:422-446, 2013

Antithrombotics vs Warfarin in Nonvalvular Atrial Fibrillation

Efficacy Results	RELY	ROCKET AF	ARISTOTLE	ACTIVE W
Primary outcome	110 mg: 1.53 vs 1.69 (p<0.001 NINF), p=0.34 (superior) 150 mg; 1.11 vs 1.69 (p<0.001 NINF)	Per protocol: 1.7 vs 2.2 (p<0.001 for NINF), as treated: 1.7 vs 2.2 (p=0.02 for superior), Intent-to-treat: 2.1 vs 2.4 (p<0.001 for NINF; p=0.12 for superior)	Intent-to-treat: 1.27 vs 1.60 (p=0.01 for superior)	Intent-to-treat: 5.60 vs 3.93 (p=0.0003 for superior)
Ischemic CVA	110 mg: 1.34 vs 1.2 (p=0.35) 150 mg: 0.92 vs 1.20 (p=0.03)	1.34 vs 1.42 (p=0.581)	1.19 vs 1.51 (p=0.01)	2.15 vs 1.00 (p<0.0001)
Hemorrhagic CVA	110 mg: 0.12 vs 0.38 (p<0.001) 150 mg: 0.10 vs 0.38 (p<0.001)	0.26 vs 0.44 (p=0.024)	0.24 vs 0.47 (p<0.001)	1.12 vs 0.36 (p=0.036)
INR TTR, % (mean)	64	55	66	64

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Danelich et al: Pharmacotherapy 33:422-446, 2013

Antithrombotics vs Warfarin in Nonvalvular Atrial Fibrillation

Safety Results	RELY	ROCKET AF	ARISTOTLE	ACTIVE W
Major bleeding	110 mg: 2.71 vs 3.36 (p=0.003) 150 mg: 3.11 vs 3.36 (p=0.31)	3.6 vs 3.4 (p=0.58)	2.13 vs 3.09 (p<0.001)	2.42 vs 2.21 (p=0.53)
Intracranial hemorrhage	110 mg: 0.23 vs 0.74 (p<0.001) 150 mg: 0.30 vs 0.74 (p<0.001)	0.5 vs 0.7 (p=0.02)	0.33 vs 0.80 (p<0.001)	0.005 vs 0.003 (p=0.08)
GI bleeding	110 mg: 1.12 vs 1.02 (p=0.43) 150 mg: 1.51 vs 1.02 (p<0.001)	3.2 vs 2.2 (p<0.001)	0.76 vs 0.86 (p=0.37)	Not reported

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Danelich et al: Pharmacotherapy 33:422-446, 2013

Background
Meta Analysis

- 44,733 patients enrolled in 4 trials
  - PETRO, RE-LY, ROCKET-AF, ARISTOTLE
- "In general the composite of stroke or systemic emboli and any stroke were significantly reduced with new oral AC versus warfarin. Significant heterogeneity was seen with any stroke, major bleed, hemorrhage stroke and GI bleed."

Baker WL et al: Circ Cardiovasc Qual Outcomes 5:711-19, 2012

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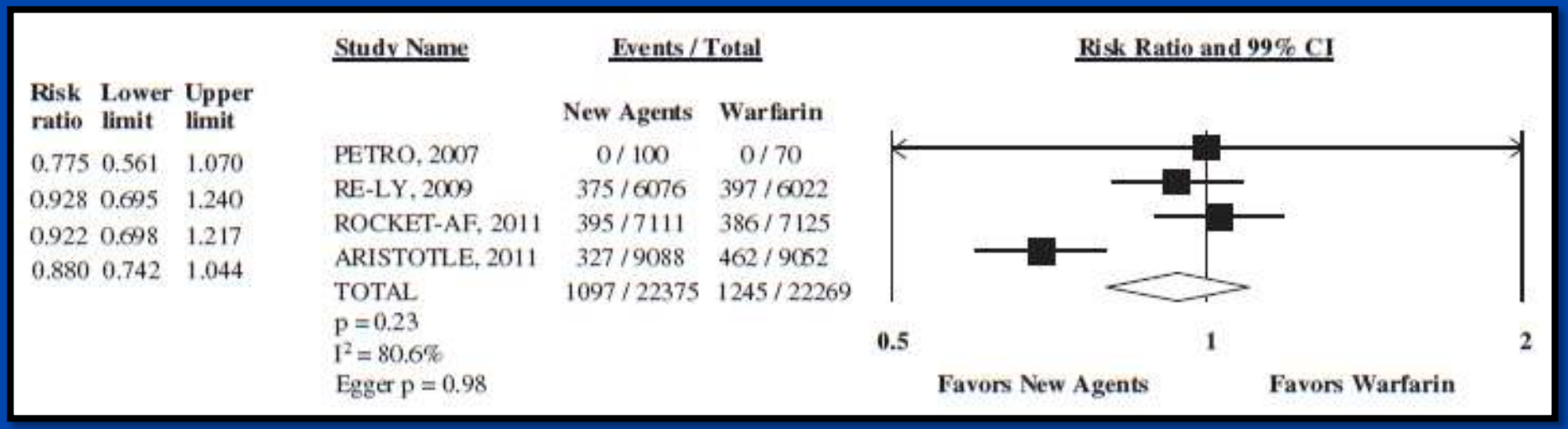
Safety of Anticoagulant Therapy
Major Bleed



Baker WL et al: Circ Cardiovasc Qual Outcomes 5:711-19, 2012

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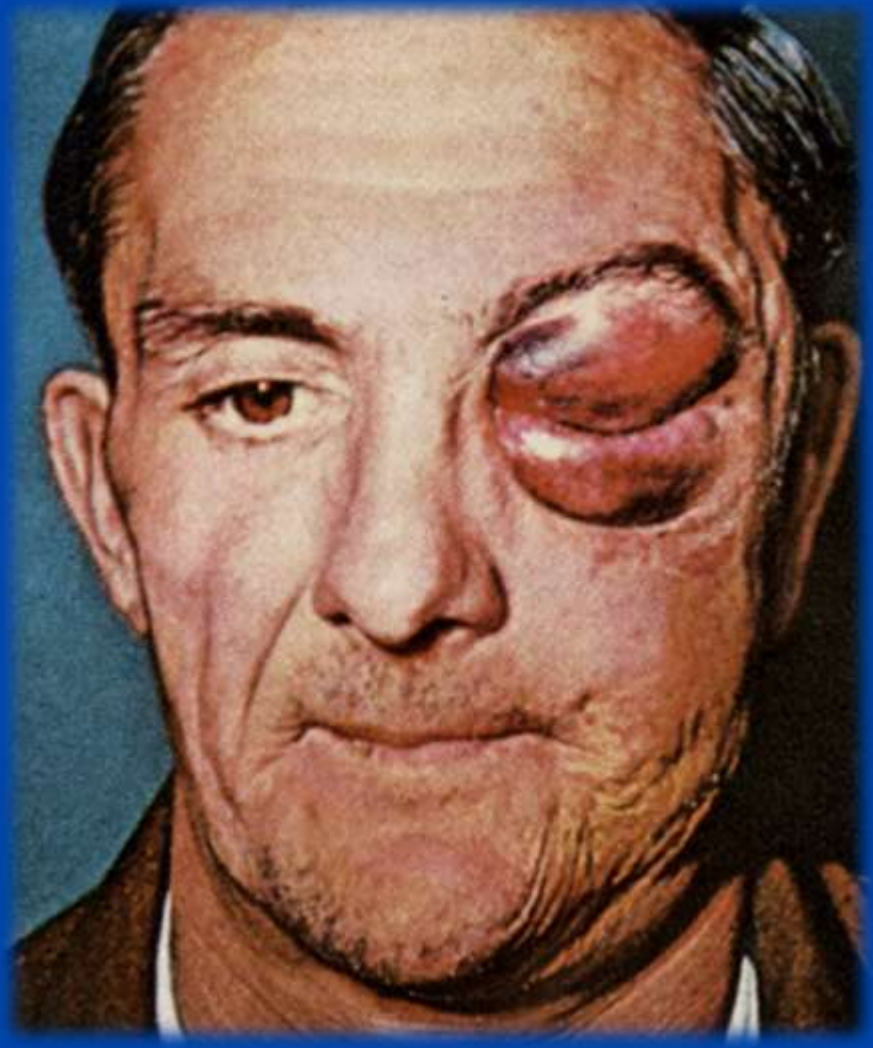

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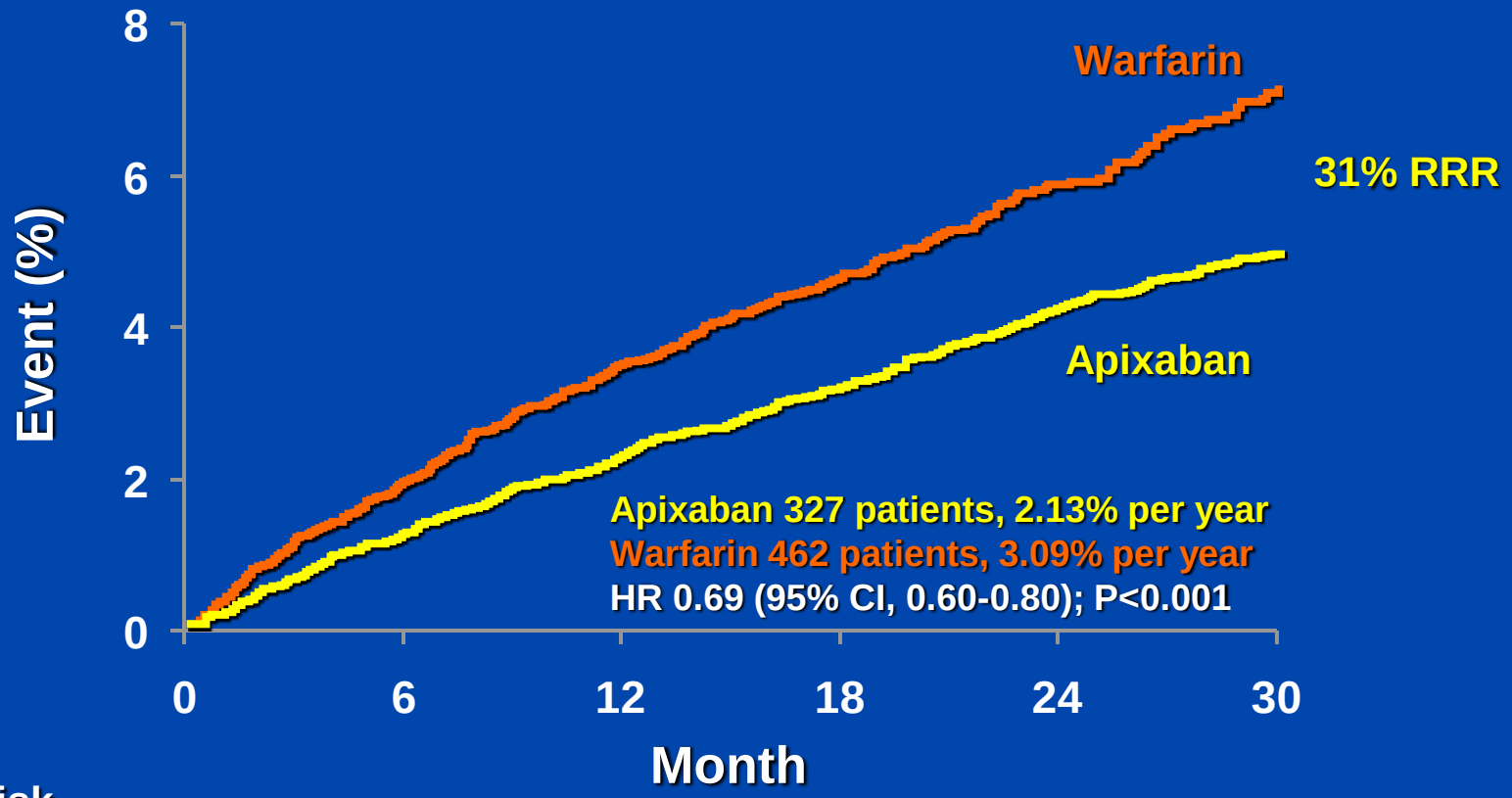
Major Bleeding
ISTH Definition



No. at risk						
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

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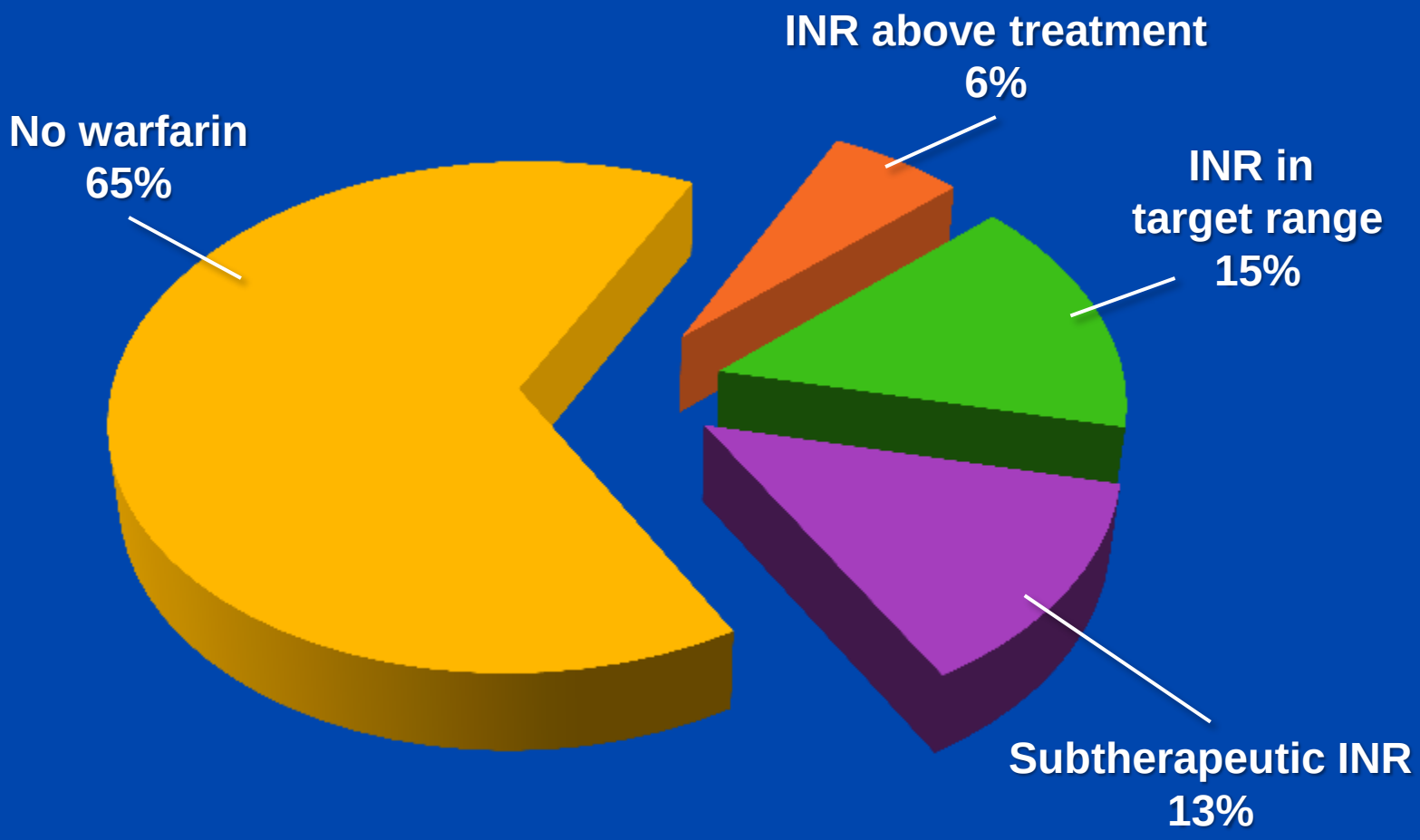
Inadequate VKA Treatment for AF



Samsa: Arch Int Med 160:967, 2000

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Patient/Family Perspective on Bleeding

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  - Sure, but what about "meaningful bleeds"
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- 26% of patients ≥80 stop at 1 year
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Reynolds: Am J Cardio, 2006; Hylek: Circulation, 2007

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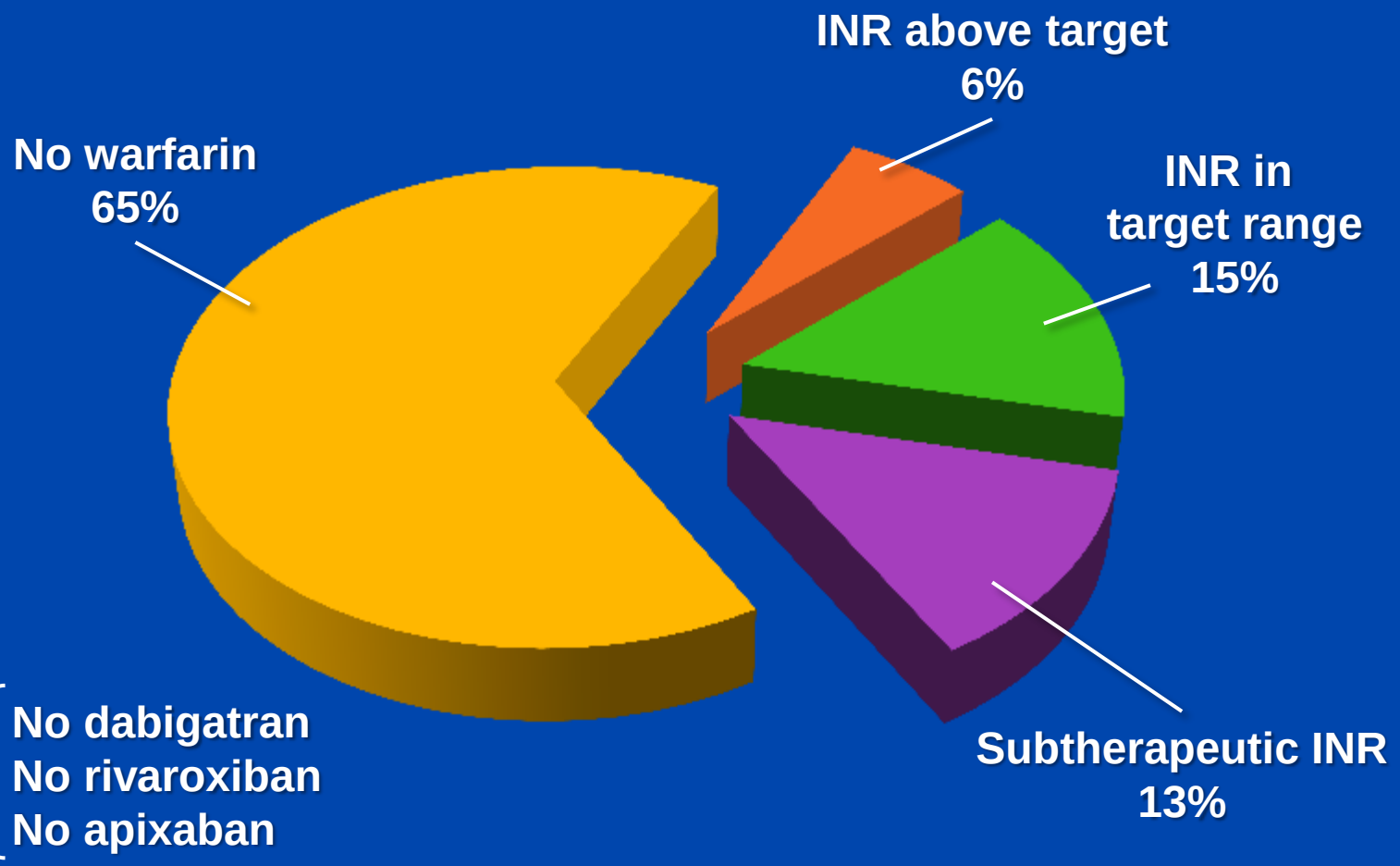
What will this Look Like in 2015?

