

Left Atrial Appendage Occlusion:
How strong is the evidence of
efficacy (or does it prevent stroke?)

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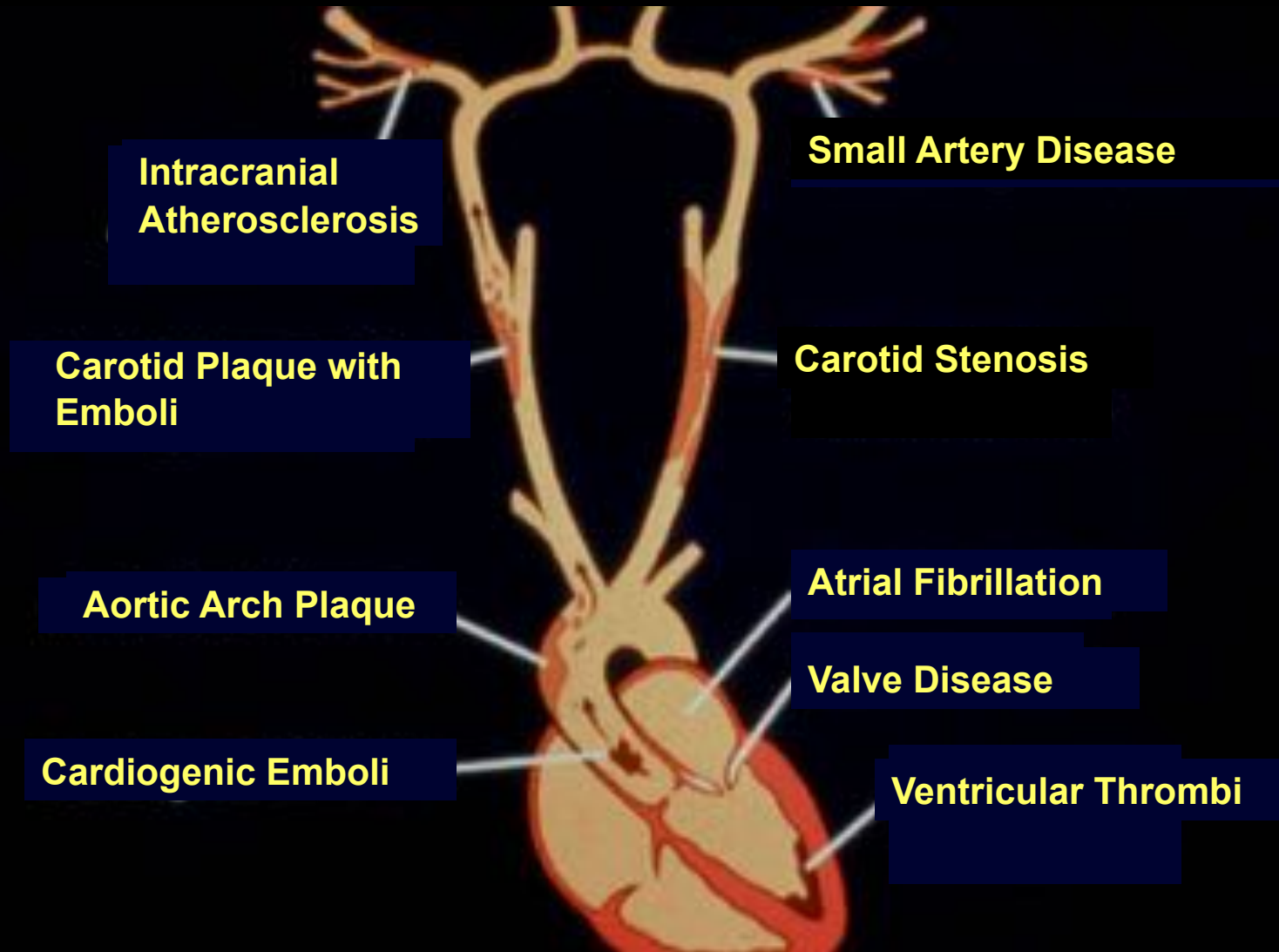
Disclosures

- Research Support, Consulting and Lecture fees from
 - BMS, Pfizer, Boehringer Ingelheim, Bayer, Portola, sanofi aventis, Boston Scientific, St. Jude Medical,

