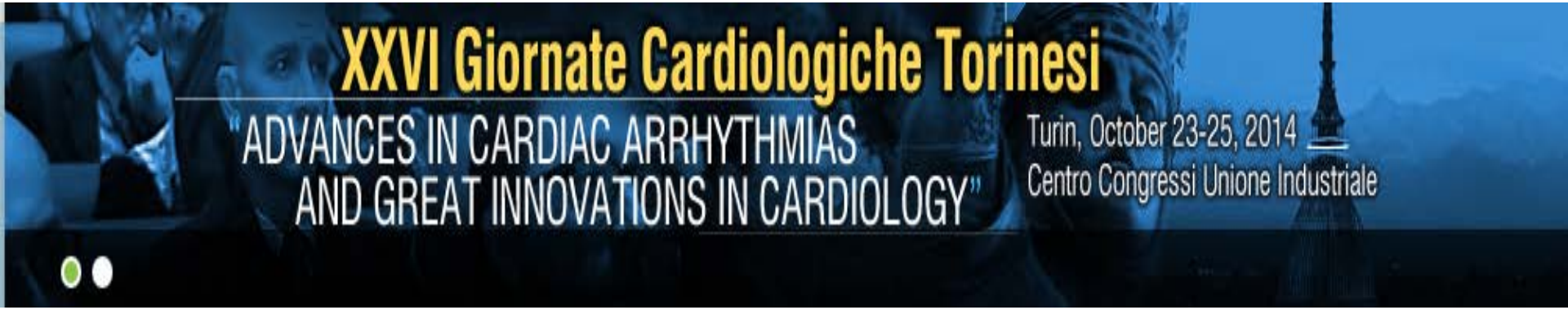
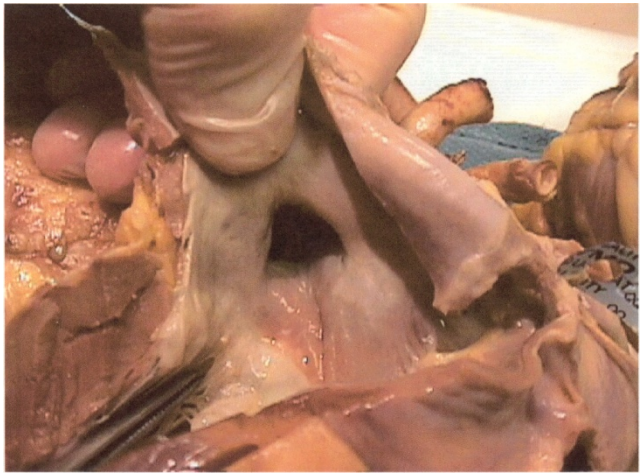


Prevention of Thromboembolic Events by Left Atrial Appendage Occlusion

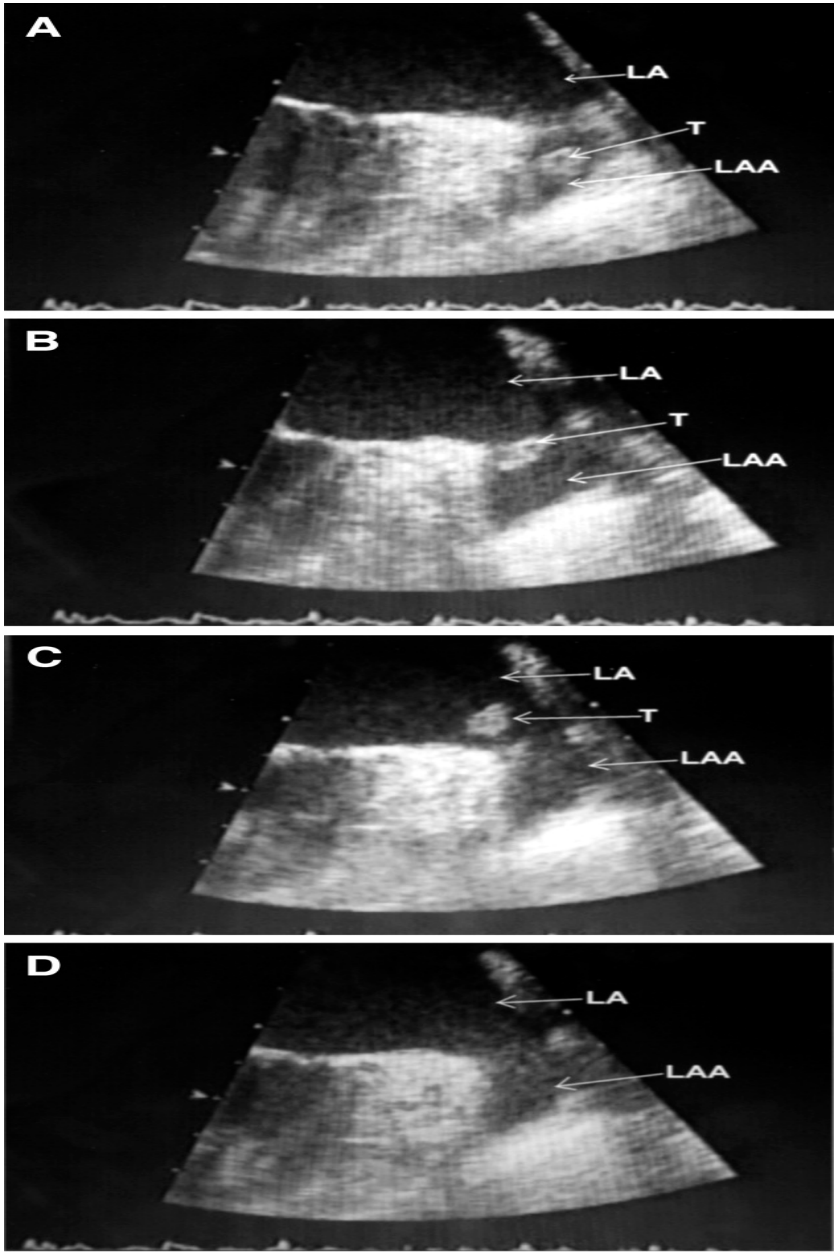
Raphael Rosso MD
Tel Aviv Sourasky Medical Center
Torino 2014



≈15-20% of all strokes due to AF

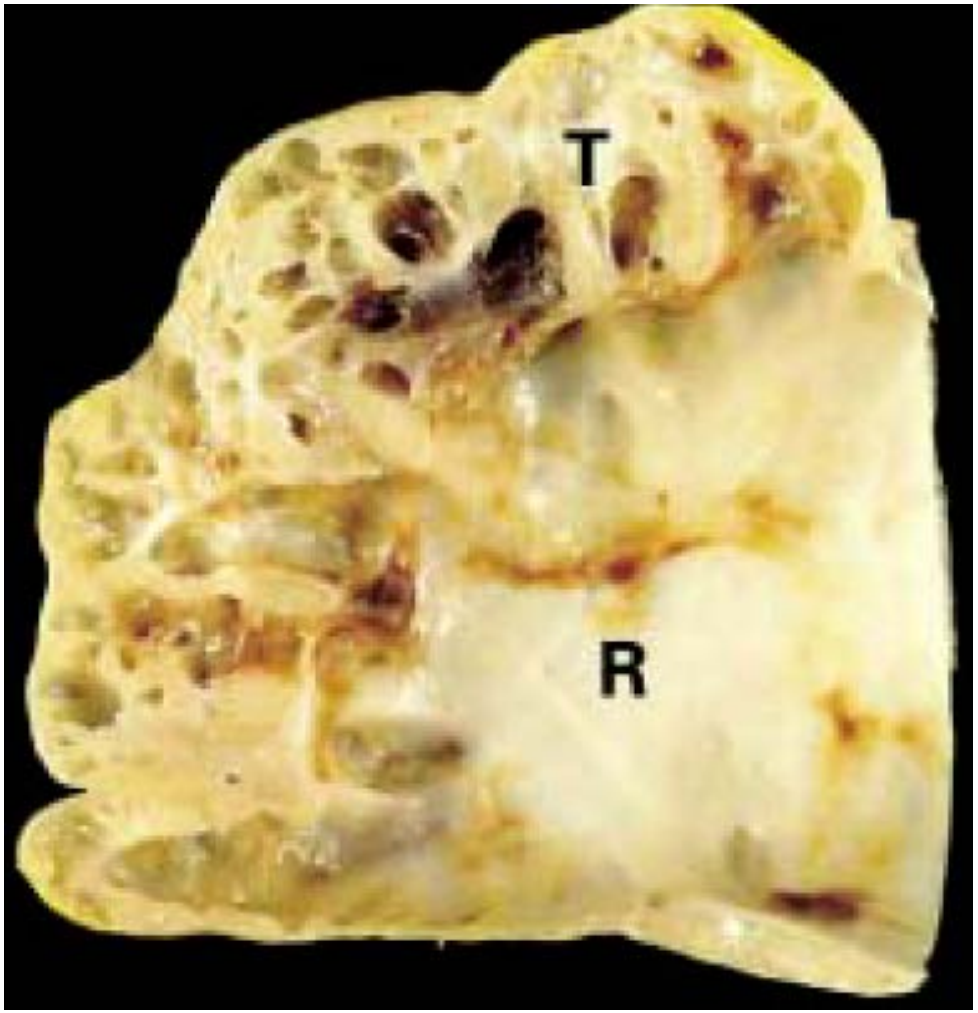
≈90% of AF strokes cardioembolic

≈90% of emboli forms In the LAA



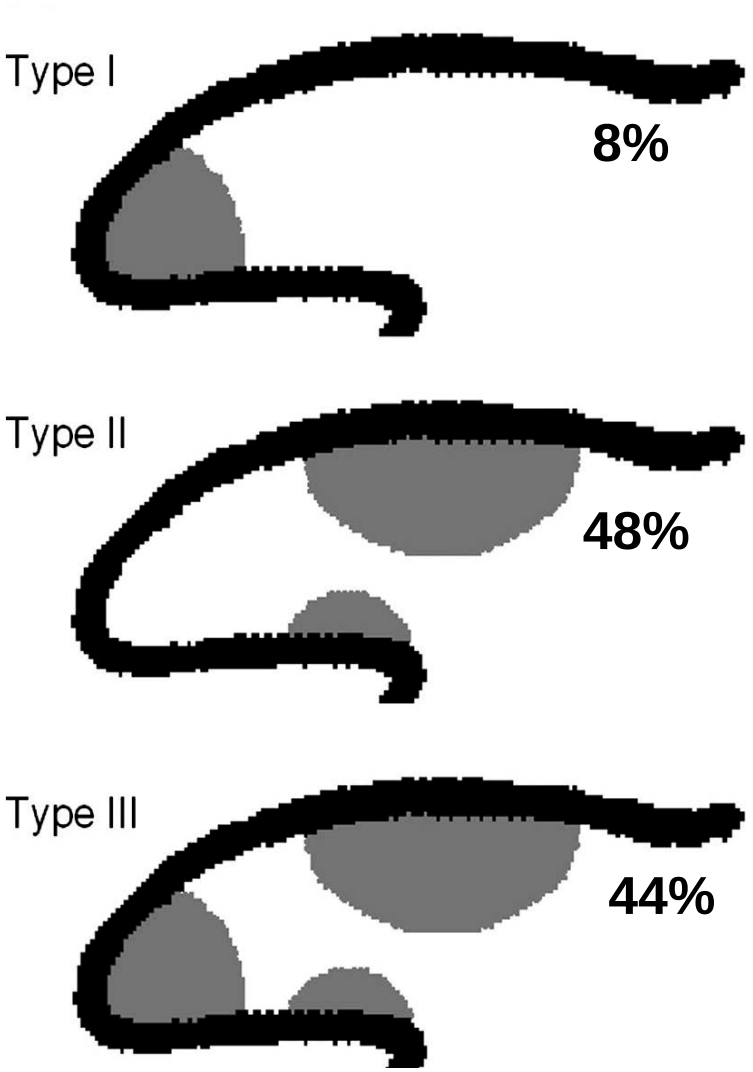
Parekh A et al. Circulation. 2006;114:e513-e514