Adequacy of Anticoagulation in Patients with AF in Primary Care Practice



Samsa et al: Arch Int Med 160:967, 2000

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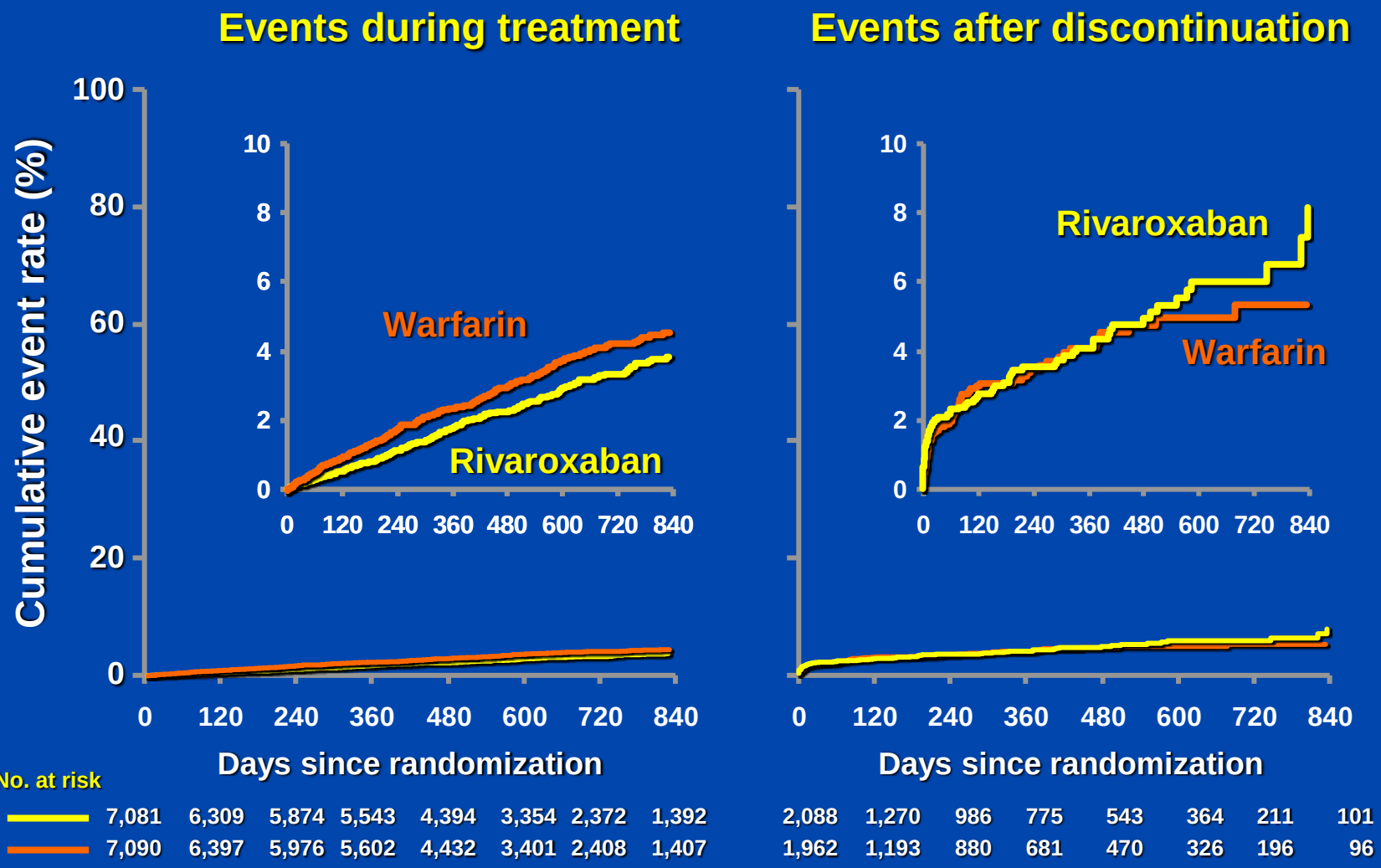
ROCKET AF



Patel MR et al: NEJM Aug 10, 2011

Other Warfarin Issues

- Drug-drug interactions
  - Challenging in elderly patient with frequent changes in concomitant medications (antibiotics/antiarrhythmics)
- Pharmacokinetic challenges (slow onset/offset)
  - Periprocedural challenges (Vit K, FFP)
  - Lovenox/heparin bridging for interruptions in therapy
- QOL
  - Frequent INR checks
  - Food-drug interactions
- Genetic variability

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New medicines and new methods of cure always work miracles for awhile

William Heberden
1710-1801

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ESC Guidelines for Management of AF
2012 Focused Update

Recommendations for LAA closure/occlusion/excision

Recommendation	Class	Level
Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contra-indications for long-term OAC	IIb	B

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RELY-ABLE Study

- Longer-term follow-up of RELY trial
- Only 48% of patients were still on the randomly assigned dabigatran
- During the next 28 month visit follow-up 13.8-14.6% discontinued the Dabigatran
- Major bleeding occurred in 2.99-3.74%

Connolly et al: Circ 128:237-243, 2013

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Of interest, in terms of GI bleeding, not all studies documented less bleeding compared with warfarin. There was increased GI bleeding with dabigatran and rivaroxaban in RELY and ROCKET AF but not with apixaban in ARISTOTLE.

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An analysis of the cost effectiveness of left atrial appendage closure for the prevention of stroke in patients with atrial fibrillation and absolute contraindications to warfarin therapy

David R. Holmes Jr.

EuroPCR 2013

An analysis of the cost effectiveness of left atrial appendage closure for the prevention of stroke in patients with atrial fibrillation and absolute contraindications to warfarin therapy

Vivek Y Reddy[1], Ron Akehurst[2], Shannon Armstrong[3], Stacey L Amorosi[4], Nic Brereton[5], David R Holmes[6]

[1]Mt. Sinai School of Medicine, New York, NY, USA; [2]University of Sheffield, Sheffield, UK; [3]GfK Bridgehead, Wayland, MA, USA; [4]Boston Scientific, Natick, MA, USA; [5]BresMed, Sheffield, UK; [6]Mayo Clinic, Rochester, MN, USA

Disclosure Information

The following relationships exist related to this presentation:

David R. Holmes:

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

Stacey L Amorosi

Paid employee of Boston Scientific

All other authors

Paid consultants of Boston Scientific

This research was funded by Boston Scientific

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Objective

- This analysis sought to estimate the cost effectiveness of treating warfarin-ineligible patients with left atrial appendage closure (LAAC) as compared to standard aspirin therapy for stroke prevention in atrial fibrillation (AF)

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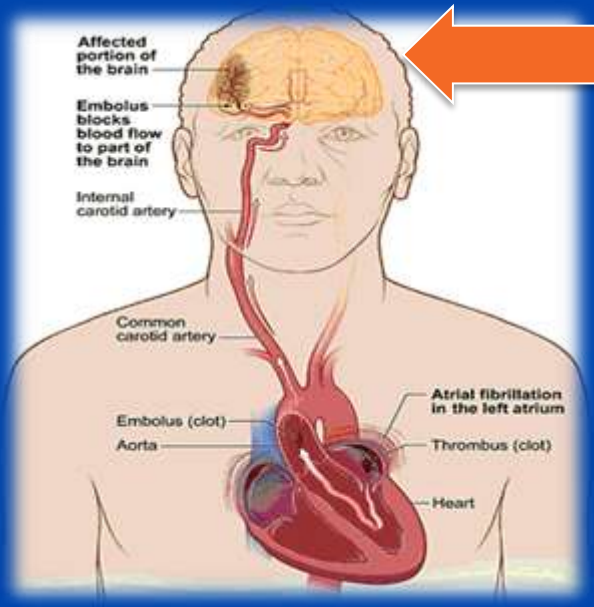
Stroke in AF

- 20% of all strokes occur in people with AF[1]



The embolism lodges itself in the blood vessels of the brain, restricting blood flow and causing a stroke

The blood clot dislodges from the LAA and travels through arterial system

The stagnant blood becomes an ideal environment for a thrombus or blood clot to form

Fibrillation causes blood to stagnate in the left atrial appendage

- AF-associated strokes affect a larger area of the brain than non-AF stroke[2], leading to a 70% chance of death or permanent disability[3]
- 91% of stroke in AF is caused by blood clots which have formed in the left atrial appendage[4]

1.Hart RG, Halperin JL. Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention. Ann Intern Med. 1999;131(9):688-95.
2.Tu HT et al, Pathophysiological determinants of worse stroke outcome in atrial fibrillation, Cerebrovascular Disease 2010;30(4):389-95.
3.Holmes DR, Atrial Fibrillation and Stroke Management: Present and Future, Seminars in Neurology 2010;30:528–536.
4.Blackshear JL, Odell JA, Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann of Thor Surgery, 1996;61:755-759.

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How Big is the Problem?

- AF is the most common arrhythmia
  - Affects more than 3 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
  - >90% of thrombus originates in the left atrial appendage
- Stroke is the #1 cause of long-term disability and the third leading cause of death in patients with AF

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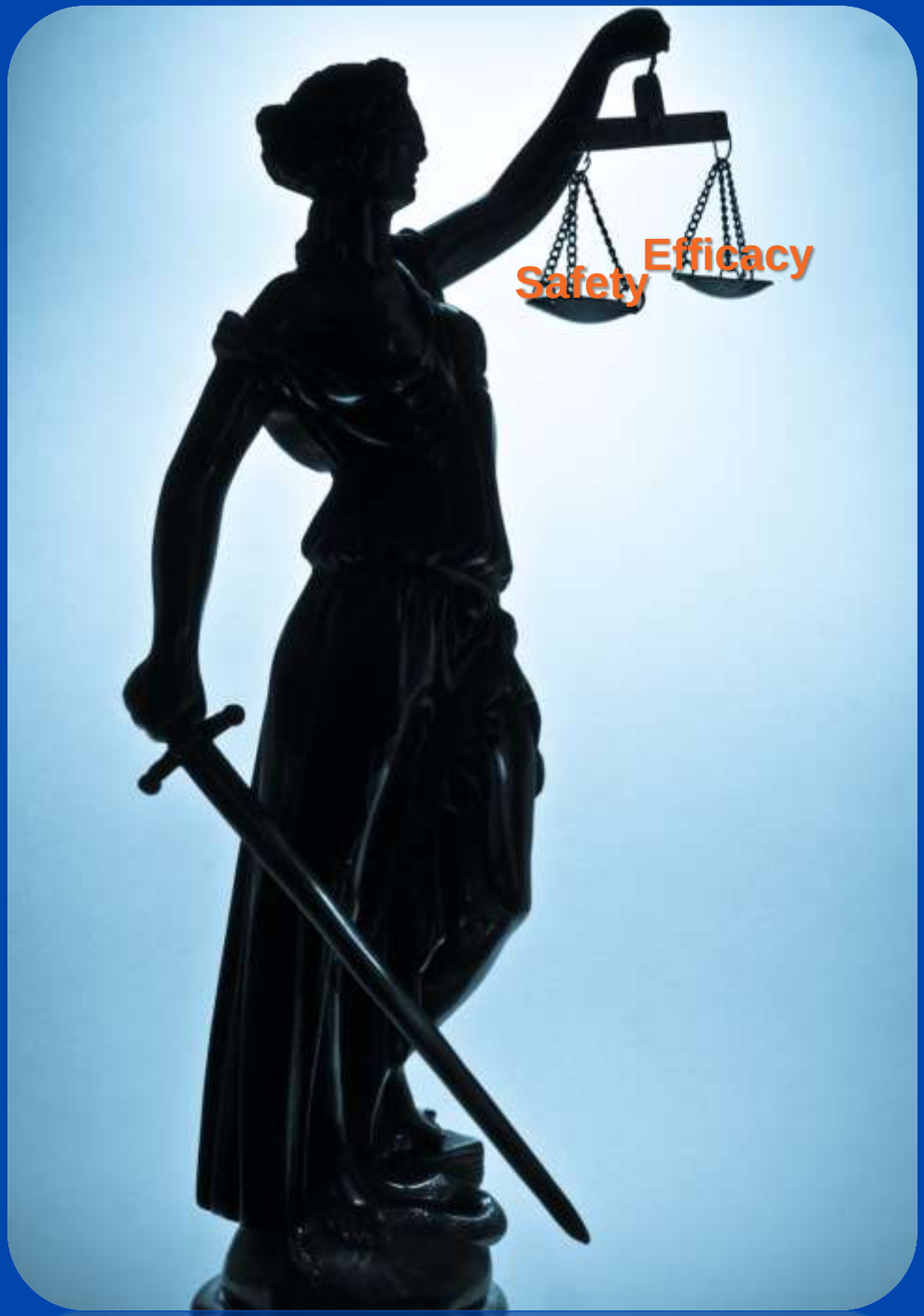

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ENGAGE AF-TIMI 48
Edoxaban vs Warfarin

- Multicenter RCT of 21,105 patients with AF
  - $CHADS_2$ 2.8±1.0
- Randomization
  - Warfarin
  - High dose Edoxaban
  - Low dose Edoxaban
- Non-inferiority design
- Primary efficacy endpoint
  - Stroke/systemic embolism
- Primary safety endpoint
  - Major bleeding

Guigliano et al: N Engl J Med 369:2093-104, 2013

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ENGAGE AF-TIMI 48

	Annualized Primary Endpoint
Warfarin (TTR 68.4%)	1.50%
High dose Edoxaban	1.18%
Low dose Edoxaban	1.61%
	Annualized Major Bleeding
Warfarin	3.43%
High dose Edoxaban	2.75%
Low dose Edoxaban	1.61%

Guigliano et al: N Engl J Med 369:2093-104, 2013

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ENGAGE AF-TIMI 48
Exclusions

- AF from reversible disorder
- CrCL <30 ml/min
- High risk bleeding
- DAPT
- ACS, coronary revasc or stroke <30 days

Guigliano et al: N Engl J Med 369:2093-104, 2013

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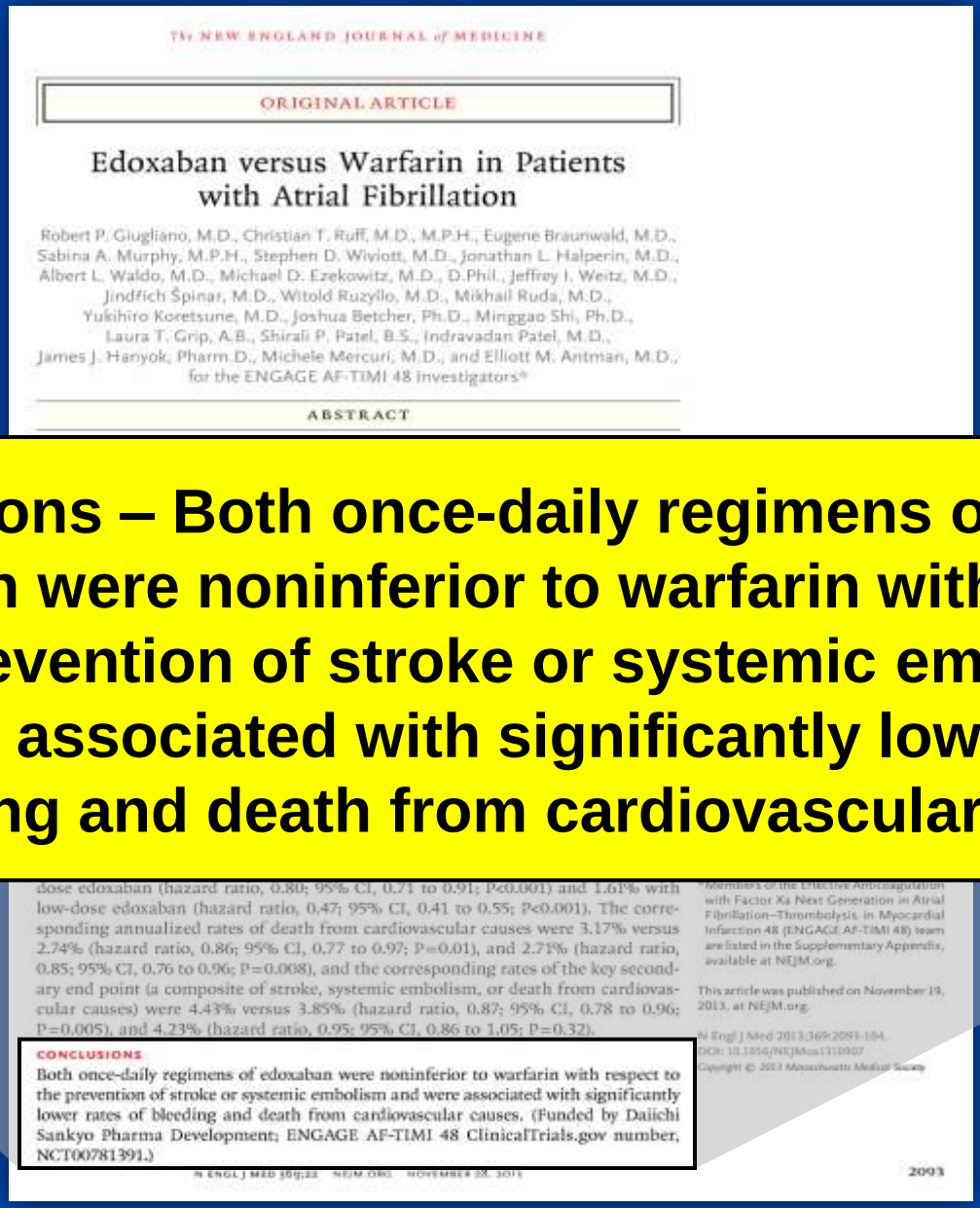

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

ABSTRACT

Conclusions – Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

dose edoxaban (hazard ratio, 0.80; 95% CI, 0.71 to 0.91; P<0.001) and 1.61% with low-dose edoxaban (hazard ratio, 0.47; 95% CI, 0.41 to 0.55; P<0.001). The corresponding annualized rates of death from cardiovascular causes were 3.17% versus 2.74% (hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.01), and 2.71% (hazard ratio, 0.85; 95% CI, 0.76 to 0.96; P=0.008), and the corresponding rates of the key secondary end point (a composite of stroke, systemic embolism, or death from cardiovascular causes) were 4.43% versus 3.85% (hazard ratio, 0.87; 95% CI, 0.78 to 0.96; P=0.005), and 4.23% (hazard ratio, 0.95; 95% CI, 0.86 to 1.05; P=0.32).

