

Etiology of Stroke and the Pros and Cons of Device-Based LAA Closure

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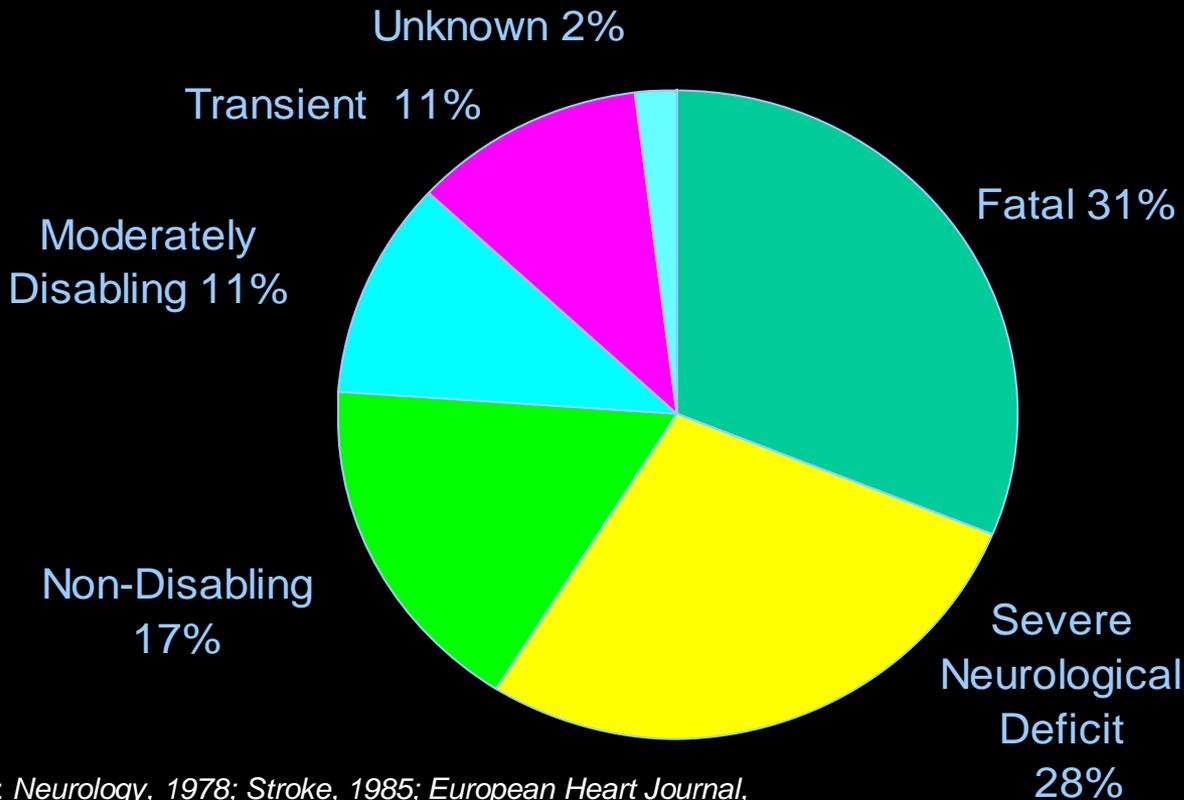
Disclosures

- Grant support:
 - Atritech Inc, Coherex Medical Inc, Sentreheart Inc
- I will be discussing the use of non-FDA approved or off-label use of investigational catheter-based devices.



AF-Related Stroke

- 500,000 strokes per year
- 15 – 20% of strokes/year are related to AF
- Functional Impact of AF-Related Stroke:



Sources: *Neurology*, 1978; *Stroke*, 1985; *European Heart Journal*, 1987; *Lancet*, 1987; *Fisher. Geriatrics*. 1979;34:59



Efficacy of Warfarin

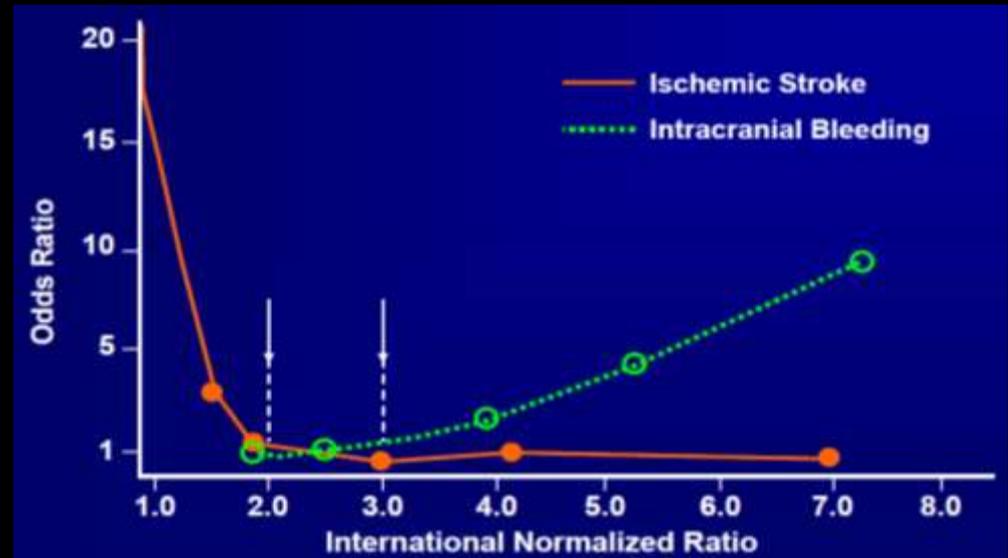
	No. of Patient-Events	years
AFASAK	27	811
BAATAF	15	922
CAFA	14	478
SPAF	23	508
SPINAF	29	972
Combined*	108	3691



