Transcatheter LAA Occlusion: More than Anticoagulation

Con: Enough!

Potent New Medication

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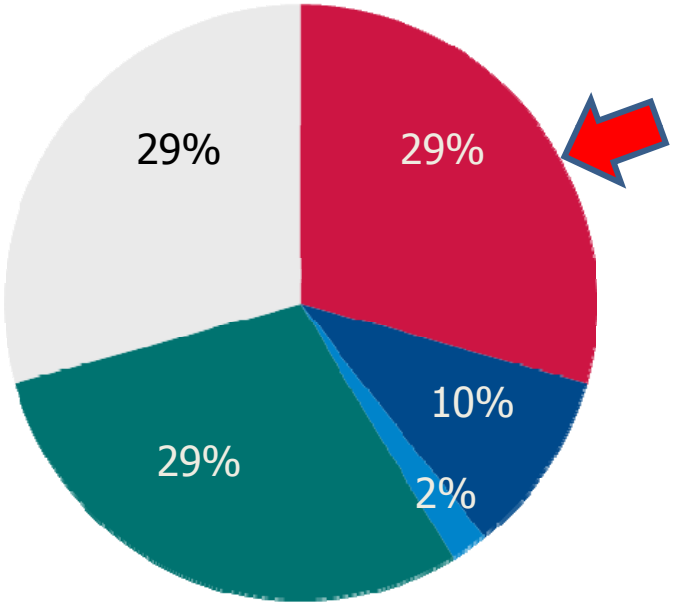
Contents

- Post warfarin era
  - New Oral Anti-Coagulant (NOAC)
- LAA occluder
  - Safety concern
  - Drawbacks of device, not yet completely convincing

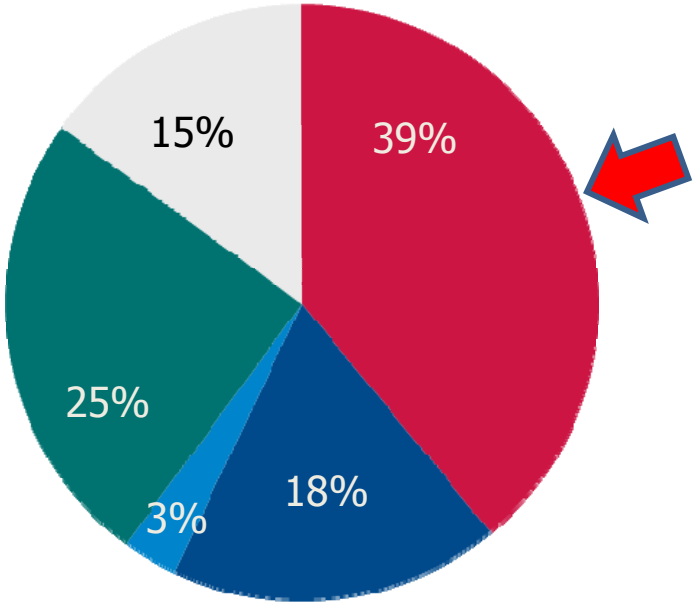
Most ischaemic strokes occur in patients who are under-anticoagulated

- >70% of ischaemic stroke patients with AF had an INR <2.0
  - Only 10% were within the therapeutic range (INR ≥2.0)

First ischaemic stroke



History of stroke or TIA



Subtherapeutic warfarin (INR <2.0)
Therapeutic warfarin (INR ≥2.0)
Dual antiplatelet therapy
Single antiplatelet therapy
No antithrombotics