CONCLUSIONS

Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. (Funded by Daiichi Sankyo Pharma Development; ENGAGE AF-TIMI 48 ClinicalTrials.gov number, NCT00781391.)

*Members of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) team are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on November 19, 2013, at NEJM.org.

N Engl J Med 2013;369:2093-104.
DOI: 10.1056/NEJMoa1310907

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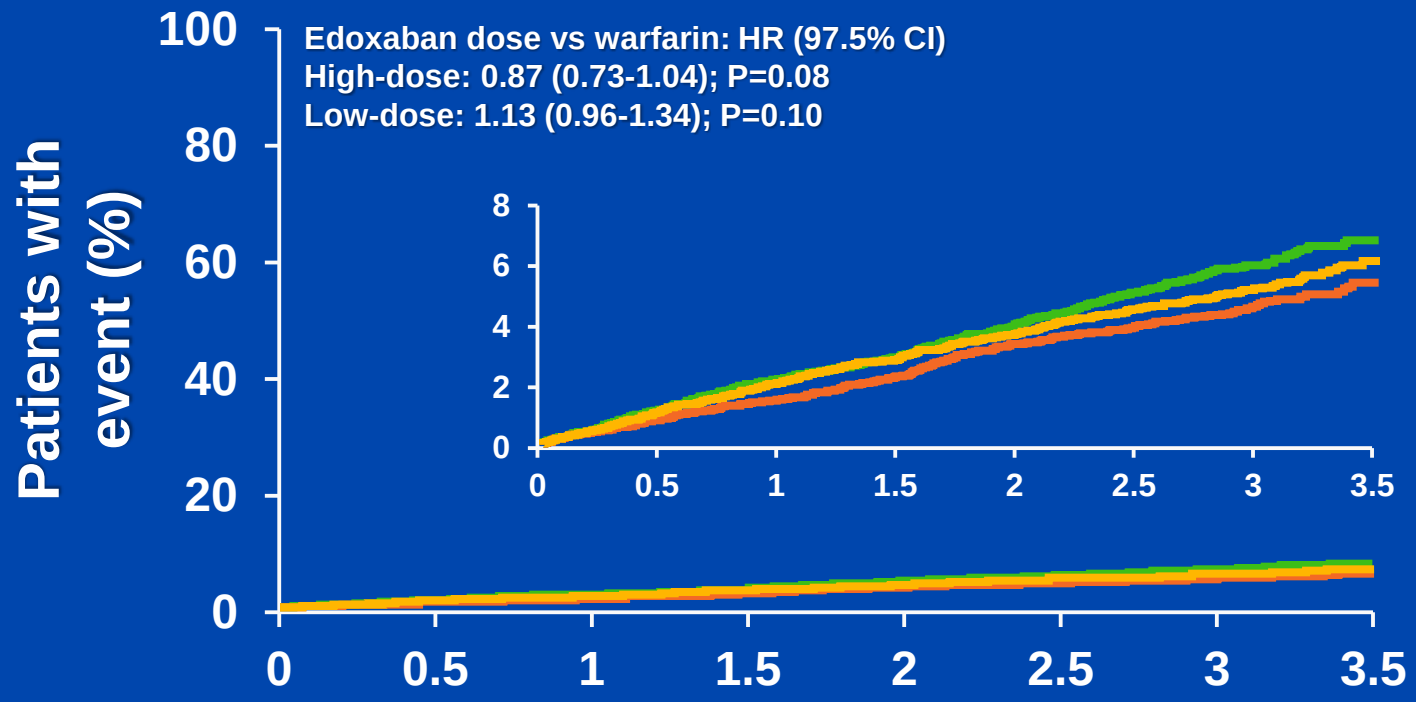
ENGAGE AF-TIMI 48

Stroke or Systemic Embolic Event



No. at Risk								
Warfarin	7,036	6,798	6,615	6,406	6,225	4,593	2,333	536
High-dose edoxaban	7,035	6,816	6,650	6,480	6,283	4,659	2,401	551
Low-dose edoxaban	7,034	6,815	6,631	6,461	6,277	4,608	2,358	534

Giugliano et al: NEJM 369(22):2093, 2013

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Primary Endpoint
Efficacy Endpoints

End Point	Warfarin (n=7,036) Pt with event (no.)	Warfarin (n=7,036) Patients per yr (%)	High-dose edoxaban (n=7,035) Pt with event (no.)	High-dose edoxaban (n=7,035) Patients per yr (%)	High-dose edoxaban vs warfarin HR (95% CI)	High-dose edoxaban vs warfarin P	Low-dose edoxaban (n=7,034) Pt with event (no.)	Low-dose edoxaban (n=7,034) Patients per yr (%)	Low-dose edoxaban vs warfarin HR (95% CI)	Low-dose edoxaban vs warfarin P
Primary end point										
Modified intention-to-treat population in treatment period	232	1.50	182	1.18	0.79 (0.63–0.99)	<0.001	253	1.61	1.07 (0.87–1.31)	0.005
Intention-to-treat population in the overall study period	337	1.80	296	1.57	0.87 (0.73–1.04)	0.08	383	2.04	1.13 (0.96–1.34)	0.10
Stroke	317	1.69	281	1.49	0.88 (0.75–1.03)	0.11	360	1.91	1.13 (0.97–1.31)	0.12
Hemorrhagic	90	0.47	49	0.26	0.54 (0.38–0.77)	<0.001	30	0.16	0.33 (0.22–0.50)	<0.001
Ischemic	235	1.25	236	1.25	1.00 (0.83–1.19)	0.97	333	1.77	1.41 (1.19–1.67)	<0.001
Nondisabling and nonfatal**	190	1.01	154	0.81	0.80 (0.65–0.99)	0.044	214	1.13	1.12 (0.92–1.36)	0.26
Disabling or fatal	135	0.71	132	0.69	0.97 (0.76–1.23)	0.81	152	0.80	1.11 (0.89–1.40)	0.36
Fatal	86	0.45	80	0.42	0.92 (0.68–1.25)	0.61	73	0.38	0.84 (0.61–1.15)	0.27
Systemic embolic event	23	0.12	15	0.08	0.65 (0.34–1.24)	0.19	29	0.15	1.24 (0.72–2.15)	0.43

Giugliano et al: NEJM 369(22):2093, 2013

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What Have We Learned

- Scope of AF and stroke
- Challenges of anticoagulation therapy including NOACS
- Issues of trial design
  - Invasive devices versus oral medications
- Regulatory pathways for new devices
- Long-term efficacy – Watchman
  - Patients eligible for AC
  - Patients not eligible for AC
- Safety
  - New operators versus inexperienced operators
- Total picture

MAYO CLINIC

Non-Valvular AF Patients

- AF increases the risk of stroke 4 - 5 times[1]
  - Highest risk: older patients and those with prior stroke or TIA[2]
  - AF is responsible for 15 - 20% of all strokes, particularly in the elderly[3]
- Typically >70 years old[4]
- Taking multiple medications[5]

1. Wolf PA: Stroke, 1991
2. Gage BF: JAMA, 2001
3. Go AS: Am J Geriatr Cardiol, 2005
4. Lloyd-Jones D: Circulation, 2010
5. Hayes BD: Clin Geriatric Med, 2007

MAYO CLINIC

Stroke in AF Patients

- Greater disability compared to non-AF related stroke
  - Larger infarcts[1]
  - More severe hemorrhagic transformation[2]
- High recurrence rate of stroke[3]
- Higher mortality[4]

1. Jorgensen HS: Stroke, 1996
2. Tu HT: Int J Stroke, 2013
3. Penado S: Am J Med, 2003
4. McGrath ER: Neurology, 2013

MAYO CLINIC

Guidelines for Anticoagulation Use Based on $CHADS_2$ Scores

CHADS2 score	Recommendation
0	Aspirin or no therapy
1	Anticoagulation or aspirin
≥2	Anticoagulation

ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation

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Factors Increasing Stroke Risk in Patients with $CHADS_2$ Score of 1

Warfarin therapy recommended for patients with $CHADS_2$ score of 1 if any of the following apply

- Female and age ≥75
- Baseline LVEF <35%
- Age 65-74 and diabetes or coronary artery disease
- Age ≥65 and has documented congestive heart failure

ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation

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Fundamental Treatment Dilemma: Stroke and Bleeding Risks Overlap

$CHADS_2$ Risk Criteria

Risk Factor	Score
Prior stroke or TIA	2
Age >75	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

HAS-BLED

Condition	Points
Hypertension	1
Abnormal liver and renal function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Age >65	1
Drugs or alcohol (1 point each)	1 or 2

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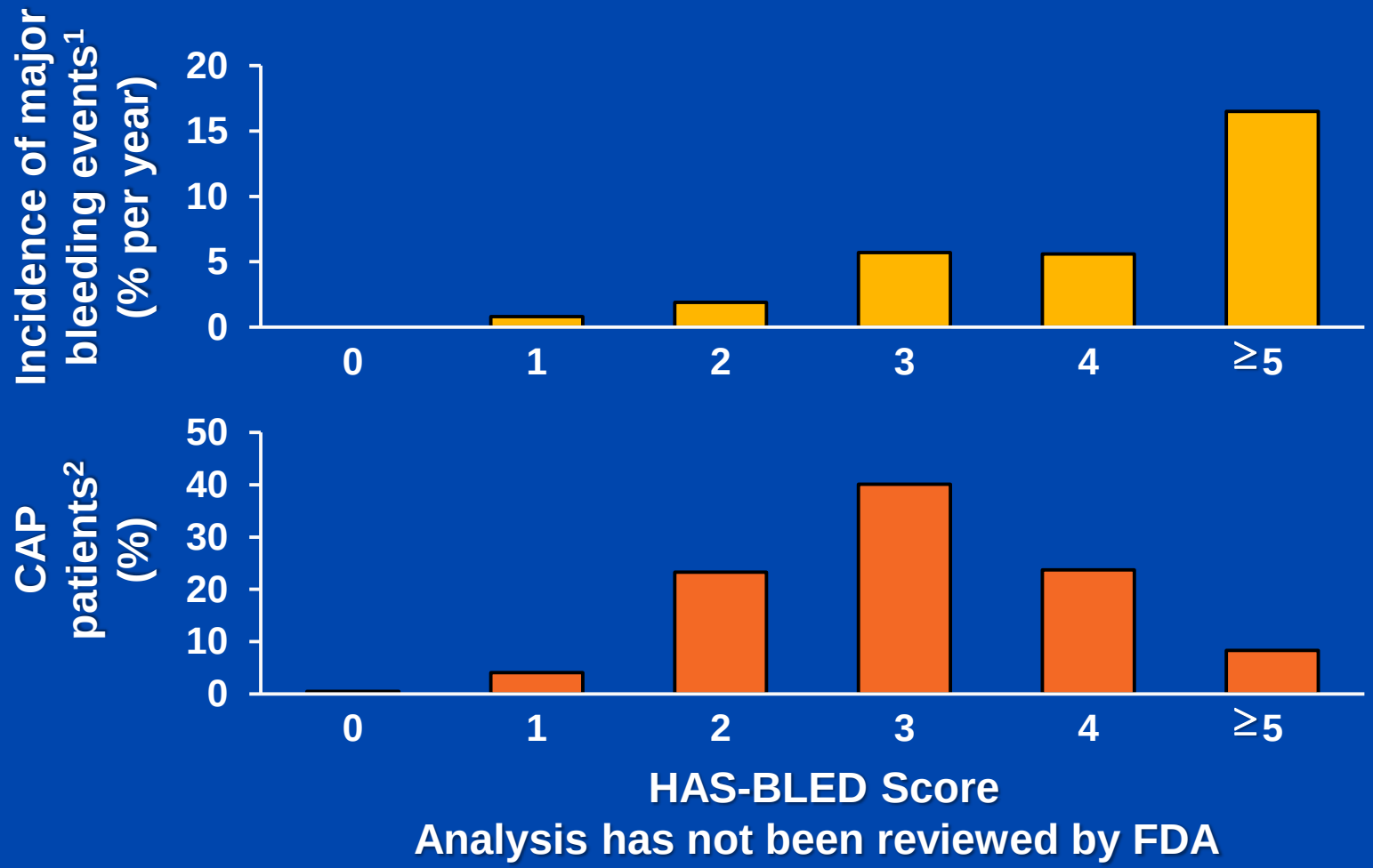
CAP: Bleeding Risks Based on HAS-BLED



Analysis has not been reviewed by FDA

1. Lip G, Chest (2013)
2. Post-hoc analysis, assumed no point for factors not collected

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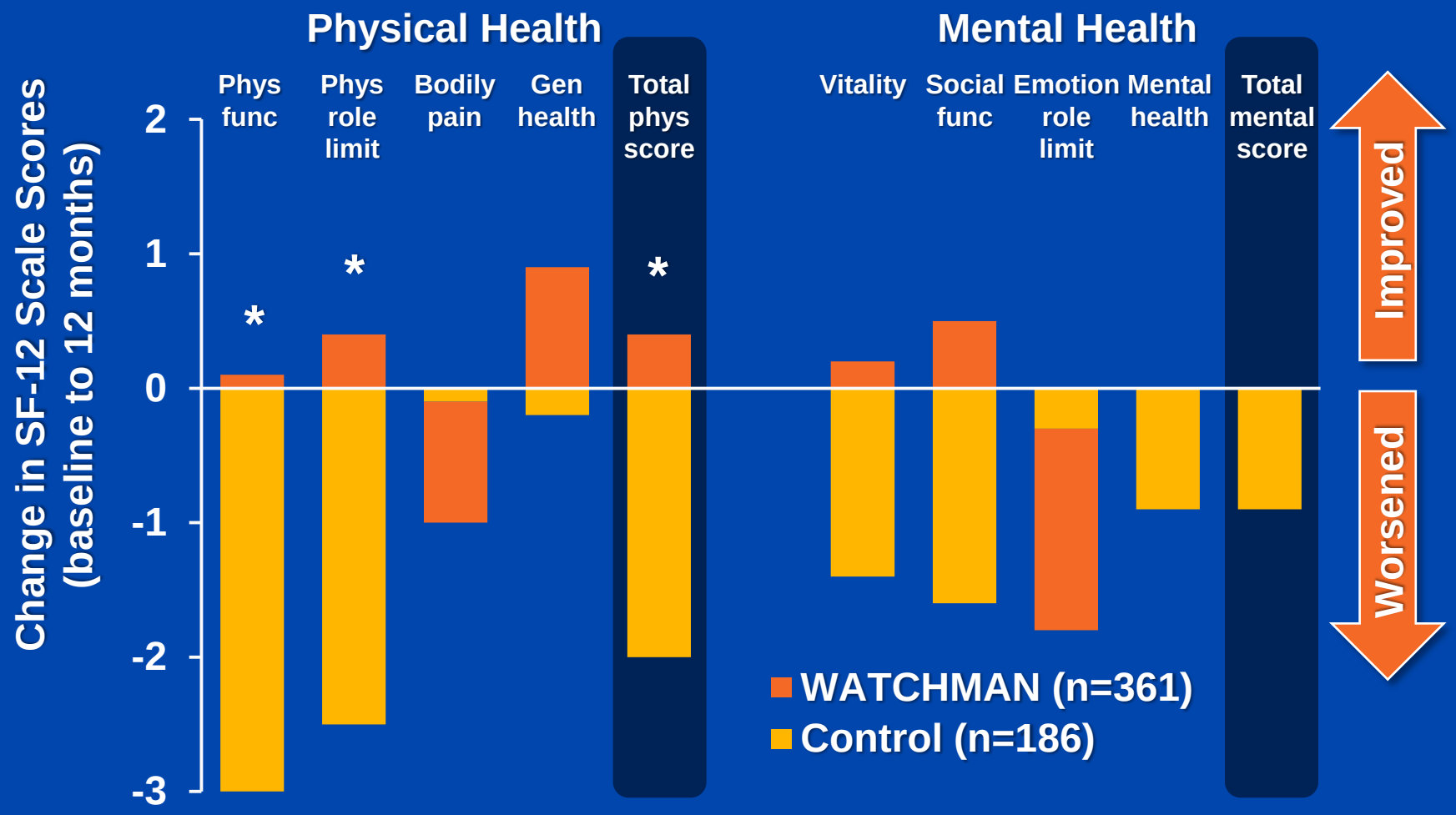
PROTECT AF: Quality of Life



* P<0.005

Alli O: JACC, 2013

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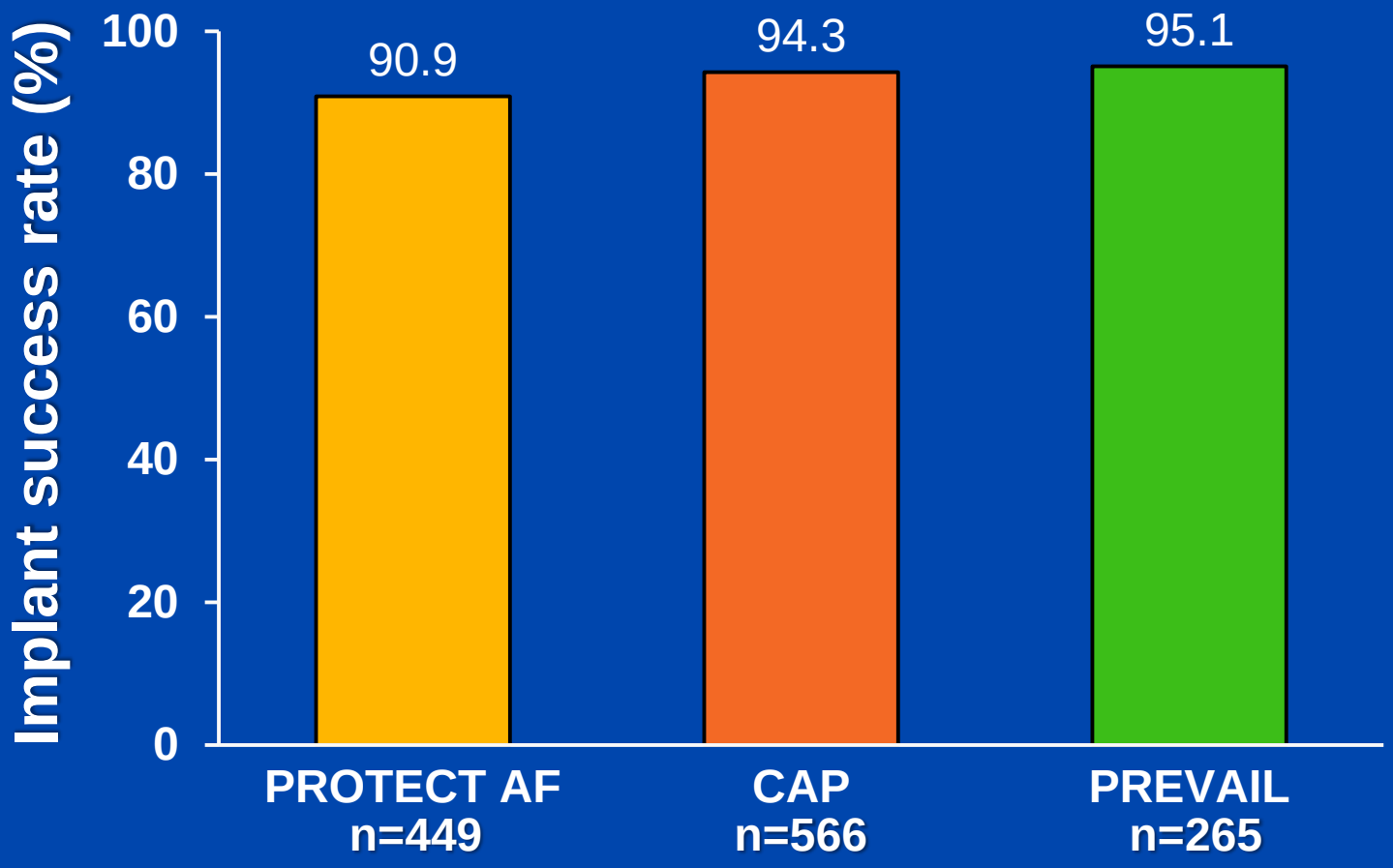
Implant Success Across Trials