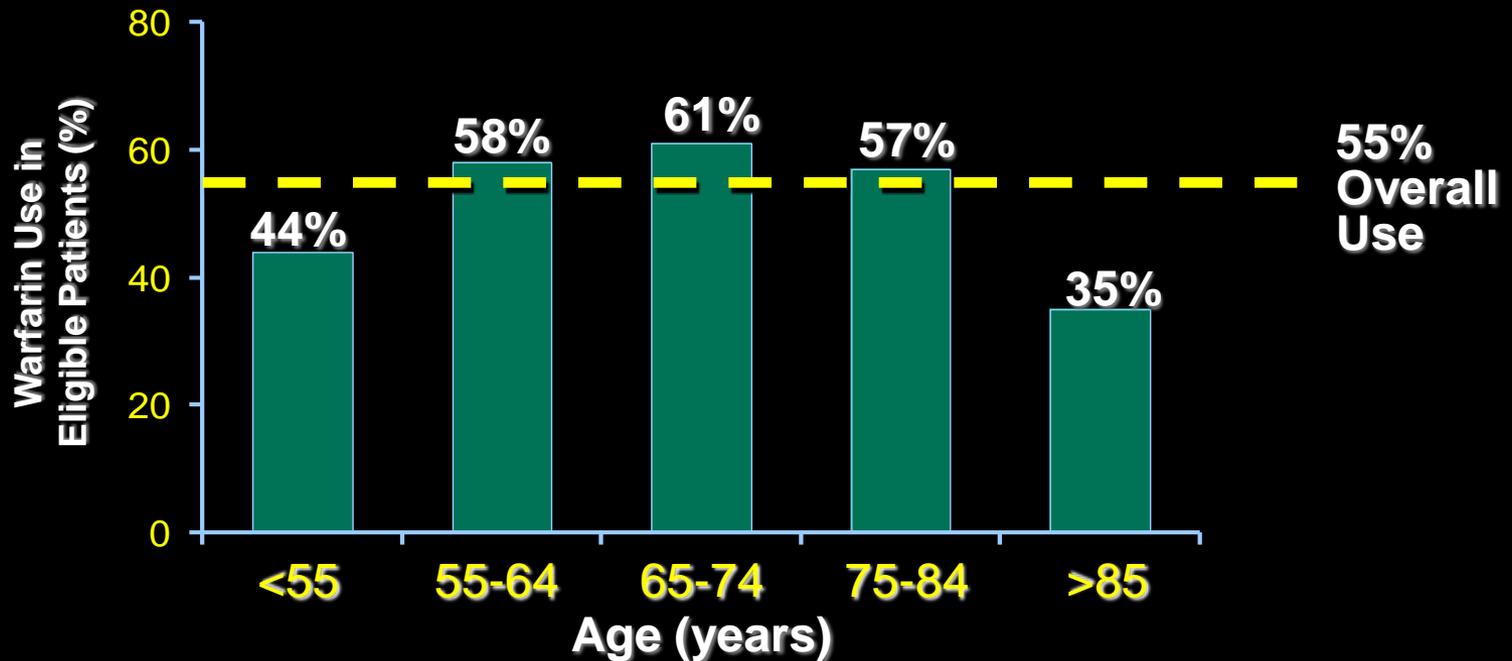
*Total risk reduction for all 5 studies combined is 69%

Difficulties with Warfarin Use

- Narrow therapeutic profile
 - Frequent blood draws
- Bleeding risk
 - Intracranial Hemorrhage
- Drug/Diet Interactions
- Physician Reluctance to prescribe to elderly patients
 - Risk of falling
 - Compliance issues