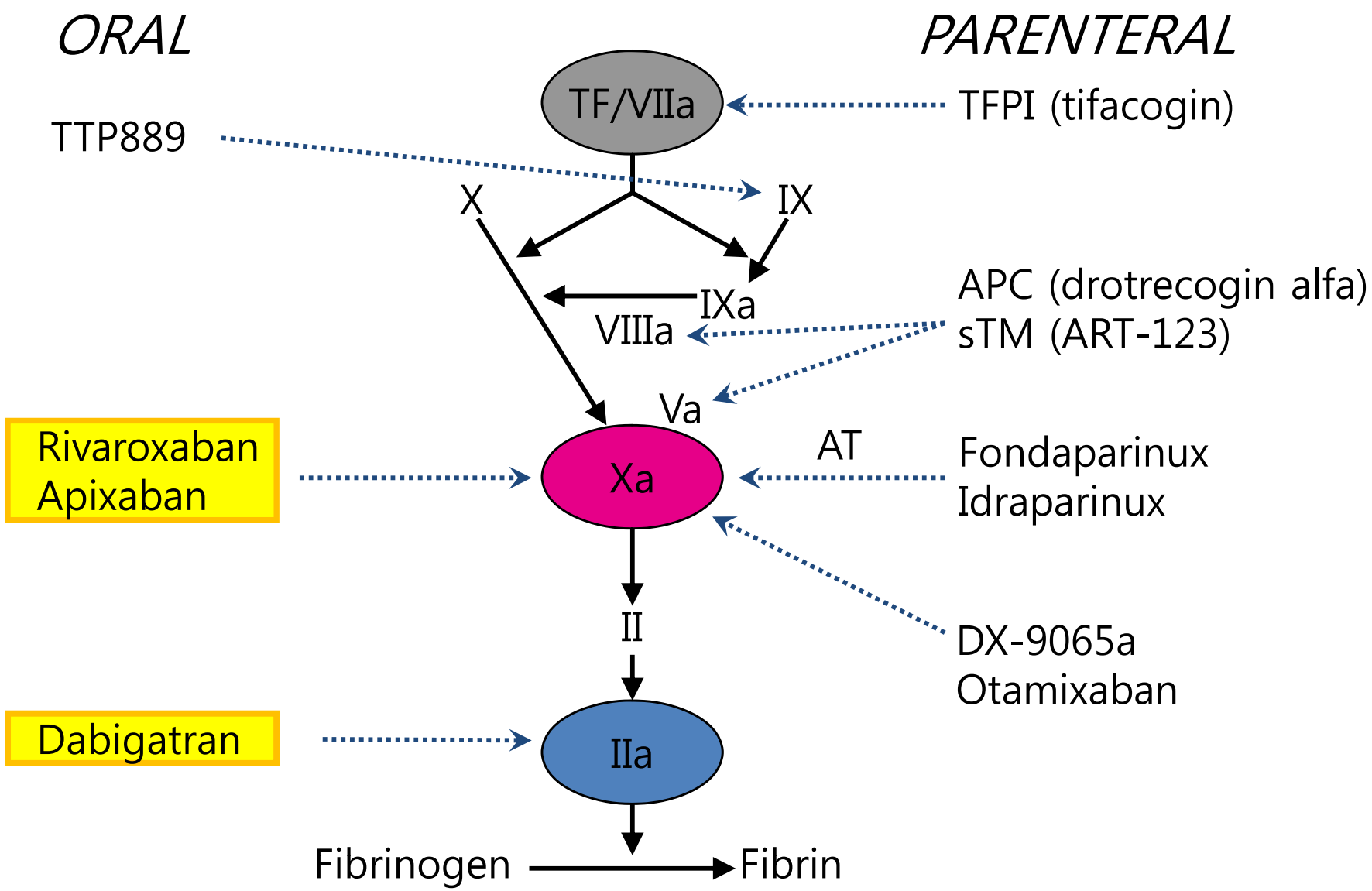
Data from a prospective stroke registry of 597 patients with AF
INR = international normalized ratio; TIA = transient ischaemic attack