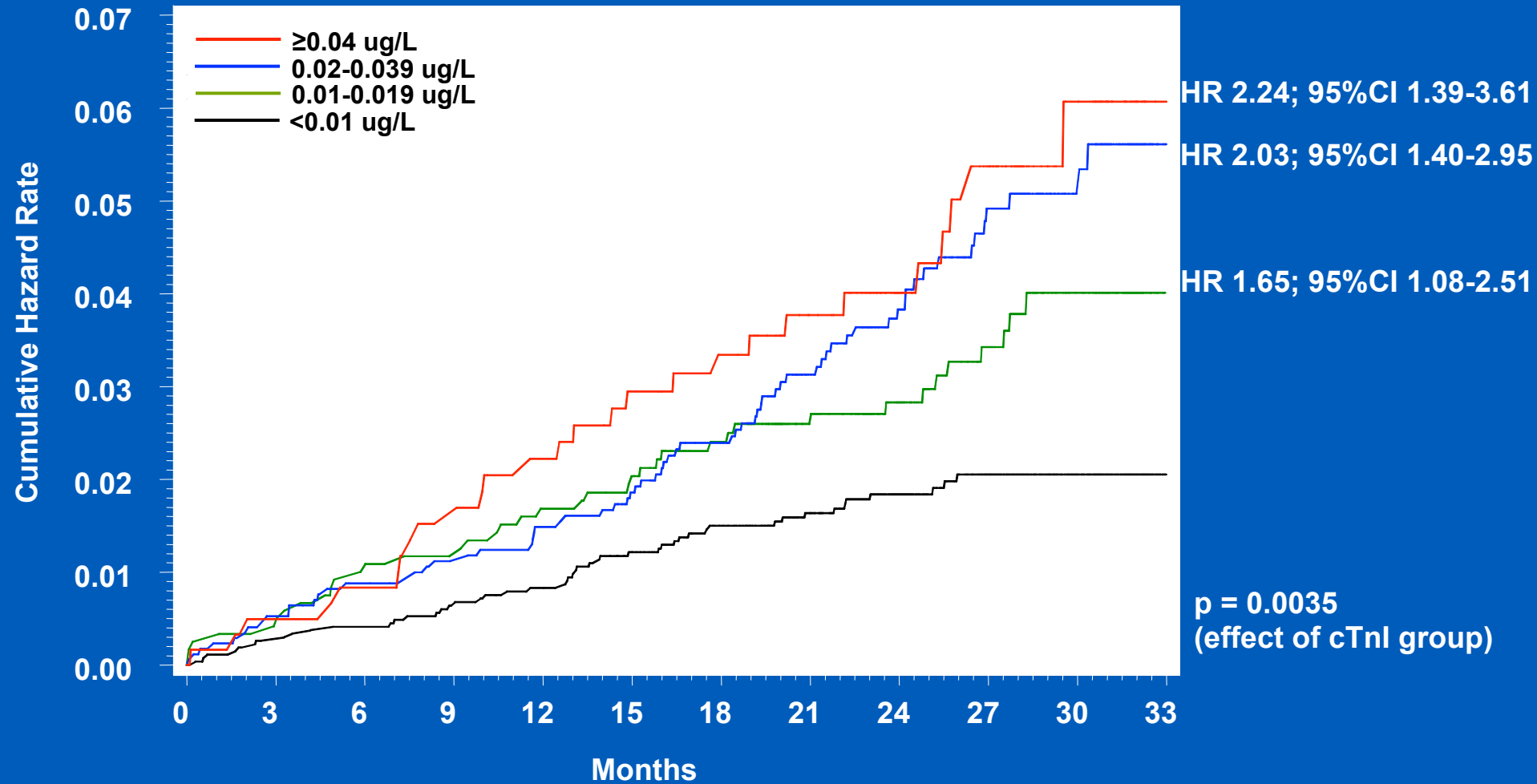
Stroke in AF

- Stroke risk factors are systemic not local
 - Age, hypertension, diabetes, renal failure, etc
 - Left atrial enlargement is NOT a risk factor
- Many sources of embolic stroke other than LAA
- Circulating biomarker abnormalities suggest a more systemic abnormality