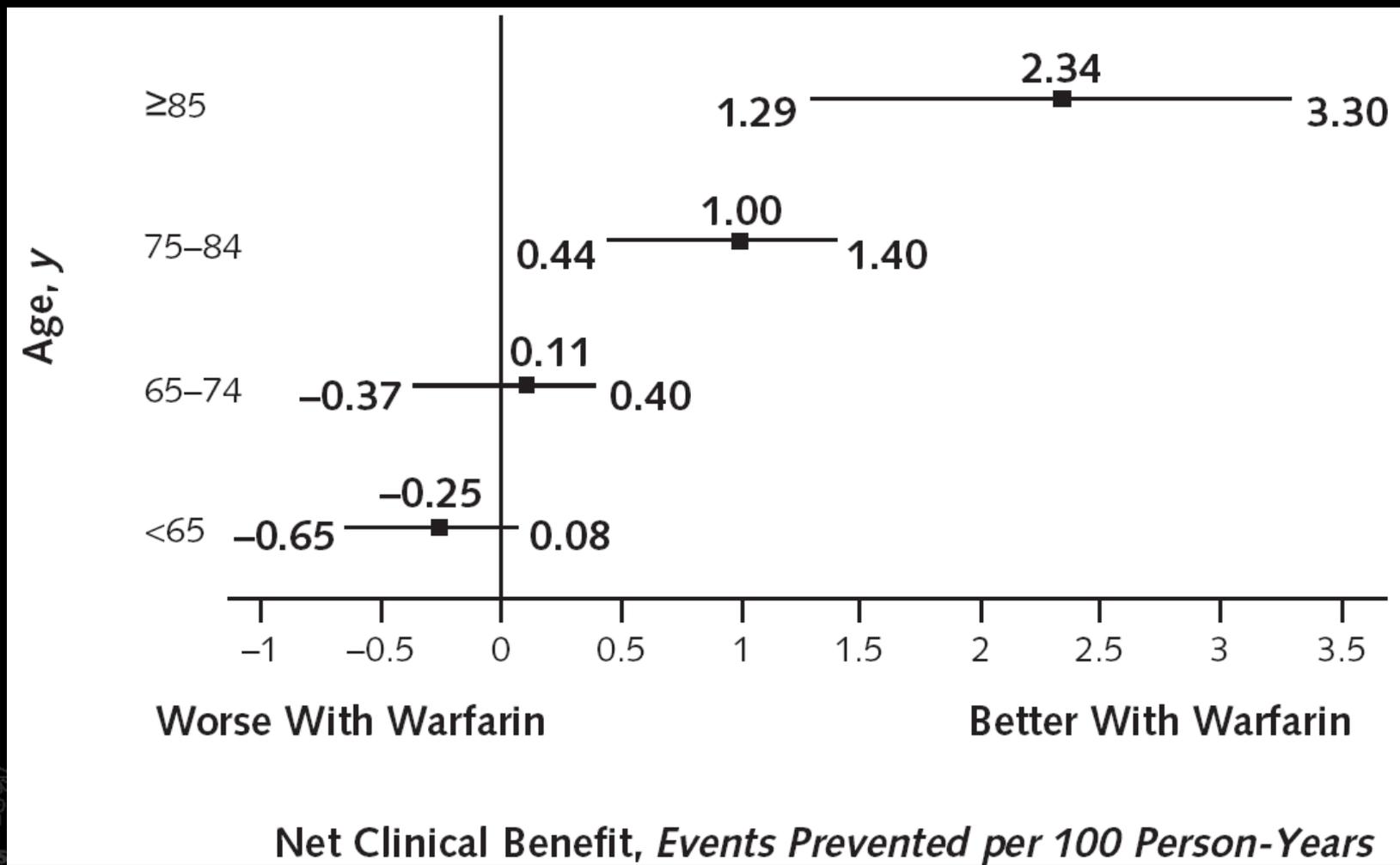
Warfarin Use in AF Patients



- Only 55% of AF patients with no contraindications to warfarin had evidence of warfarin use in previous 3 months
- Other studies site warfarin use among AF patients from 17% - 50%
- Elderly patients with an increased absolute risk of stroke were least likely to be taking warfarin



Warfarin Net Clinical Benefit: Impact of Age

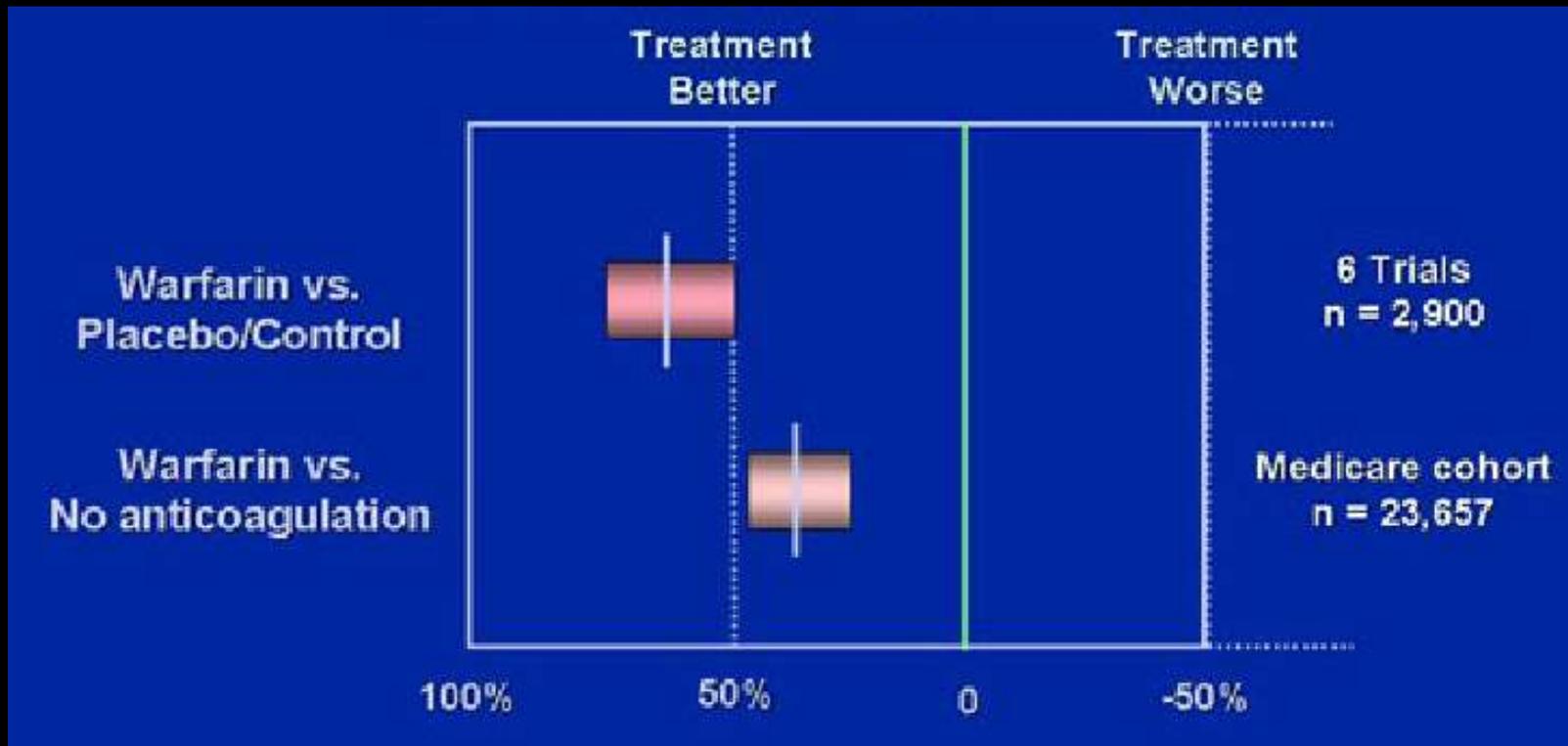


Singer D, *Ann Int Med.* 2009; 2009;151:297-305.