NVAF

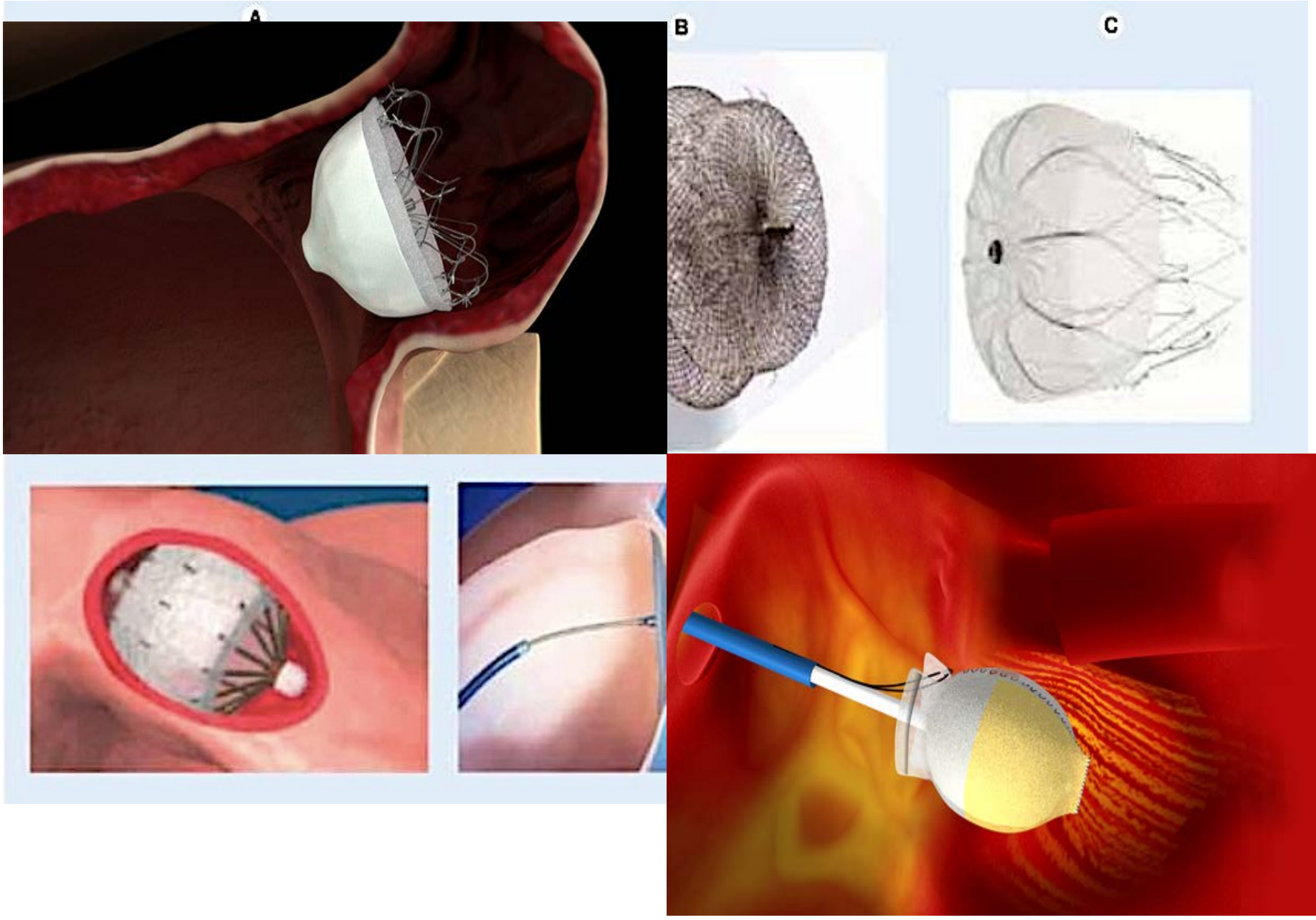


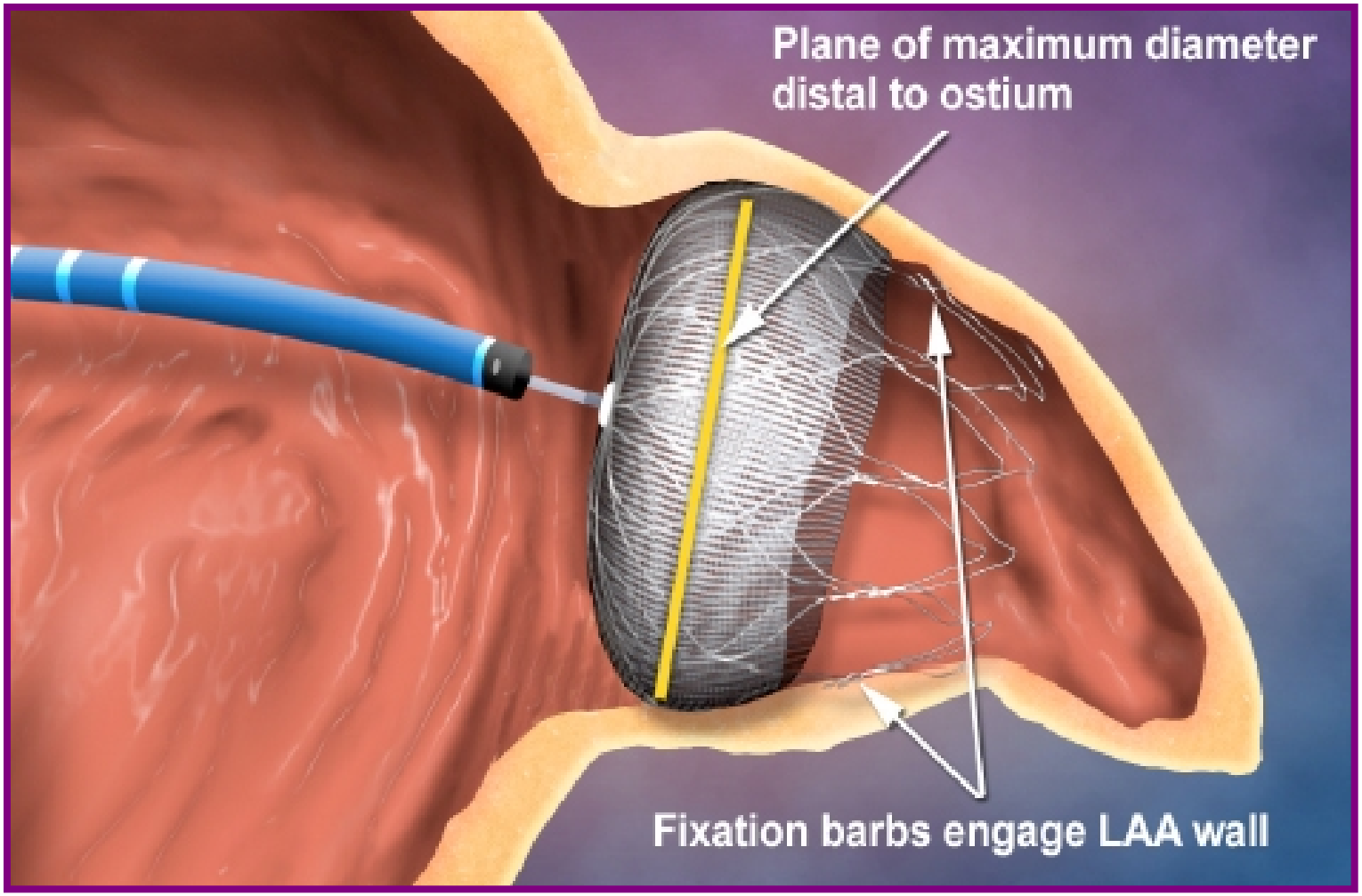
Yamaji, et al.Cardiology2002;97:104

Valvular AF

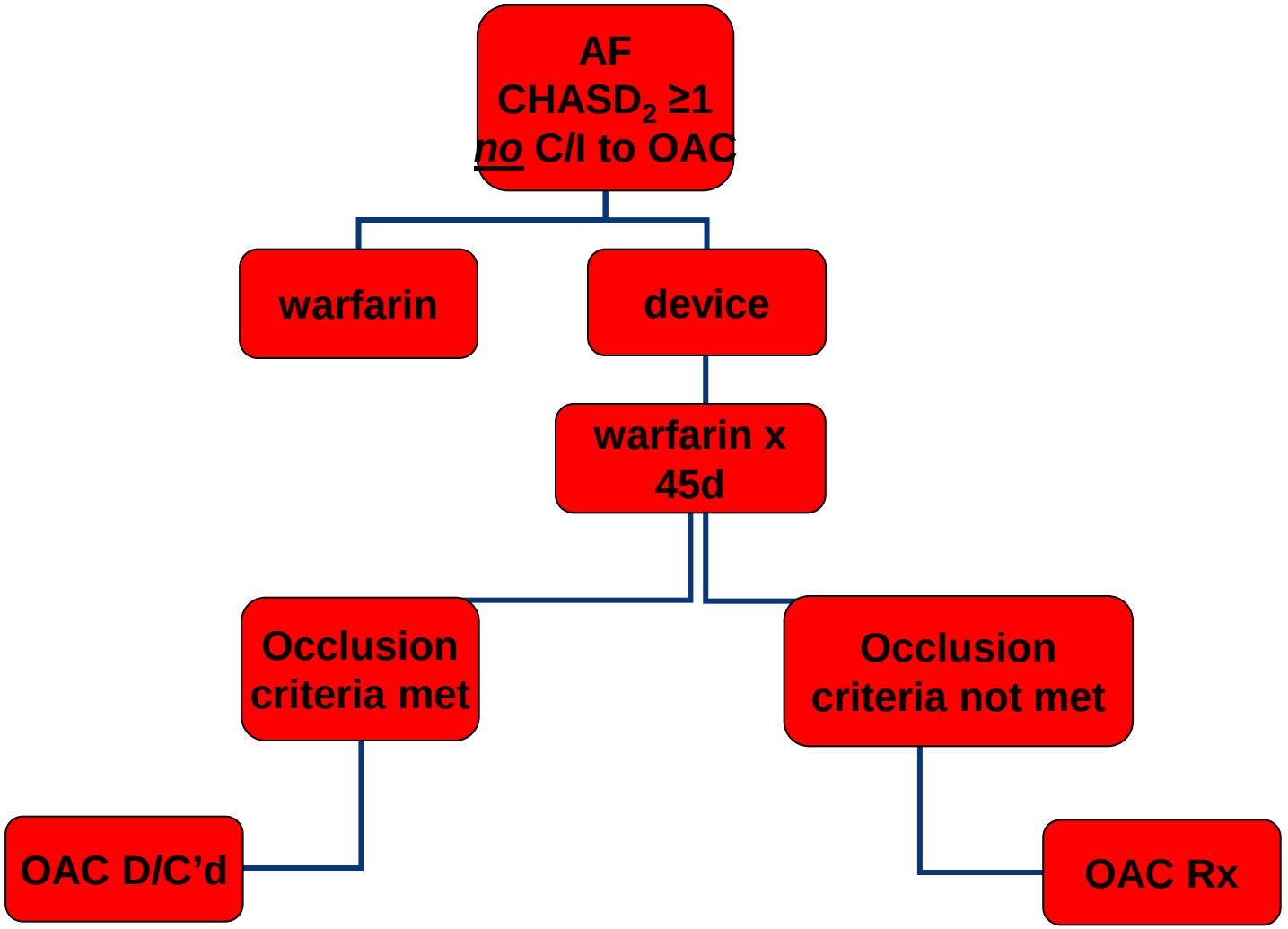


Saito, et al. AHJ 2007;153:704


A
B
C

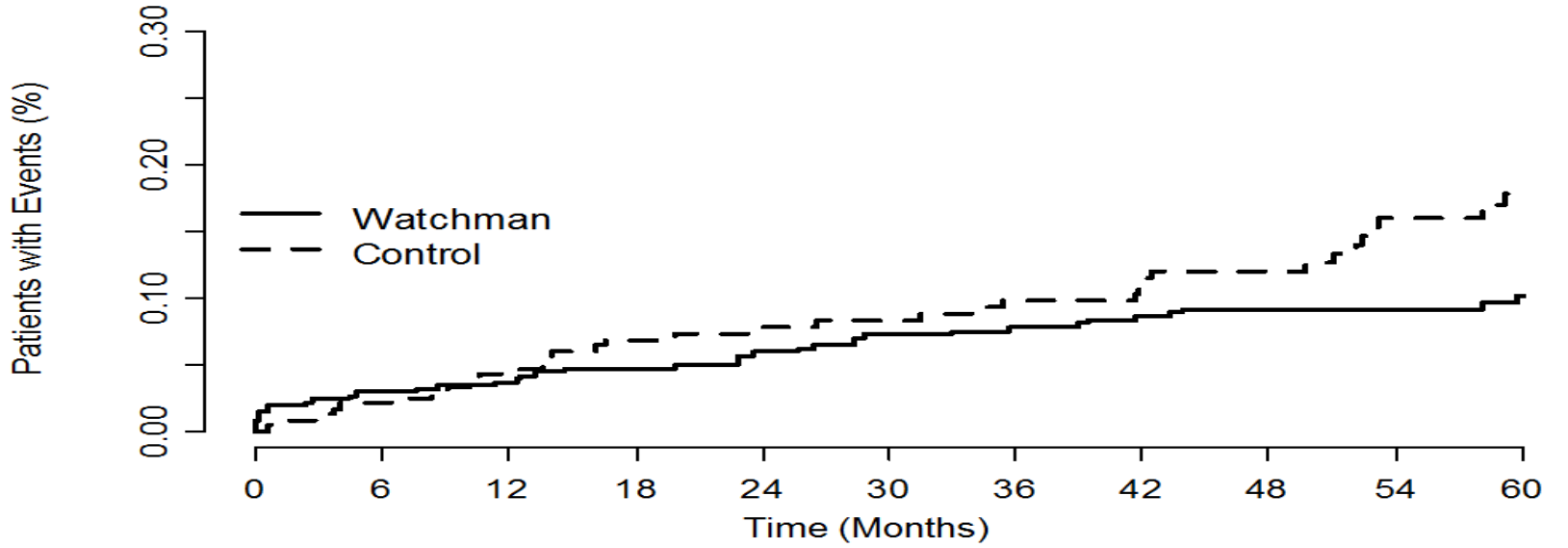

Plane of maximum diameter
distal to ostium
Fixation barbs engage LAA wall

Is the LAAO better then warfarin?



Protect AF
Holmes. Lancet 2009

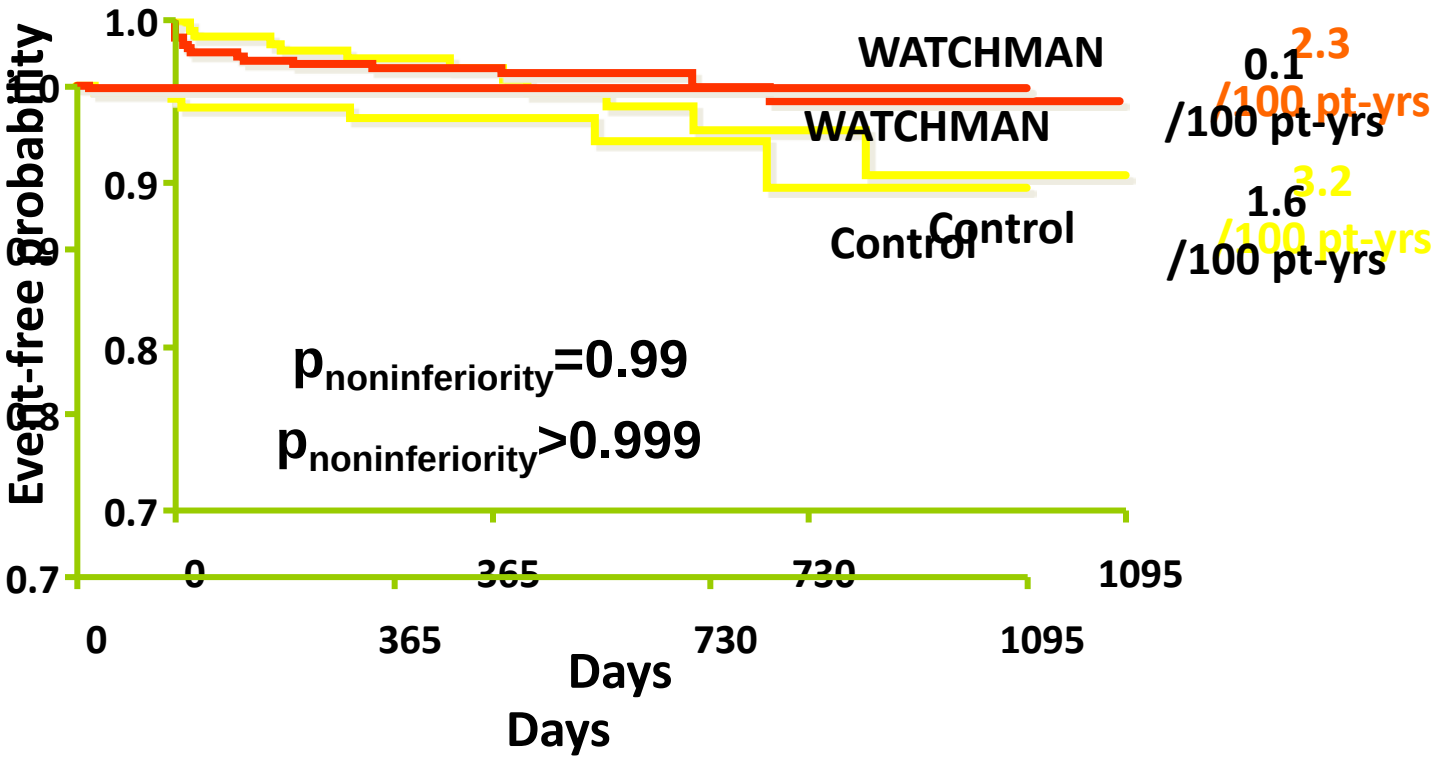
Event	Watchman Group (n = 463) Events/ Patient-Years	Watchman Group (n = 463) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Warfarin Group (n = 244) Events/ Patient-Years	Warfarin Group (n = 244) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	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



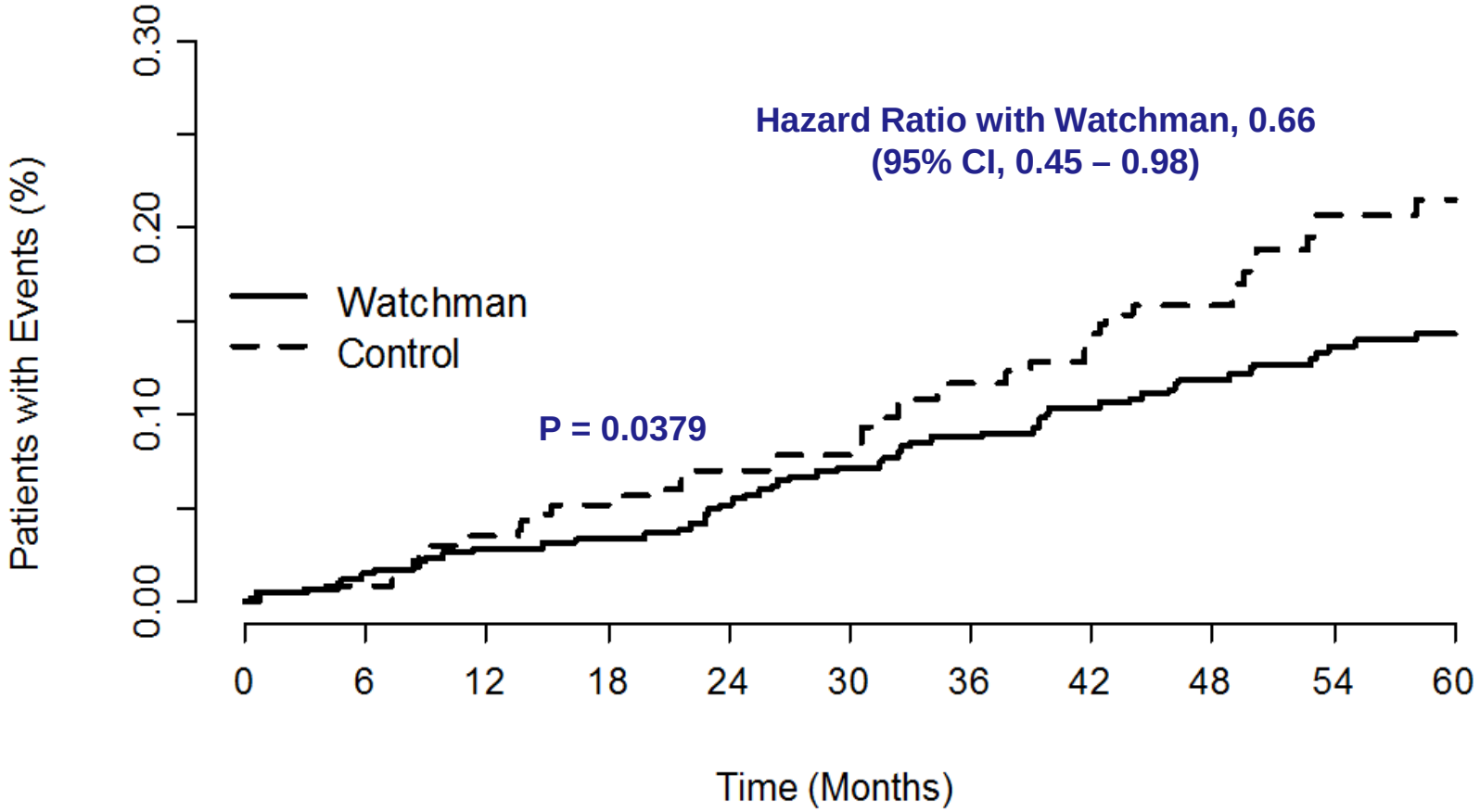
No. at Risk

Watchman	463	398	382	370	360	345	337	327	317	285	196
Control	244	230	218	210	200	188	173	159	147	121	87

Intent-to-Treat: Hemorrhagic stroke



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

PROTECT AF Patient Risk Factors

	WATCHMAN N= 463	Control N= 244	p-value
$CHADS_2$ Score:			0.37
1	34.1%	27.0%	
2	33.9%	36.1%	
3	19.0%	20.9%	
4	8.0%	9.8%	
5	4.1%	4.1%	
6	0.9%	2.0%	
AF Pattern:			0.76
Paroxysmal	43.2%	40.6%	
Persistent	21.0%	20.5%	
Permanent	34.6%	38.1%	
Unknown	1.3%	0.8%	
LVEF (%)	57.3 ± 9.7	56.7 ± 10.1	0.42

PROTECT-AF:Long-Term Follow-Up Analysis

- Mean follow-up 45 months (range 0–77.5) = 2,621 patient-years
- RELY (2.0 yrs), ROCKET-AF (1.9 yrs), ARISTOTLE (1.8 yrs)

- All analyses by intention-to-treat
- Primary Efficacy and Safety endpoints
  - Bayesian model stratified for CHADS2 score
- All Secondary Analyses (including All-Cause Mortality)
  - Used Cox proportional hazards model

Circulation 2013

Event at 1500 pts per year

	Primary Efficacy	All Strokes	CV/unexplained death	Systemic Embolism
Watchman	3	2	1	0,3
Warfarin	4,3	2,7	2,8	0

PROTECT AF: WATCHMAN Final Primary Efficacy (2717 Pt Yrs)

	Event Rate (per 100 Pt-Yrs)		Rate Ratio	Posterior Probability	
	WATCHMAN	Warfarin	(95% CrI)	Non-inferiority	Superiority
Primary efficacy	**2.2**	**3.7**	**0.61 (0.42, 1.07)**	**>99%**	**95.4%**
Stroke (all)	1.5	2.2	0.68 (0.42, 1.37)	>99%	83%
Ischemic	1.3	1.1	1.25 (0.72, 3.27)	78%	15%
Hemorrhagic	0.2	1.1	0.15 (0.03, 0.49)	>99%	>99%
Systemic embolism	0.2	0.0	N/A	N/A	N/A
Death (CV/unexpl)	1.0	2.3	0.44 (0.26, 0.90)	>99%	99%

Reddy V. et al TCT 2014

Randomized Trial of LAA Closure vs Warfarin for Stroke/ Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation (PREVAIL)

	PROTECT AF	PREVAIL
Randomization	2:1	2:1
Time from randomization to implant	7-14[1] days	2 days
Roll-in	New implanter: 1st 3 patients[2]	New implanter: 1st 2 patients Experienced: 1st patient
Exclusion of clopidogrel	No exclusion	Indication for clopidogrel therapy or has taken clopidogrel within 7 days prior to enrollment
Inclusion differences	$CHADS_2 \geq 1$	CHADS2 > 2 or CHADS2 = 1 if any of the following apply*: • Female age >75 • Baseline LVEF > 30 and < 35% • Age 65-74 and has diabetes or coronary artery disease • Age 65 or greater and has documented congestive heart failure

Demographics

Device Patients

Characteristic	PROTECT AF N=463	CAP N=566	PREVAIL N=269	P value
Age, years	71.7 ± 8.8 (463) (46.0, 95.0)	74.0 ± 8.3 (566) (44.0, 94.0)	74.0 ± 7.4 (269) (50.0, 94.0)	<0.001
Gender (Male)	326/463 (70.4%)	371/566 (65.5%)	182/269 (67.7%)	0.252
$CHADS_2$ Score (Continuous)	2.2 ± 1.2 (1.0, 6.0)	2.5 ± 1.2 (1.0, 6.0)	2.6 ± 1.0 (1.0, 6.0)	<0.001
$CHADS_2$ Risk Factors				
CHF	124/463 (26.8%)	108/566 (19.1%)	63/269 (23.4%)	
Hypertension	415/463 (89.6%)	503/566 (88.9%)	238/269 (88.5%)	
Age ≥ 75	190/463 (41.0%)	293/566 (51.8%)	140/269 (52.0%)	
Diabetes	113/463 (24.4%)	141/566 (24.9%)	91/269 (33.8%)	
Stroke/TIA	82/463 (17.7%)	172/566 (30.4%)	74/269 (27.5%)	

Most notable differences:
Age, Diabetes, and Prior Stroke/TIA

PROTECT AF and CAP data
from Reddy, VY et al. *Circulation*. 2011;123:417-424.

Prevail Primary Endpoints

- Acute (7-day) occurrence of death, ischemic stroke, systemic embolism and procedure or device related complications requiring major cardiovascular or endovascular intervention
  - Timepoint = 7 days post randomization
- Comparison of composite of stroke, systemic embolism, and cardiovascular/unexplained death
  - Timepoint = 18 months
- Comparison of ischemic stroke or systemic embolism occurring >7 days post randomization
  - Timepoint = 18 months

TABLE 4 Late-Ischemic Coprimary Endpoint: PREVAIL Subjects Only (Intention-to-Treat)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Noninferiority Criterion	18-Month Rate Difference (95% CrI)	Rate Difference Noninferiority Criterion
0.0253	0.0200	1.6 (0.5 to 4.2)	95% CrI upper bound <2.0	0.0053 (-0.0190 to 0.0273)	95% CrI upper bound <0.0275

Abbreviations as in Tables 2 and 3.