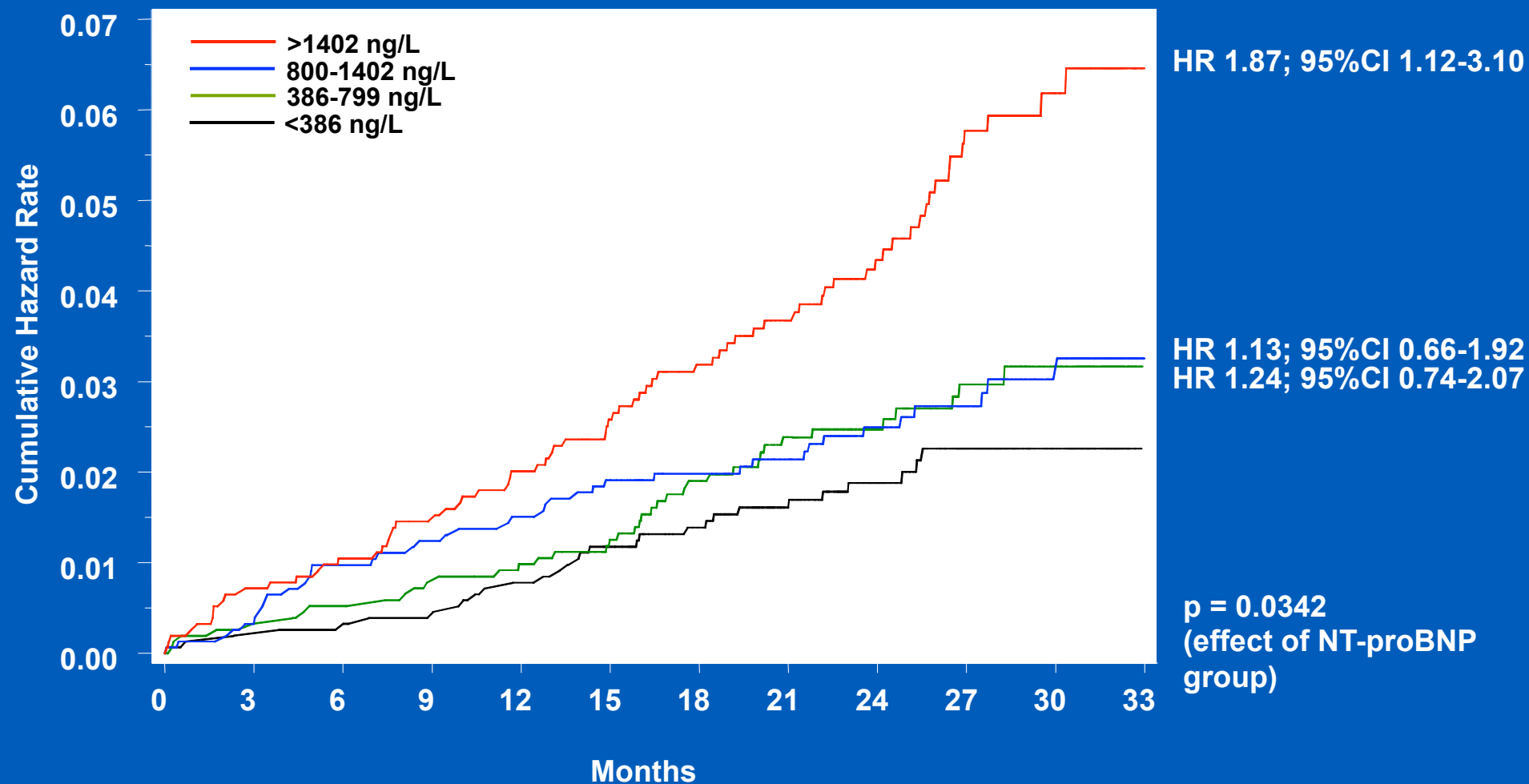
Major Causes of Ischemic Stroke