Warfarin Efficacy: Trial vs Practice

Stroke Risk Reductions

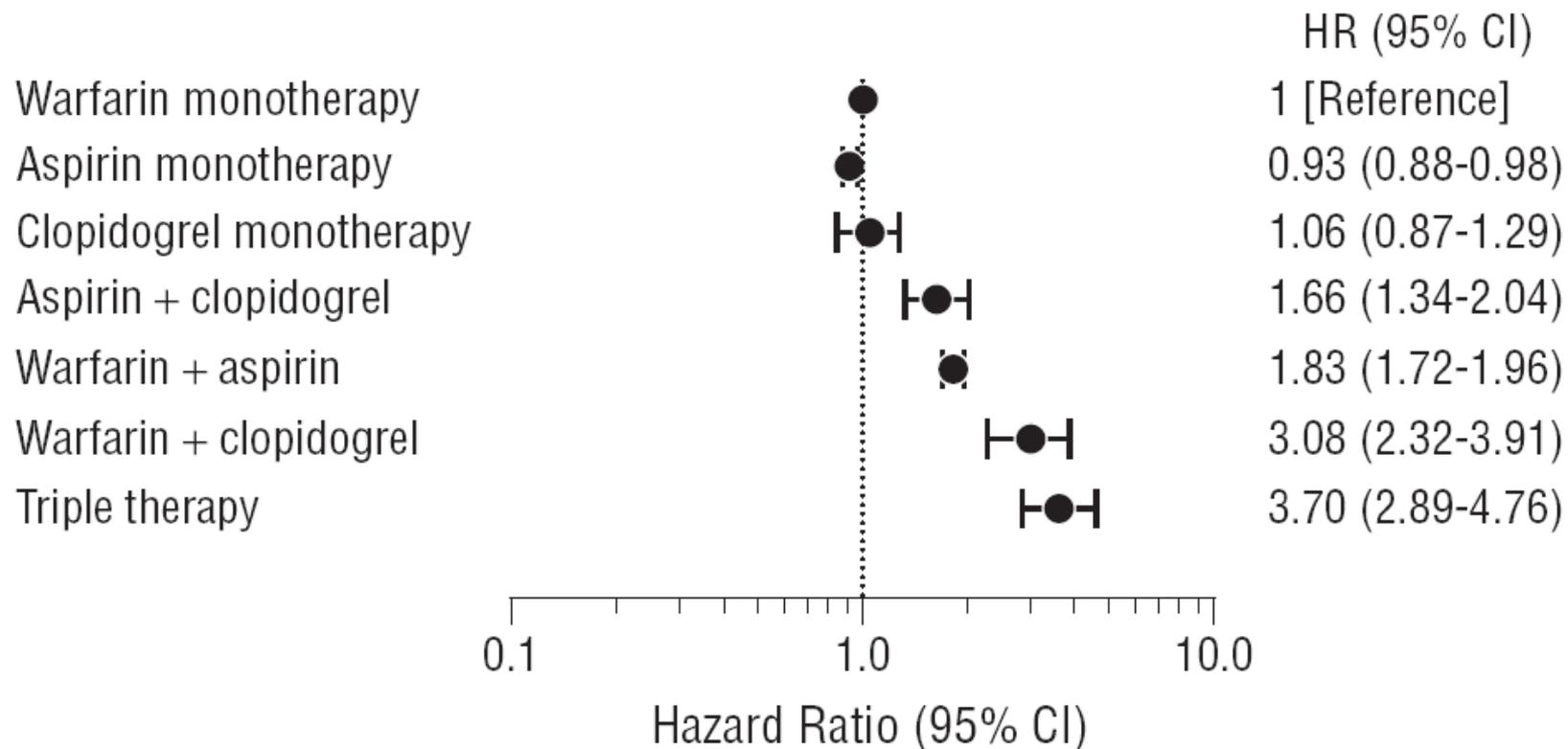


Hart R et al, *Ann Intern Med.* 2007; 146:587.
Birman-Deych E, *Stroke.* 2006; 37:1070.



Effect of multiple antithrombotics on serious bleeding rates

A cohort study using Danish Registry of >100,000 AF patients



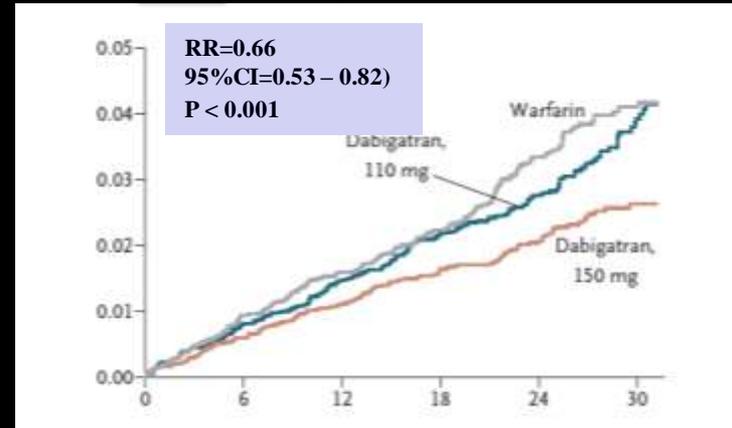
Hansen ML et al. *Arch Intern Med.* 2010; 170:1433.