Gladstone DJ et al. Stroke 2009;40:235–40

New or Novel Oral Anti-coagulants

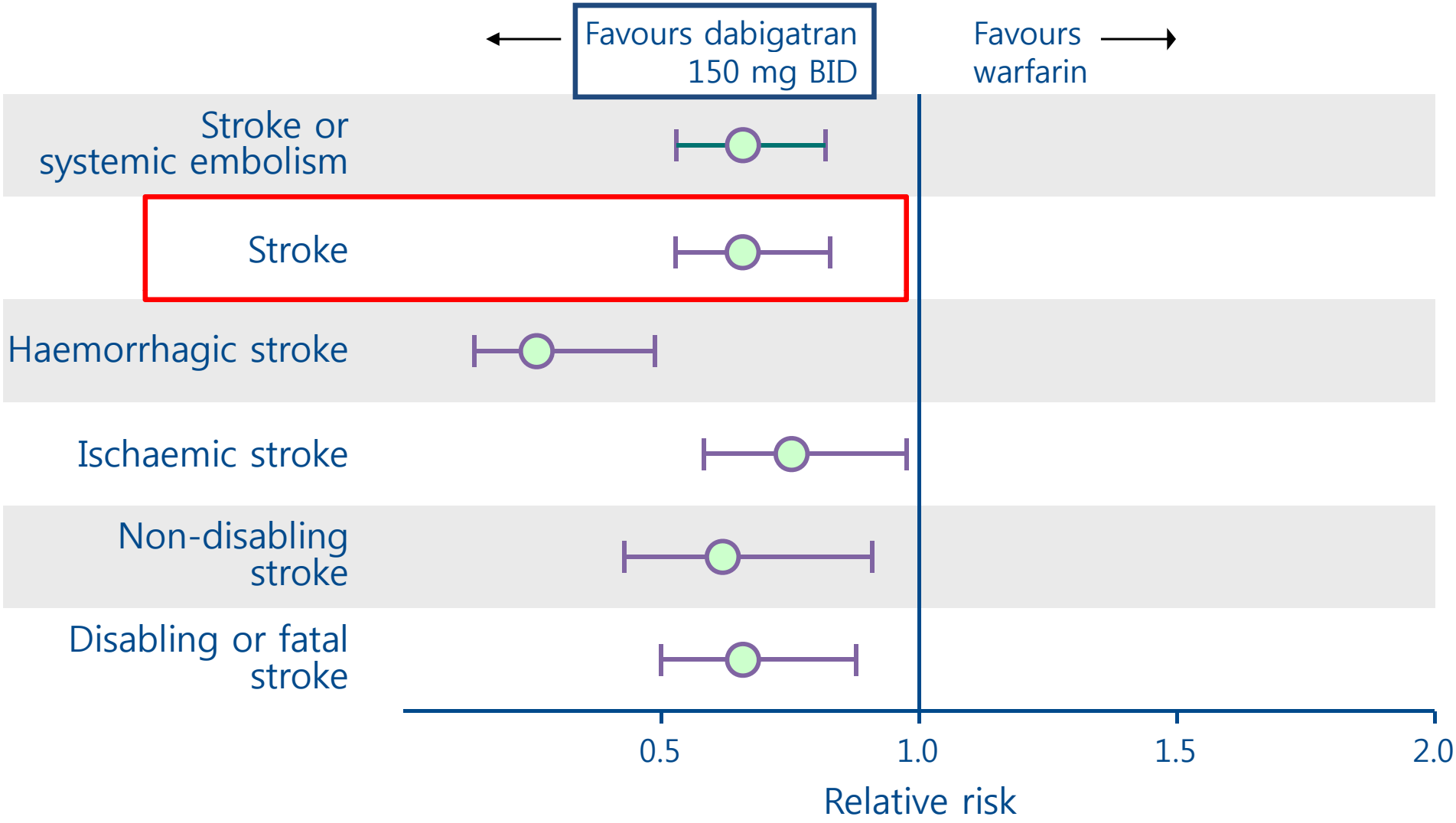
POST WARFARIN ERA

New anticoagulants



Adapted from Weitz & Bates, *J Thromb Haemost* 2005

Dabigatran etexilate 150 mg BID compared with warfarin for stroke prevention in AF

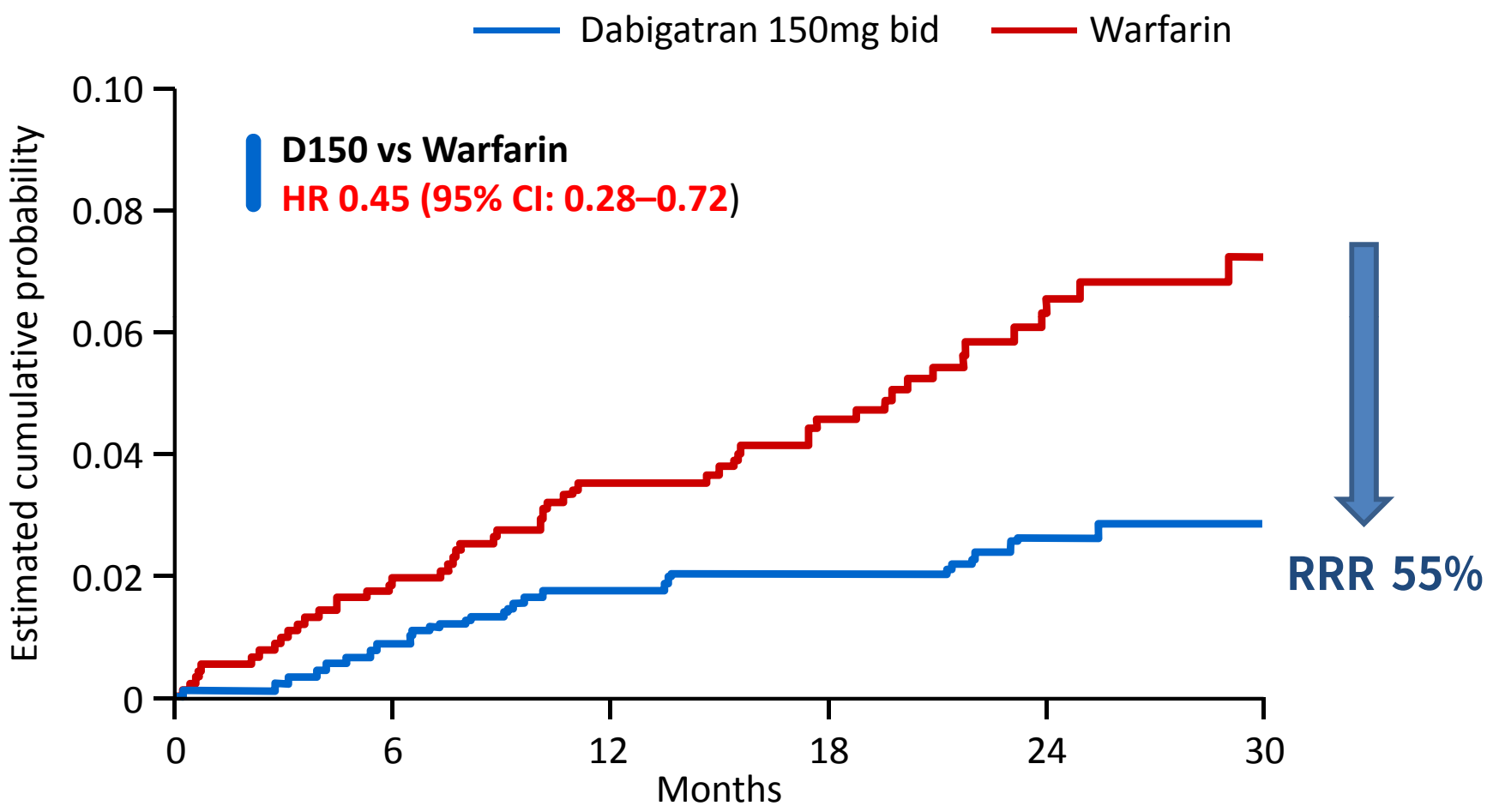


Error bars = 95% CI; BID = twice daily

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6; Pradaxa®: EU SmPC 2011

Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please check local prescribing information for further details