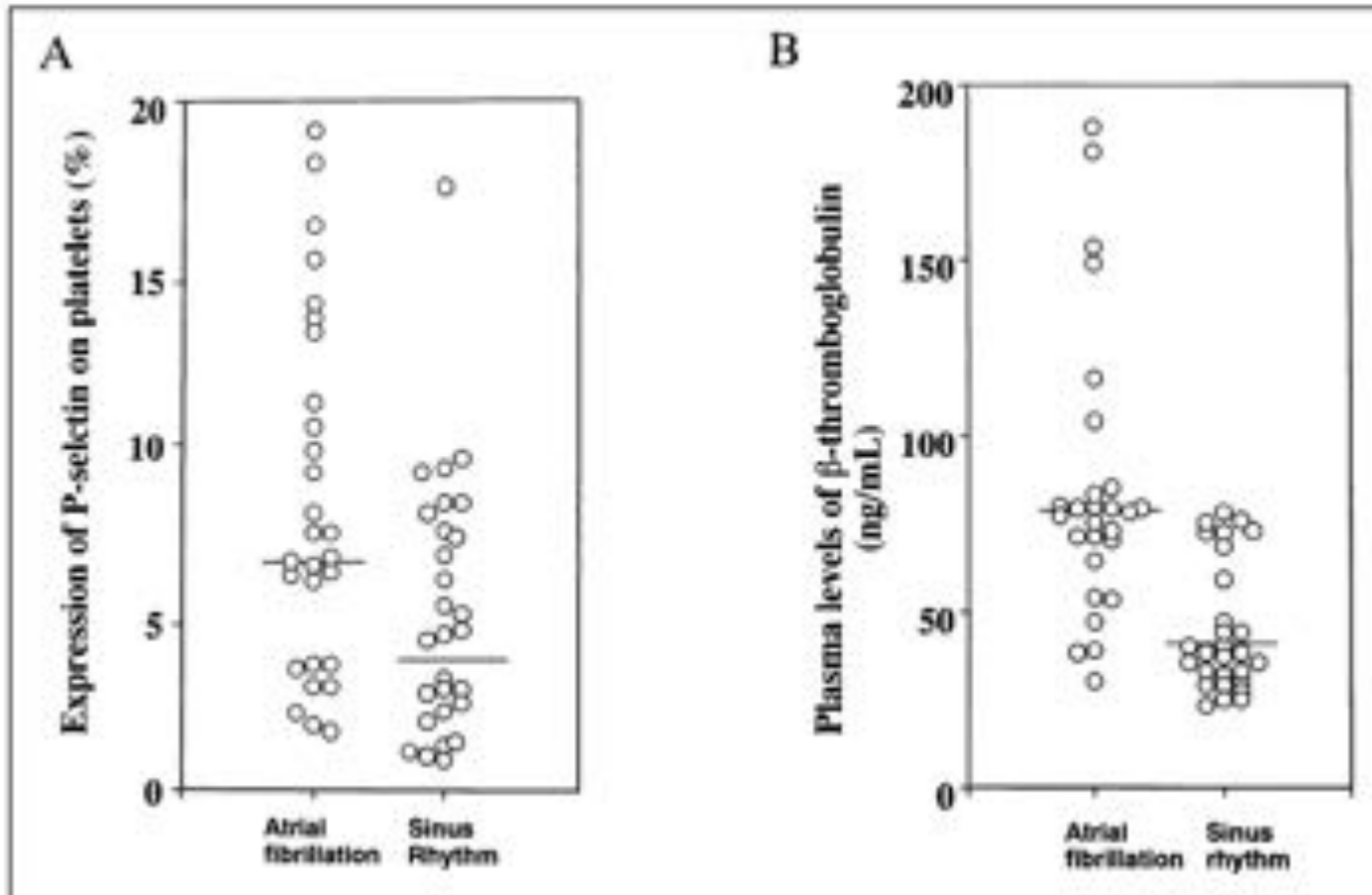
Stroke and systemic embolism in relation to troponin I