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Warfarin Cessation Rates High in WATCHMAN Patients

	PROTECT AF (n=408)		CAP (n=534)		PREVAIL (n=253)	
Visit	n/N	%	n/N	%	n/N	%
45-day	348/401	86.8	507/529	95.8	227/246	92.2
6-month	355/385	92.2	493/500	98.6	235/239	98.3
12-month	345/370	93.2	455/472	96.4	141/142	99.3

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Long-Term PROTECT AF Results

	Mean follow-up (years)	Event Rate			Posterior Probabilities	
		WATCHMAN	Control	Rate ratio	Non inferiority	Superiority
900 pt-yr	1.3	3.4	5.0	0.68	0.998	0.837

Composite primary efficacy

- All stroke
- Cardiovascular / unexplained death
- Systemic embolism

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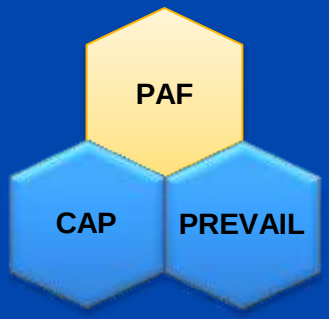
Long-term PROTECT AF Results

	Mean follow-up (years)	Event rate			Posterior probabilities	
		WATCHMAN	Control	Rate ratio	Non-inferiority	Superiority
900 pt-yr	1.3	3.4	5.0	0.68	0.998	0.837
1,588 pt-yr	2.3	3.0	4.3	0.71	>0.999	0.846
2,621 pt-yr	3.8	2.3	3.8	0.60	>0.999	0.960



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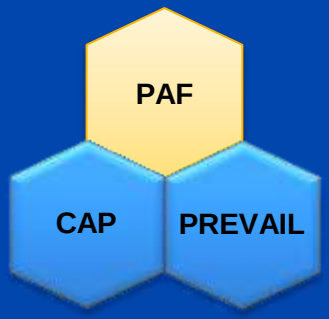
PROTECT AF: Long-Term Efficacy Results (2,621 Patient-Years of Follow-Up)

	Event rate (per 100 pt-yr)			Posterior probabilities	
	WATCHMAN n=463	Control n=244	Rate ratio (95% CrI)	Non-inferiority	Superiority
Primary efficacy	2.3	3.8	0.60 (0.41, 1.05)	>0.999	0.960
Stroke (all)	1.5	2.2	0.68 (0.42, 1.37)	0.999	0.825
Ischemic	1.4	1.1	1.26 (0.72, 3.28)	0.779	0.147
Hemorrhagic	0.2	1.1	0.15 (0.03, 0.49)	0.999	0.999
Systemic embolism	0.2	0.0	NA	NA	NA
Death (CV & unexplained)	1.0	2.4	0.40 (0.23, 0.82)	>0.999	0.995



MAYO CLINIC

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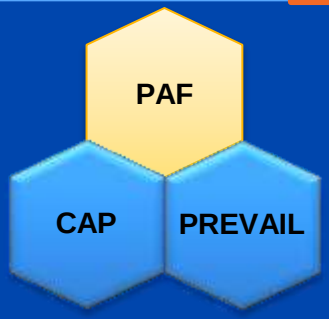
Systemic Embolism	0.2	0.0	n/a	n/a	n/a
Death (CV & unexplained)	1.0	2.4	0.40 (0.23, 0.82)	>0.999	0.995



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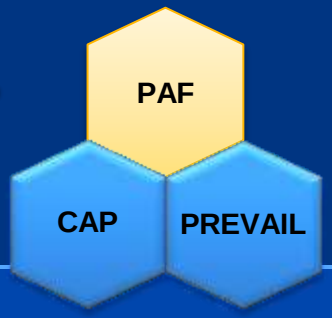
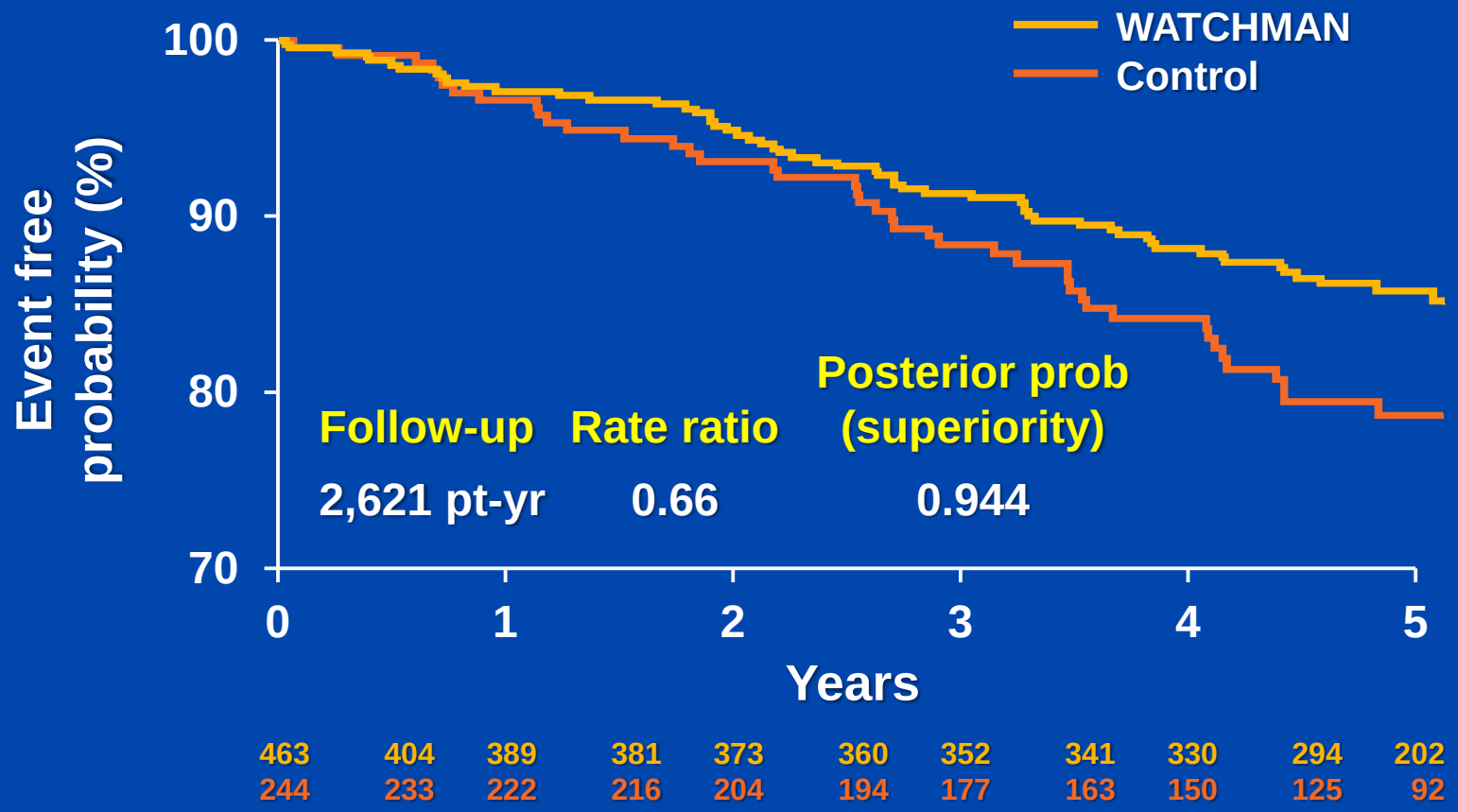
Long Term PROTECT AF All-Cause Mortality





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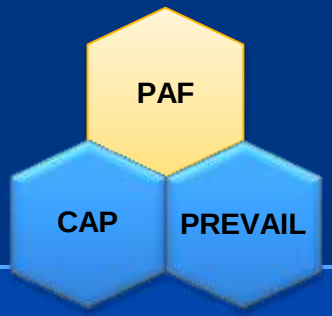
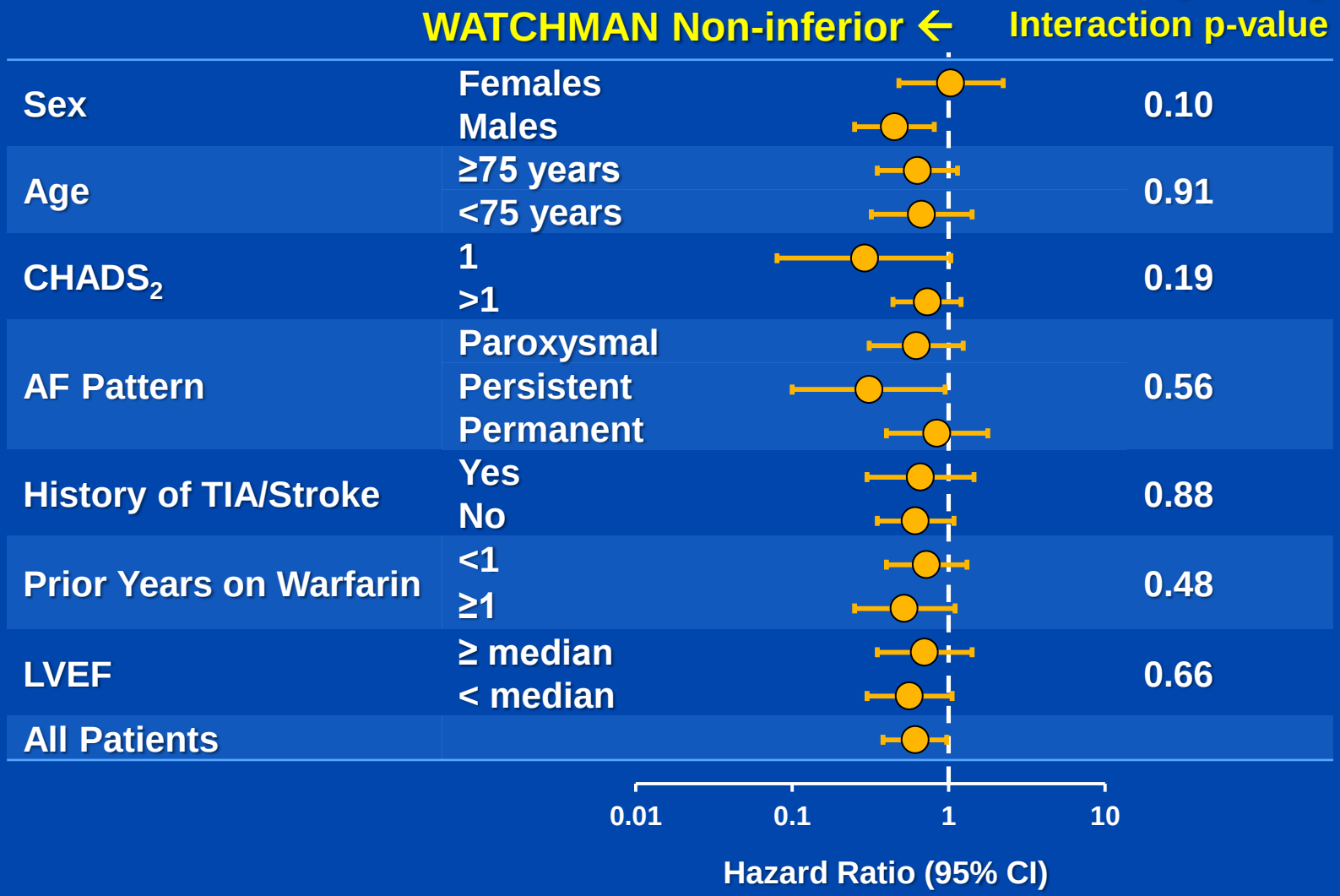
Long-term PROTECT AF Primary Efficacy Endpoint: Hazard Ratios by Subgroup





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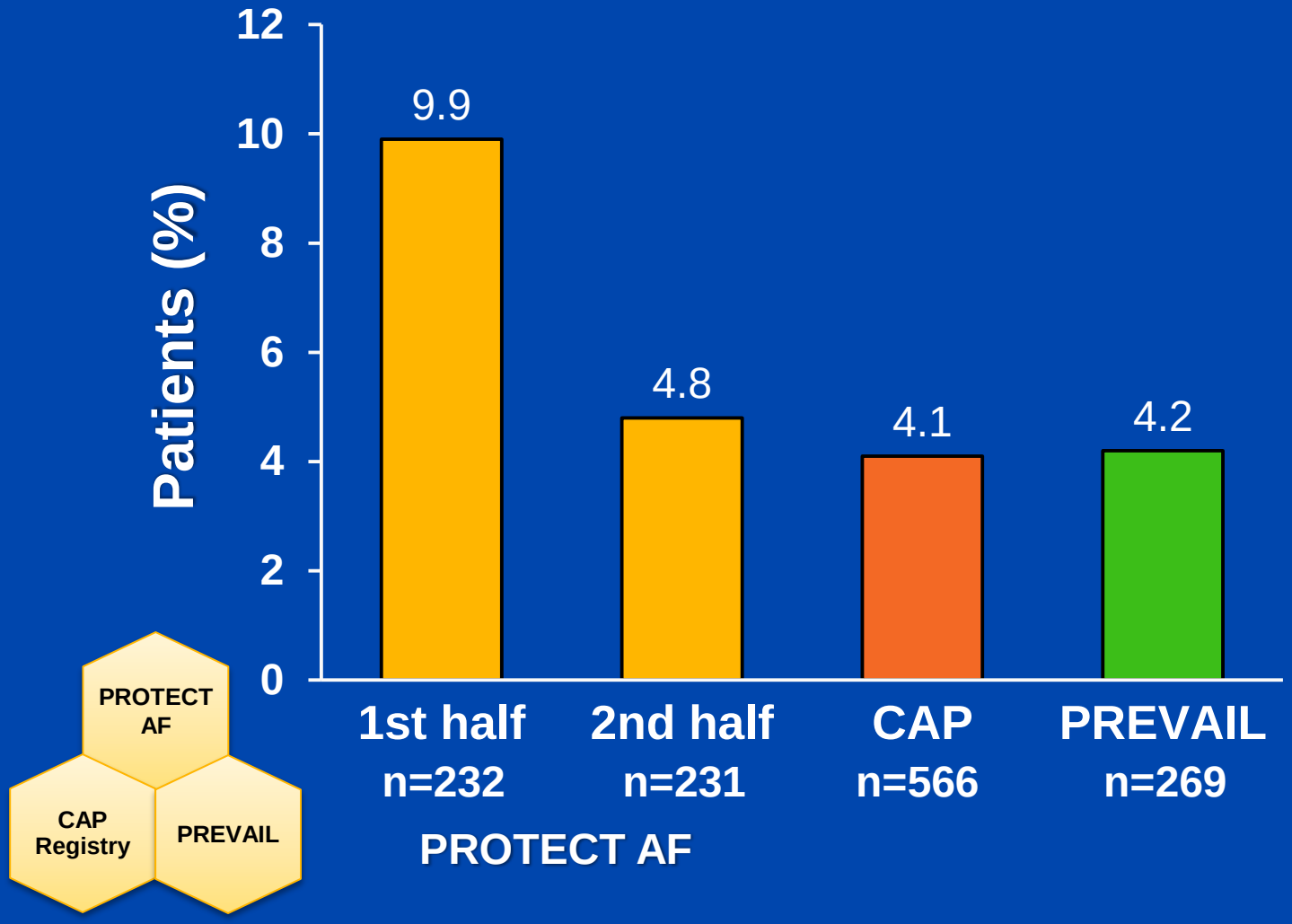
Safety Events: PROTECT AF, CAP, PREVAIL



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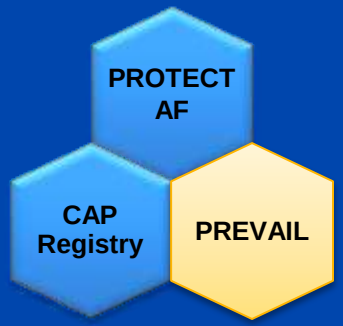
PREVAIL Safety Assessment

- Included new operators and centers
- Safety primary endpoint: Safety events occurring in the peri-procedural period*
  - All-cause death, ischemic stroke, systemic embolism

or

  - Device or procedure related events requiring surgical or major endovascular intervention



*Between randomization and within 7 days of procedure or by hospital discharge, whichever is later