Cumulative Hazard Rates for Stroke or Systemic Embolism in ASIA (RELY-subanalysis)



Subjects at risk						
DE 150mg bid	933	906	875	697	420	237
DE 110mg bid	923	888	866	683	401	216
Warfarin	926	886	858	664	382	198

Am Heart J 157, 805-810, 2009
N Engl J Med 361, 1139-1151, 2009

Prior stroke subgroup analysis in RE-LY: stroke or systemic embolism

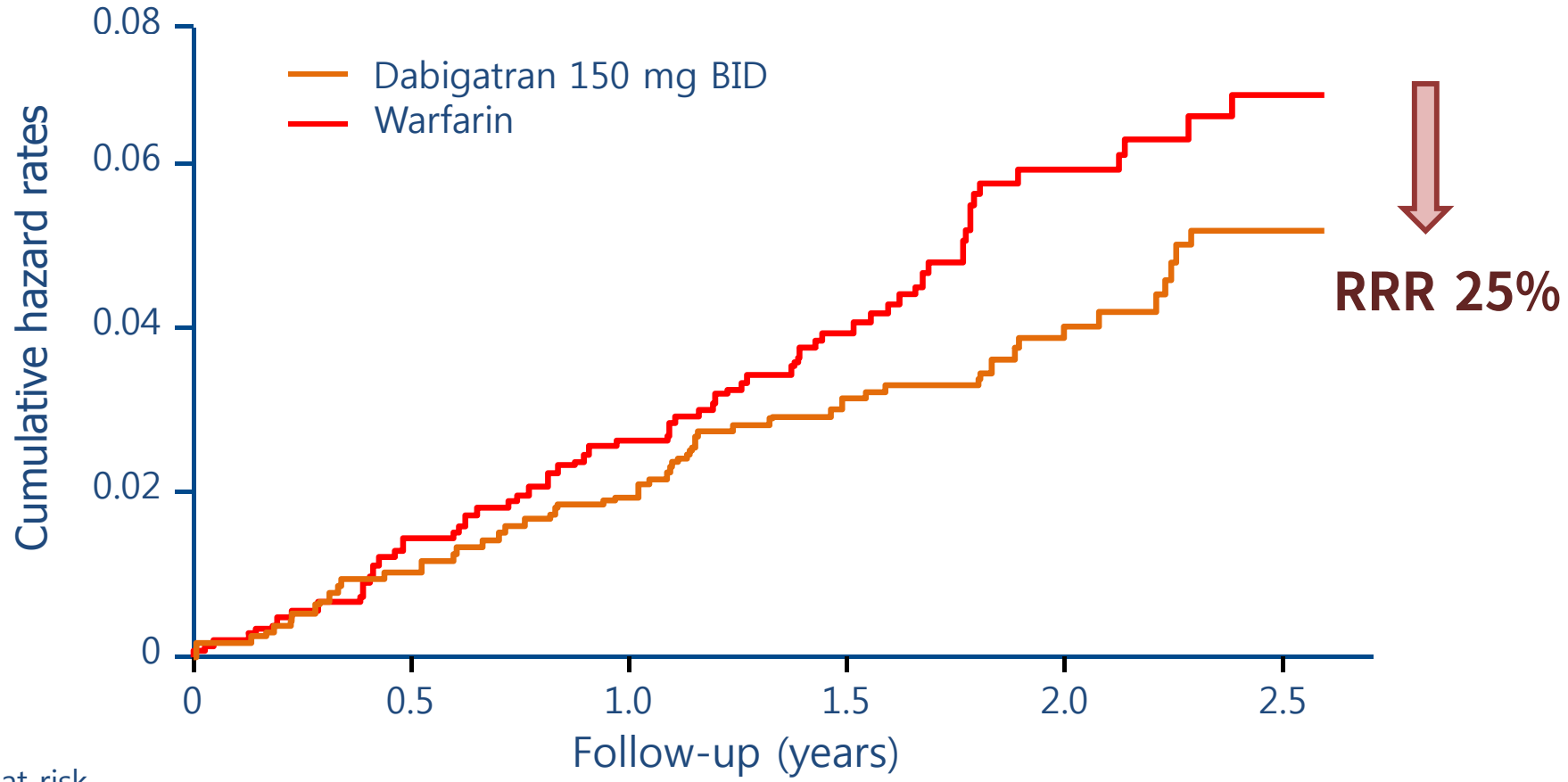
- Higher rate of stroke/systemic embolism in patients with prior stroke/TIA vs those without across treatment groups (2.38% vs 1.22 %/yr; P<0.001)