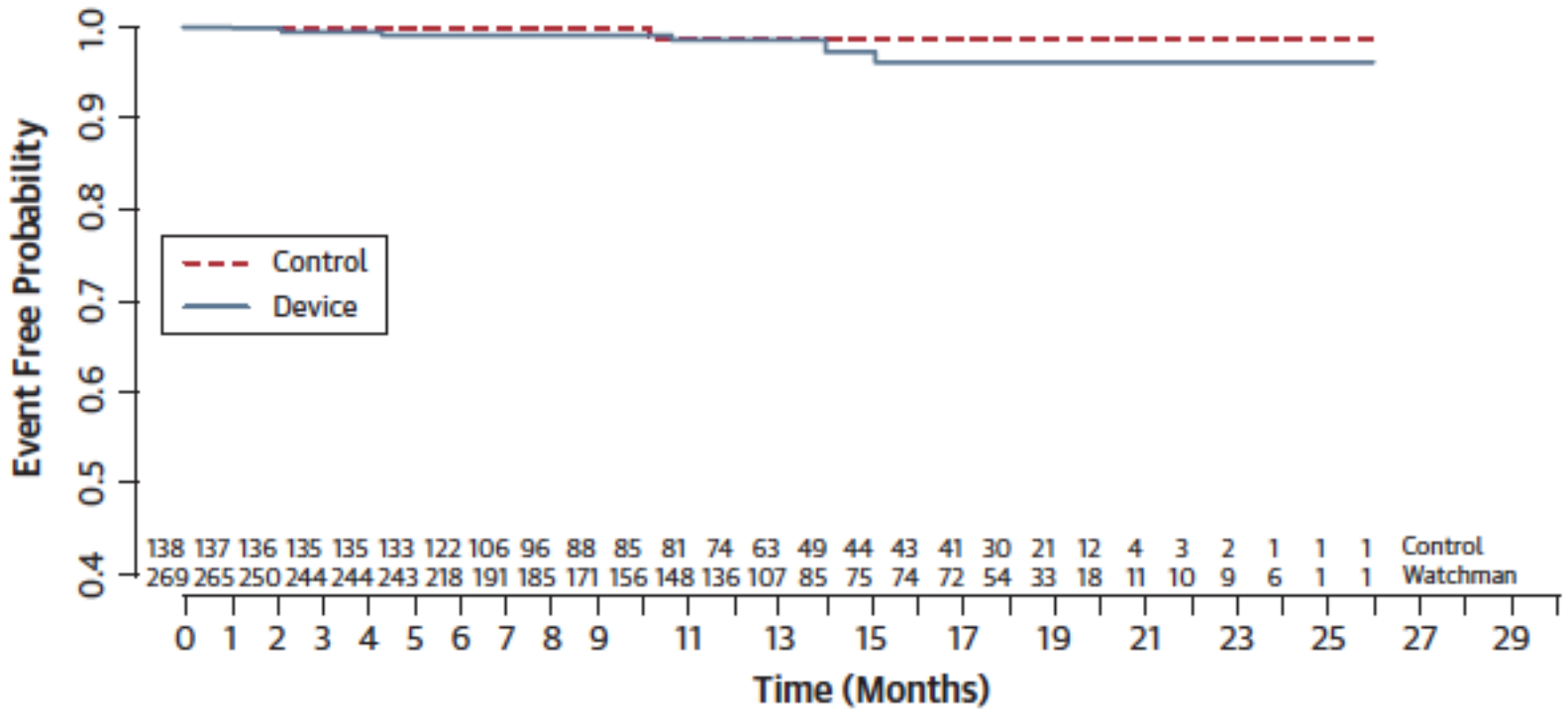
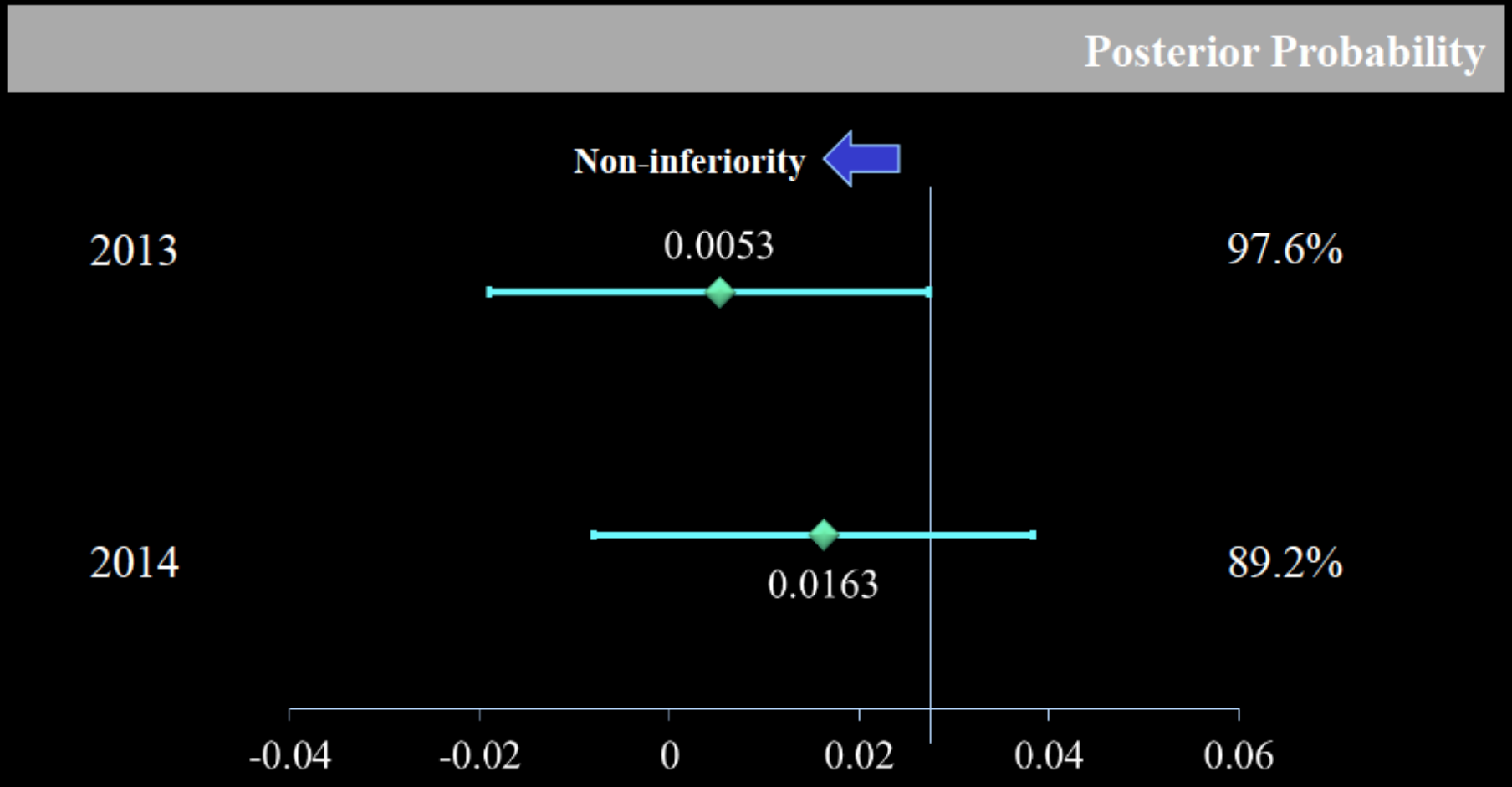


FIGURE 3 Kaplan-Meier Curve: Freedom From Second Primary Endpoint Event (Intention-to-Treat)

J Am Coll Cardiol. 2014 Jul 8;64

PREVAIL Ad hoc Analysis: Second Primary Endpoint (2013 vs 2014)



Bayesian model results

PREVAIL-only: New First Events Since 2013 Panel

	New First Events Since 2013 Panel			
	WATCHMAN N=269		Warfarin N=138	
Endpoint Event	n	%	n	%
Primary Efficacy	**10**	**3.7**	**5***	**3.6**
All Stroke	9	3.3	2	1.4
Ischemic	8	3.0	0	0
Hemorrhagic	1	0.4	2*	1.4
Systemic Embolism	0	0	0	0
Death (CV or Unexplained)	1	0.4	4*	2.9

* One patient had a hemorrhagic stroke followed by death. This was only counted as a single event for the combined primary endpoint per the statistical analysis plan

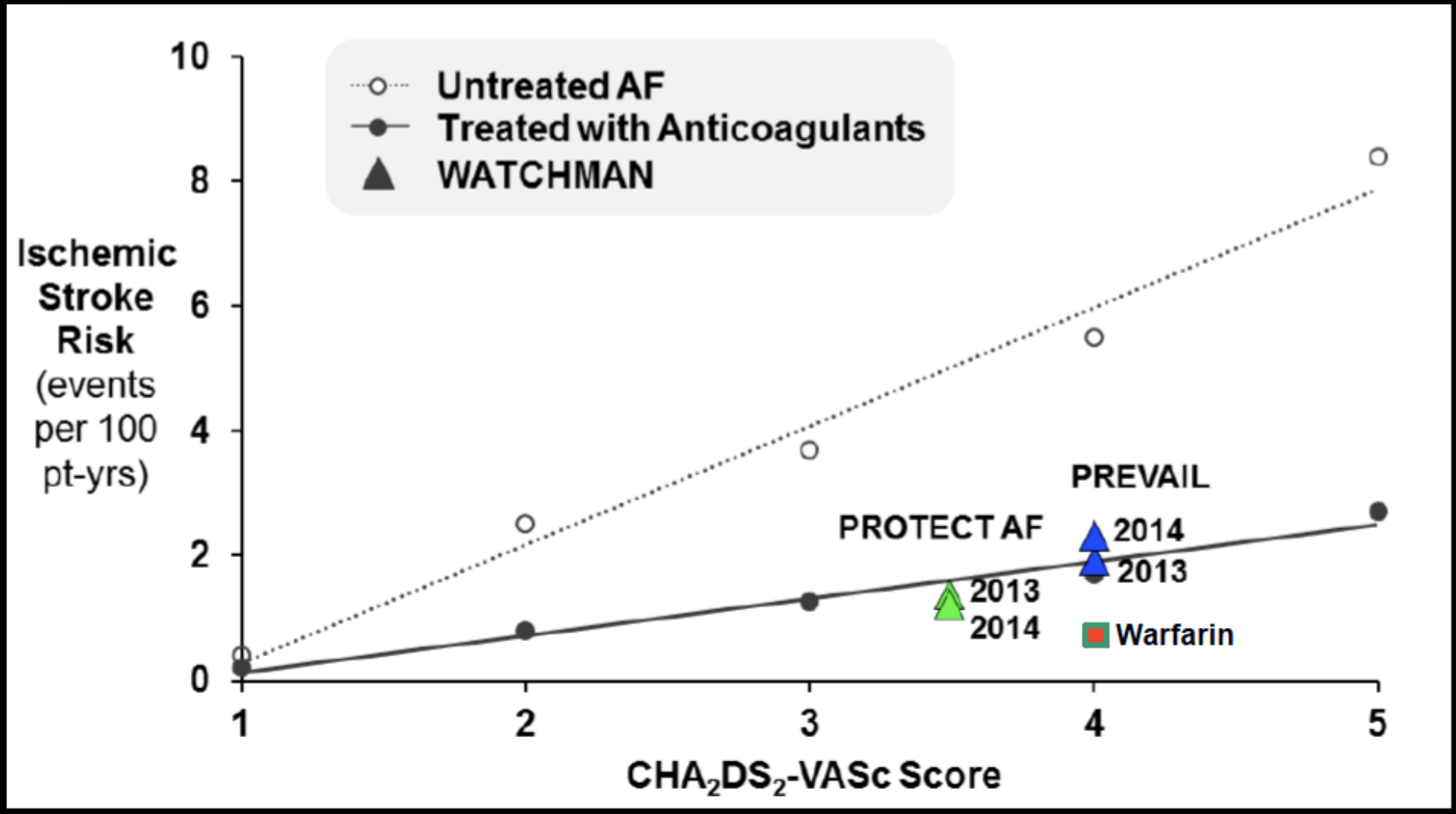
* One patient had a hemorrhagic stroke followed by death. This was only counted as a single event for the combined primary endpoint per the statistical analysis plan

PREVAIL-only: Primary Efficacy Rates

Endpoint Event	Total Endpoint Events Event Rate (per 100 pt-yrs) WATCHMAN N=269	Warfarin N=138
Composite Primary Efficacy	**4.3**	**3.0**
Individual Components		
All Stroke	2.7	1.0
Ischemic	2.3	0.3
Hemorrhagic	0.4	0.7
Systemic Embolism	0.2	0
Death (CV or Unexplained)	1.4	2.3

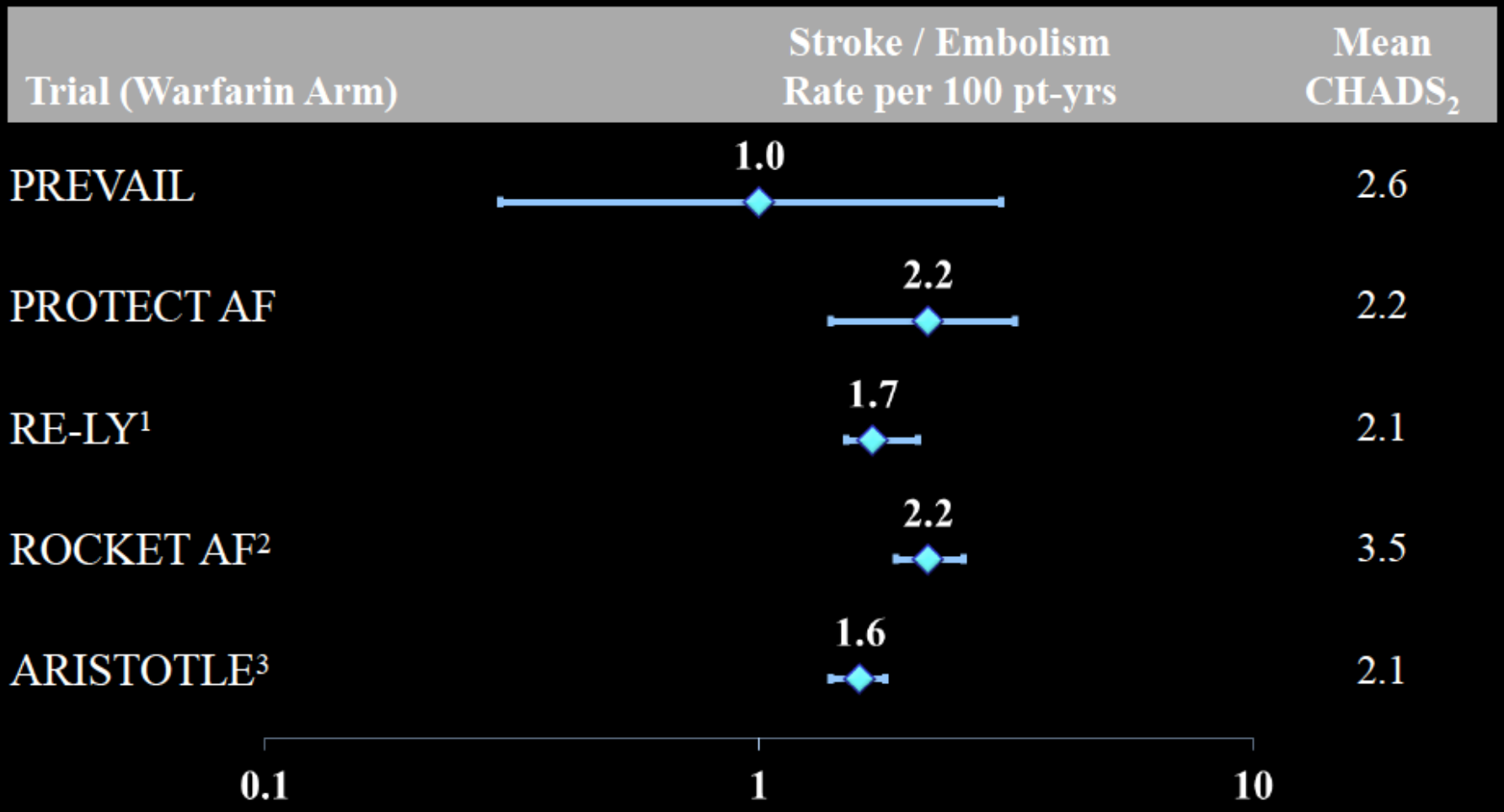
*** One patient had a hemorrhagic stroke followed by death. This was only counted as a single event for the combined primary endpoint per the statistical analysis plan**

PREVAIL Ischemic Stroke Rate Aligns with Expected Rate



Friberg. Eur Heart J (2012); NICE UK (2014)

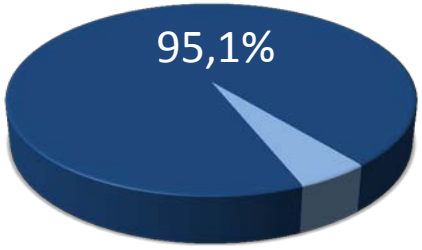
PREVAIL: Warfarin Stroke Rate Differs from Other Trials



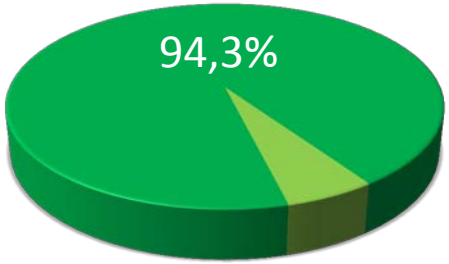
1. Connolly SJ. N Engl J Med (2009); 2. Patel MR. N Engl J Med (2011); 3. Granger CB. N Engl J Med (2011)

Is LAAO with the Watchman safe and feasible?

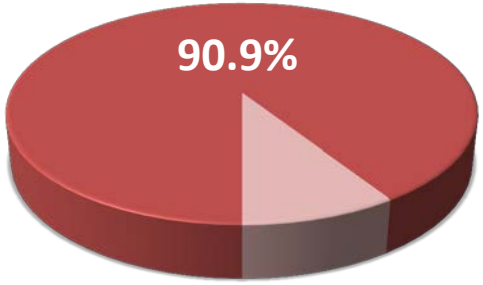
PREVAIL
Implant success



CAP
Implant success



PROTECT AF
Implant success

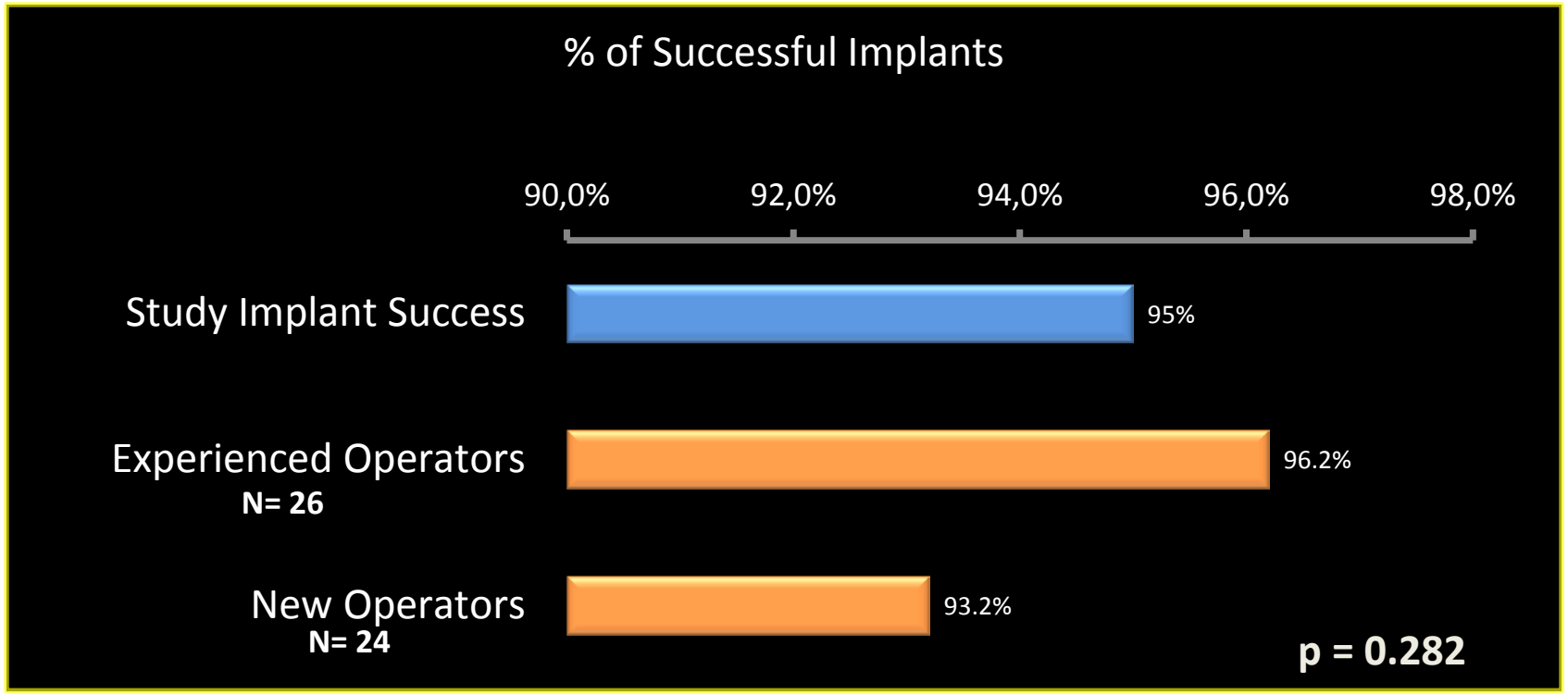


P=0.04

PROTECT AF and CAP data
from Reddy, VY et al. *Circulation*. 2011;123:417-424.