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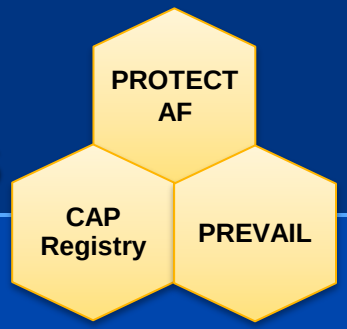
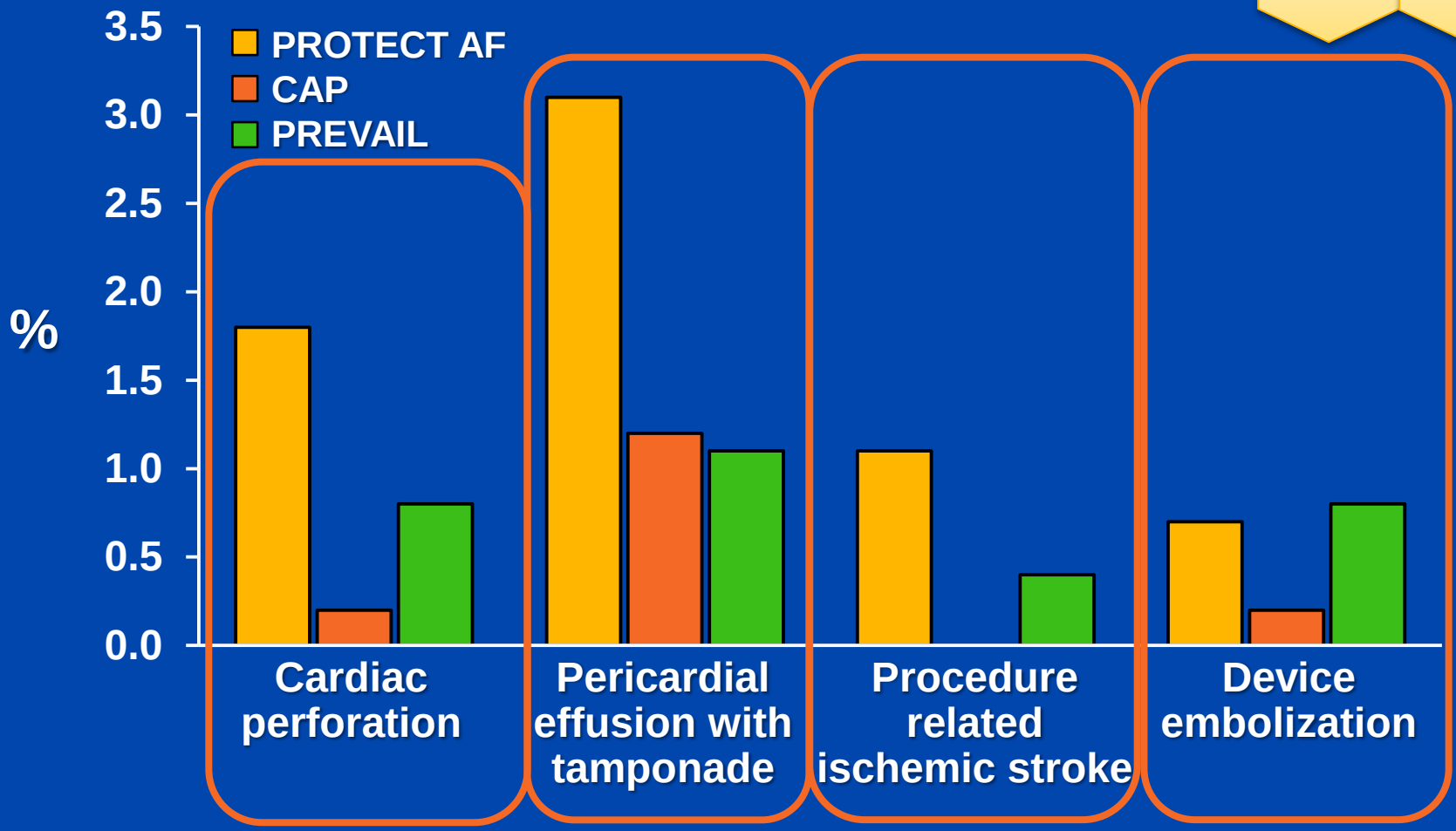
Trends in Key Procedural Safety Events Across Trials





* Overall embolization rate across studies is 0.5%

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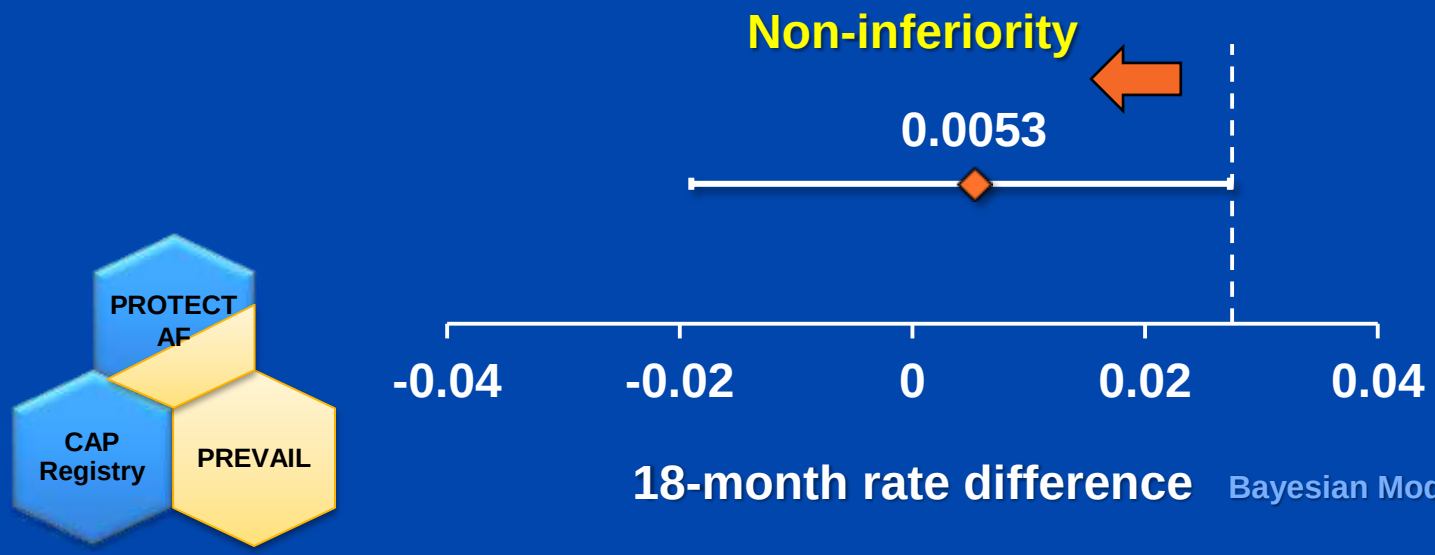
PREVAIL: Mechanism-of-Action Endpoint Results

Event rate		Rate difference (95% CrI)	Non-inferiority	
WATCHMAN	Control		Rate difference criterion	Posterior probability
0.0253	0.0200	0.0053 (-0.0190, 0.0273)	95% CrI Upper Bound < 0.0275	0.976



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ASAP Trial

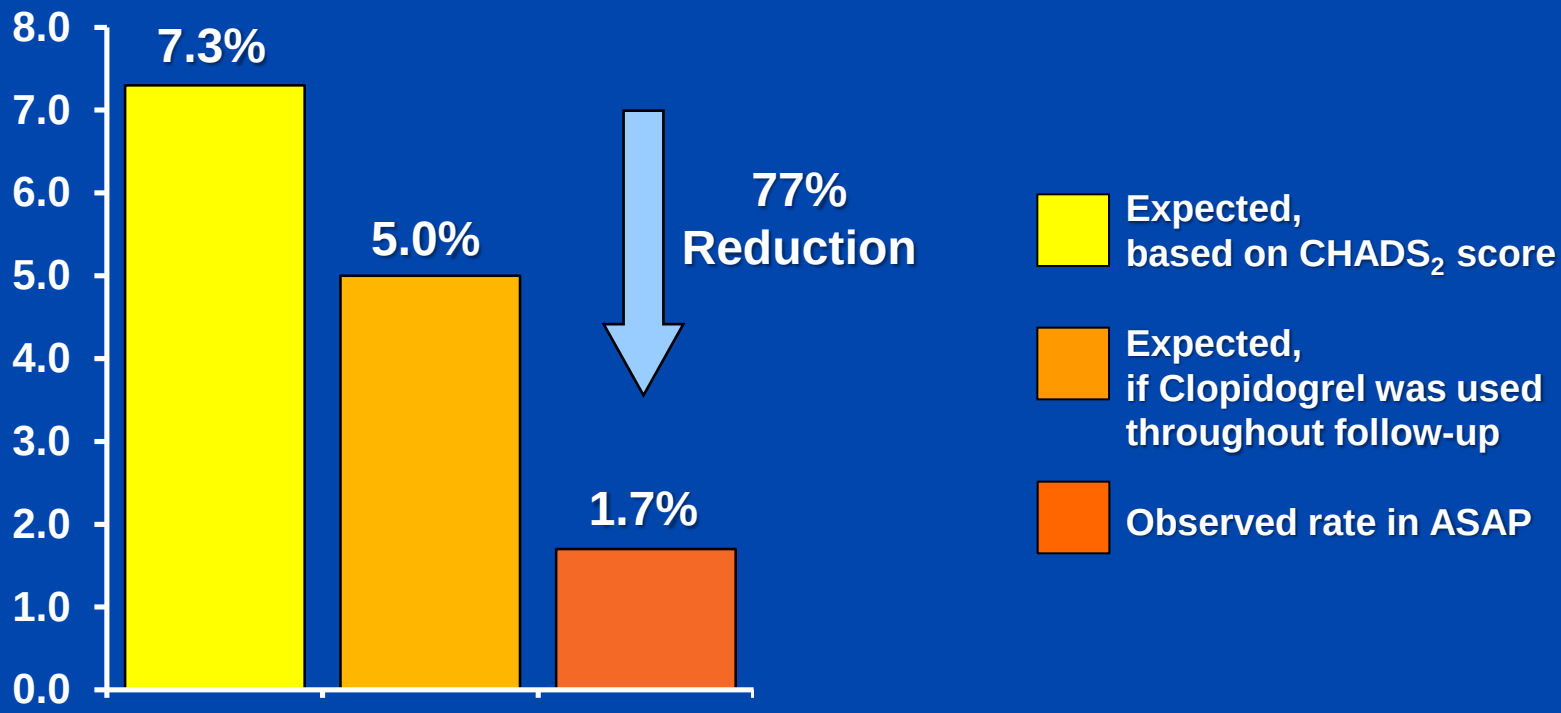
- Multicenter prospective registry
- 150 patients with nonvalvular atrial fibrillation and $CHADS_2$ ≥1, ineligible for warfarin
- Watchman Device without warfarin
- Primary endpoint of ischemic stroke, hemorrhagic stroke, systemic embolism and CV/unexplained death

MAYO CLINIC

Reddy V et al: JACC 2013
doi:10.1016/j.jacc.2013.03.035

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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ASAP Trial
Conclusions

- **LAA closure with the Watchman device can be safely performed without a warfarin transition, and is a reasonable alternative to consider for patients at high risk for stroke but with contraindications to systemic oral anticoagulation.**

Reddy V et al: JACC 2013
doi:10.1016/j.jacc.2013.03.035

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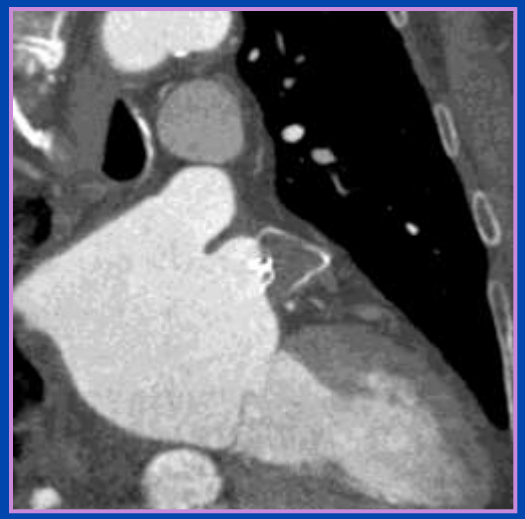
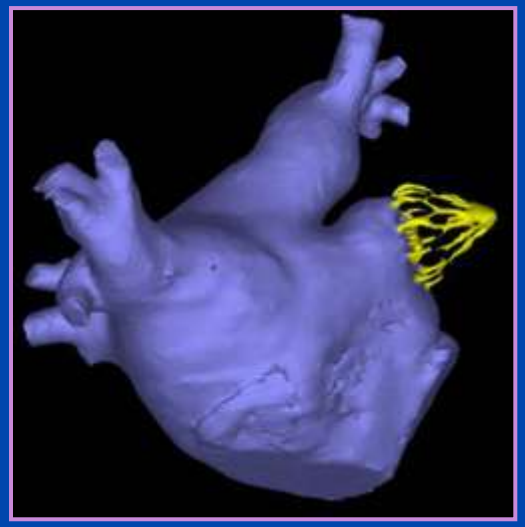
Stroke and Atrial Fibrillation
Alternative to Warfarin or NOACS





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

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XARELTO® DOSING SUMMARY

Reduce stroke risk in NONVALVULAR AF	 **20 mg ONCE DAILY**	**Patients with CrCl >50 mL/min:** with the evening meal
	▲ OR ▼	
	 **15 mg ONCE DAILY**	**Patients with CrCl 15 to 50 mL/min:** with the evening meal
Treatment of DVT and PE	 **15 mg TWICE DAILY**	with food for first 21 days
	▼ ON DAY 22 TRANSITION TO ▼	
	 **20 mg ONCE DAILY**	with food, at approximately the same time each day for remaining treatment
Reduce risk of recurrent DVT and PE	 **20 mg ONCE DAILY**	with food, at approximately the same time each day
Prophylaxis of DVT which may lead to PE after KNEE or HIP replacement surgery	 **10 mg ONCE DAILY**	**KNEE: 12 days** **HIP: 35 days** The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established

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Standard of Care to Prevent Strokes in AF Patients

- Warfarin
- Novel oral anticoagulants (NOACs)
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban
- All increase risk of bleeding

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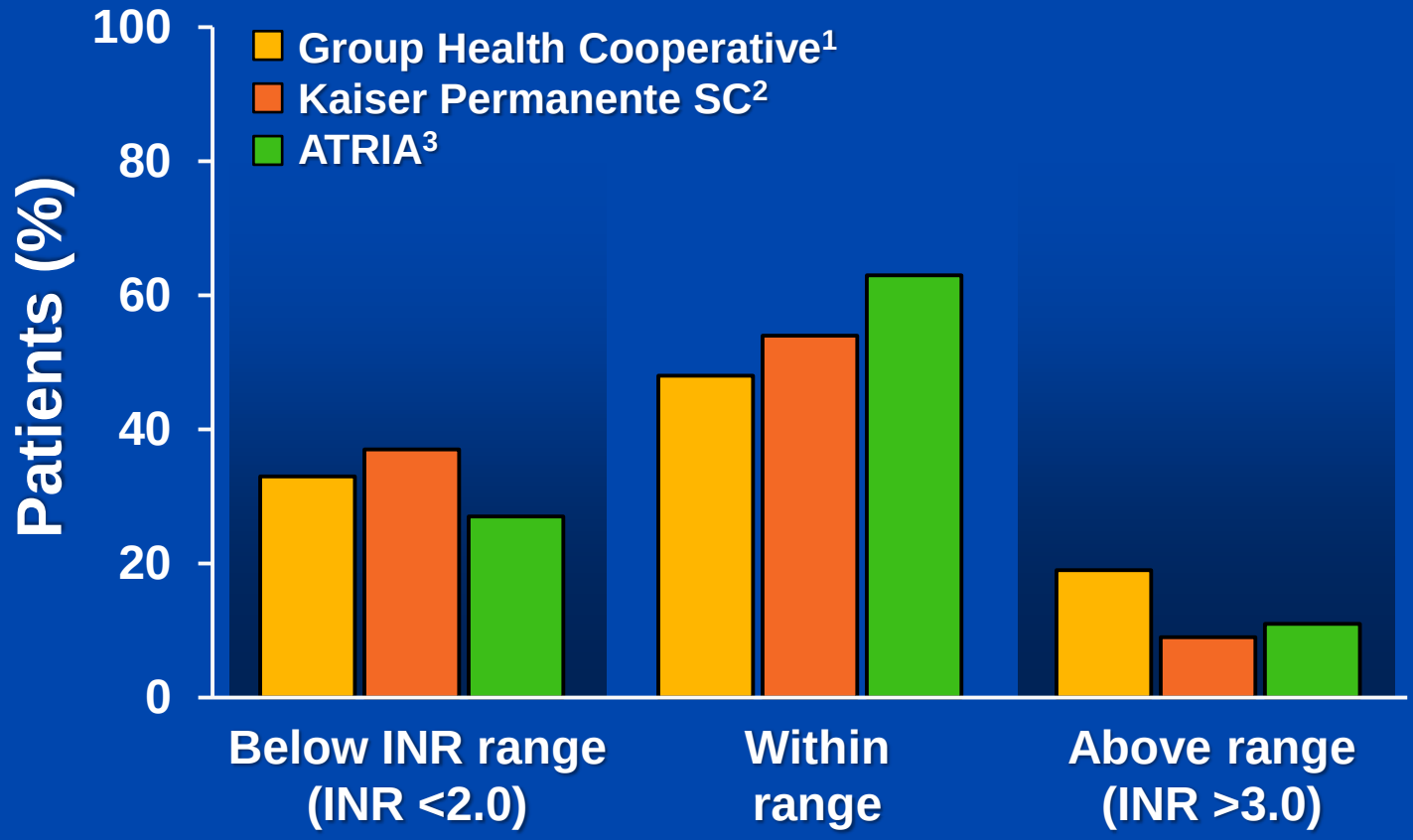
INR Control is Difficult With Warfarin Treatment and Impacts Risk



1. Glazer NL: Arch Intern Med, 2007
2. Shen AY: J Am Coll Cardiol, 2007
3. Go AS: JAMA, 2003

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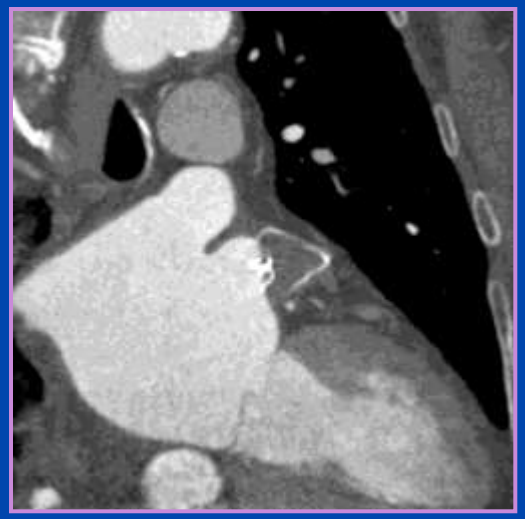
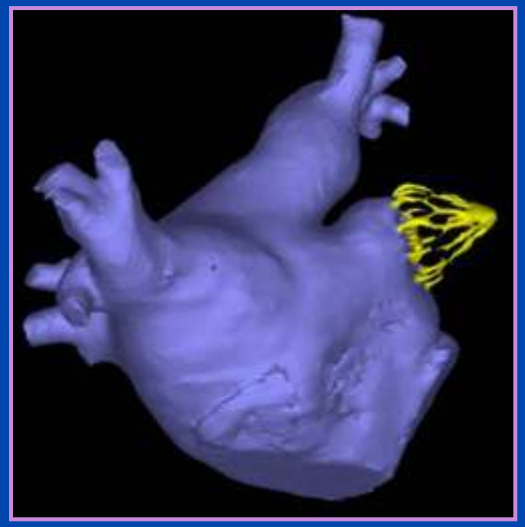
Stroke and Atrial Fibrillation
Alternative to Warfarin or NOACS





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

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“Nancy always had thick ankles, but no one really noticed.”