Stroke and systemic embolism in relation to NT-proBNP



Systemic Antiplatelet Effects of AF



Clinical Trial Evidence of Efficacy

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

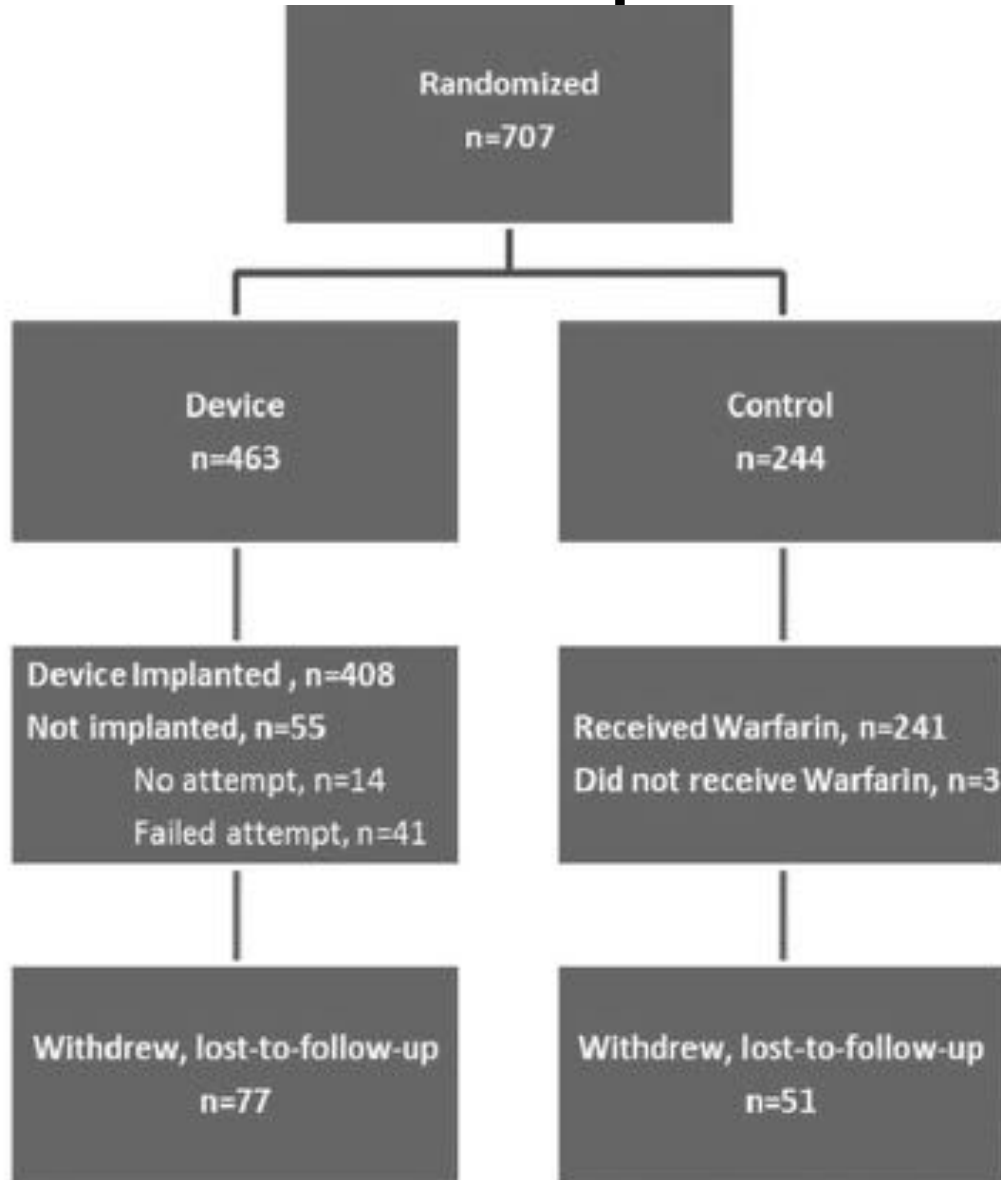


American
Heart
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Percutaneous Left Atrial Appendage Closure for Stroke Prophylaxis in Patients With Atrial Fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) Trial
Vivek Y. Reddy, Shephal K. Doshi, Horst Sievert, Maurice Buchbinder, Petr Neuzil, Kenneth Huber, Jonathan L. Halperin and David Holmes
on behalf of the PROTECT AF Investigators

Circulation. 2013;127:720-729; originally published online January 16, 2013;

Patient Disposition



Efficacy Results

Table 2. Efficacy and Safety Results

	Device		Control		Rate Ratio (Intervention/Control) (95% CrI)
	Events/ Patient-Years	Observed Rate: Events per 100 Patient-Years (95% CrI)	Events/Patient- Years	Observed Rate: Events per 100 Patient-Years (95% CrI)	
Primary efficacy	31/1025.7	3.0 (2.1–4.3)	24/562.7	4.3 (2.6–5.9)	0.71 (0.44–1.30)
Ischemic stroke	19/1026.3	1.9 (1.1–2.9)	8/564.9	1.4 (0.6–2.4)	1.30 (0.66–3.60)
Cardiovascular/unexplained death	11/1050.4	1.0 (0.5–1.8)	16/573.2	2.8 (1.5–4.2)	0.38 (0.18–0.85)
Hemorrhagic stroke	3/1050.3	0.3 (0.1–0.7)	7/571.0	1.2 (0.5–2.3)	0.23 (0.04–0.79)
Systemic embolism	3/1049.8	0.3 (0.1–0.7)	0/573.2	0	...

Safety

Table 4. Primary Safety Results

Analysis	Device	
	Events/Total Patient-Years	Rate (95% CI)
ITT	54/979.9	5.5 (4.2–7.1)
Postprocedure	27/969.8	2.8 (1.9–4.0)
Per-protocol	14/921.8	1.5 (0.9–2.5)
Terminal therapy	9/708.8	1.3 (0.6–2.4)

Safety

	Intervention (n=463)	Control (n=244)
Serious pericardial effusion*	22 (4.8%)	0
Major bleeding†	16 (3.5%)	10 (4.1%)
Procedure-related ischaemic stroke	5 (1.1%)	0
Device embolisation	3 (0.6%)	0
Haemorrhagic stroke‡	1 (0.2%)	6 (2.5%)
Other§	2 (0.4%)	0

**Prospective Randomized Evaluation
of the Watchman Left Atrial Appendage
Closure Device in Patients With
Atrial Fibrillation Versus
Long-Term Warfarin Therapy**

The PREVAIL Trial

Patients

TABLE 1 Baseline Demographic Characteristics and Risk Factors (Randomized Subjects)