	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin
Prior stroke/TIA			
Annual rate, %	2.32	2.07	2.78
RR (95% CI) vs warfarin	0.84 (0.58–1.20)	0.75 (0.52–1.08)	
No prior stroke/TIA			
Annual rate, %	1.34	0.87	1.45
RR (95% CI) vs warfarin	0.93 (0.73–1.18)	0.60 (0.45–0.78)	
P value for interaction	0.62	0.34	

BID = twice daily; RR = relative risk; TIA = transient ischaemic attack
Diener HC et al. Lancet Neurol 2010;9:1157–63

Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries.
Please check local prescribing information for further details

Prior stroke subgroup analysis: time to stroke or systemic embolism in patients with previous stroke or TIA



Number at risk

Dabigatran 110 mg	1195	1159	1131	908	573	289
Dabigatran 150 mg	1233	1200	1163	938	517	321
Warfarin	1195	1159	1125	895	565	251

BID = twice daily; TIA = transient ischaemic attack

Diener HC et al. Lancet Neurol 2010;9:1157–63

Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please check local prescribing information for further details

Prior stroke patients in PROTECT-AF

	Intervention group (n=463)	Control group (n=244)
Characteristics		
Age (years)	71·7 (8·8;46·0–95·0)	72·7 (9·2;41·0–95·0)
Male	326 (70·4%)	171 (70·1%)
Race/ethnicity		
Asian	4 (0·9%)	1 (0·4%)
Black/African-American	6 (1·3%)	5 (2·0%)
White	425 (91·8%)	222 (91·0%)
Hispanic/Latin American	25 (5·4%)	15 (6·1%)
Hawaiian/Pacific Islander	1 (0·2%)	1 (0·4%)
Other	2 (0·4%)	0
Risk factors		
CHADS2 score*		
Previous transient ischaemic attack/ischaemic stroke	82 (17·7%)	49 (20·1%)
4	37 (8·0%)	24 (9·8%)
5	19 (4·1%)	10 (4·1%)
6	4 (0·9%)	5 (2·0%)
Congestive heart failure	124 (26·8%)	66 (27·0%)

Table 1: Baseline characteristics and risk factors of study participants

(Holmes DR et al, Lancet 2009)