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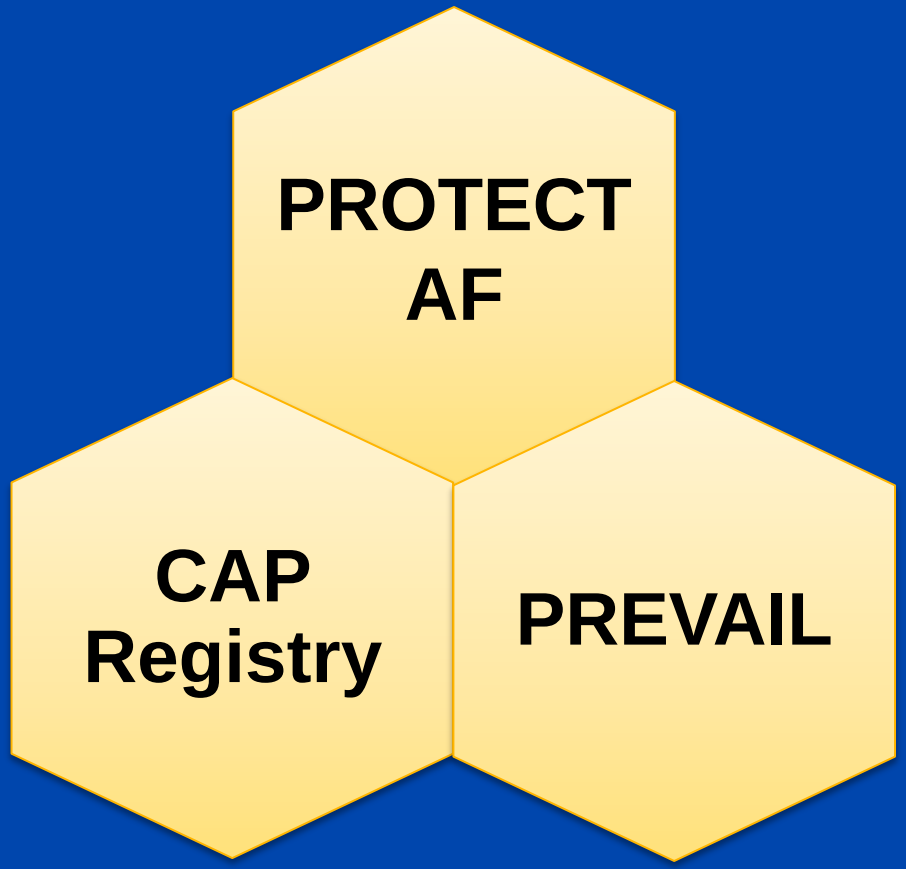
Totality of Data Support Safety and Efficacy of WATCHMAN



- ~2000 clinical patients
- ~4900 patient-years of follow-up
- Approved in 55 countries
- ~ 5,000 commercial implants

MAYO CLINIC

Anticoagulant Therapy Carries Risk of Intracerebral Hemorrhage

- More disabling and more often fatal than ischemic stroke[1]
- Impacts physician prescribing behavior[2] and patient adherence to therapy[3]

1. Broderick J: Circulation, 2007
2. Hylek EM: Stroke, 2006
3. Ghate SR: Circulation, 2013

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Novel Oral Anticoagulants Discontinuation and Bleeding Rates

Treatment	Discontinuation rate in study (%)	Major bleeding (rate/year) (%)
Dabigatran[1] (150 mg)	21	3.1
Rivaroxaban[2]	24	3.6
Apixaban[3]	22	2.1

1. Connolly SJ: N Engl J Med, 2009
2. Patel MR: N Engl J Med, 2011
3. Granger CB: N Engl J Med, 2011

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FDA Executive Summary: Primary Concerns

Patient Population

- Enrollment of $CHADS_2$=1 patients, for whom aspirin could have been used

Efficacy

- Concomitant use of clopidogrel therapy

Safety

- Serious peri-procedural adverse events

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Warfarin Time in Therapeutic Range (TTR) for Control Groups

Study	Warfarin Control Group Mean TTR (%)
PROTECT AF	**70**
PREVAIL	**68**
RE-LY[1] (Dabigatran)	**64**
ARISTOTLE[2] (Apixaban)	**62**
ROCKET AF[3] (Rivaroxaban)	**55**

1. Connolly SJ et al: NEJM, 2009
2. Granger CB et al: NEJM, 2011
3. Patel MR et al: NEJM, 2011

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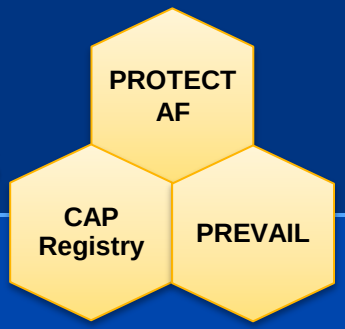
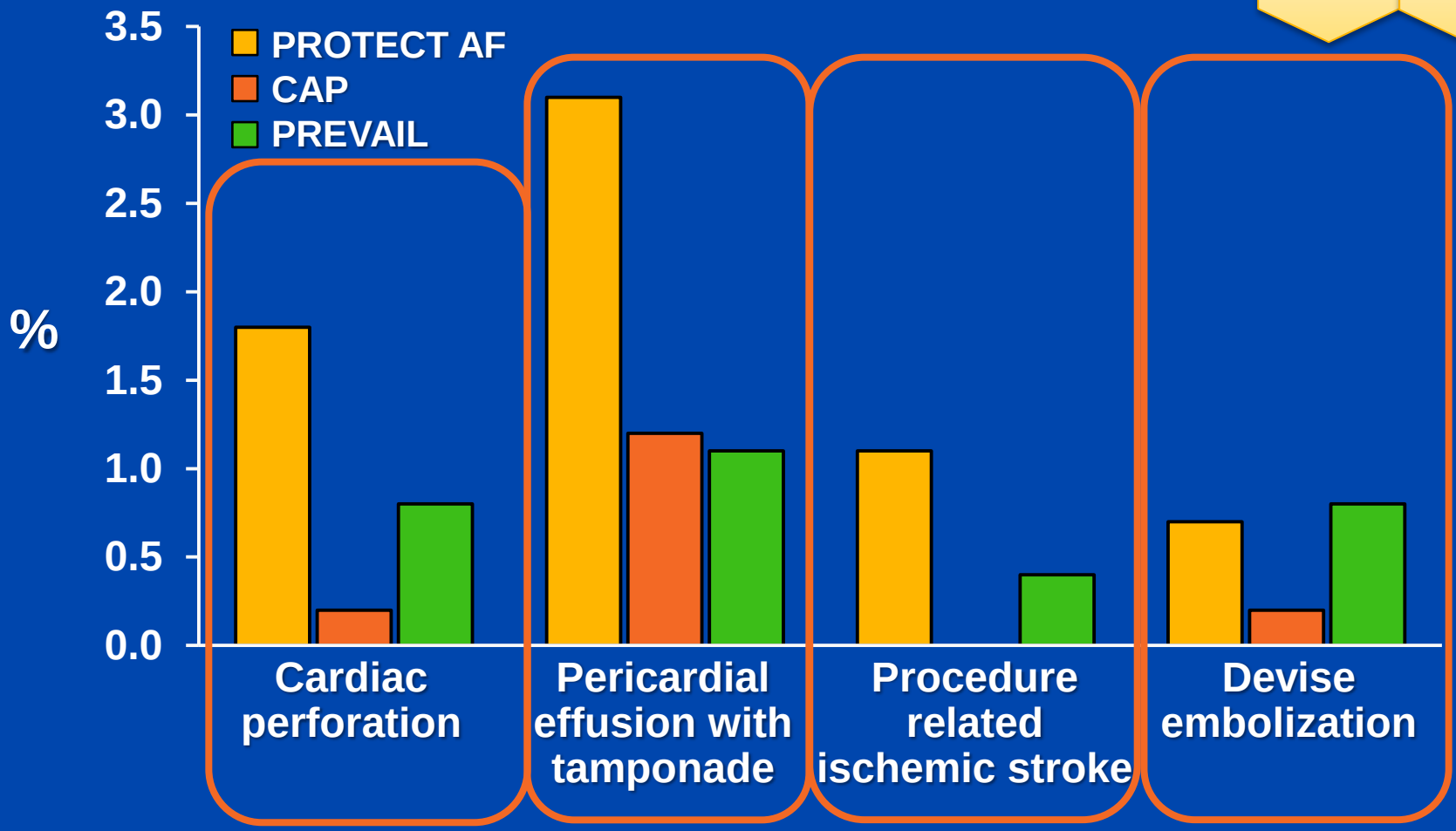
Trends in Key Procedural Safety Events Across Trials





* Overall embolization rate across studies is 0.5%

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Not all Patients are Candidates for Referral to WATCHMAN Therapy

Patients should not be referred if

- **Patient is already doing well or is likely to do well on anticoagulation**
- **Upfront risk of implant outweighs long-term risk of excessive bleeding**

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Fundamental Treatment Dilemma: Stroke and Bleeding Risks Overlap

$CHADS_2$ Risk Criteria

Risk Factor	Score
Prior stroke or TIA	2
Age >75	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

HAS-BLED

Condition	Points
Hypertension	1
Abnormal liver and renal function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Age >65	1
Drugs or alcohol (1 point each)	1 or 2

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How Big is the Problem?

- AF is the most common arrhythmia
  - Affects more than 3 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
  - >90% of thrombus originates in the left atrial appendage
- Stroke is the #1 cause of long-term disability and the third leading cause of death in patients with AF

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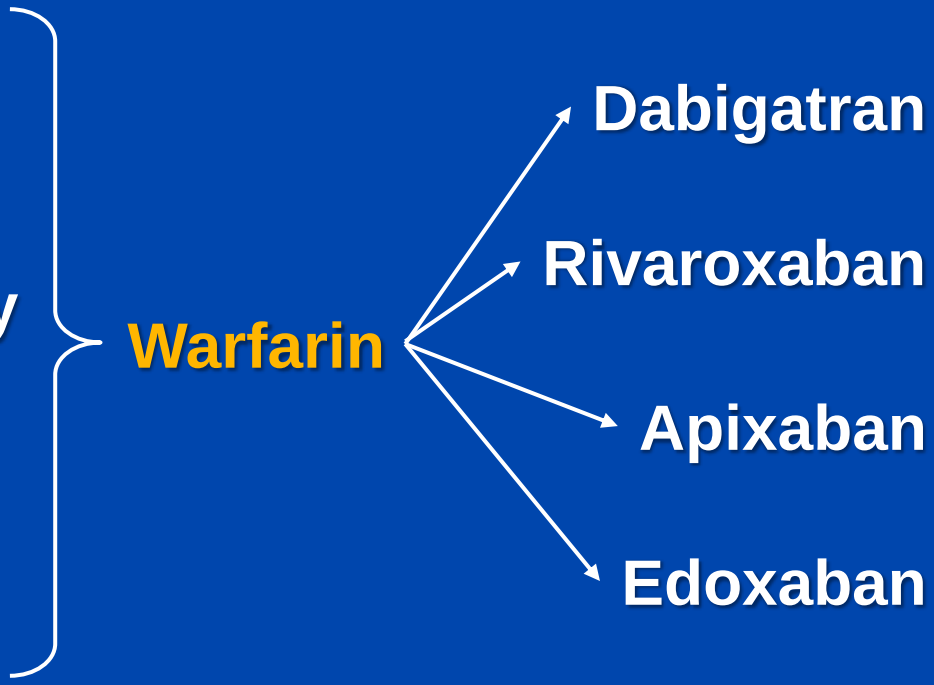
New OAC Strategies

- Underused
- Suboptimally applied
- Difficult pharmacology
- Inappropriately discontinued
- Bleeding concerns



Game changer?

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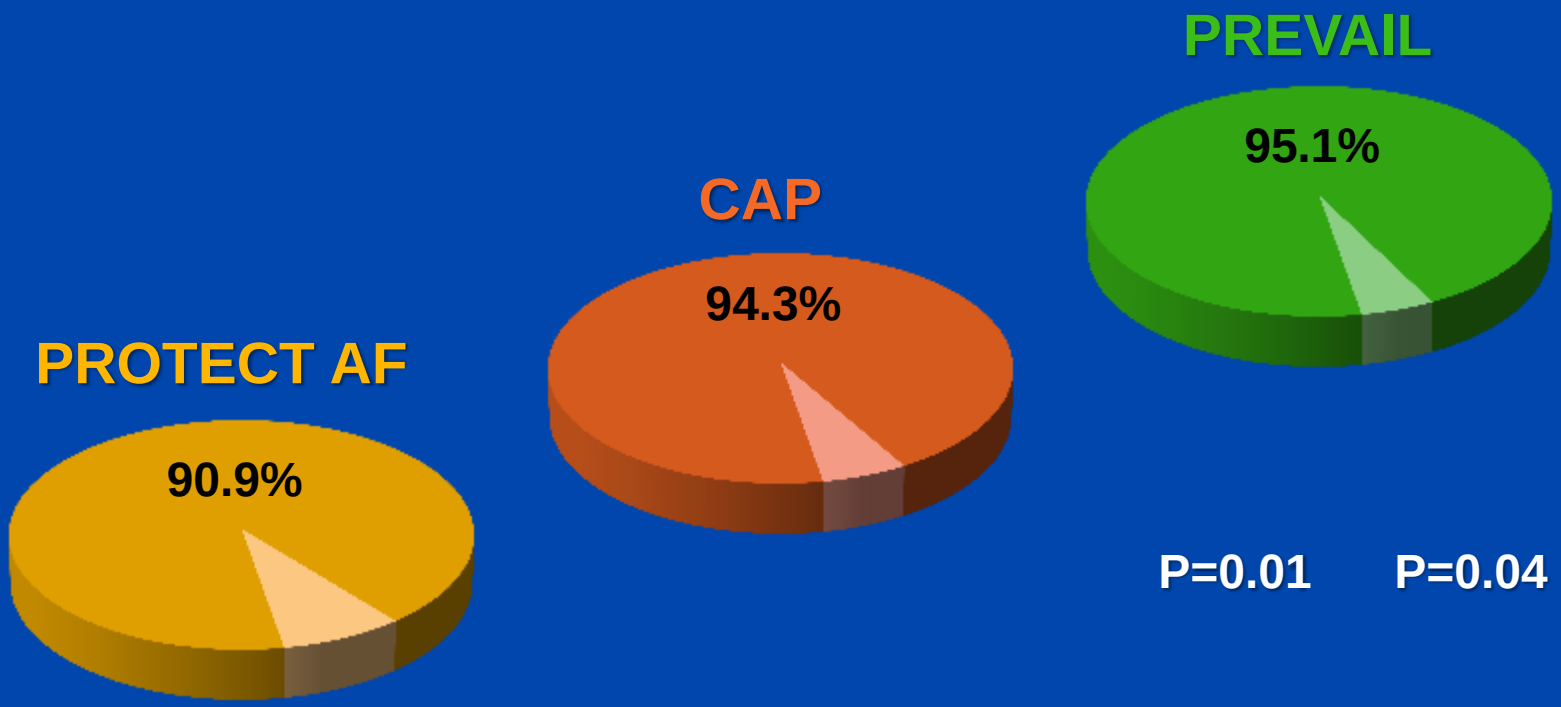
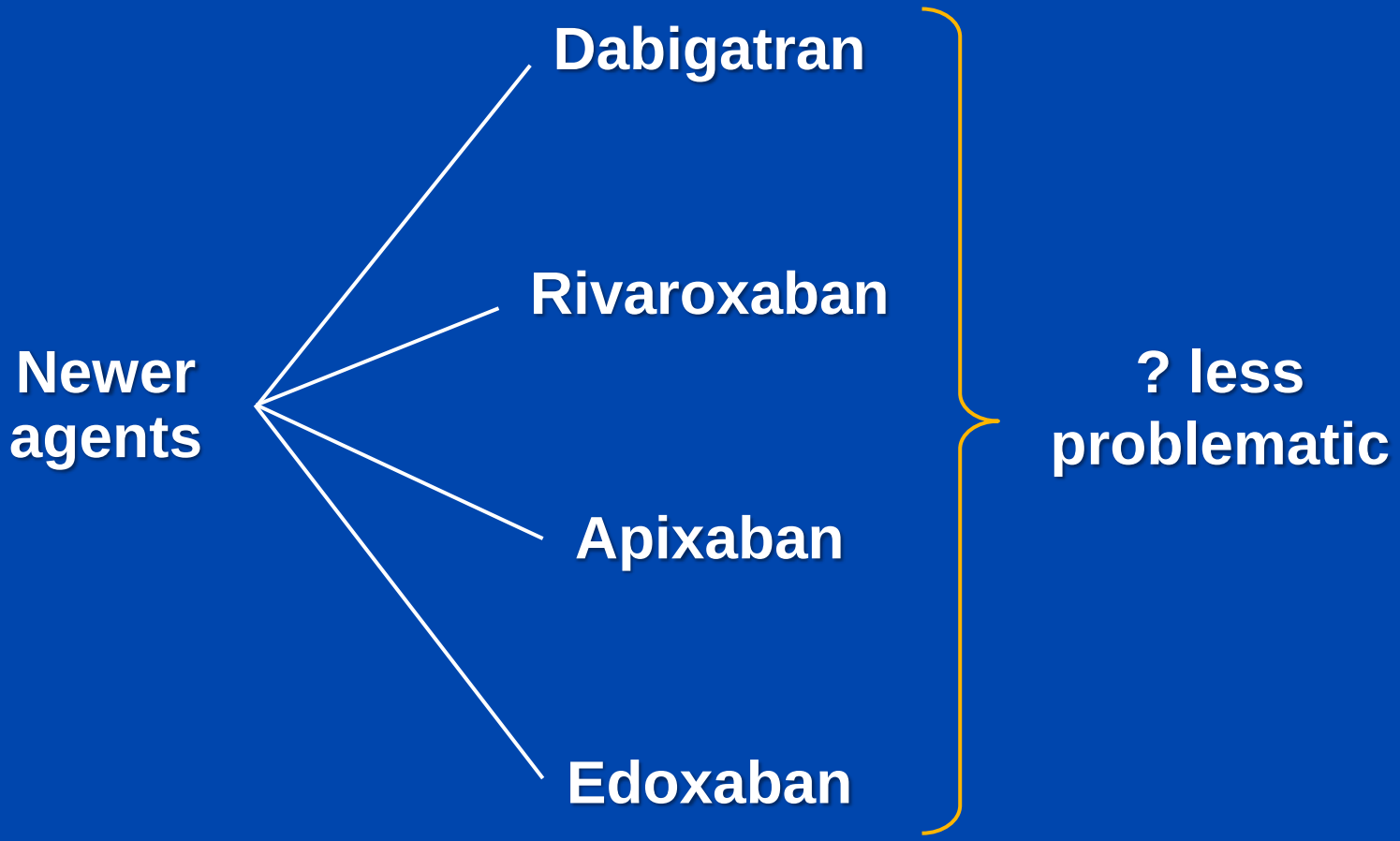
Procedure Implant Success



Implant success defined as deployment and release of the device into the left atrial appendage

MAYO CLINIC

Warfarin Problematic



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Antithrombotics vs Warfarin in Nonvalvular Atrial Fibrillation

	RELY	ROCKET AF	ARISTOTLE	ACTIVE W
Intervention	Dab 110 mg bid or 150 mg bid	Rivar 20 mg once/day	Apix 5 mg bid	Plavix 75 mg/day + aspirin 75-100 mg/day
# Pts.	18,113	14,264	18,201	6.706
Primary outcome	CVA/Emb	CVA/Emb	CVA/Emb	CVA, Emb, MI or CVD
F/U (yrs, median)	2.0	1.9	1.8	1.3
Age (yrs, median)	71.5	73	70	70
$CHADS_2$ score (mean)	2.1	3.5	2.1	2.0