Novel Anticoagulant Strategies

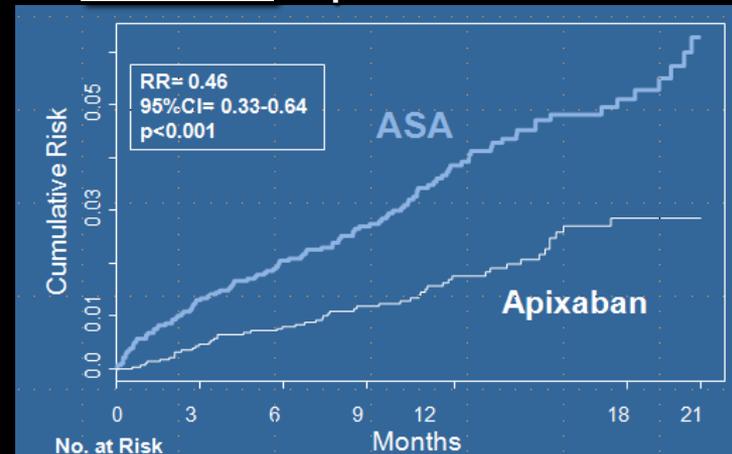
- Novel Anticoagulants
 - Anti-Platelet Agents
 - Thrombin Inhibitors
 - Dabigatran (RELY)
 - Factor Xa Inhibitors
 - Apixaban (AVERROES)
 - Rivaroxaban (ROCKET AF)

- LA Appendage Closure
 - Surgical
 - PLAATO
 - Amplatzer Cardiac Plug
 - WATCHMAN
 - Epicardial

RELY: Dabigatran vs Warfarin



AVERROES: Apixaban/ASA vs ASA



Connolly SJ, *NEJM*, 2009; 361:1139.
Connolly SJ, presented at ESC – 2010.



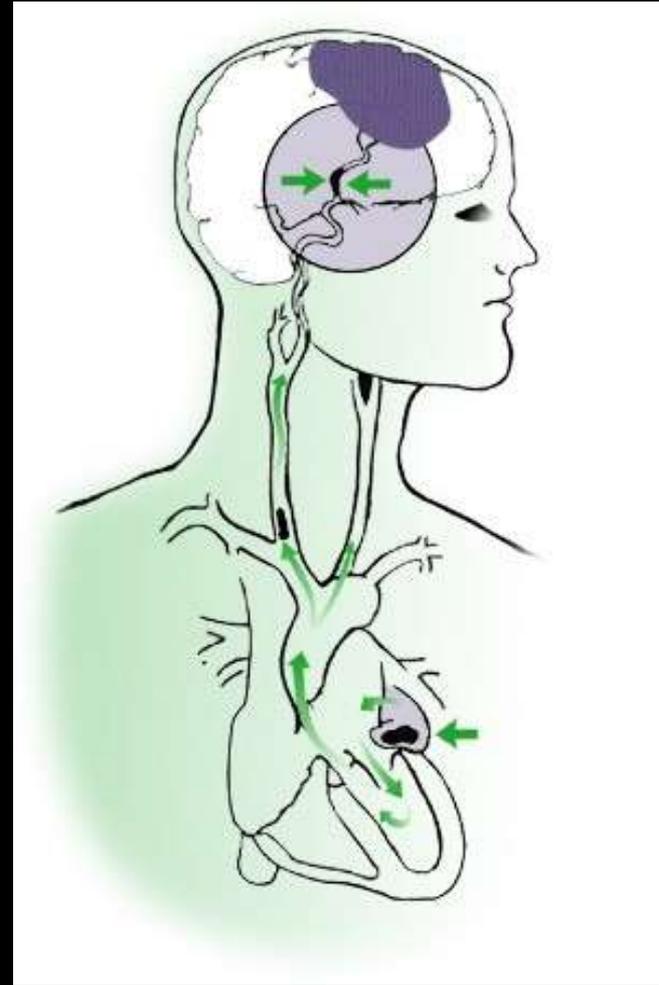
Dabigatran: Musings on Cost

- Costs in Ireland:
 - Warfarin (at 5 mg / day) = \$3.55 / month
 - Dabigatran (110 mg BID) = \$239.55 / month
 - Currently, > 32,500 patients in Ireland take the medication
 - If 50% switched, \$45 million / year
 - Equivalent to 10% of total cost of CV drugs in Ireland
- Estimates for the US:
 - Dabigatran (150 mg BID) = \$339 / month
 - Is 10 x cost of Warfarin (including INR monitoring)
 - In RELY, NNT to prevent 1 stroke w/ Dabigatran-150 is 357
 - Translates to \$1.3 million to prevent 1 stroke (vs Warfarin)
 - If double the risk (eg, CHADS₂ = 3-4), cost halved
 - [Not take into account cost of care of a stroke patient ... estimated at \$28,500 over 1st year]



Stroke Prophylaxis: Alternatives to Drugs

- Novel Anticoagulants
 - Anti-Platelet Agents
 - Thrombin Inhibitors
 - Dabigatran
 - Factor Xa Inhibitors
 - Rivaroxaban
- LA Appendage Closure
 - Surgical
 - Epicardial
 - Vascular
 - PLAATO
 - Amplatzer Cardiac Plug
 - WATCHMAN