	Device Group (n = 269)	Control Group (n = 138)	p Value
Characteristics			
Age, yrs	74.0 ± 7.4 (269) (50.0, 94.0)	74.9 ± 7.2 (138) (53.0, 90.0)	0.260
Height, in	68.4 ± 4.3 (269) (57.0, 80.0)	68.5 ± 4.0 (138) (57.0, 78.0)	0.944
Weight, lbs	196.3 ± 44.9 (269) (106.0, 333.0)	197.1 ± 43.3 (138) (112.0, 317.0)	0.851
Sex			0.146
Female	87/269 (32.3%)	35/138 (25.4%)	
Male	182/269 (67.7%)	103/138 (74.6%)	
Race/ethnicity			0.603
Asian	1/269 (0.4%)	1/138 (0.7%)	
Black/African American	6/269 (2.2%)	1/138 (0.7%)	
White	253/269 (94.1%)	131/138 (94.9%)	
Hispanic/Latino	6/269 (2.2%)	5/138 (3.6%)	
Native American Indian/Alaskan Native	1/269 (0.4%)	0/138 (0.0%)	
Other	2/269 (0.7%)	0/138 (0.0%)	
Risk			
CHADS ₂ score (categorical)			0.484
1	21/269 (7.8%)	12/138 (8.7%)	
2	137/269 (50.9%)	62/138 (44.9%)	
3	65/269 (24.2%)	36/138 (26.1%)	
4	33/269 (12.3%)	21/138 (15.2%)	
5	12/269 (4.5%)	7/138 (5.1%)	
6	1/269 (0.4%)	0/138 (0.0%)	
CHADS ₂ score (continuous)	2.6 ± 1.0 (269)	2.6 ± 1.0 (138)	0.838

PREVAIL – Efficacy Results

TABLE 3 Coprimary Efficacy Endpoint Observed Events by Type: PREVAIL Subjects Only (Intention-to-Treat)*

	Device Group			Control Group		
	No. of Events	% of Subjects	% of Endpoints	No. of Events	% of Subjects	% of Endpoints
Ischemic stroke	5	1.9	35.7	1	0.7	25.0
Hemorrhagic stroke	1	0.4	7.1	0	0.0	0.0
Death (cardiovascular/unexplained)	7	2.6	50.0	3	2.2	75.0
Systemic embolism	1	0.4	7.1	0	0.0	0.0

Safety

TABLE 5 Safety Coprimary Endpoint Results and Events by Type
(Intention-to-Treat): Device Group Only

	% (n/N)	95% CrI
Safety primary endpoint results	2.2% (6/269)	2.652%
	No. of Events	% of Subjects
Safety events by type		
Device embolization	2	0.7
Arteriovenous fistula	1	0.4
Cardiac perforation	1	0.4
Pericardial effusion with cardiac tamponade	1	0.4
Major bleed requiring transfusion	1	0.4