Prior stroke patients in PROTECT-AF 2y F/U

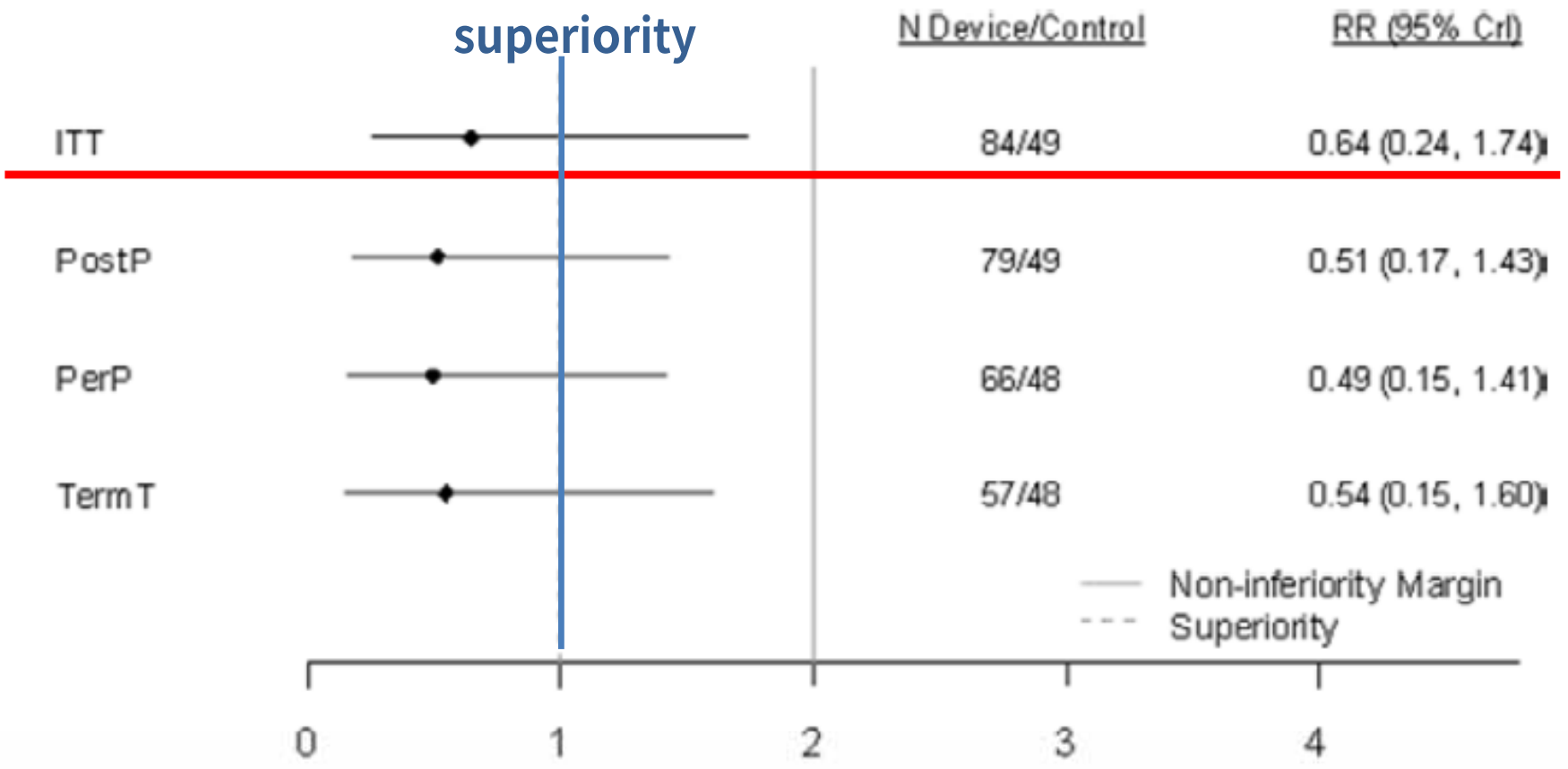


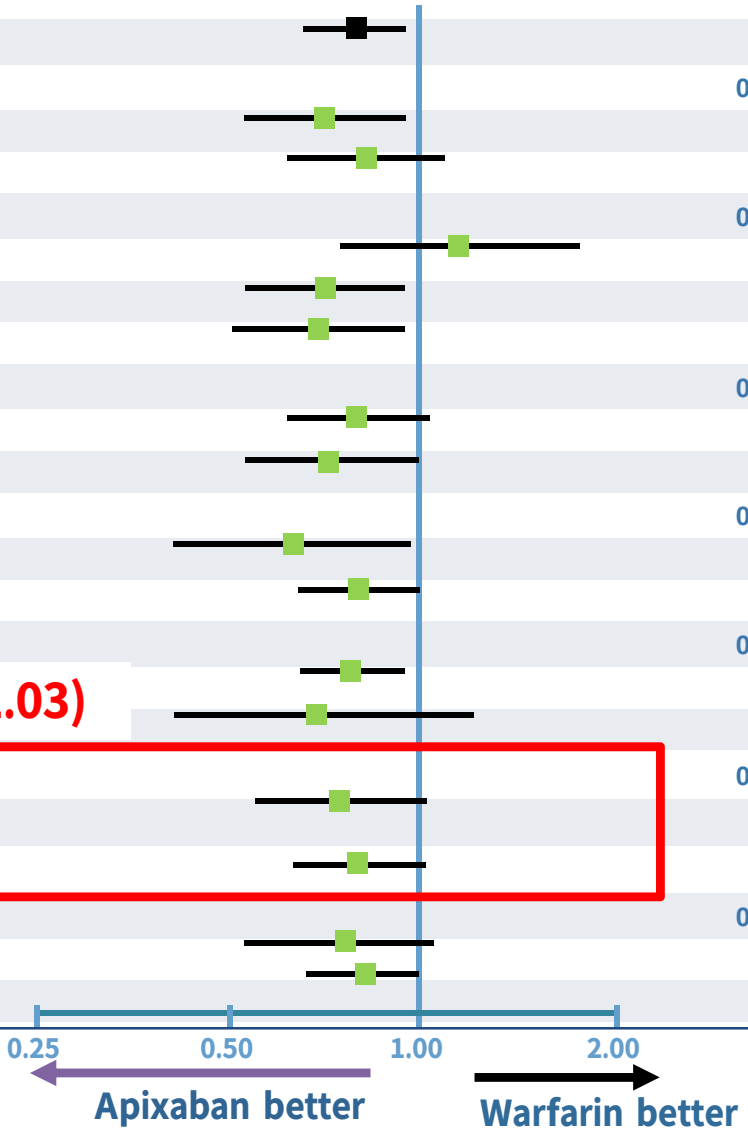
Figure 6. Primary efficacy results of the secondary prevention group. The rate ratios (RR) and 95% credible intervals (CrI)

Circulation 2013;127:720-729

Primary efficacy results for apixaban in subgroup of ARISTOTLE

Characteristics	No. of patients	Apixaban	Warfarin	Hazard Ratio (95% CI)	P value for interaction
		No. of events (%/yr)			
All patients	**18,201**	**212 (1.27)**	**265 (1.60)**		
Prior warfarin/VKA					**0.39**
Yes	10,401	102 (1.1)	138 (1.5)		
No	7,800	110 (1.5)	127 (1.8)		
Age					**0.12**
< 65 yrs	5,471	51 (1.0)	44 (0.9)		
65 to < 75 yrs	7,052	82 (1.3)	112 (1.7)		
≥ 75 yrs	5,678	79 (1.6)	109 (2.2)		
Sex					**0.60**
Male	11,785	132 (1.2)	160 (1.5)		
Female	6,416	80 (1.4)	105 (1.8)		
Weight					**0.26**
≤ 60 kg	1,985	34 (2.0)	52 (3.2)		
> 60 kg	16,154	177 (1.2)	212 (1.4)		
Type of AF					**0.70**
Permanent/Persistent	15,412				
Paroxysmal	2,786				
Prior stroke or TIA					**0.71**
Yes	3,436	73 (2.5)	98 (3.2)		
No	14,765	139 (1.0)	167 (1.2)		
Diabetes mellitus					**0.71**
Yes	4,547	57 (1.4)	75 (1.9)		
No	13,654	155 (1.2)	190 (1.5)		

HR 0.76(95% CI 0.56-1.03)



Primary efficacy endpoint: stroke or systemic embolism

Adapted from Granger et al. N Engl J Med 2011;365:981-92.