Blackshear and Odell, Ann Thoracic Surgery 1996



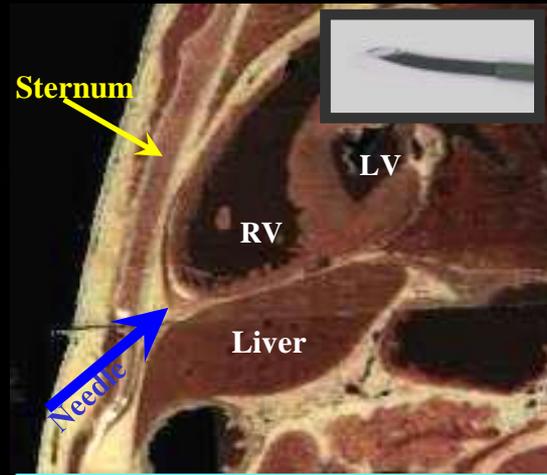
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Stroke Prophylaxis: Alternatives to Drugs

- Novel Anticoagulants
 - Anti-Platelet Agents
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 - Factor Xa Inhibitors
 - Rivaroxaban



Modified from slide from: E Sosa, M Scanavacca, A d'Avila

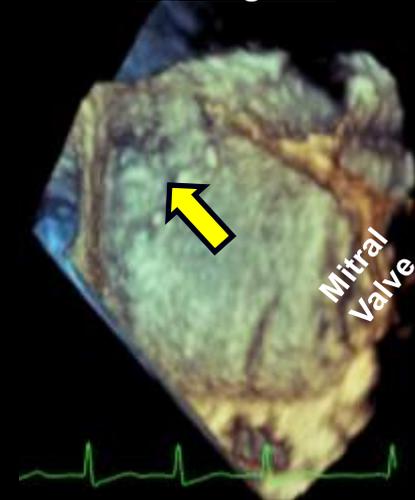


- LA Appendage Closure
 - Surgical
 - Epicardial
 - Vascular
 - PLAATO
 - Amplatzer Cardiac Plug
 - WATCHMAN

Pre-Ligation



Post-Ligation



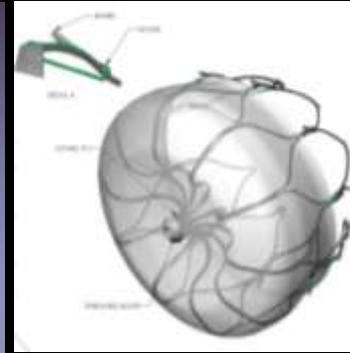
Stroke Prophylaxis: Alternatives to Drugs

- Novel Anticoagulants
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PLAATO



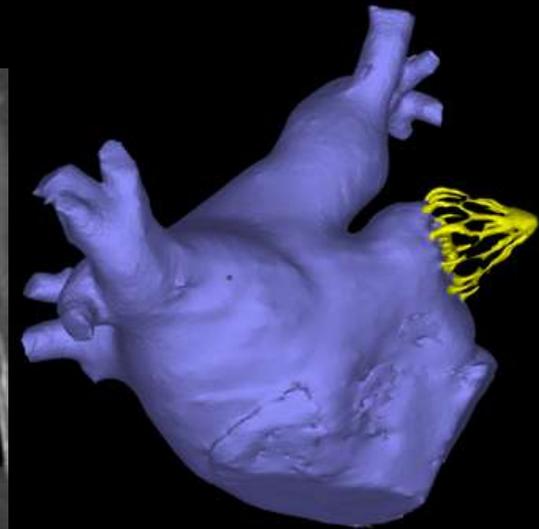
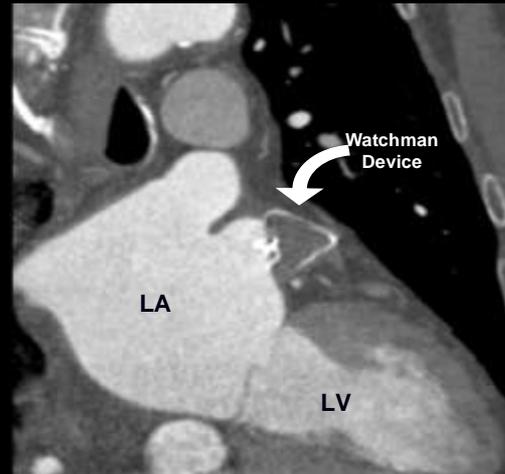
Watchman



Cardiac Plug

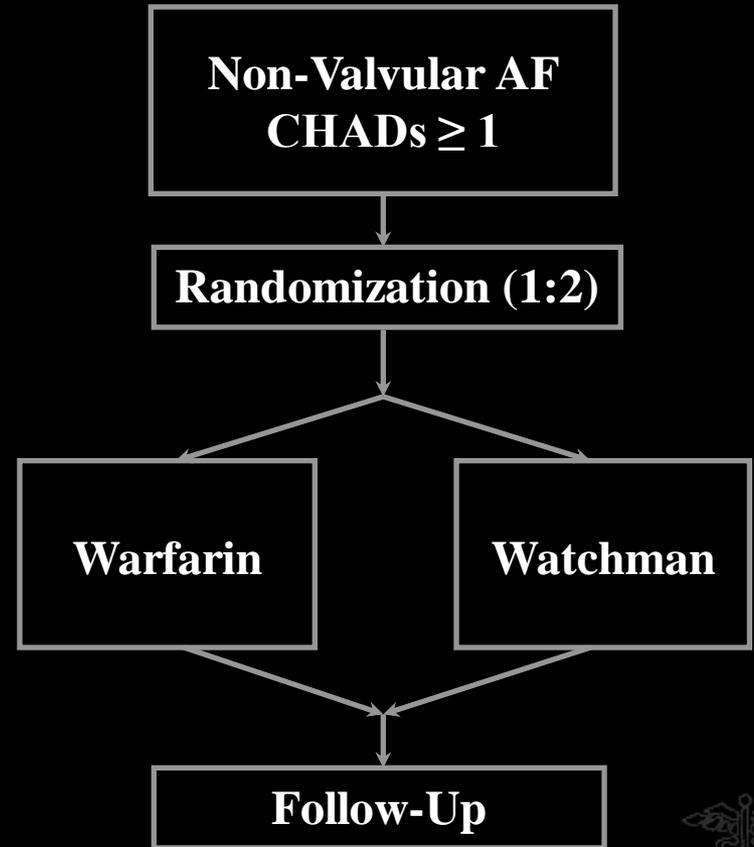


- LA Appendage Closure
 - Surgical
 - Epicardial
 - Vascular
 - PLAATO
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 - Amplatzer Cardiac Plug