Meta-analysis

TABLE 1 PROTECT AF and CAP: Largest Data Sets to Evaluate Totality of Data

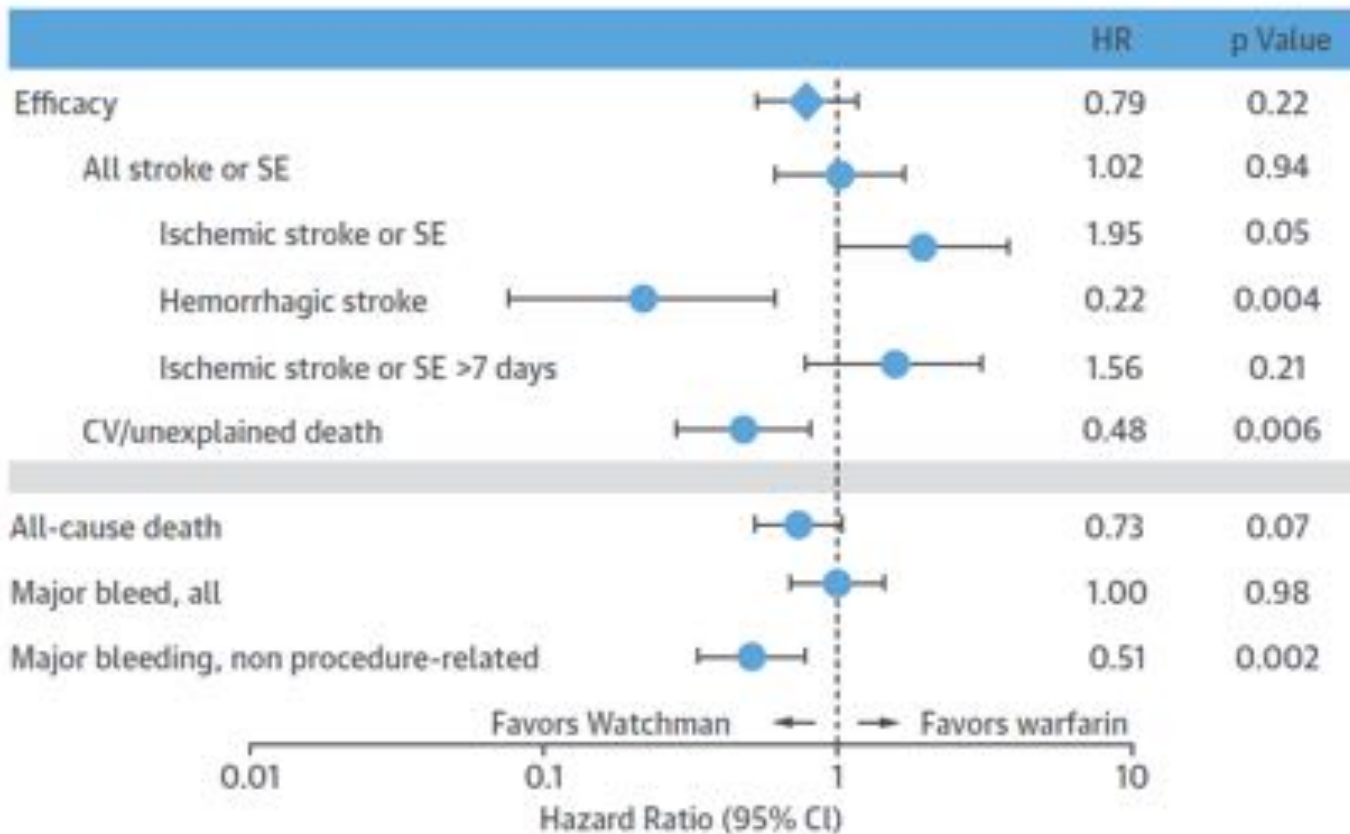
	PROTECT AF	PREVAIL	CAP	CAP2	Total
Enrollment	2005-2008	2010-2012	2008-2010	2012-2014	
Enrolled	800	461	566	579	2,406
Randomized	707	407	—	—	1,114
Watchman:warfarin (2:1)	463:244	269:138	566	579	1,877:382
Mean follow-up, yrs	4.0	2.2	3.7	0.58	N/A
Patient-years	2,717	860	2,022	332	5,931

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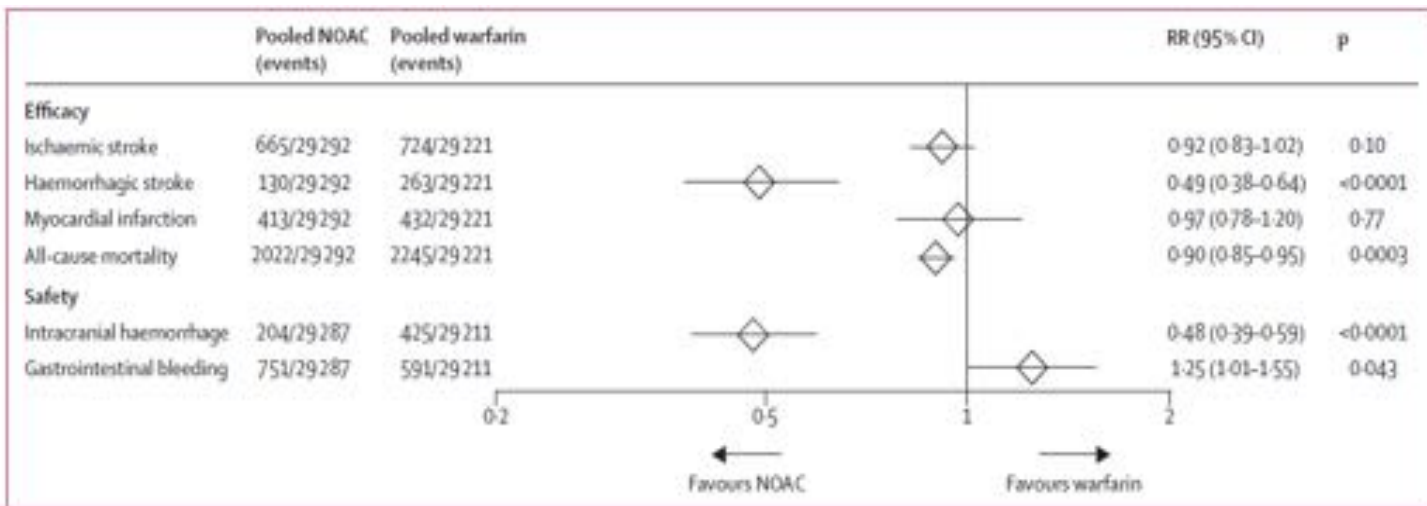
Efficacy