NOAC vs. warfarin in *secondary stroke prevention*

Outcome	Any NOAC (dabigatran 150 mg twice daily, apixaban, rivaroxaban*) *v* warfarin	
	Weighted average effect—hazard ratio (95% CI)	P value
Stroke or systemic embolism	0.86 (0.73 to 1.00)	0.047
Stroke	0.86 (0.74 to 1.01)	0.070
Ischaemic or uncertain type of stroke	0.98 (0.82 to 1.17)	0.825
Haemorrhagic stroke	0.51 (0.35 to 0.75)	0.001
Disabling or fatal stroke	0.87 (0.70 to 1.07)	0.174
Death from anycause	0.94 (0.84 to 1.07)	0.350
Death from vascular causes	0.98 (0.84 to 1.14)	0.793
Myocardial infarction	1.06 (0.80 to 1.40)	0.682
ISTH major bleeding	0.91 (0.79 to 1.06)	0.221
Intracranial bleeding	0.53 (0.39 to 0.73)	<0.001
Gastrointestinal bleeding	1.34 (0.94 to 1.90)	0.106
Other location bleeding	1.05 (0.84 to 1.31)	0.675

Rasmussen LH et al. BMJ 2012

Device, procedural, medication related complications

SAFETY CONCERN

Complications

- ***Device related***
  - Device embolization
  - Device erosion
  - Failure to obliterate residual flow
  - Compromise pulmonary vein
- ***Procedural related***
  - Trans-septal puncture
  - Pericardial effusion
  - Vascular access
  - Stroke: embolization of air and thrombi

Device related complication

(Circulation 2011;123:417-424)

- **Device embolization**
  - **3 of 542 (0.6%) attempted**
  - Experience-related improvement
    - No cases in last~250 cases in PROTECT AF
    - No cases in CAP registry
- **Device thrombus**
  - **16 of 542 (3.0%) attempted**
  - 1 of 16 had an ischemic stroke

Complication, complication, complication!

Serious Complications from Dislocation of a Watchman Left

CLAUD

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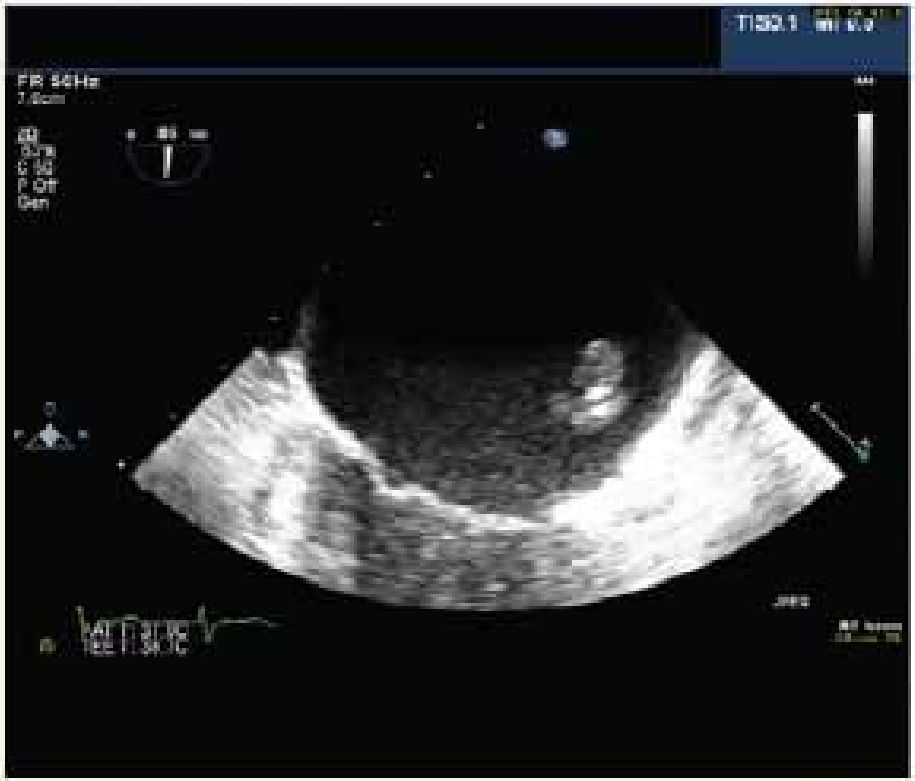
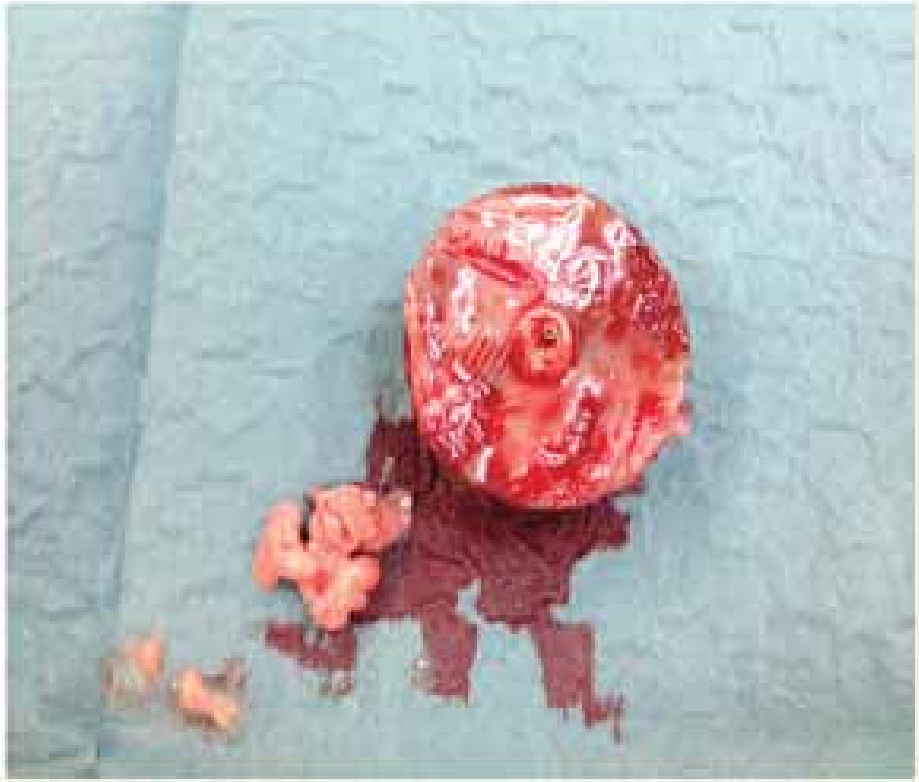
CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehs437
Online publish-ahead-of-print 13 December 2012