PROTECT-AF: Overview

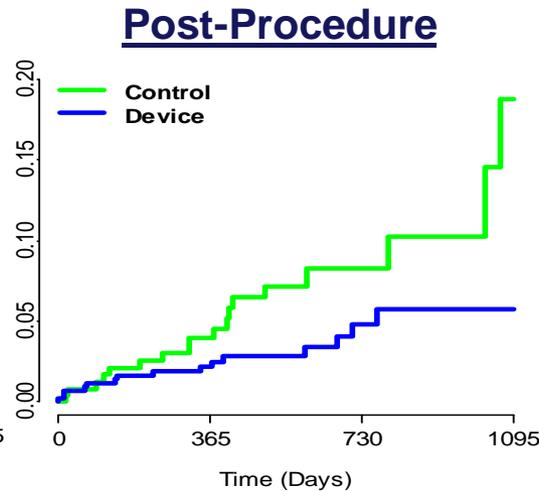
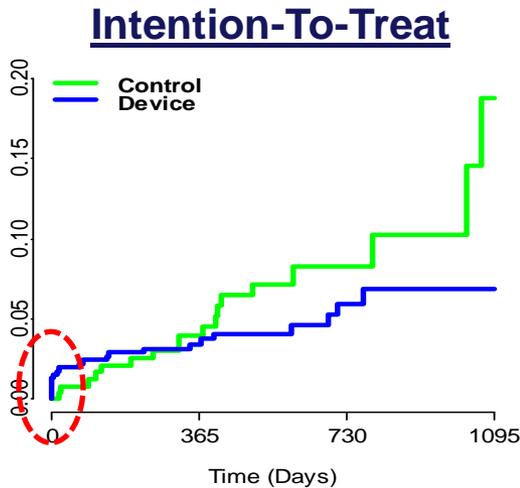
- Randomized FDA-IDE Trial
 - Can the WATCHMAN device *replace* Warfarin?
- Inclusion / Exclusion Criteria
- Efficacy Endpoint:
 - Stroke
 - CV death (& Unknown)
 - Systemic embolism
- Safety Endpoint
- Non-inferiority Study
 - Bayesian Sequential Design
 - Analysis at 600 pt-yrs & every 150 pt-yrs thereafter → to 1500 pt-yr



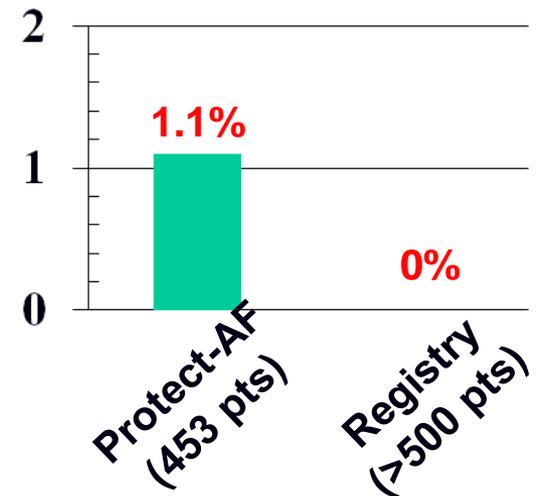
Primary Efficacy Results

Cohort 1050 Pt-Yrs	WATCHMAN		Control		Relative Risk	95% CI
	Rate (Events/100 Pt-Yrs)	Rate (Events/100 Pt-Yrs)	Rate (Events/100 Pt-Yrs)	Rate (Events/100 Pt-Yrs)		
Intention-To-Treat	3.0	21/694.1	4.9	18/370.8	0.62	0.33, 1.17*
Post-Procedure	2.2	15/684.0	4.9	18/370.8	0.45	0.23, 0.90

* Using Cox Proportional Model



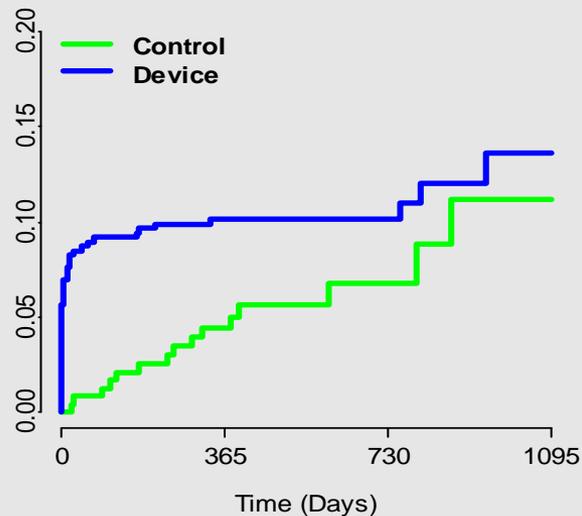
Procedure-Related Stroke



Primary Safety Results: Intent-To-Treat

Cohort 1050 Pt-Yrs	WATCHMAN		Control		Relative Risk	95% CI
	Rate (Events/100 Pt-Yrs)		Rate (Events/100 Pt-Yrs)			
All Patients	7.4	49/658.8	4.4	16/364.2	1.69	0.96, 2.97

Primary Safety



- **Pericardial Effusion / Tamponade**
 - **22 requiring Tx (4.8% of patients)**
 - 15 treated percutaneously
 - 7 underwent surgical intervention
 - **Extended hospitalization**
 - **No Death or Long-term Disability**
- **Effect of operator experience**
 - **< 2% (CAP Registry)**

→ → How do we interpret this safety data?