New vs Experienced Operators

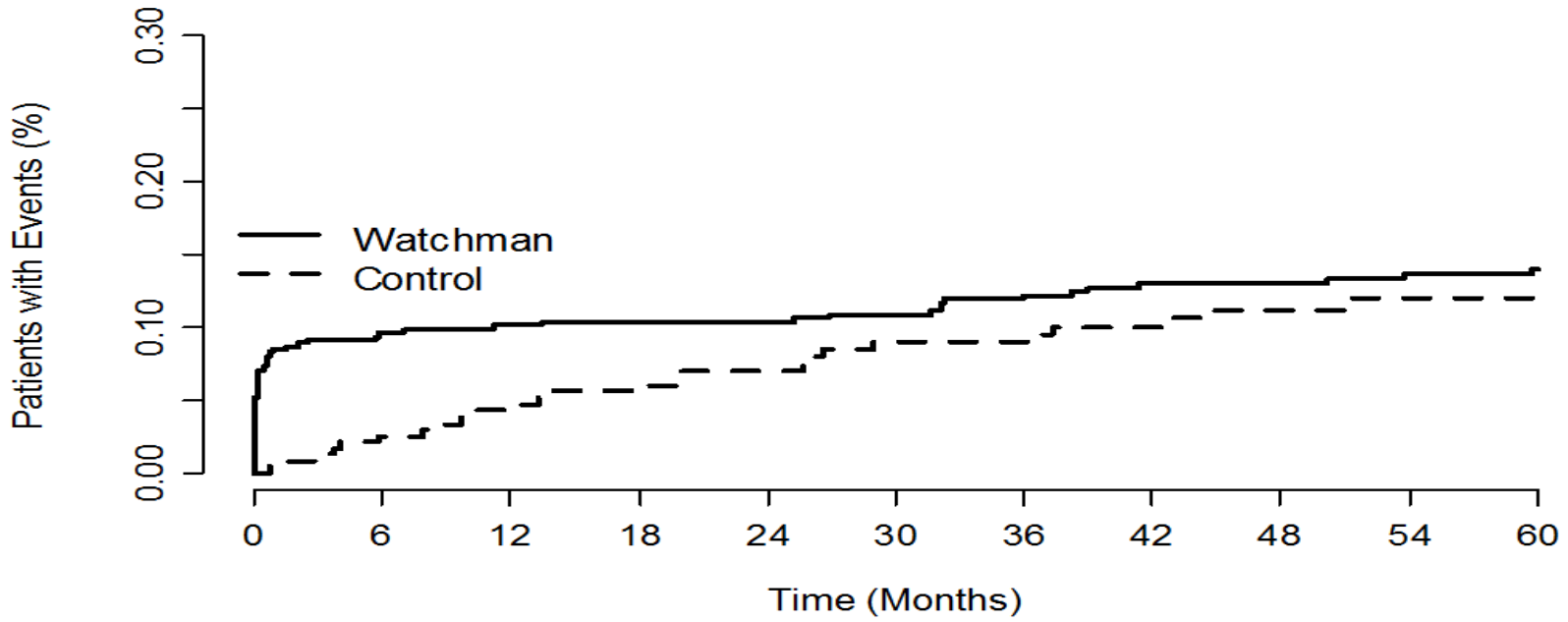
- Protocol required a minimum of 20% of subjects enrolled at new centers and 25% of subjects enrolled by new operators
- 18 out of 41 centers did not have prior WATCHMAN experience
- 40% of patients enrolled at new sites by new operators



Prevail data

PROTECT AF:Primary Safety 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 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

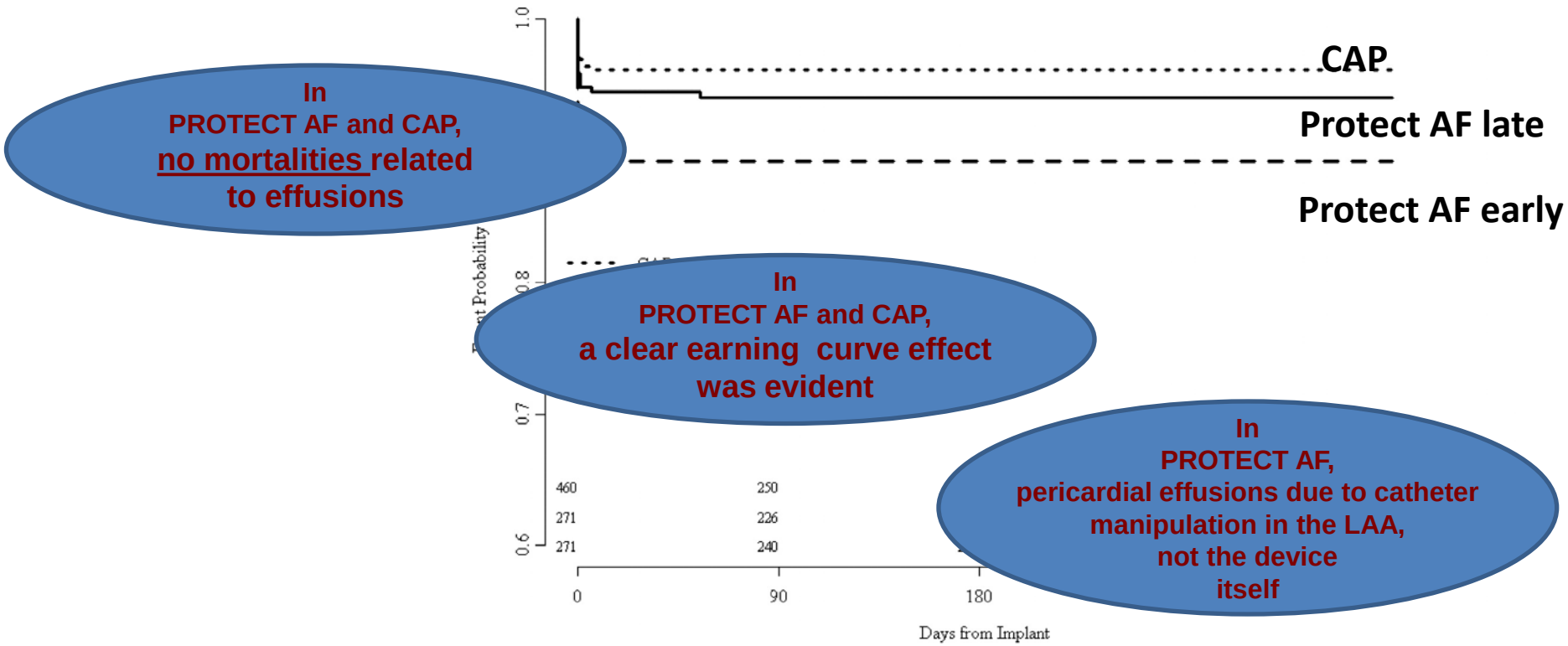


No. at Risk

Watchman	463	376	364	357	353	341	332	320	310	277	190
Control	244	228	214	207	195	183	169	153	139	117	86

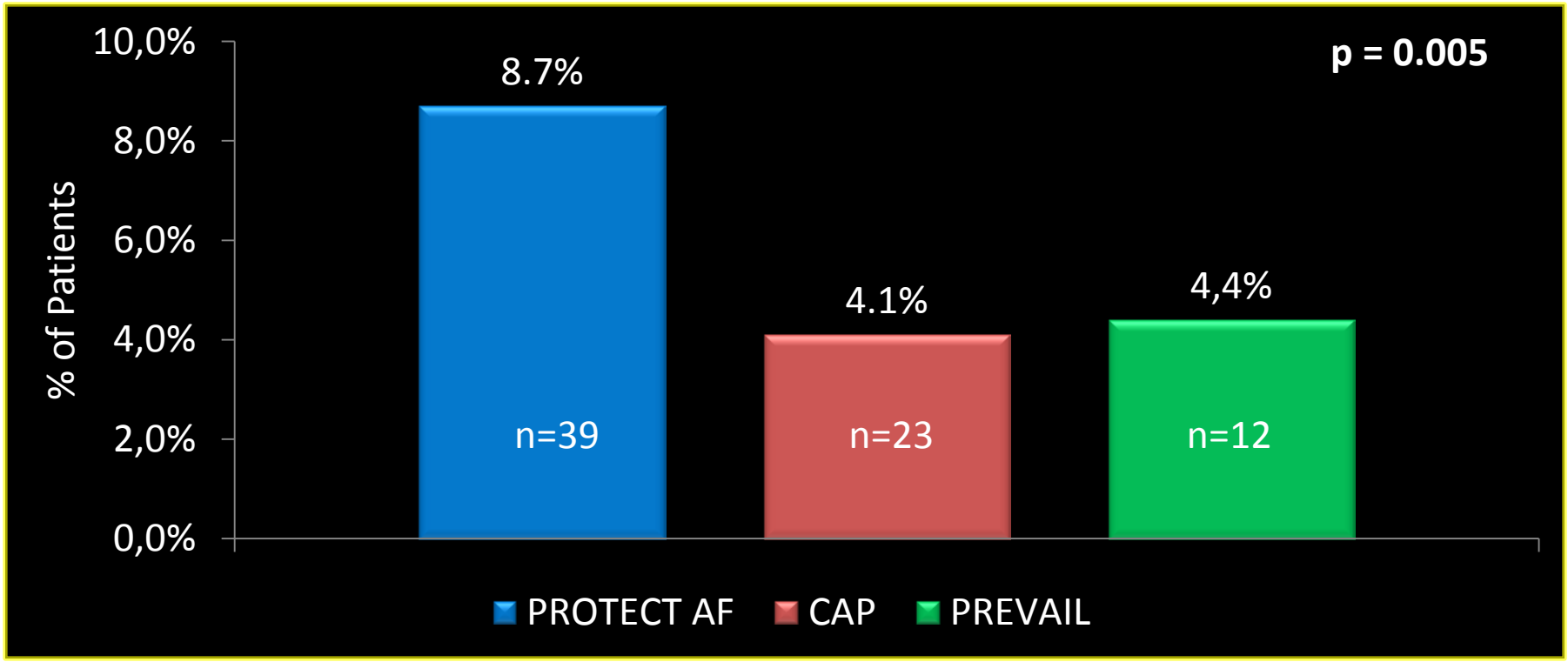
LAA closure - Adverse Events
PROTECT AF randomized arm vs. CAP Registry

Event	Protect AF (n=463)	CAP (n=460)	p
Serious pericardial effusion	4.8%	2.2%	0.007
Any serious adverse event	7.7%	3.7%	0.02



Vascular Complications
7 Day Serious Procedure/Device Related

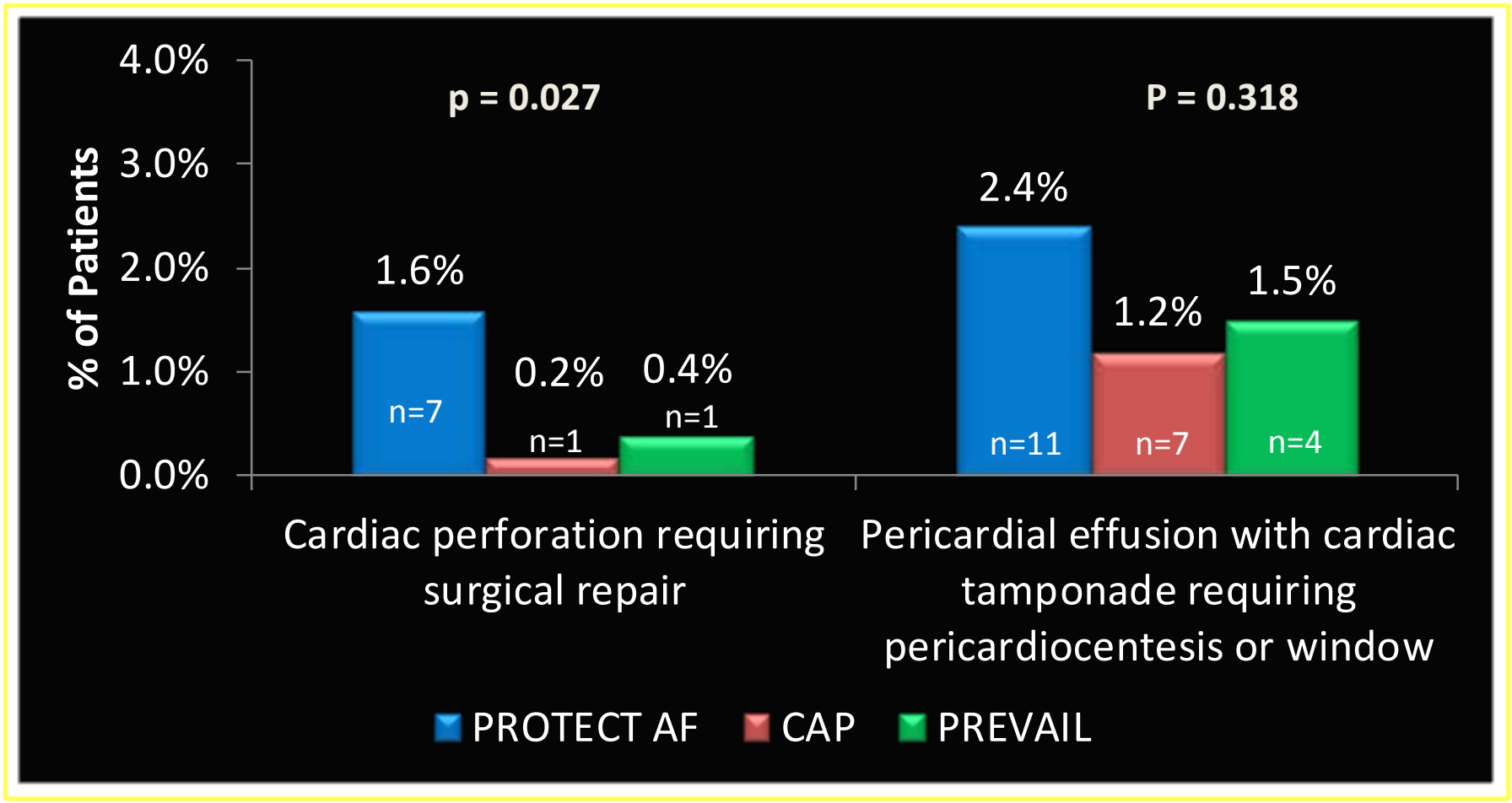
Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications[1]



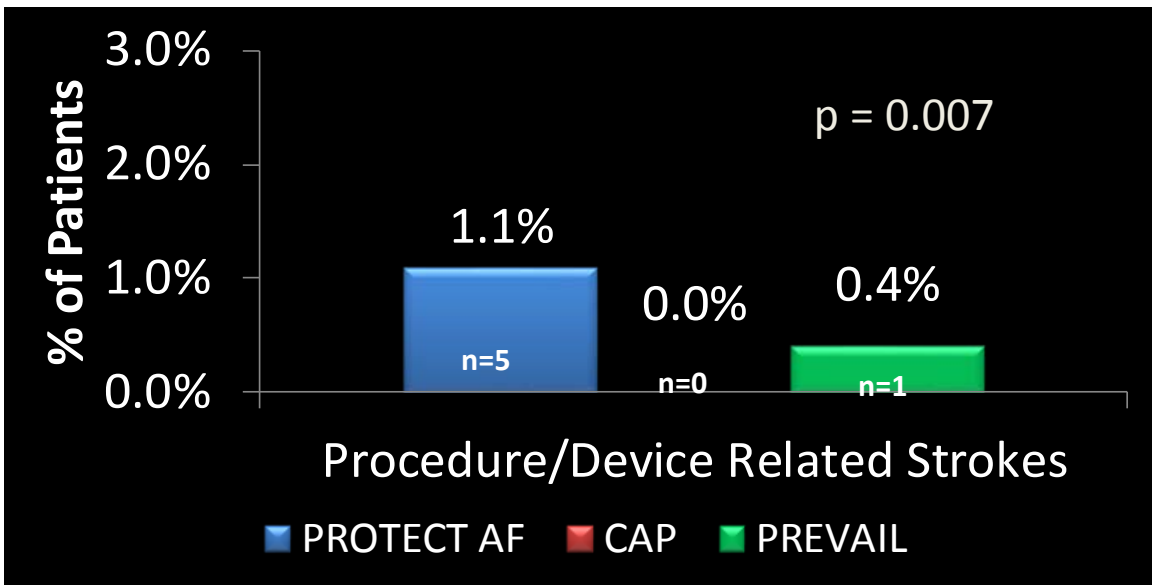
No procedure-related deaths reported in any of the trials

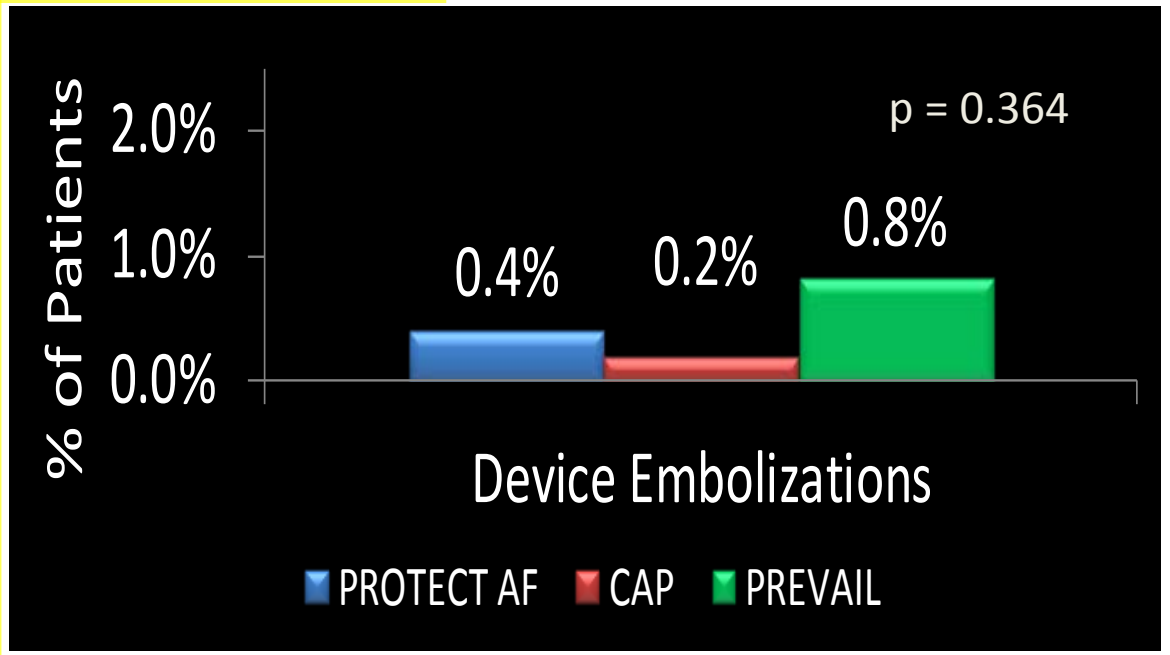
PROTECT-AF and CAP data from Reddy, VY et al. *Circulation*. 2011;123:417-424.