MAYO CLINIC

Danelich et al: Pharmacotherapy 33:422-446, 2013

Antithrombotics vs Warfarin in Nonvalvular Atrial Fibrillation

Efficacy Results	RELY	ROCKET AF	ARISTOTLE	ACTIVE W
Primary outcome	110 mg: 1.53 vs 1.69 (p<0.001 NINF), p=0.34 (superior) 150 mg; 1.11 vs 1.69 (p<0.001 NINF)	Per protocol: 1.7 vs 2.2 (p<0.001 for NINF), as treated: 1.7 vs 2.2 (p=0.02 for superior), Intent-to-treat: 2.1 vs 2.4 (p<0.001 for NINF; p=0.12 for superior)	Intent-to-treat: 1.27 vs 1.60 (p=0.01 for superior)	Intent-to-treat: 5.60 vs 3.93 (p=0.0003 for superior)
Ischemic CVA	110 mg: 1.34 vs 1.2 (p=0.35) 150 mg: 0.92 vs 1.20 (p=0.03)	1.34 vs 1.42 (p=0.581)	1.19 vs 1.51 (p=0.01)	2.15 vs 1.00 (p<0.0001)
Hemorrhagic CVA	110 mg: 0.12 vs 0.38 (p<0.001) 150 mg: 0.10 vs 0.38 (p<0.001)	0.26 vs 0.44 (p=0.024)	0.24 vs 0.47 (p<0.001)	1.12 vs 0.36 (p=0.036)
INR TTR, % (mean)	64	55	66	64

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Danelich et al: Pharmacotherapy 33:422-446, 2013

Antithrombotics vs Warfarin in Nonvalvular Atrial Fibrillation

Safety Results	RELY	ROCKET AF	ARISTOTLE	ACTIVE W
Major bleeding	110 mg: 2.71 vs 3.36 (p=0.003) 150 mg: 3.11 vs 3.36 (p=0.31)	3.6 vs 3.4 (p=0.58)	2.13 vs 3.09 (p<0.001)	2.42 vs 2.21 (p=0.53)
Intracranial hemorrhage	110 mg: 0.23 vs 0.74 (p<0.001) 150 mg: 0.30 vs 0.74 (p<0.001)	0.5 vs 0.7 (p=0.02)	0.33 vs 0.80 (p<0.001)	0.005 vs 0.003 (p=0.08)
GI bleeding	110 mg: 1.12 vs 1.02 (p=0.43) 150 mg: 1.51 vs 1.02 (p<0.001)	3.2 vs 2.2 (p<0.001)	0.76 vs 0.86 (p=0.37)	Not reported

MAYO CLINIC

Danelich et al: Pharmacotherapy 33:422-446, 2013

Stroke Prophylaxis

- Cornerstone of therapy: OAC with warfarin
  - 60-70% risk reduction vs placebo
  - 30-40% risk reduction vs antiplatelet Rx/ASA
- Antiplatelet therapy: 22% risk reduction vs placebo
- ACTIVE W: Warfarin vs DAPT; 42% RRR
- ASA only: 19% risk reduction vs placebo (P=NS)
- Older patients (>65): Absolute benefit of OAC increases while effect of ASA declines

Warfarin "preferred therapy"

MAYO CLINIC

Hart: Ann Int Med, 2007
Connoly: Lancet, 2006

Conclusions

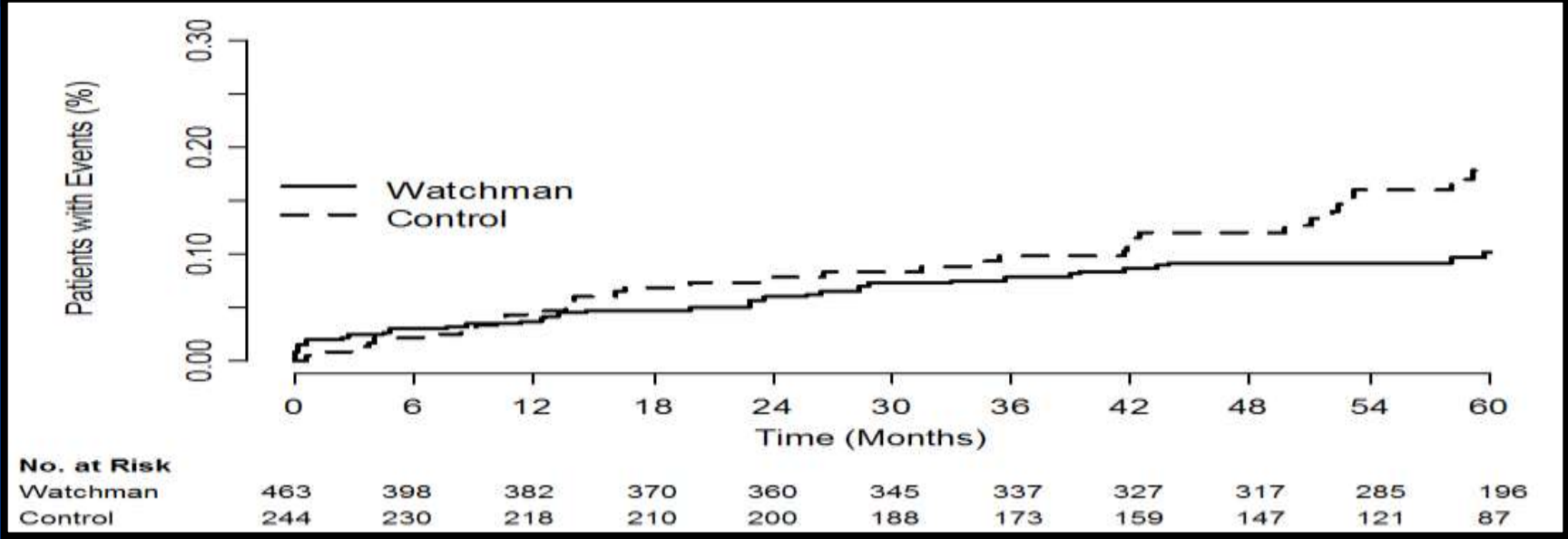
- OAC with warfarin effective → problematic
  - Underused leaving thousands unprotected
- New OAC agents show greater efficacy and safety vs warfarin
  - Stroke risk vs warfarin

- Complexities, cost and current state of CDS tools make it unlikely to move the bar significantly (vs warfarin)
- Effectiveness of any OAC will always be mitigated by risks of major bleeding and hemorrhagic stroke
  - Tools to predict that risk and "tailor" therapy inadequate at best
- Fear of bleeding

MAYO CLINIC

PROTECT-AF:
Primary Efficacy Endpoint

Event	Watchman Group (n = 463) Events/ Patient-Years	Watchman Group (n = 463) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Warfarin Group (n = 244) Events/ Patient-Years	Warfarin Group (n = 244) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	Posterior Probabilities Non-inferiority	Posterior Probabilities Superiority
Primary Efficacy Endpoint	39/1720.2	2.3 (1.7, 3.2)	34/900.8	3.8 (2.5, 4.9)	0.60 (0.41, 1.05)	>0.999	0.960



Reddy, V et al. HRS 2013

MAYO CLINIC

PROTECT-AF:
Primary Efficacy Endpoint

Event	Watchman Group (n = 463)		Warfarin Group (n = 244)			Posterior Probabilities	
	Events/ Patient-Years	Observed Rate (Events per 100 Patient-Years) (95% CrI)	Events/ Patient-Years	Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	Non-inferiority	Superiority
Primary Efficacy Endpoint	39/1720.2	2.3 (1.7, 3.2)	34/900.8	3.8 (2.5, 4.9)	0.60 (0.41, 1.05)	>0.999	0.960
Stroke	26/1720.7	1.5 (1.0, 2.2)	20/900.9	2.2 (1.3, 3.1)	0.68 (0.42, 1.37)	0.999	0.825
Ischemic Stroke	24/1720.8	1.4 (0.9, 2.1)	10/904.2	1.1 (0.5, 1.7)	1.26 (0.72, 3.28)	0.780	0.147
Hemorrhagic Stroke	3/1774.2	0.2 (0.0,0.4)	10/916.2	1.1 (0.5, 1.8)	0.15 (0.03, 0.49)	>0.999	0.999
Systemic Embolization	3/1773.6	0.2 (0.0, 0.4)	0/919.5	0.0	NA	-	-
Cardiovascular Death	17/1774.3	1.0 (0.6, 1.5)	22/919.4	2.4 (1.4, 3.4)	0.40 (0.23, 0.82)	>0.999	0.995

Reddy, V et al. HRS 2013

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Hemorrhagic Stroke:
Comparison to Other Major Stroke Trials

Clinical Trial	$CHADS_2$ Score (mean ± S.D.)	TTR	Event rate (per 100 pt-yrs)	95% CI
PROTECT AF (Warfarin Group)	2.3 ± 1.2	70%	1.1	(0.6, 2.0)
RELY	2.1 ± 1.1	64%	0.4	(0.3, 0.5)
ROCKET AF	3.5 ± 0.95	55%	0.4	(0.3, 0.6)
ARISTOTLE	2.1 ± 1.1	66%	0.5	(0.4, 0.6)
ACTIVE W	2.0 ± 1.1	64%	0.4	(0.2, 0.6)
SPORTIF V	N.R.*	68%	0.1	(0.0, 0.2)
SPORTIF III	N.R.	66%	0.4	(0.3, 0.9)
SPAF III	N.R.	61%	0.5	(0.1, 1.5)
SPAF II > 75 years	N.R.	—	1.8	(0.6, 3.5)

*** N.R. = Not reported**

Reddy, V et al. HRS 2013

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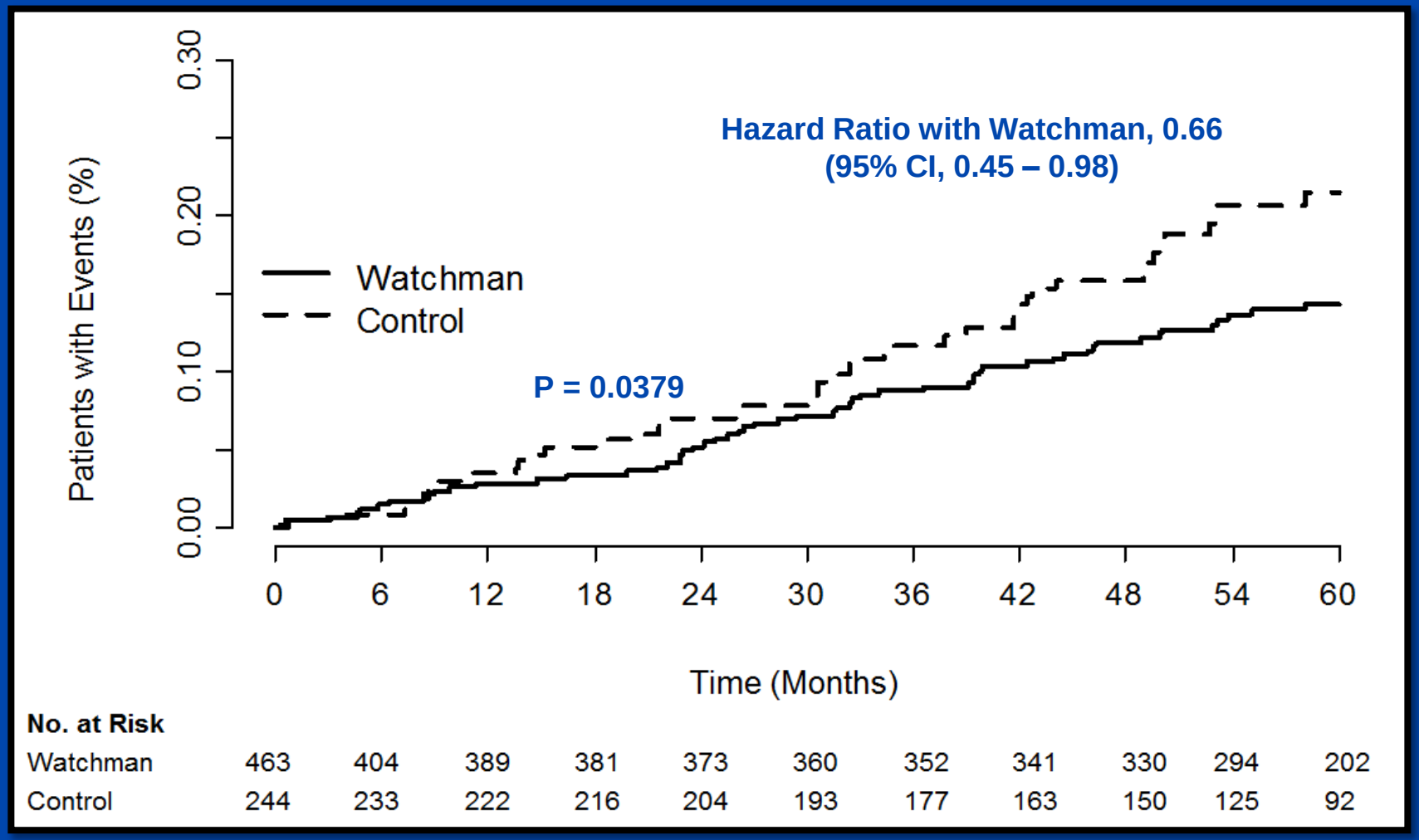
Intention-to-Treat:
All-Cause Mortality



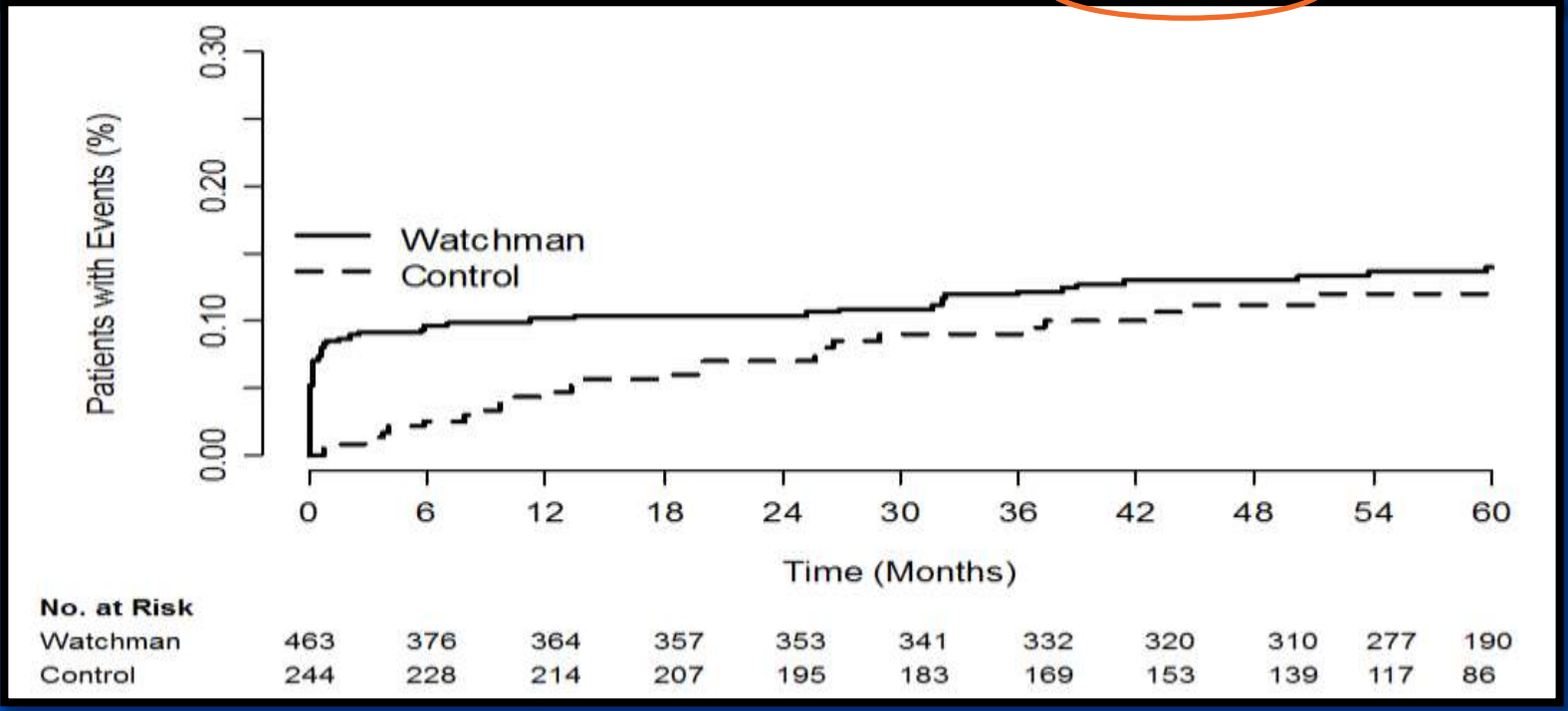
No. at Risk											
Watchman	463	404	389	381	373	360	352	341	330	294	202
Control	244	233	222	216	204	193	177	163	150	125	92

Reddy, V et al. HRS 2013

MAYO CLINIC

PROTECT AF:
Primary Safety Endpoint

Event	Watchman Group (n = 463) Events/ Patient-Years	Watchman Group (n = 463) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Warfarin Group (n = 244) Events/ Patient-Years	Warfarin Group (n = 244) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	Posterior Probabilities Non-inferiority	Posterior Probabilities Superiority
Primary Safety Endpoint	60/1666.2	3.6 (2.8, 4.6)	27/878.2	3.1 (2.0, 4.3)	1.17 (0.78, 1.95)	0.980	0.196



Reddy, V et al. HRS 2013

PREVAIL Trial
Primary Endpoints

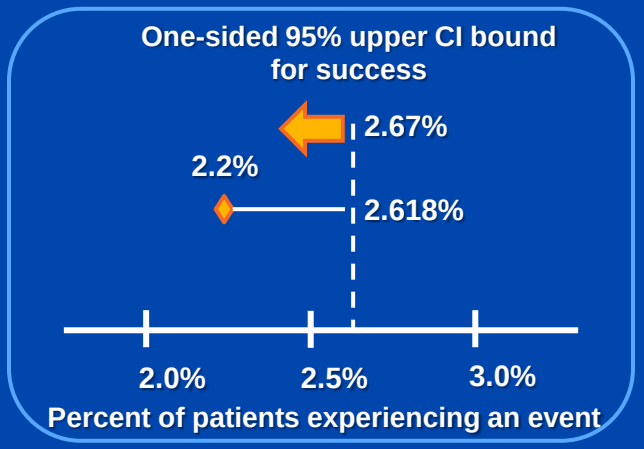
- **Early Safety:** Acute (7-day) occurrence of death, ischemic stroke, systemic embolism and procedure or device related complications requiring major cardiovascular or endovascular intervention
  - (Time-point = 7 days post randomization)
- **Primary Efficacy:** Comparison of composite of stroke, systemic embolism, and cardiovascular/unexplained death
  - (Time-point = 18 months)
- **Late-Ischemic Efficacy:** Comparison of ischemic stroke or systemic embolism occurring >7 days post randomization
  - (Time-point = 18 months)