FIGURE 2 PROTECT AF/PREVAIL Combined: Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin



NOACs versus Warfarin

Published Online December 4, 2013 [http://dx.doi.org/10.1016/S0140-736\(13\)62343-0](http://dx.doi.org/10.1016/S0140-736(13)62343-0)

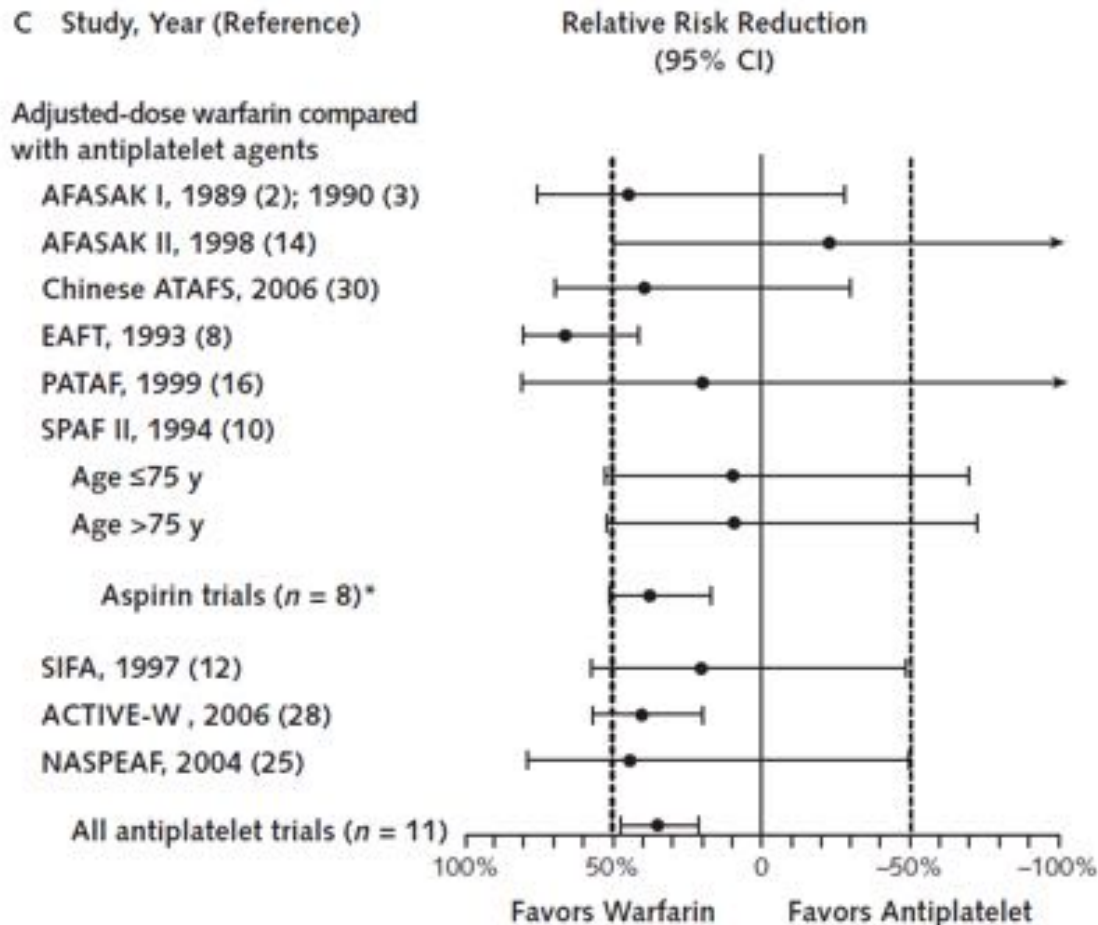


Conclusions: Device efficacy remains in sufficiently proven

- LAA occlusion less effective than warfarin for reduction of ischemic stroke
 - Rate is about double with the device
- Watchman device failed to meet even modest non-inferiority criteria in one trial and barely met them in another
- Warfarin is no longer the reasonable standard of care
 - NOACs are safer and more effective than warfarin

Meta-analysis of Warfarin Versus Aspirin

Risk reduction with warfarin is 37% (95% CI 23% to 48%).
 This is equivalent to 59% increase in The risk of stroke with aspirin.



Conclusions

- Insufficient evidence of efficacy to recommend LAA occlusion devices, except in exceptional circumstances
- Safety concerns as the implant is technically demanding
- Effective and safe alternatives to warfarin now available
- More research is needed for this promising concept