Pericardial Effusions Requiring Intervention



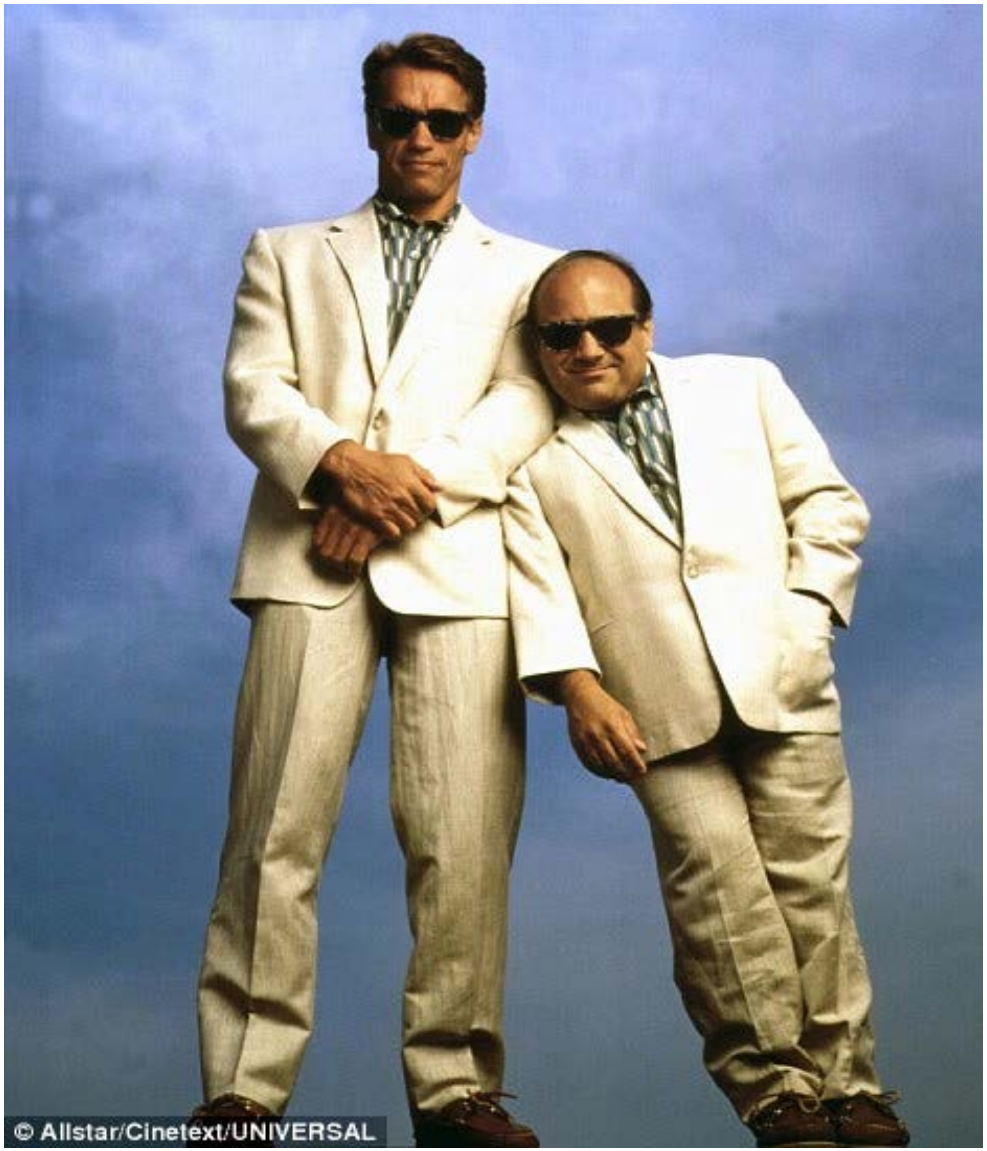
Stroke and Device Embolization





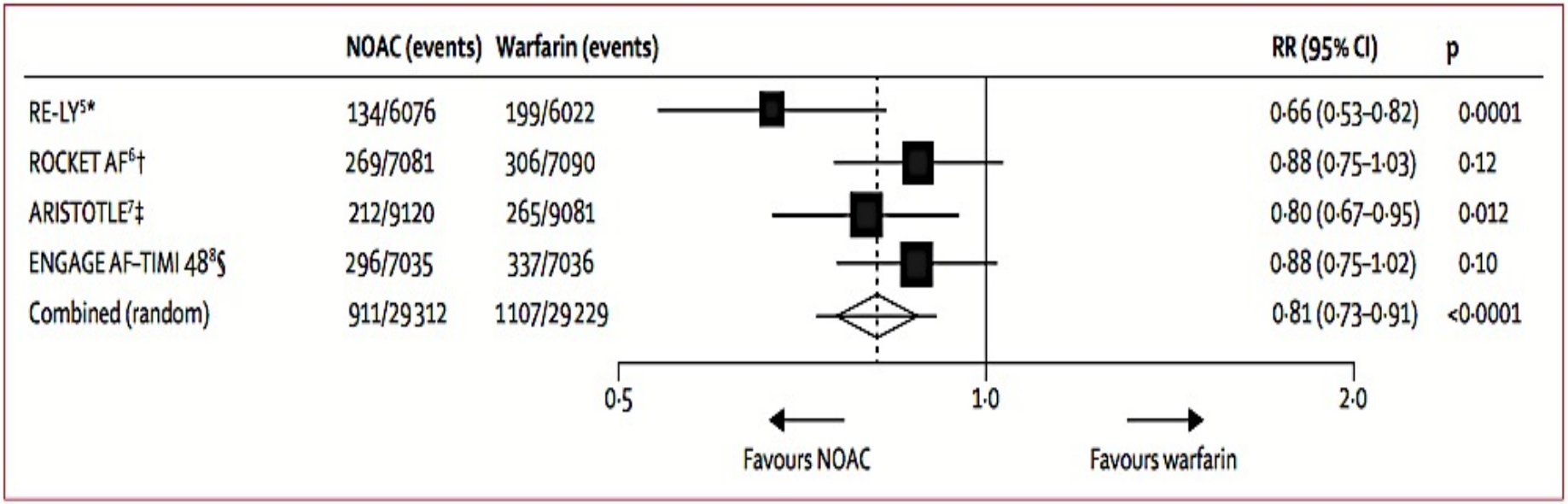
PROTECT-AF and CAP data from Reddy VY et al. *Circulation*. 2011;123:417-424

LAAOs vs NOACS



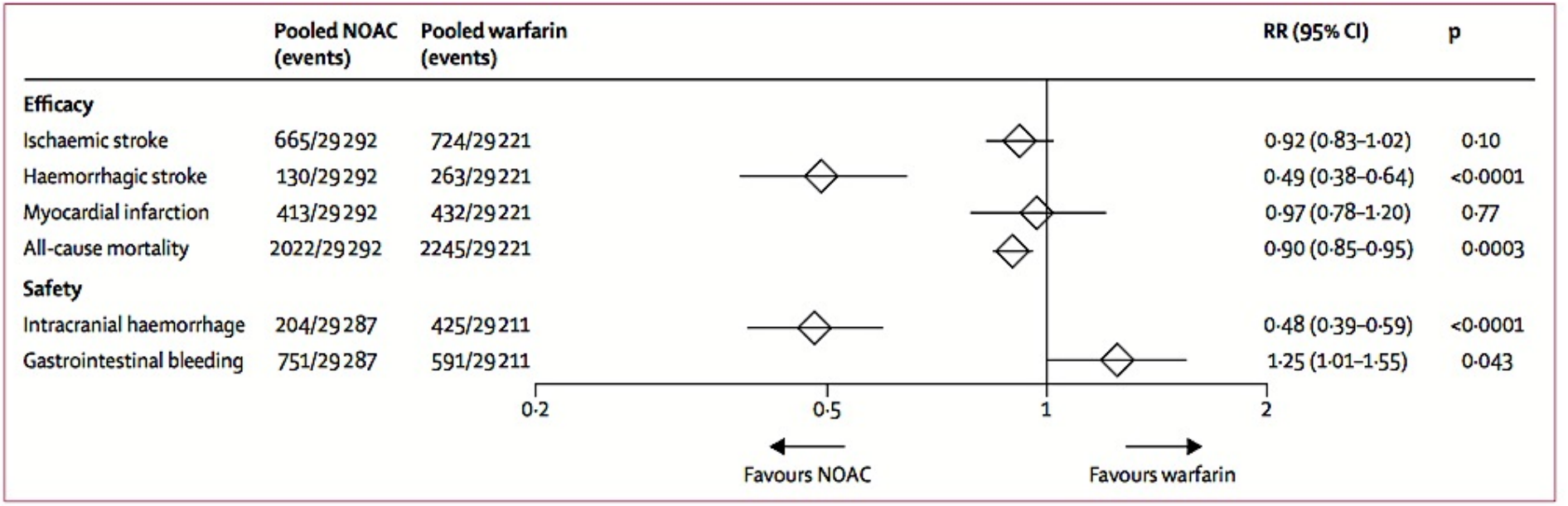
Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

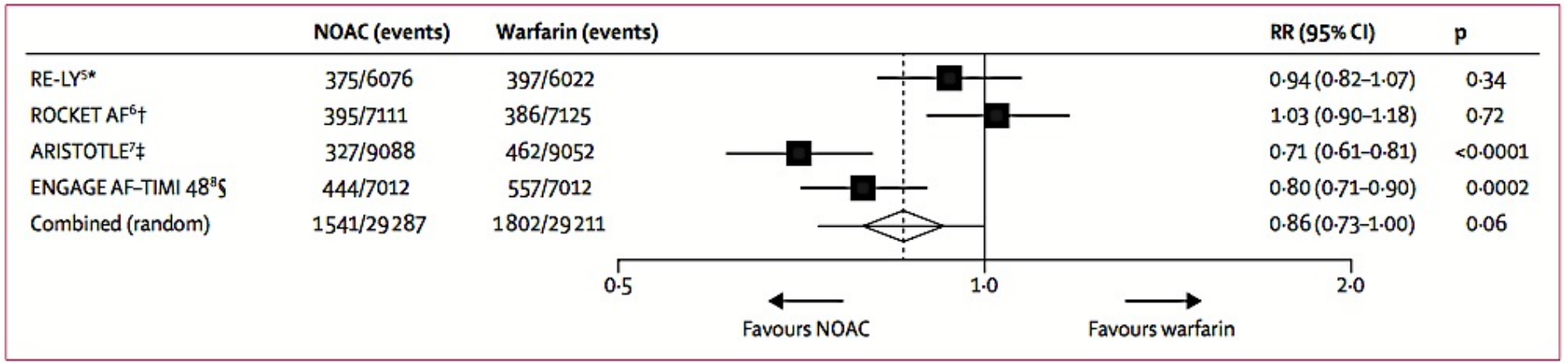
Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman



Stroke and systemic embolism

Lancet March 2014





Major bleeding

Rate of drug discontinuation

- Rely trial:

-warfarin at 1 year 10%

-warfarin 2 years 17%

-Dabi 110mg bid at 1 year 15%

-Dabi 110mg bid at 2 years 16%

-Dabi 150mg bid at 2 years 21%

- Aristotle:

-warfarin discontinued in 28%

-apixaban discontinues in 25%

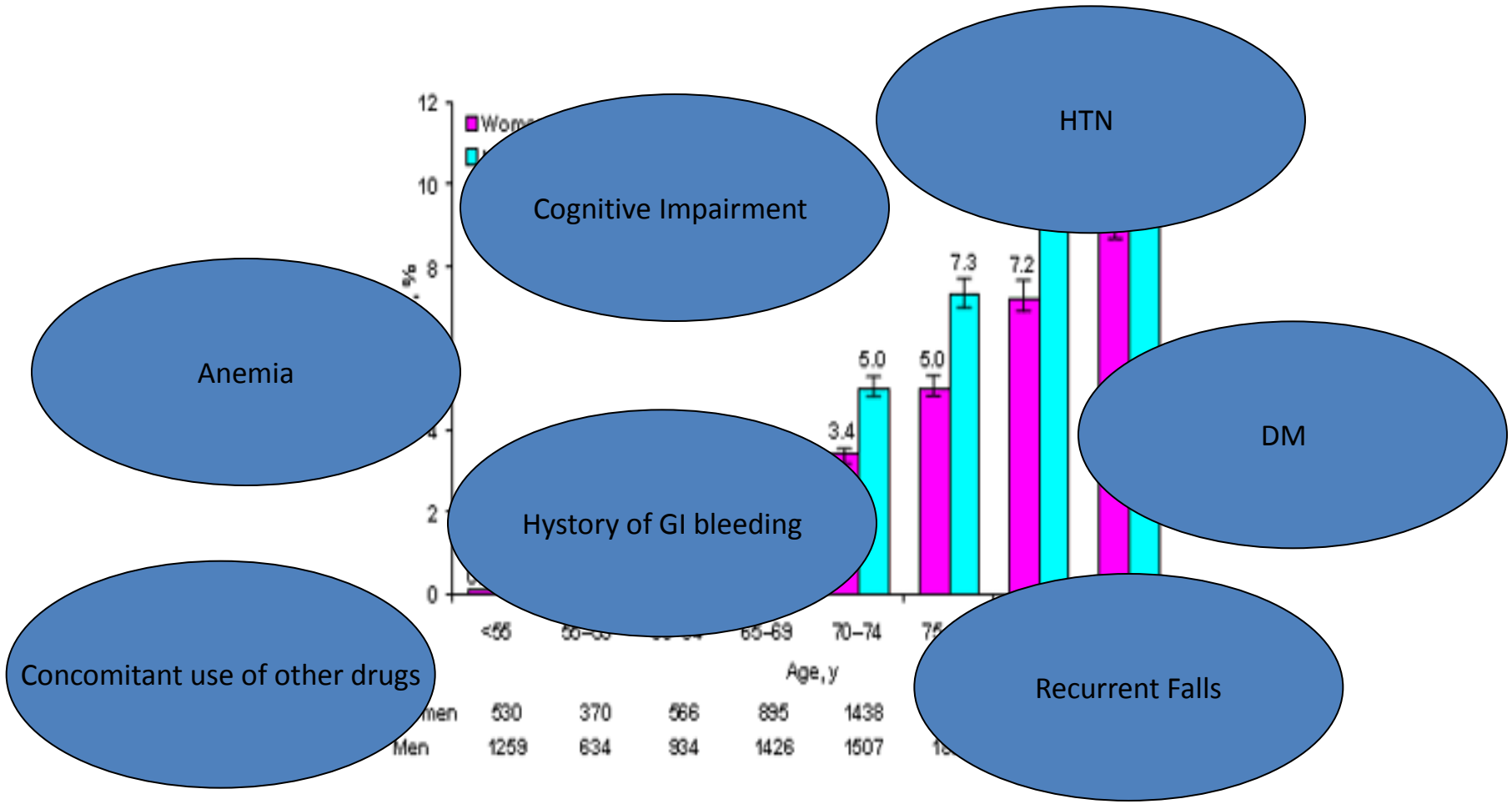
- Rocket AF:

-warfarin discontinued in 22%

-riva discontinued in 24%

- No head to head study NOACs vs LAAO

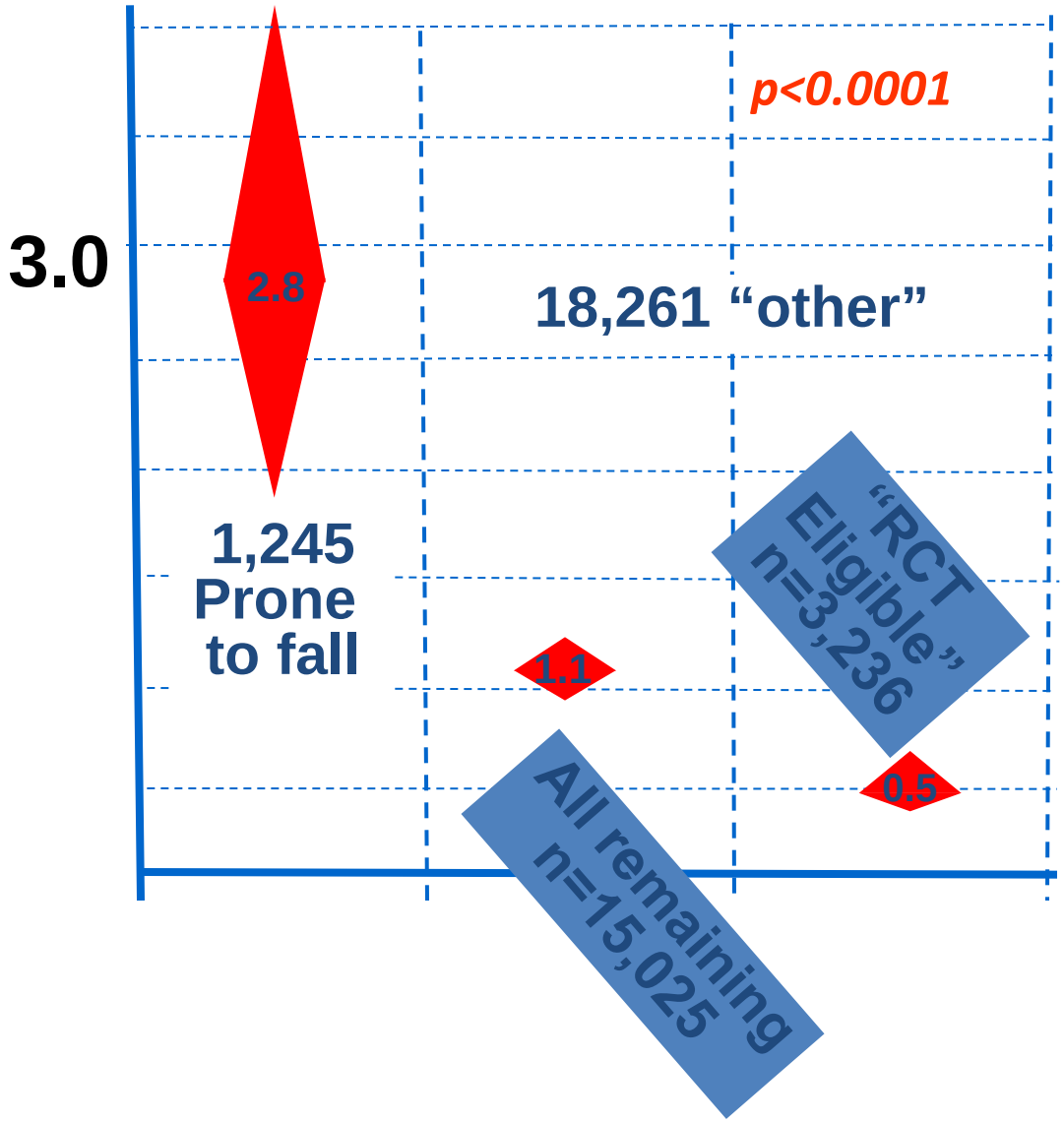
- History of bleeding and high risk for bleeding represent an exclusion criteria for any NOACs study



Go As et al.JAMA 2001

Proneness to Falls and the Risk for Intracranial Bleeds (per 100 pt-yrs)

n=1,245 prone vs. 18, 261 other (National registry of Atrial Fibrillation II)

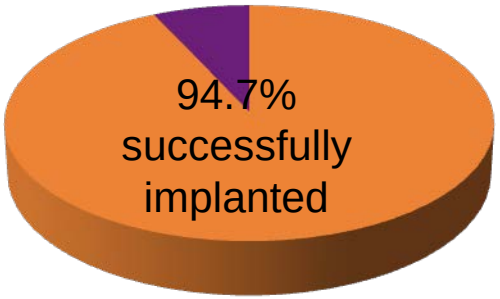


Gage, *AJM* 2005

ASAP (Aspirin Plavix) Study

- Patients history of hemorrhagic & bleeding tendencies or a warfarin hypersensitivity
- 150 patients, 4 European centers
- Average $CHADS_2$ = 2.8
- Post procedure anti-platelet regimen
  - Clopidogrel through 6 months
  - Aspirin indefinitely
- Patients followed to 2 years
  - Follow up @ 3, 6, 12, 18 & 24 months
  - TEE at 3 and 12 months
  - Average follow-up was 14.4 months

Rate of success with implantation in warfarin contraindicated patients[1]



Ave Procedure Time = 51.5 mins

[1] Braut A et al, LAA closure with the WATCHMAN Device in patients with contraindications to warfarin: preliminary results from the ASA Plavix registry (ASAP), ESC Congress 2011, Paris 27-31 August 2011

JACC 2013

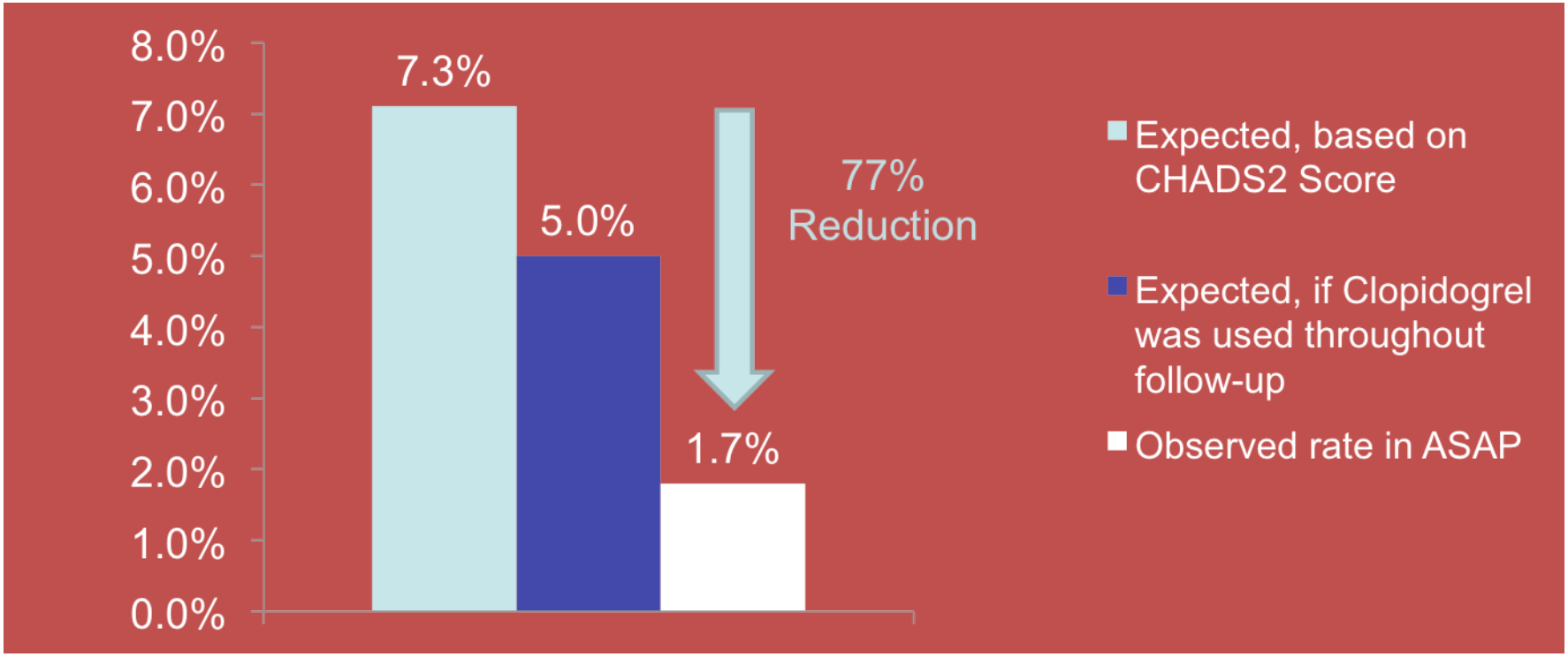
Characteristic	All patients (n=150)
Clinical	
Age (year)	72.5 ± 7.4
Male	96 (64.0%)
Stroke risk factors*	
Heart failure or reduced LV EF	43 (28.7%)
Hypertension	142 (94.7%)
Age ≥ 75 yrs	64 (42.7%)
Diabetes	48 (32.0%)
Prior stroke or TIA	61 (40.7%)
Vascular disease	27 (18.0%)
Age 65-74 yrs	64 (42.7%)
Female gender	54 (36.0%)