Holmes, DR et al. JACC. In Press

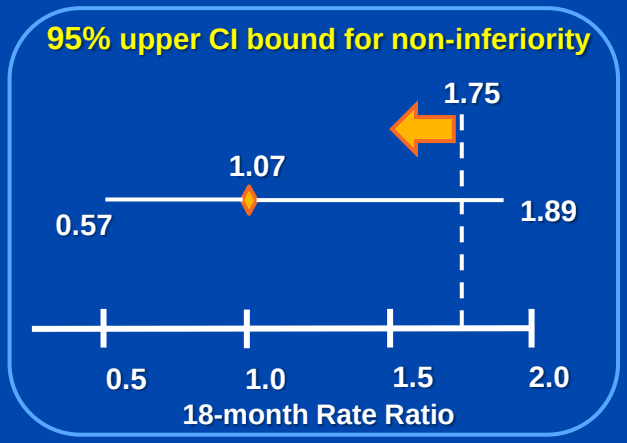
MAYO CLINIC

PREVAIL Trial: Co-Primary Endpoints

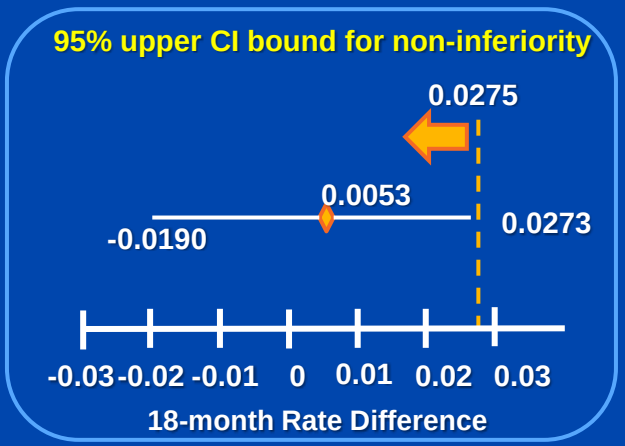
Early Safety



Primary Efficacy



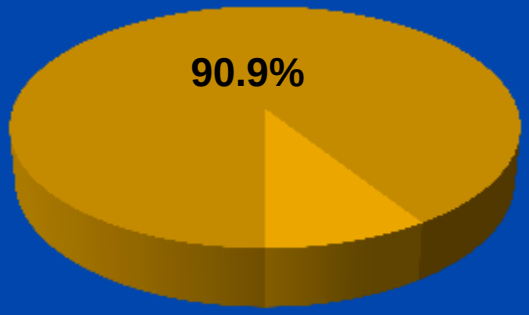
Late Ischemic Efficacy



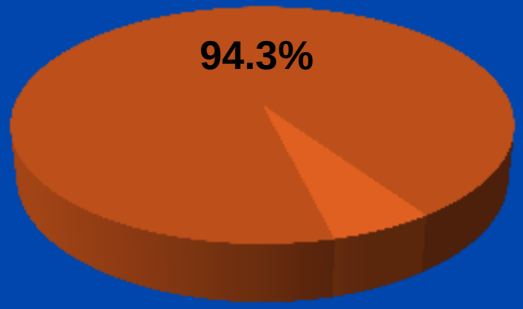
Holmes, DR et al. JACC. In Press

Procedure Implant Success

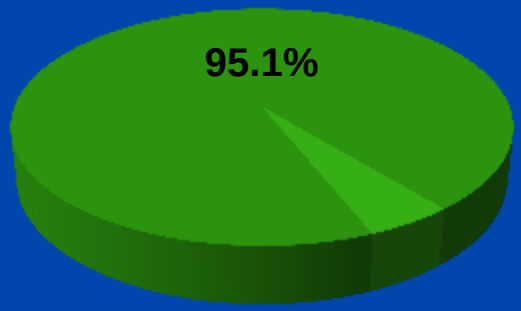
PROTECT AF
Implant success



CAP
Implant success



PREVAIL
Implant success



p = 0.04

Warfarin Discontinuation

Study	45-Day	6-Month	12-Month
PROTECT AF	86.6%	92.2%	93.2%
PREVAIL	92.2%	98.3%	99.3%

PROTECT-AF and CAP: Reddy, VY et al. *Circulation*. 2011;123:417-424; PREVAIL: Holmes, DR et al. JACC *In Press*

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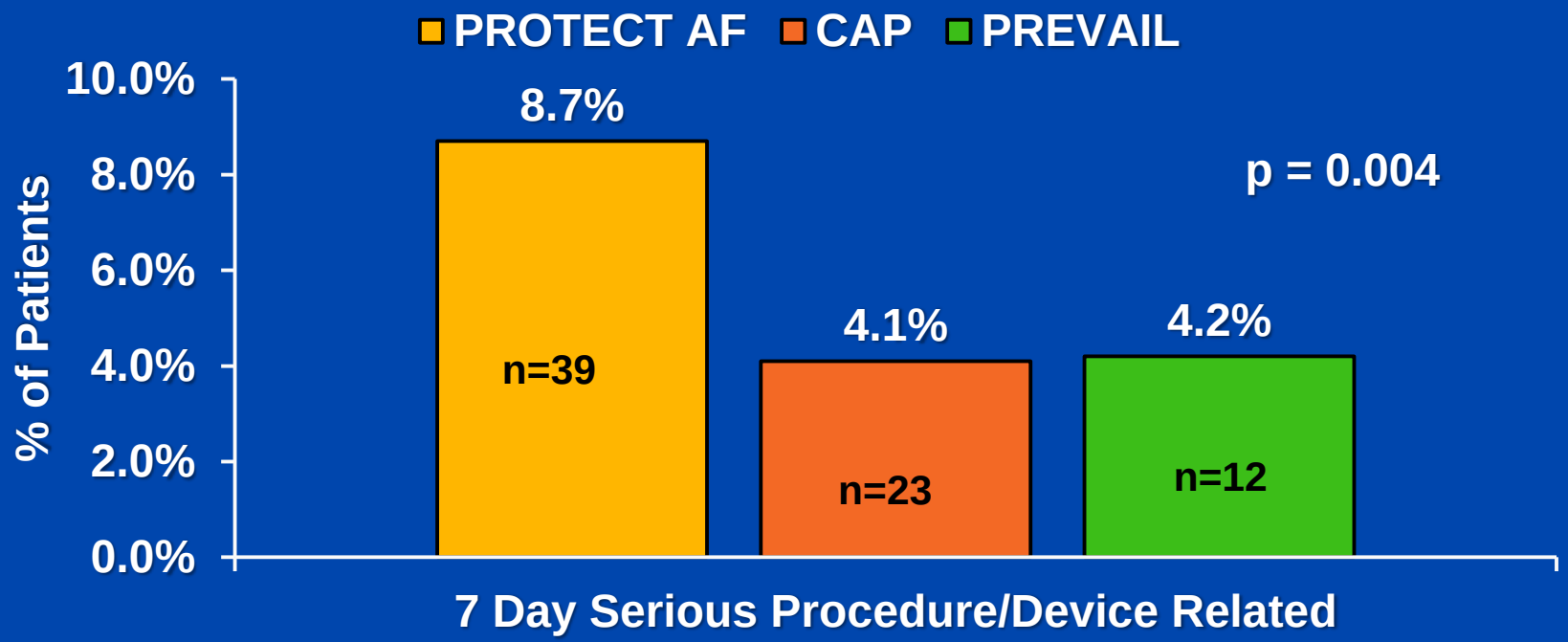
In the US, WATCHMAN is an investigational device, limited by applicable law to investigational use only and not available for sale. CE Mark 2005

Vascular Complications

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



No procedure-related deaths reported in any of the trials

PROTECT-AF and CAP: Reddy, VY et al. *Circulation*. 2011;123:417-424; PREVAIL: Holmes, DR et al. JACC *In Press*

[1]Includes observed PE not necessitating intervention, AV fistula, major bleeding requiring transfusion, pseudoaneurysm, hematoma and groin bleeding

PREVAIL
Control (Warfarin) Group Performance

- In spite of the high average $CHADS_2$ score of 2.6 in the control group, the observed rate of stroke in the PREVAIL Control group was lower than in other published warfarin studies
- PREVAIL control group rate = 0.7 (95% CI 0.1, 5.1)
  - Wide confidence bounds due to small number of patients with 18-months of follow-up

Trial	Control (Warfarin) Group Stroke, Systemic Embolism Rate (Per 100 PY)
PROTECT AF[1]	1.6
RE-LY (Dabigatran)[2]	1.7
ARISTOTLE (Apixaban)[3]	1.6
ROCKET AF (Rivaroxaban)[4]	2.2
PREVAIL[5]	**0.7**

[1]Ischemic stroke rate from Holmes et al. *Lancet* 2009; 374:534-42
[2]Connolly et al. *N Engl J Med* 2009; 361:1139-51
[3]Granger et al. *N Engl J Med* 2011; 365:981-92
[4]Patel et al. *N Engl J Med* 2011; 365:883-91
[5]PREVAIL: Holmes, DR et al. JACC *In Press*

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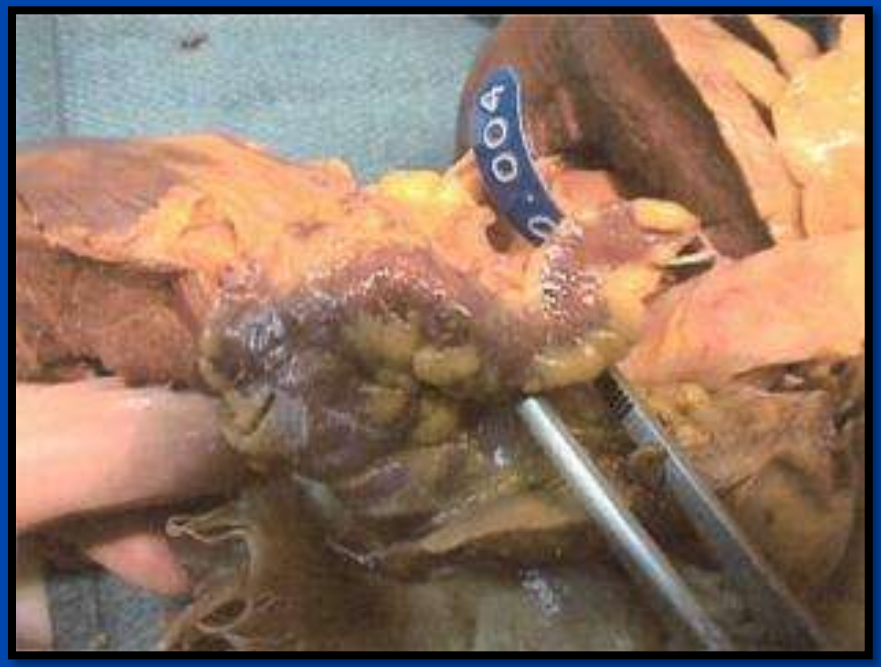
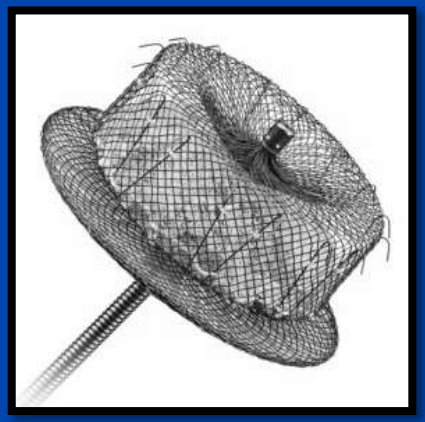
Future Predictions and Prospective
New and Next Generation Devices





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Future Predictions and Prospective
New New Oral Anti-Coagulants

The design and rationale for the Acute Medically Ill Venous Thromboembolism Prevention with Extended Duration Betrixaban (APEX) study ☆

Alexander T. Cohen, MD,[a] Robert Harrington, MD,[b] Samuel Z. Goldhaber, MD,[c] Russell Hull, MD,[d] C. Michael Gibson, MD,[c] Adrian F. Hernandez, MD, MHS,[c] Michael M. Kitt, MD,[f,g] and Todd J. Lorenz, MD[h]
London, United Kingdom

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

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Future Predictions and Prospective
Cost Effectiveness Research

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Clinical Therapeutics/Volume 36, Number 2, 2014

Cost-Effectiveness of Apixaban Versus Other New Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation☆

Gregory Y.H. Lip[1]; Thitima Kongnakorn[2]; Hemant Phatak[3]; Andreas Kuznik[4]; Tereza Lanitis[5]; Larry Z. Liu[6]; Uchenna Iloeje[7]; Luis Hernandez[8]; and Paul Dorian[9]

1142-108 - Cost Utility and Quality of Life Impact of Left Atrial Appendage Closure Compared to Warfarin for Stroke Prevention in Atrial Fibrillation

View session detail

ACC.14
63rd Annual Scientific Session & Expo

Author Block: Vivek Reddy, Ronald L. Akehurst, Stacey L. Amorosi, Shannon Armstrong, Colin Taggart, Steve Beard, Chris Knight, David Holmes, Boston Scientific, Natick, MA, USA

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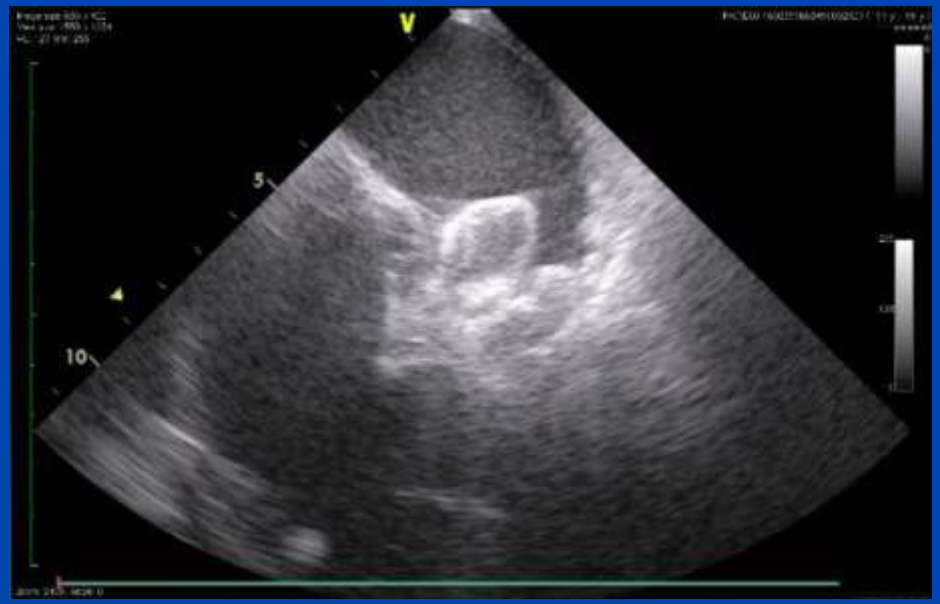
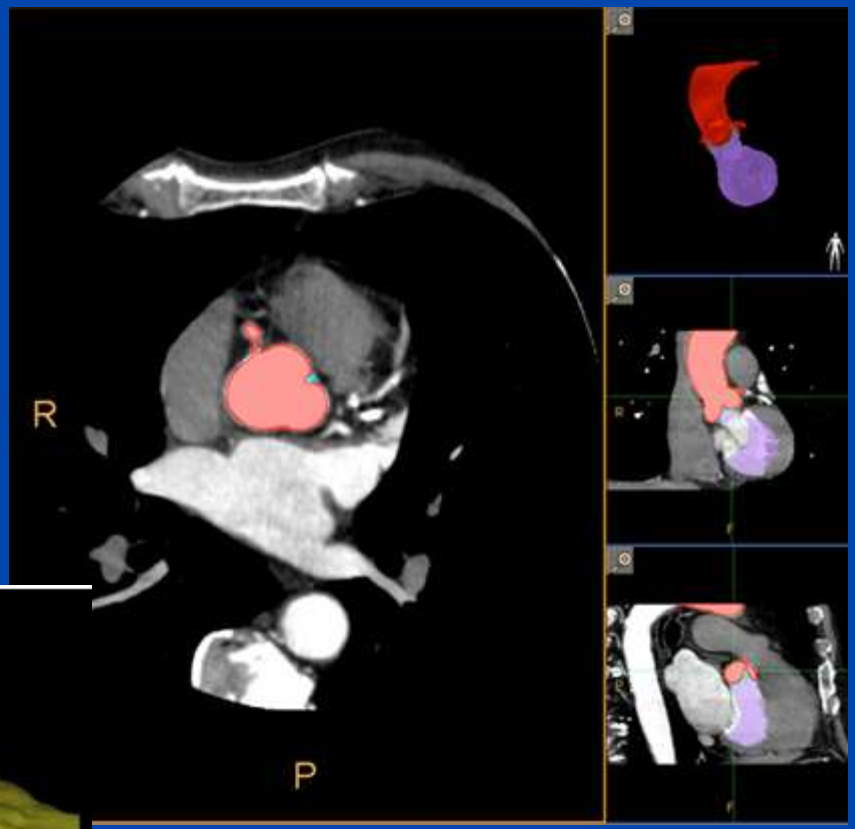
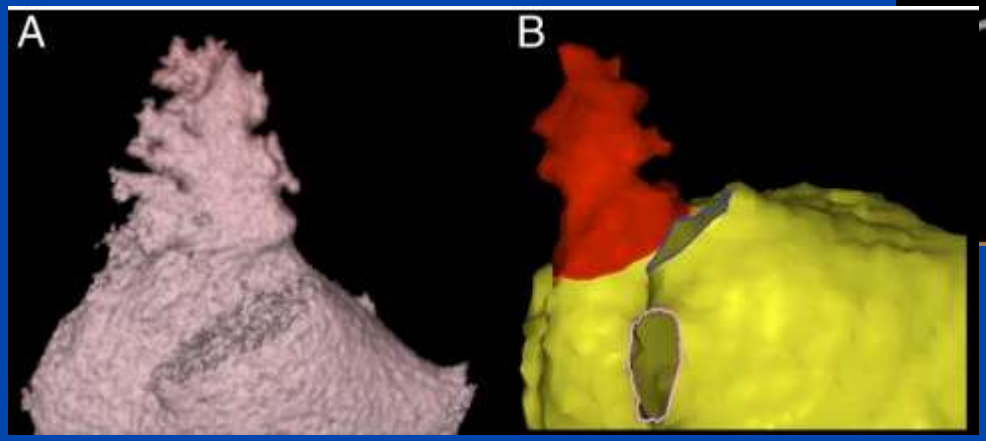
Future Predictions and Prospective Imaging







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Future Predictions and Prospective Guidelines

Accepted Manuscript

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

Craig T. January, MD, PhD, FACC L. Samuel Wann, MD, MACC, FAHA Joseph S. Alpert, MD, FACC, FAHA Hugh Calkins, MD, FACC, FAHA, FHRS Joseph C. Cleveland Jr., MD, FACC Joaquin E. Cigarroa, MD, FACC Jamie B. Conti, MD, FACC, FHRS Patrick T. Ellinor, MD, PhD, FAHA Michael D. Ezekowitz, MB, ChB, FACC, FAHA Michael E. Field, MD, FACC, FHRS Katherine T. Murray, MD, FACC, FAHA, FHRS Ralph L. Sacc
FHRS Patrick J. Tchou, MD,
Yancy, MD, FACC, FAHA

European Heart Journal (2013) **34**, 2094–2106
doi:10.1093/eurheartj/eht134

SPECIAL ARTICLE

EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary†

Hein Heidbuchel[1]*, Peter Verhamme[1], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

Risk of Triple Therapy

- AF linked to increased likelihood of vascular disease → ACS
- 82,000 patients follow-up 2.6 years
  - 3.7-fold increased risk triple therapy vs warfarin
  - 11.4% fatal or nonfatal major bleeds
  - OAC + DAPT 15.7%/patient-year
  - OAC + clopidogrel only 13.9%/patient-year

Sorensen: Lancet, 2009; Hansen: Arch Int Med, 2010

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