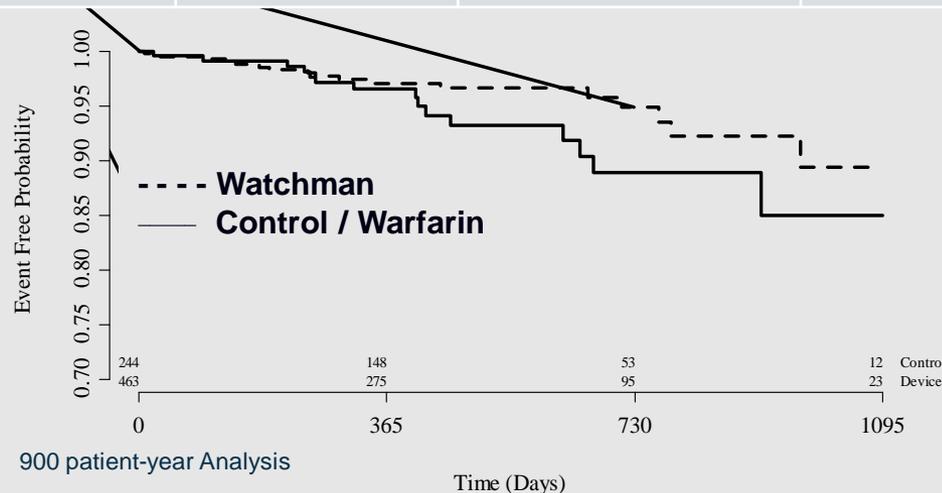
Safety Data Interpretation

- As with any Device vs Drug comparison, must balance the:
 - Higher up-front, acute risk of complications with a procedure
 - Numerically-lower, but continual, risk of drug therapy
- Since complications different in each group, how to compare?
 - Composite event rates of each group
 - Time course of the events
 - Is there evidence for experience – related improvements?
 - What is the functional impact of this heterogeneous group of events?



Intent-to-Treat: All-Cause Mortality

Cohort	Device	Control	Rel. Risk (95% CI)	Posterior Probabilities	
	Rate (95% CI)	Rate (95% CI)		Non-inferiority	Superiority
900 pt-yrs	2.9 (1.7, 4.4)	4.7 (2.5, 7.1)	0.61 (0.32, 1.32)	99.9%	88.9%
1050 pt-yrs	3.0 (1.9, 4.5)	4.8 (2.5, 7.1)	0.62 (0.34, 1.24)	99.9%	90.7%



Significant Disability or Death (1350 pt-yrs)

	Watchman	Control	Relative Risk (95% C.I.)
	Rate Events (per 100 Pt-Yrs)	Rate Events (per 100 Pt-Yrs)	
MRS Increase \geq 1 Or Death	1.6 (14 / 902.6)	4.5 (21 / 468.4)	0.35 (0.18, 0.73)
MRS Increase \geq 2 Or Death	1.2 (11 / 908.8)	3.8 (18 / 471.9)	0.32 (0.15, 0.72)
MRS Increase \geq 3 Or Death	1.1 (10 / 910.3)	3.6 (17 / 475.0)	0.31 (0.14, 0.71)

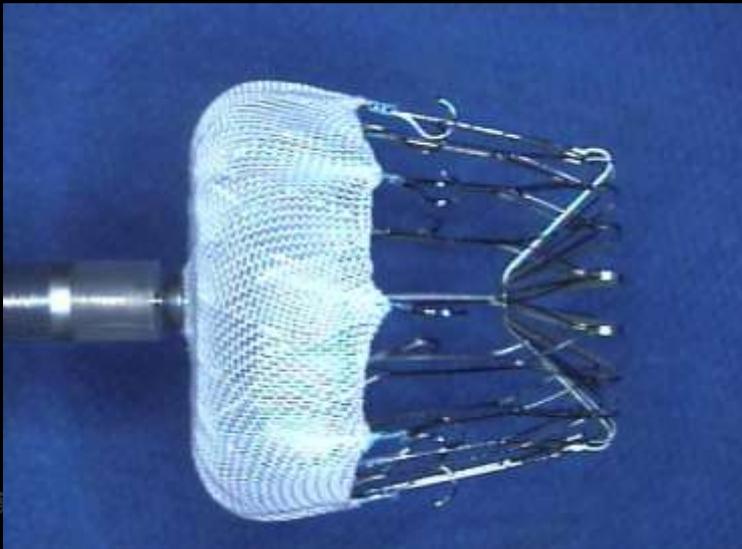
Next Generation Watchman

- **18 Splines**
- **Bumper / Stabilizer**
- **Completely Re-Capturable**

**Current
Generation**



**Next
Generation**



Next Generation Watchman



Next Generation Watchman



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Next Generation Watchman



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Final Thoughts

- Despite higher bleeding risk, the net benefit of Warfarin is even greater in the Elderly
- LAA Occlusion/Exclusion is an appropriate avenue of investigation for the prevention of stroke in patients with non-valvular AF
- LAA Closure with Implant
 - Watchman is a reasonable alternative to Warfarin
 - Safety issues related to experience
 - Need data w/ other devices





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