CHA_2DS_2-VASc score	
1	7 (4.7%)
2	12 (8.0%)
3	25 (16.7%)
4	42 (28.0%)
5	28 (18.7%)
6	18 (12.0%)
7	13 (8.7%)
8	5 (3.3%)
9	0 (0.0%)

Mean CHA_2DS_2-VASc score (entire cohort, = 150) = 4.4 ± 1.7

Reasons for Warfarin ineligibility*	
History of hemorrhagic/bleeding tendencies	140 (93.0%)
Blood dyscrasia	11 (7.3%)
Unsupervised Senility/high fall risk	6 (4.0%)
Other	8 (5.3%)

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



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

Gage et al Circ 2004 and Gage et al JAMA 2001
ACTIVE trial AHJ 2006 151(6): 1187-93

Percutaneous Left Atrial Appendage Closure With the AMPLATZER Cardiac Plug Device in Patients With Nonvalvular Atrial Fibrillation and Contraindications to Anticoagulation Therapy

Marina Urena, MD,* Josep Rodés-Cabau, MD,* Xavier Freixa, MD,† Jacqueline Saw, MD,‡ John G. Webb, MD,§ Mélanie Freeman, MD,§ Eric Horlick, MD,|| Mark Osten, MD,|| Albert Chan, MD,¶ Jean-Francois Marquis, MD,# Jean Champagne, MD,* Réda Ibrahim, MD†

Quebec City, Quebec; Montreal, Quebec; Vancouver, British Columbia; Toronto, Ontario; and Ottawa, Ontario, Canada

Age 74±8, 58% male

CHADS2 score 3 (2-4)

CHA2DS2VASc score 5 (4-6)

HAS-BLED score 4 (3-4)

Bleeding	
Intracranial hemorrhage	18 (34.6)
Gastrointestinal bleeding	12 (23.1)
Spontaneous hematoma of abdominal muscles	7 (13.5)
Otorhinolaryngological	4 (7.7)
Respiratory	3 (5.8)
Recurrent severe hematuria	1 (1.9)
Ophthalmological	1 (1.9)
Recurrent hemarthrosis	1 (1.9)
International normalized ratio lability	2 (3.8)
High risk of fall	1 (1.9)
Warfarin allergy	1 (1.9)
Severe anemia	1 (1.9)

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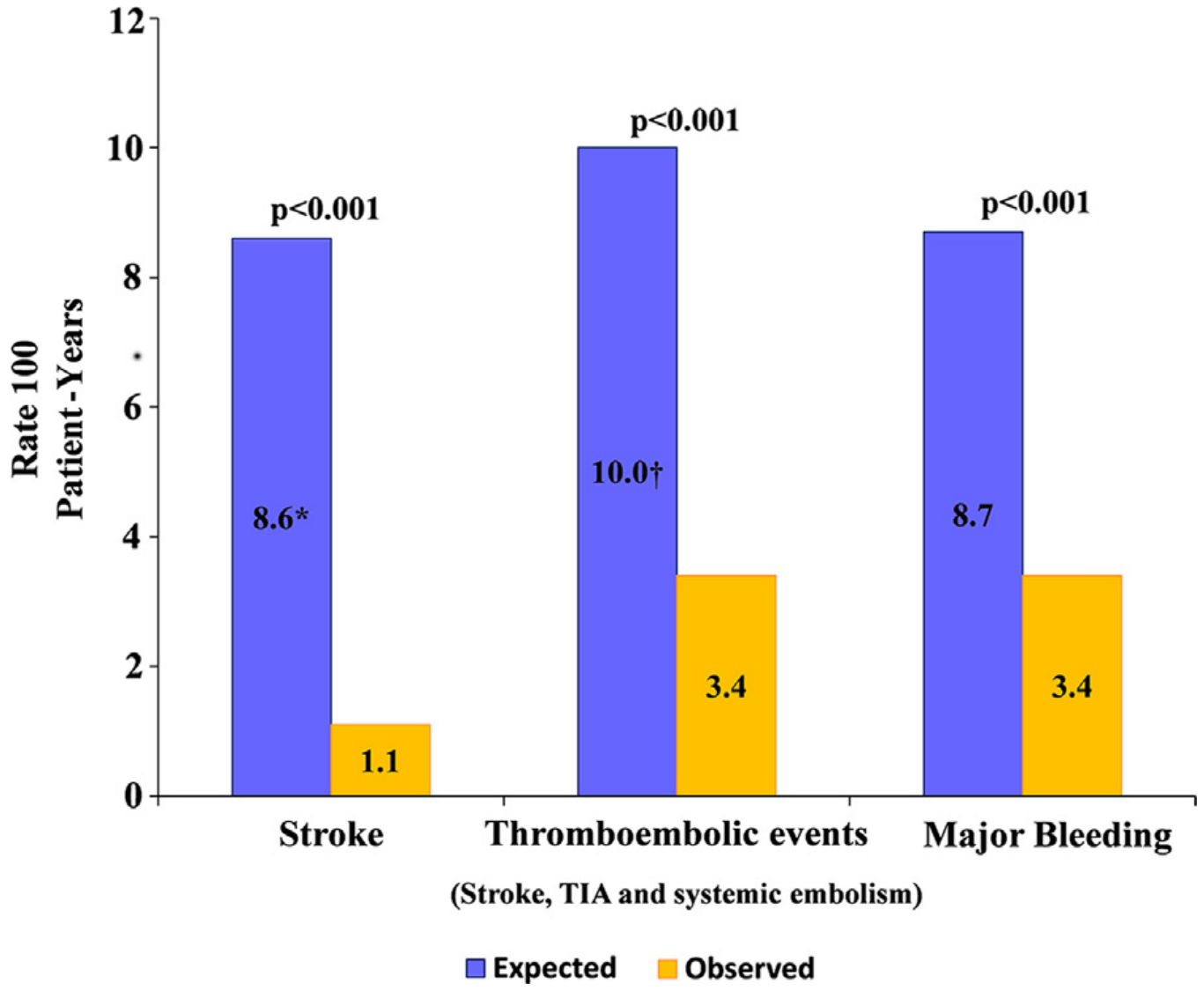
Procedural success	51 (98.1)
In-hospital outcomes	
Pericardial effusion	0 (0)
Major bleeding†	2 (3.8)
Device embolization	1 (1.9)
Myocardial infarction	0 (0)
Systemic embolism	0 (0)
Transient ischemic attack	1 (1.9)
Stroke	0 (0)
Death	0 (0)
MAEs‡	3 (5.8)
Hospitalization length, days	1 (1–1)
Device embolization	0 (0)
Cardiac tamponade	1 (1.9)
Major bleeding	1 (1.9)
Transient ischemic attack	1 (1.9)
Stroke	1 (1.9)
Systemic embolism	0 (0)
Death	
Overall	3 (5.8)
Cardiovascular or neurologic death*	1 (1.9)

F.U 20±5 months



Mean f.u 20±months

Safety of Percutaneous Left Atrial Appendage Closure with the Amplatzer Cardiac Plug in Patients with Atrial Fibrillation and Contraindications to Anticoagulation

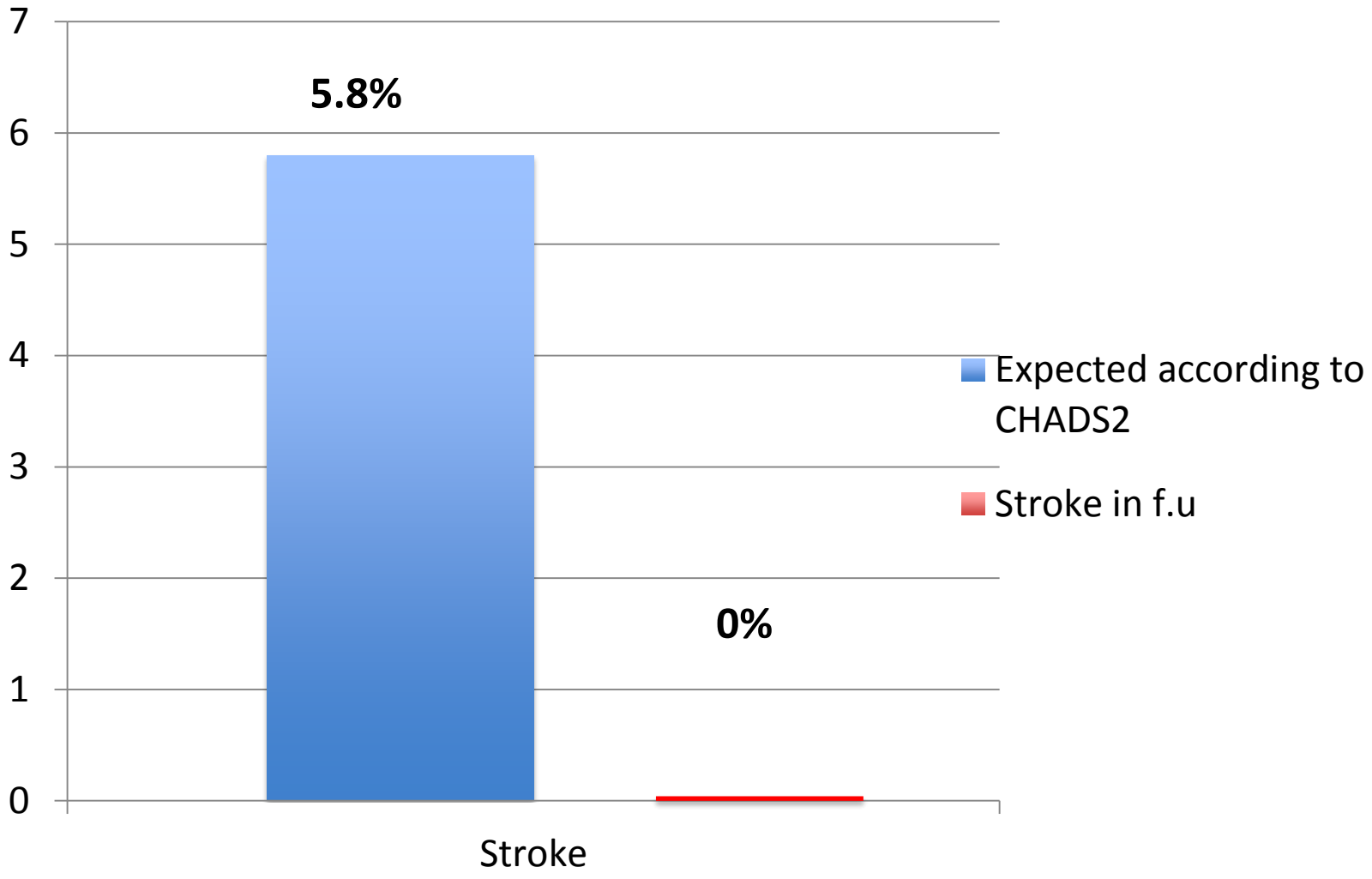
Jens Wiebe, MD, Stefan Bertog, MD, Jennifer Franke, MD, Olga Wettstein, MD, Katharina Lehn, MD, Ilona Hofmann, MD, Laura Vaskelyte, MD, and Horst Sievert,* MD

TABLE I. Baseline Characteristics

N	60		
Age (mean years ± SD)		72.9 ± 8.1	
$CHADS_2$ (mean score ± SD)		2.6 ± 1.4	
CHA_2DS_2-VASc (mean score ± SD)		4.3 ± 1.7	
HAS-BLED (mean score ± SD)		3.3 ± 1.0	
Number of Contraindications			
1	85.0		(51/60)
2	13.3		(8/60)
3	1.7		(1/60)
History of bleeding without oral anticoagulation	25.0		(15/60)
Eye	6.7		(1/15)
Gastrointestinal	60.0		(9/15)
Intracranial	33.3		(5/15)
History of bleeding under oral anticoagulation	63.3		(38/60)
Epistaxis	5.1		(2/38)
Eye	5.1		(2/38)
Gastrointestinal	33.3		(13/38)
Hematoma	17.9		(7/38)
Hematuria	5.1		(2/38)
Intracranial	23.1		(9/38)
Other locations	7.7		(3/38)
Non-hermorrhagical Contraindications	36.7		(22/60)
Elevated liver enzymes	13.6		(3/22)
Falling tendencies	4.5		(1/22)
Labile INR[a], % (n/N)	13.6		(3/22)
Other contraindications	40.9		(9/22)

TABLE IV. Follow-up

Follow-up time (median years, range)[a]	1.8 (1.0–2.8)	
Patient years	103.2	
Patient contacts (mean $n \pm$ SD)	3.7 ± 1.3	
Device-associated thrombus (%; *n*/*N*)	3.5	(2/57)
Cerebral Ischemia (% per year)	0.0	
Stroke (% per year)	0.0	
TIA[b] (% per year)	0.0	
Other thromboembolic event (% per year)	0.0	
Bleeding complications (% per year)	8.7	
Major bleeding complications (% per year)	1.9	
Minor bleeding complications (% per year)	6.8	
Major cardiovascular AE (% per year)	15.5	
Major noncardiovascular AE (% per year)	18.4	
Deaths (% per year)	4.8	



Mean Follow Up 1.8 years (1-2.8)

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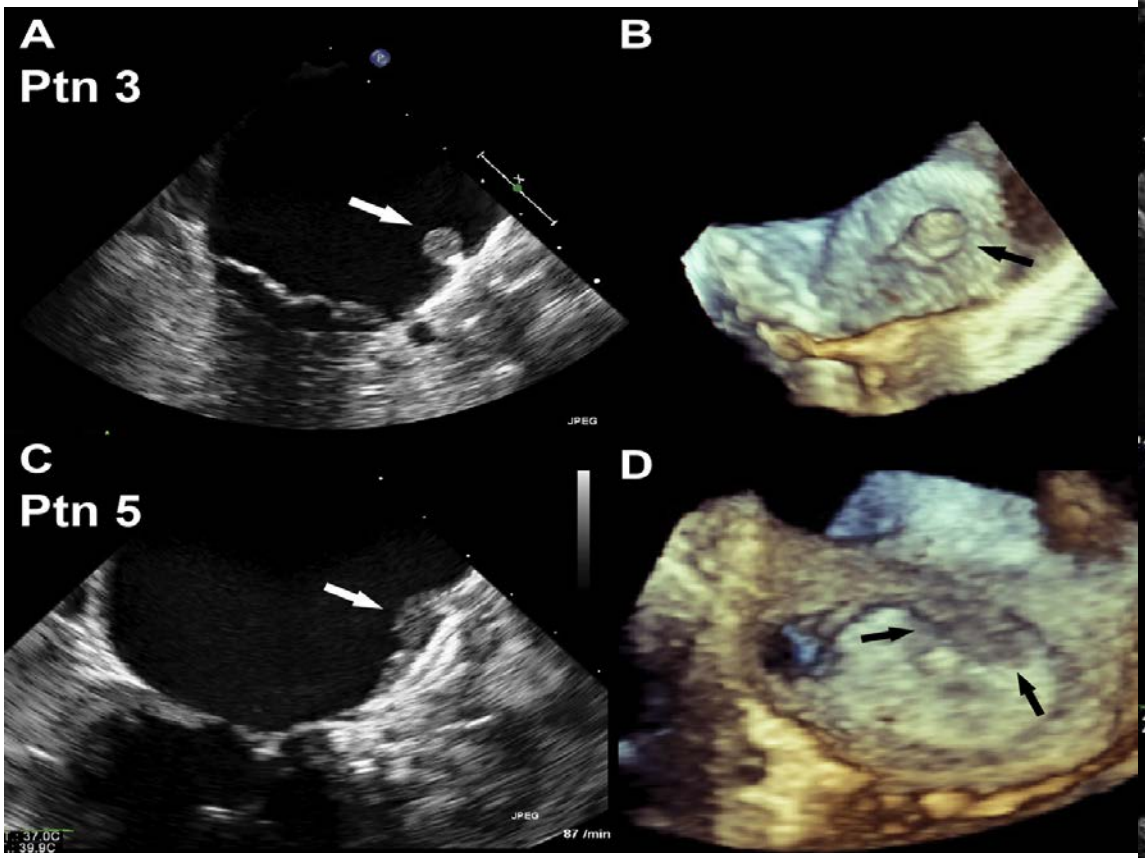
Risk Factors for Thrombus Formation on the Amplatzer Cardiac Plug After Left Atrial Appendage Occlusion

Bjoern Plicht, MD,* Thomas F. M. Konorza, MD,* Philipp Kahlert, MD,* Fadi Al-Rashid, MD,* Hagen Kaelsch, MD,* Rolf Alexander Jánosi, MD,* Thomas Buck, MD,* Hagen S. Bachmann, MD,† Winfried Siffert, MD,† Gerd Heusch, MD,‡ Raimund Erbel, MD*

Essen, Germany



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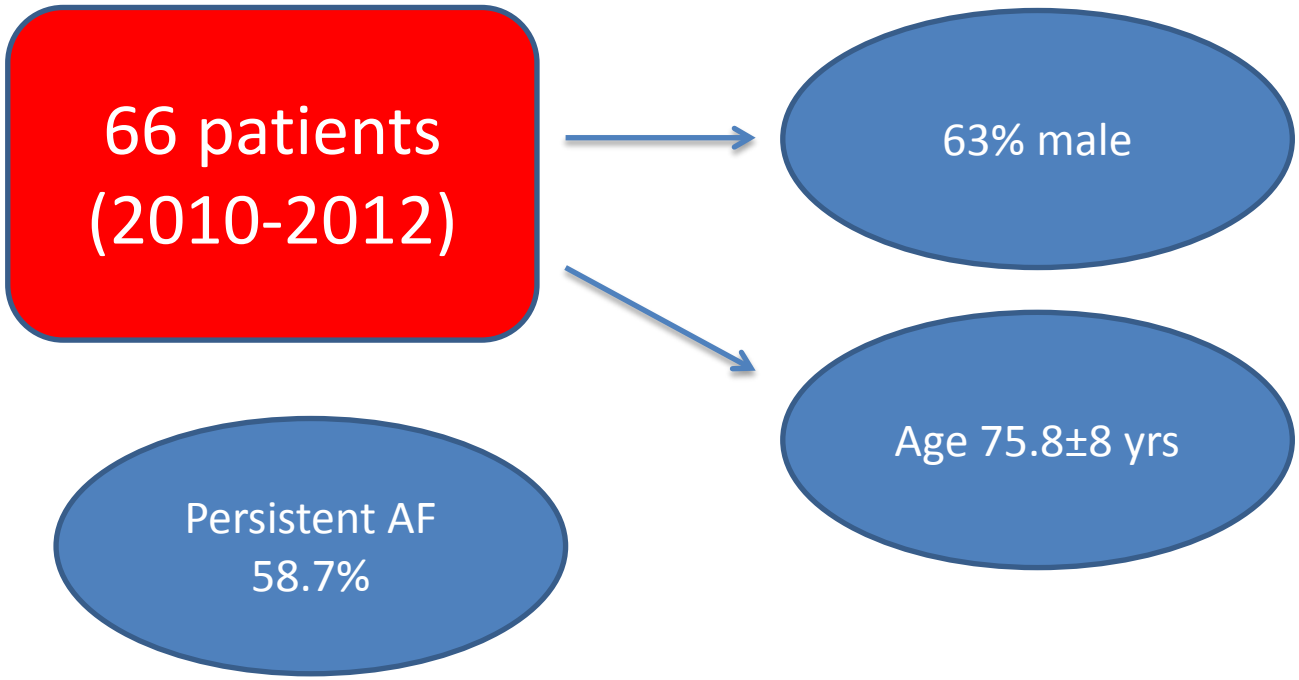
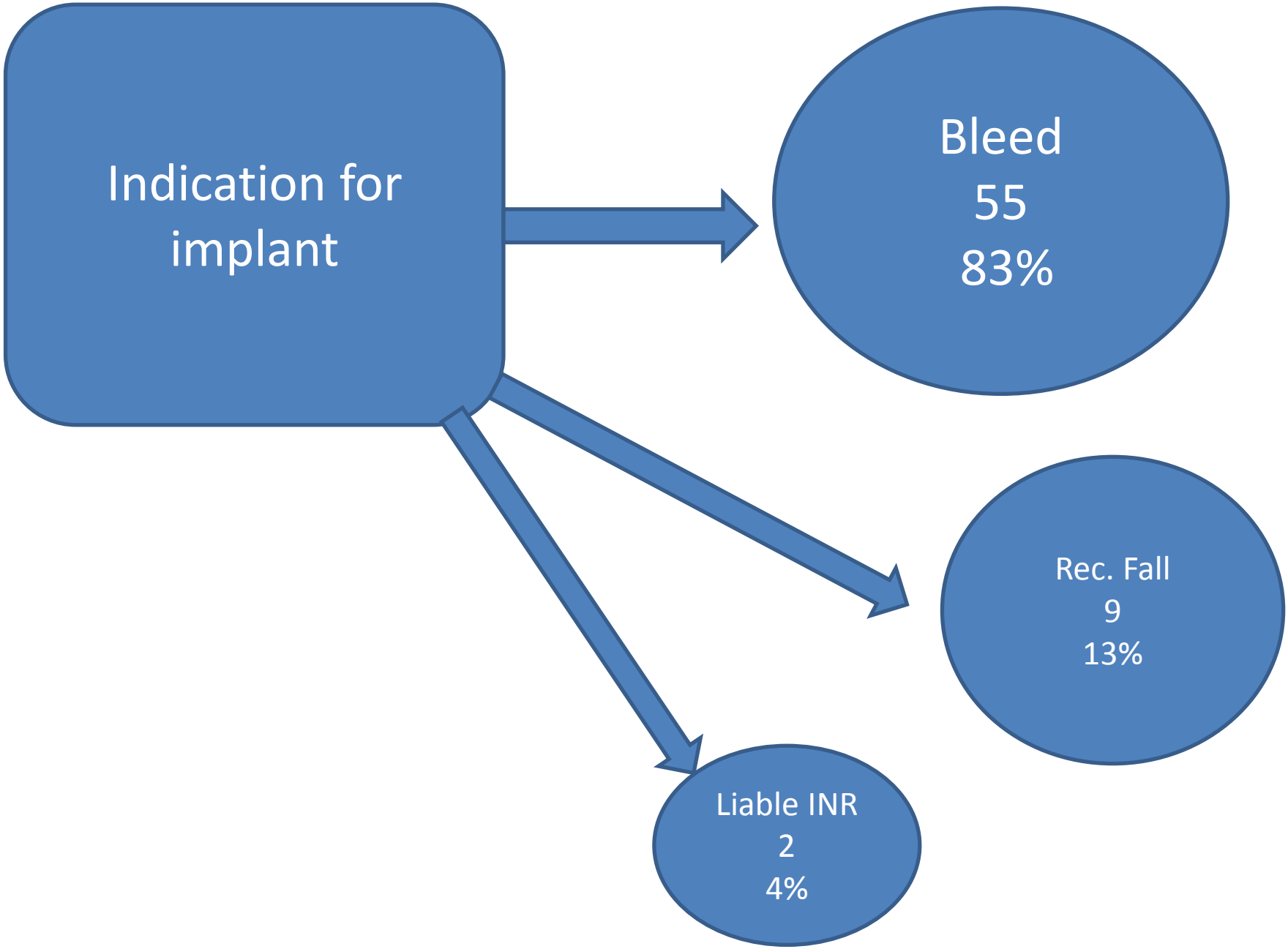
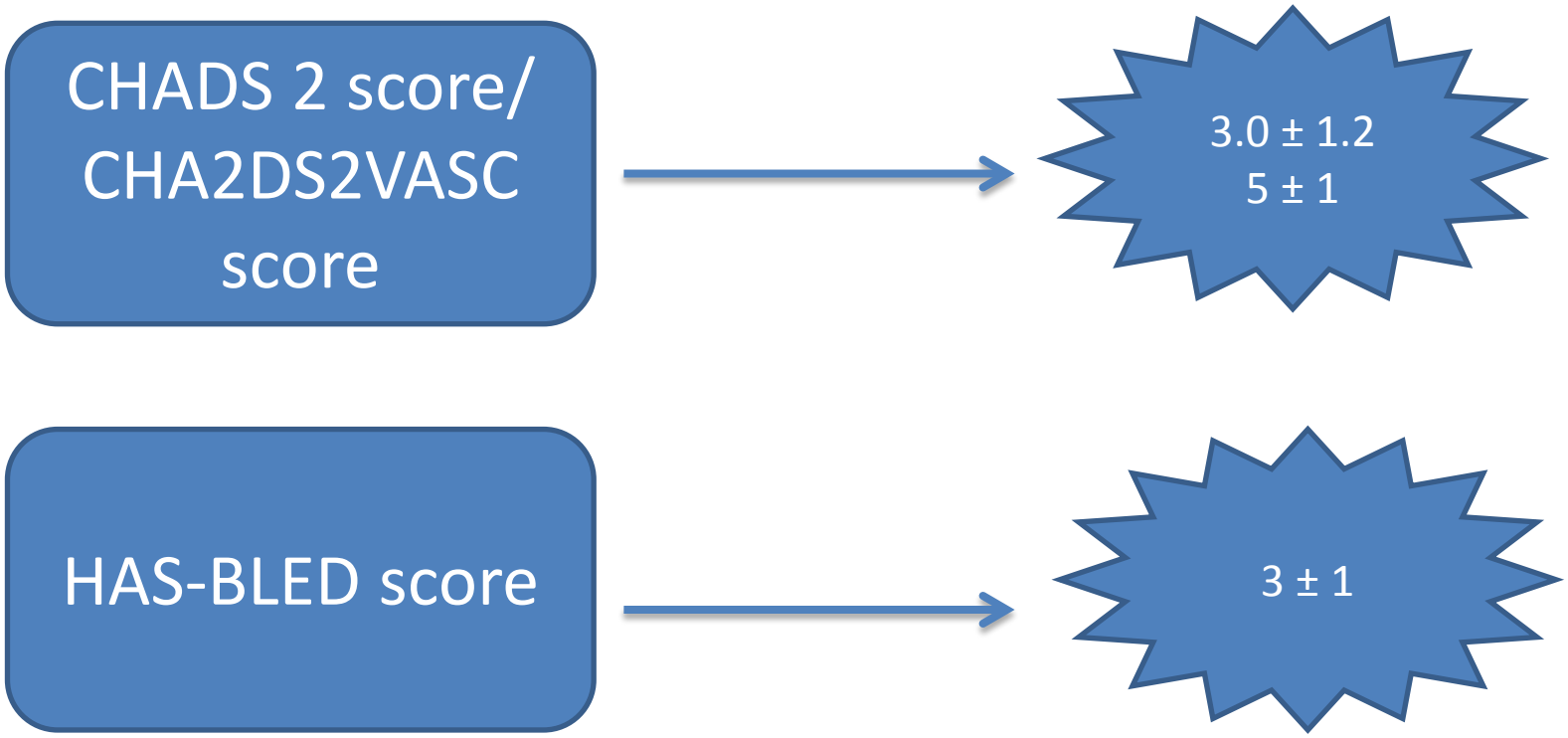
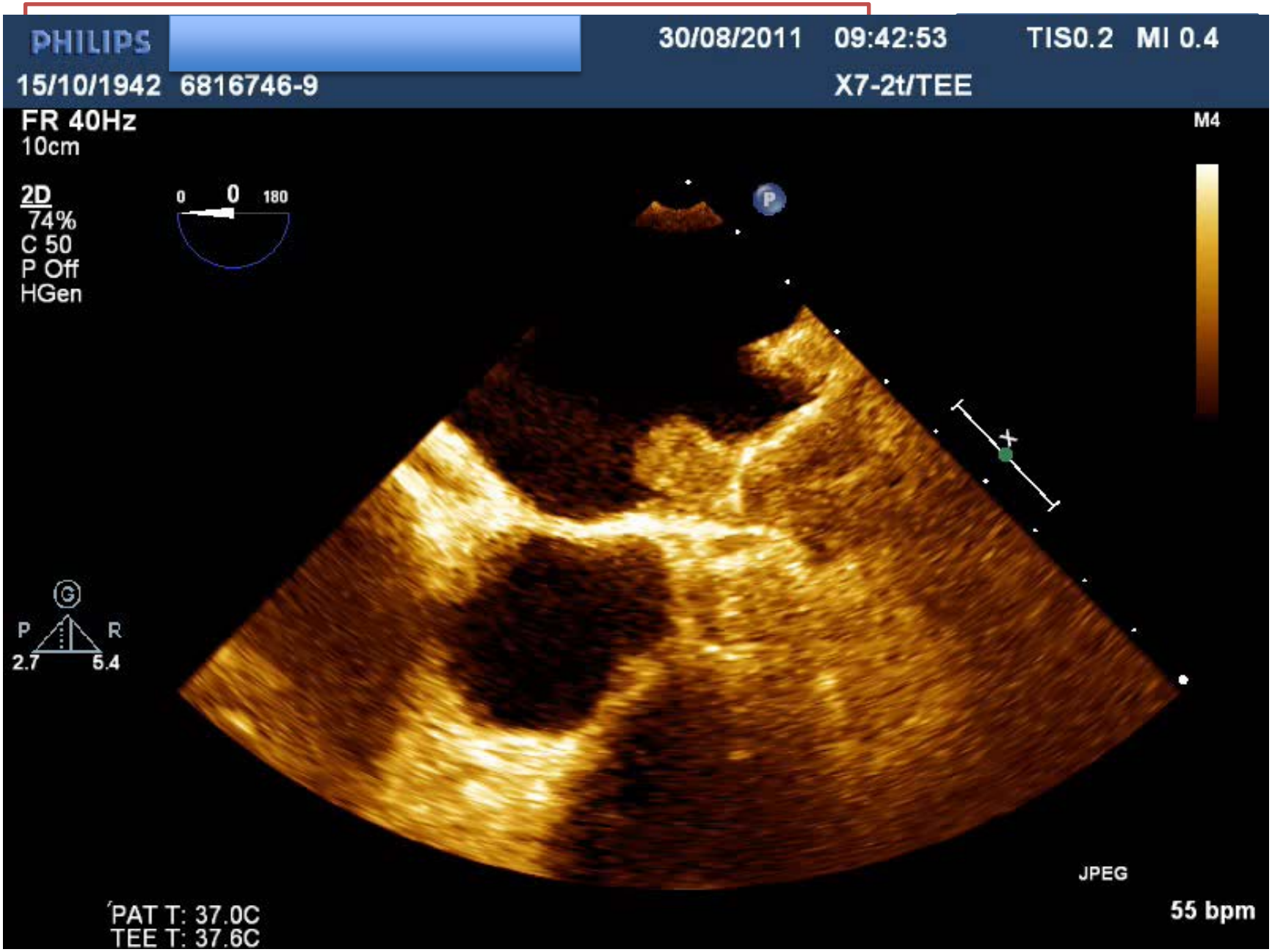
Watchman long-term efficacy from the Israeli Registry




Indication for implant
Bleed
55
83%
Rec. Fall
9
13%
Liable INR
2
4%


CHADS 2 score/
CHA2DS2VASC
score
3.0 ± 1.2
5 ± 1
HAS-BLED score
3 ± 1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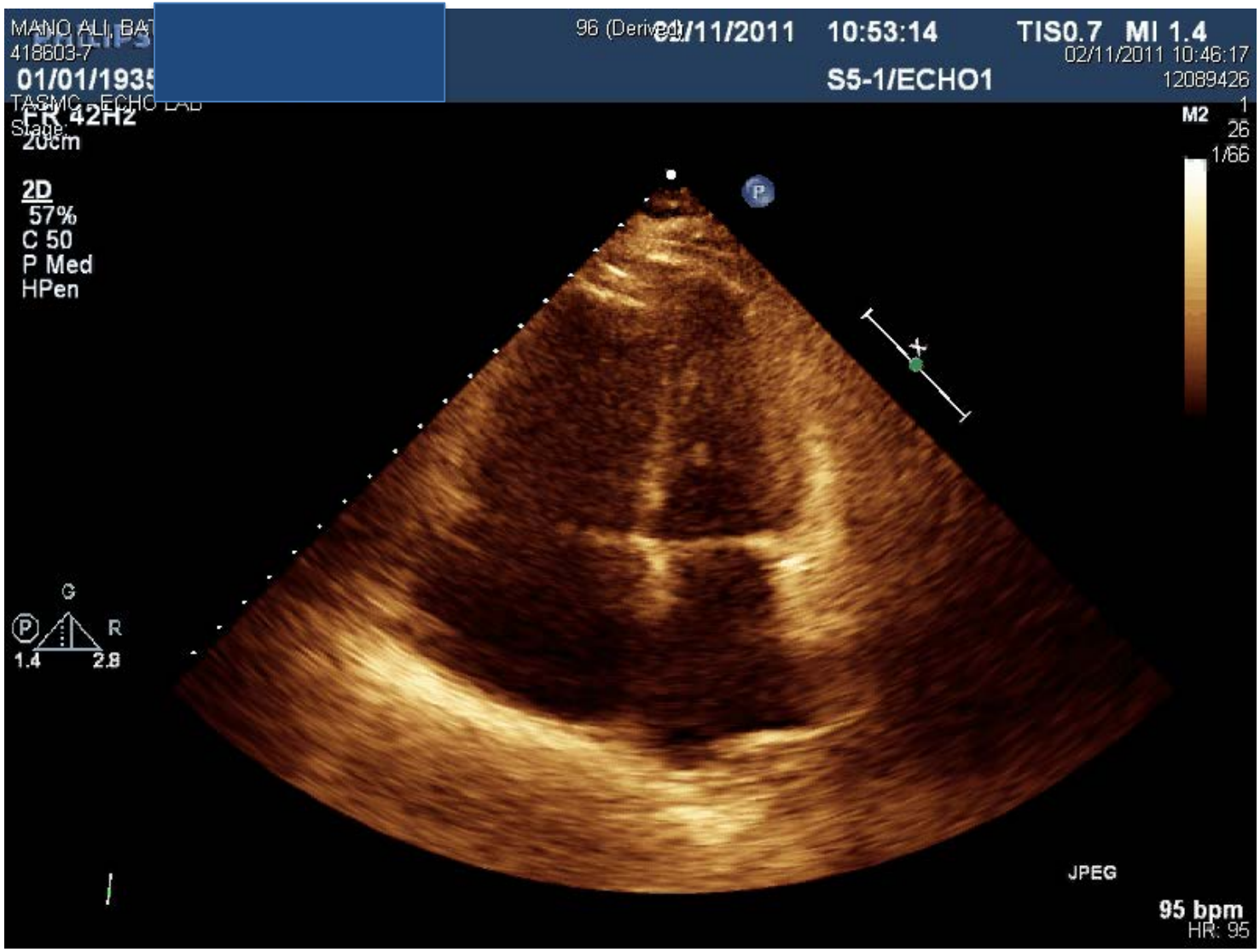
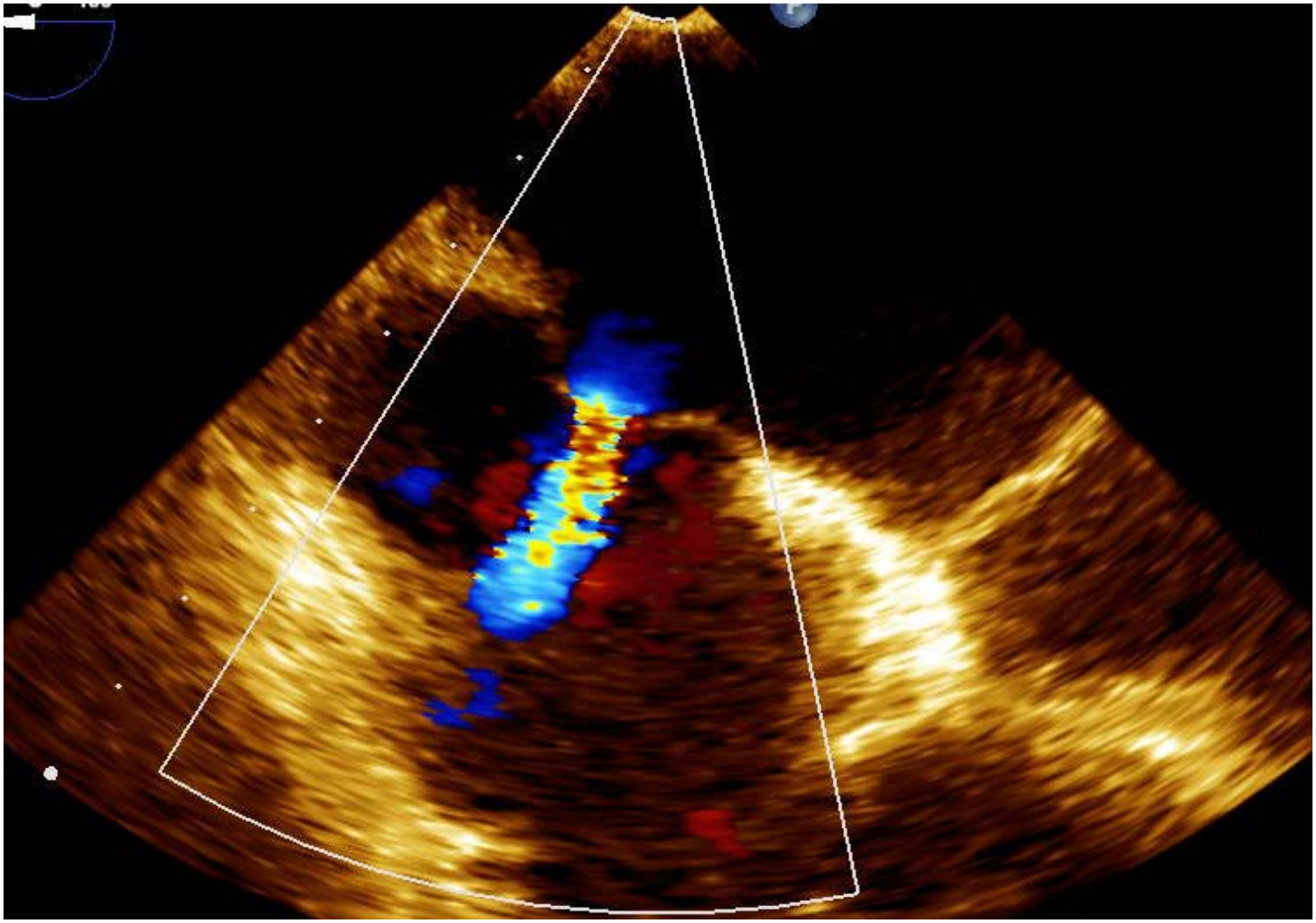
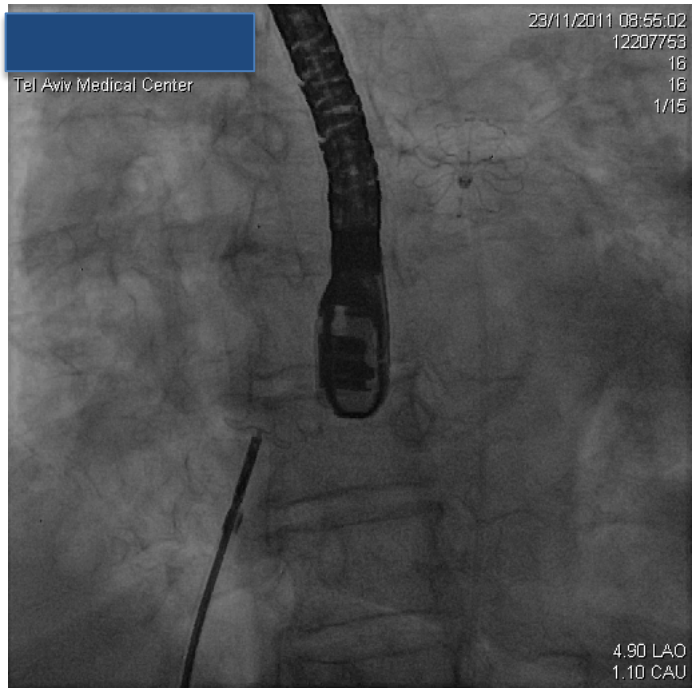
10cm
M4
2D
74%
C 50
P Off
HGen
0 0 180
P
G
P R
2.7 5.4
JPEG
PAT T: 37.0C
TEE T: 37.6C
55 bpm

4-mo post implant presents with severe right-sided CHF



PE, RVMI excluded




Tel Aviv Medical Center
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12207753
16
16
1/15
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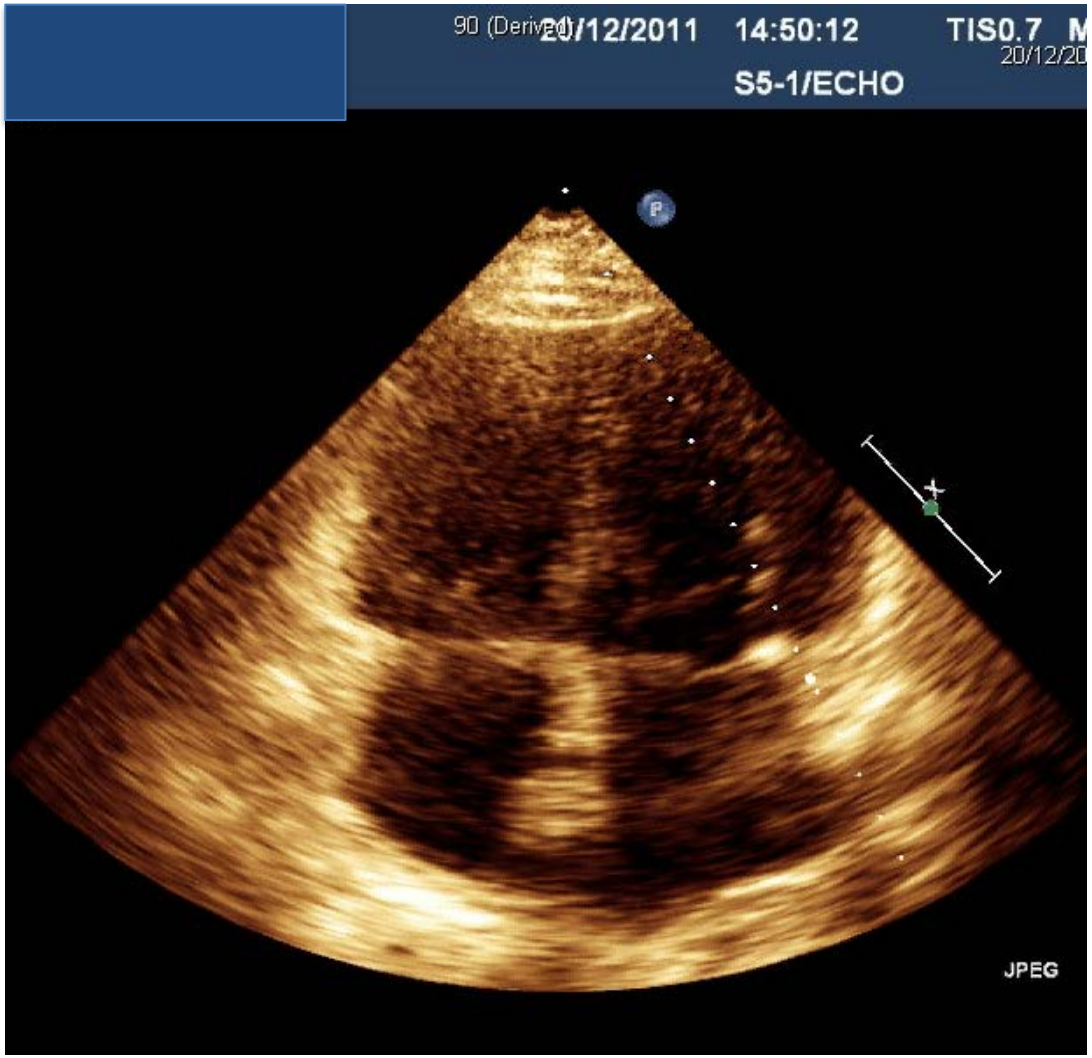
1.10 CAU


90 (Derived)
20/12/2011
14:50:12
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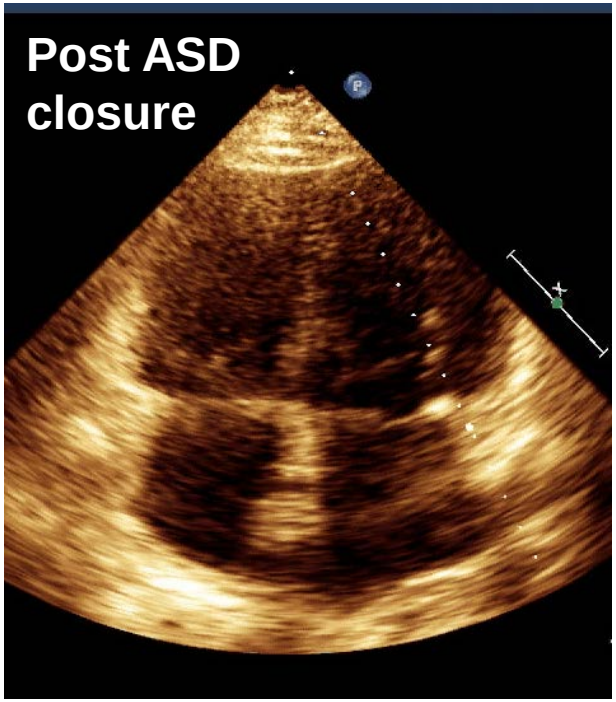
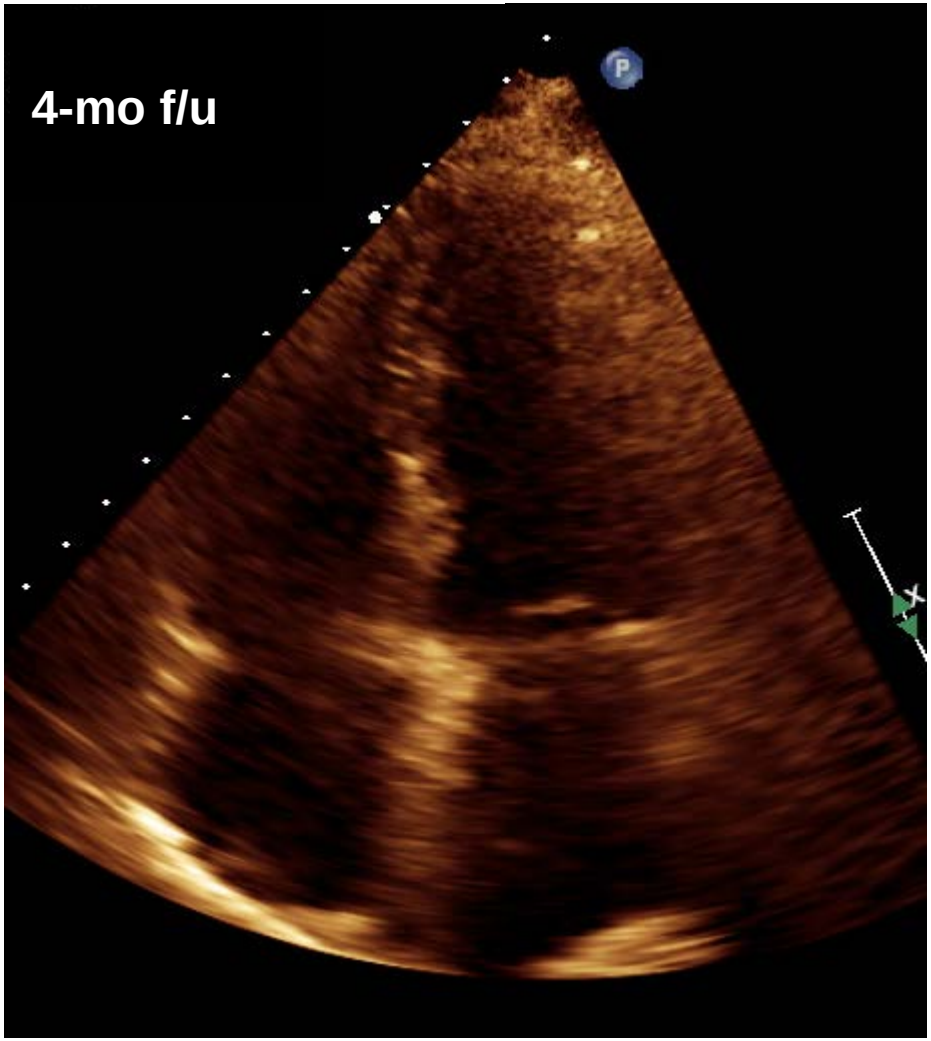
20/12/20
S5-1/ECHO
JPEG

Post-procedural Echo Guidance after LAA Closure

underwent ASD closure with gradual clinical improvement





Post LAAC symptomatic ASD

- **incidence??**
- **1st case report**

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

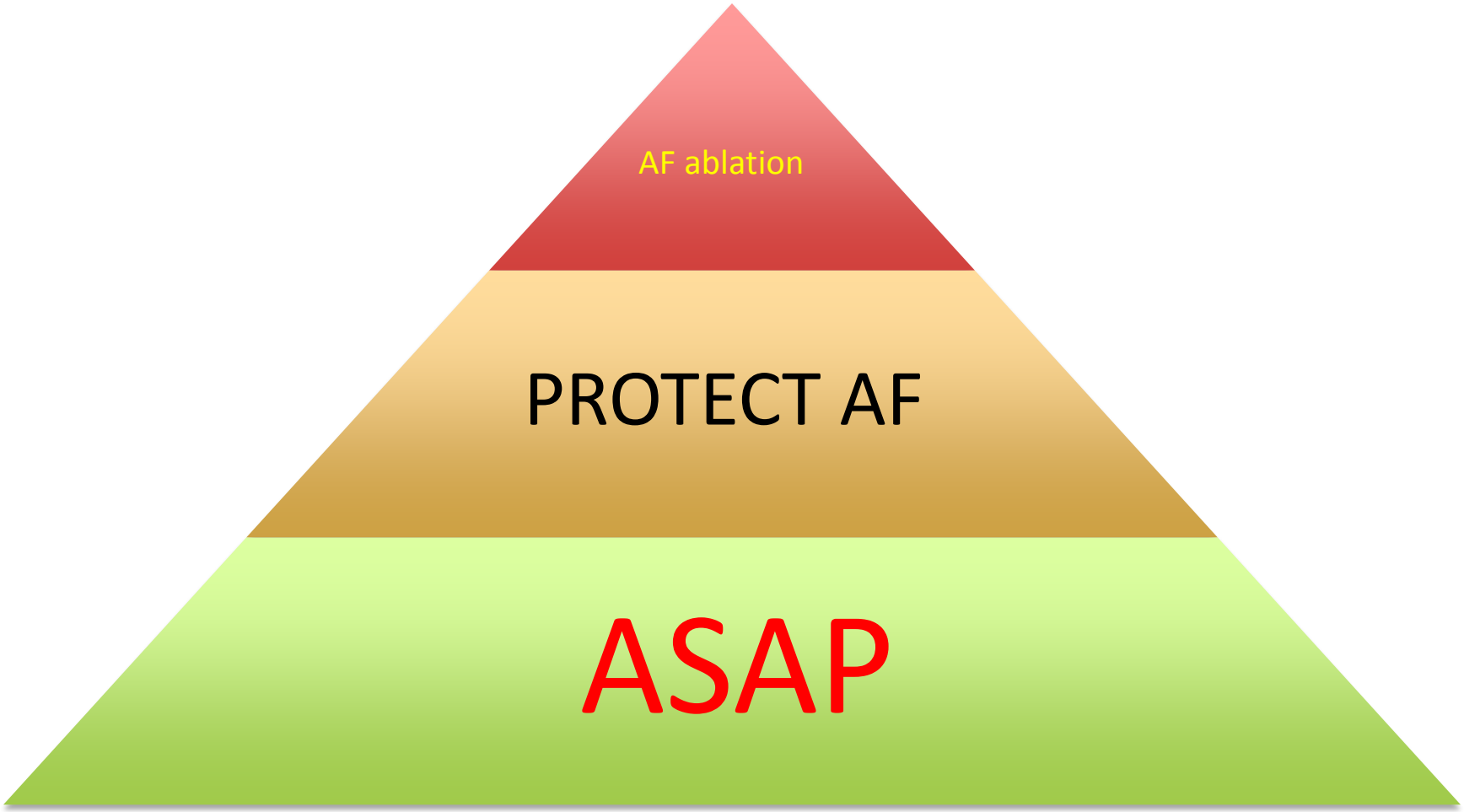
An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association

EHJ Aug 2012

Recommendations for LAA closure/occlusion/excision

Recommendations	Class[a]	Level[b]	Ref[c]
Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation.	IIb	B	115, 118
Surgical excision of the LAA may be considered in patients undergoing open heart surgery.	IIb	C	

Who are the patients we are going to implant?

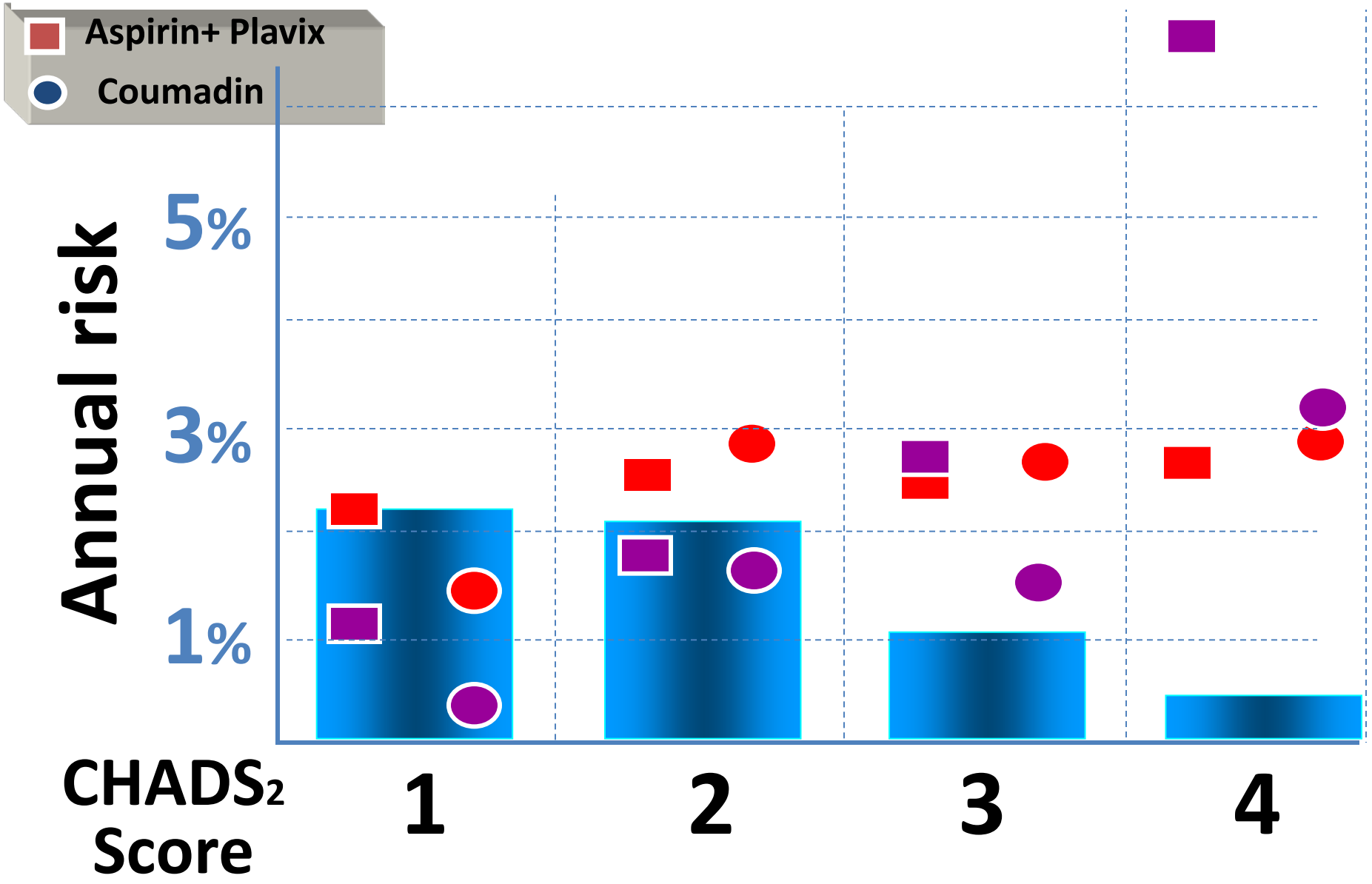


Can the PROTECT AF data be extrapolated to OACs other than warfarin?

Can the PROTECT AF data be extrapolated to devices other than Watchman?

How do we manage high bleeding-risk patients early post device implantation?

Annual Risk for Stroke and Bleeding on Aspirin/Plavix vs. Coumadin



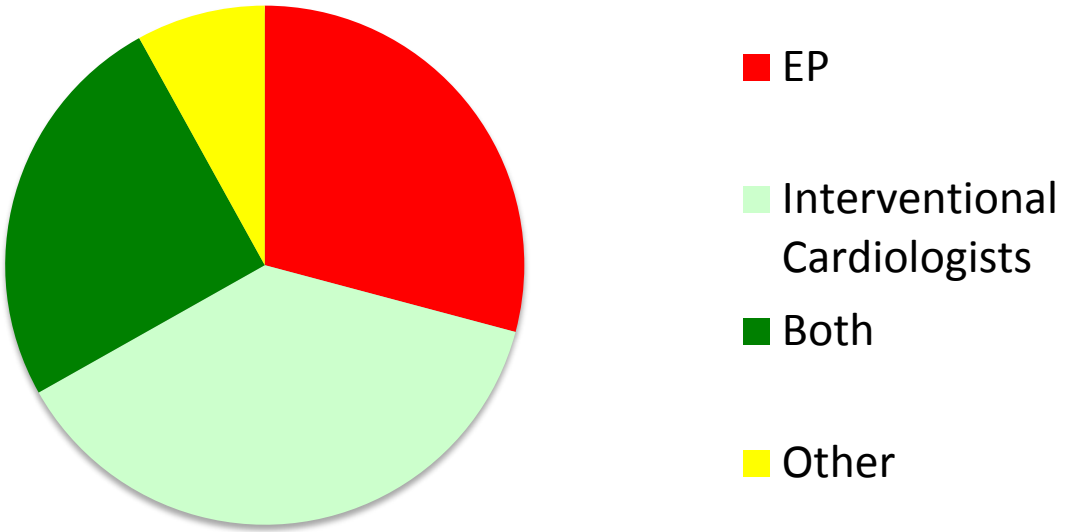
Europace (2013) 15, 141–143
doi:10.1093/europace/eus413

Left atrial appendage occlusion for stroke prevention in atrial fibrillation in Europe: results of the European Heart Rhythm Association survey

- 36 centers,24 (67%) performing LAAO , 73% <10 procedures/year

Gregory Y.H. Lip[1*†], Nikolaos Dagres[2†], Alessandro Proclemer[3], Jesper Hastrup Svendsen[4], Laurent Pison[5], and Carina Blomstrom-Lundqvist[6], conducted by the Scientific Initiative Committee, European Heart Rhythm Association

Who implants Watchman?



Indications for implant

- 86% absolute contra indication for anticoagulation
- 8% along with CPVI
- 6% patient request

50% GA and 50% conscious sedation

Periprocedural Complication Rate

- Periprocedural Stroke: 0% to 10%
- Tamponade : 0% to 10%
- Major Bleeding : 0% to 8%
- Dislodgment: 0% to 20%