Thrombus formation on an Amplatzer closure device after left atrial appendage closure

Jeroen Lammers*, Ted Elenbaas, and Albert Meijer





Pericardial effusion

(Circulation 2011;123:417-424)

- 5.2% PROTECT AF, 2.2% CAP
  - 38 patients /PROTECT AF 542, CAP registry 460 patients
- Required Treatment : 34/38 patients
  - 26 percutaneous intervention
  - 8 surgical intervention
- No mortality but prolong hospital stay
- **Late pericardial effusion** reported

Drawbacks of LAA occluders--

- Local Treatment against broader source of embolism ex) thrombus from LA wall, ↑ coagulopathy
- Limited randomized data in small population
- Thrombogenic foreign surface for several months
- Suboptimal procedure up to 30% patients ; up to 10% failed implants
- ~10% peri-procedural complications
- Learning curve and specialized training be needed
- Upfront costs
- Long-term effects and safety unknown

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, MD; Shephal K. Doshi, MD; Horst Sievert, MD; Maurice Buchbinder, MD; Petr Neuzil, MD, PhD; Kenneth Huber, MD; Jonathan L. Halperin, MD; David Holmes, MD; on behalf of the PROTECT AF Investigators

Background—The multicenter PROTECT AF study (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) was conducted to determine whether percutaneous left atrial appendage closure with a filter device (Watchman) was n... ...brillation.

Methods and Results—Patients ... ...ast 1 risk factor (age >75 years, hypertension, heart failure, diabetes, or prior stroke/transient ischemic attack) were randomized to either the Watchman device (n=463) or continued warfarin (n=244) in a 2:1 ratio. After device implantation, warfarin was continued for ≈45 days, followed by clopidogrel for 4.5 months and lifelong aspirin. Study discontinuation rates were 15.3% (71/463) and 22.5% (55/244) for the Watchman and warfarin groups, respectively. The time in therapeutic range for the warfarin group was 66%. The composite primary efficacy end point included stroke, systemic embolism, and cardiovascular death, and the primary analysis was by intention to treat. After 1588 patient-years of follow-up (mean 2.3±1.1 years), the primary efficacy event rates were 3.0% and 4.3% (percent per 100 patient-years) in the Watchman and warfarin groups, respectively (relative risk, 0.71; 95% confidence interval, 0.44%–1.30% per year), which met the criteria for noninferiority (probability of noninferiority >0.999). There were more primary safety events in the Watchman group (5.5% per year; 95% confidence interval, 4.2%–7.1% per year) than in the control group (3.6% per year; 95% confidence interval, 2.2%–5.3% per year; relative risk, 1.53; 95% confidence interval, 0.95–2.70). ...fibrillation.

Clinical Trial Registration:—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00129545. (***Circulation.*** **2013;127:720-729.**)

Lack of long-term data

Drawbacks of LAA occluders--

- Local Tx against broader source of embolism
- Limited randomized data in small population
- Long-term effects and safety unknown
- Thrombogenic foreign surface for several months
- Suboptimal procedure up to 30% patients; up to 10% failed implants
- ~10% peri-procedural complications
- Learning curve and specialized training be needed
- Upfront costs

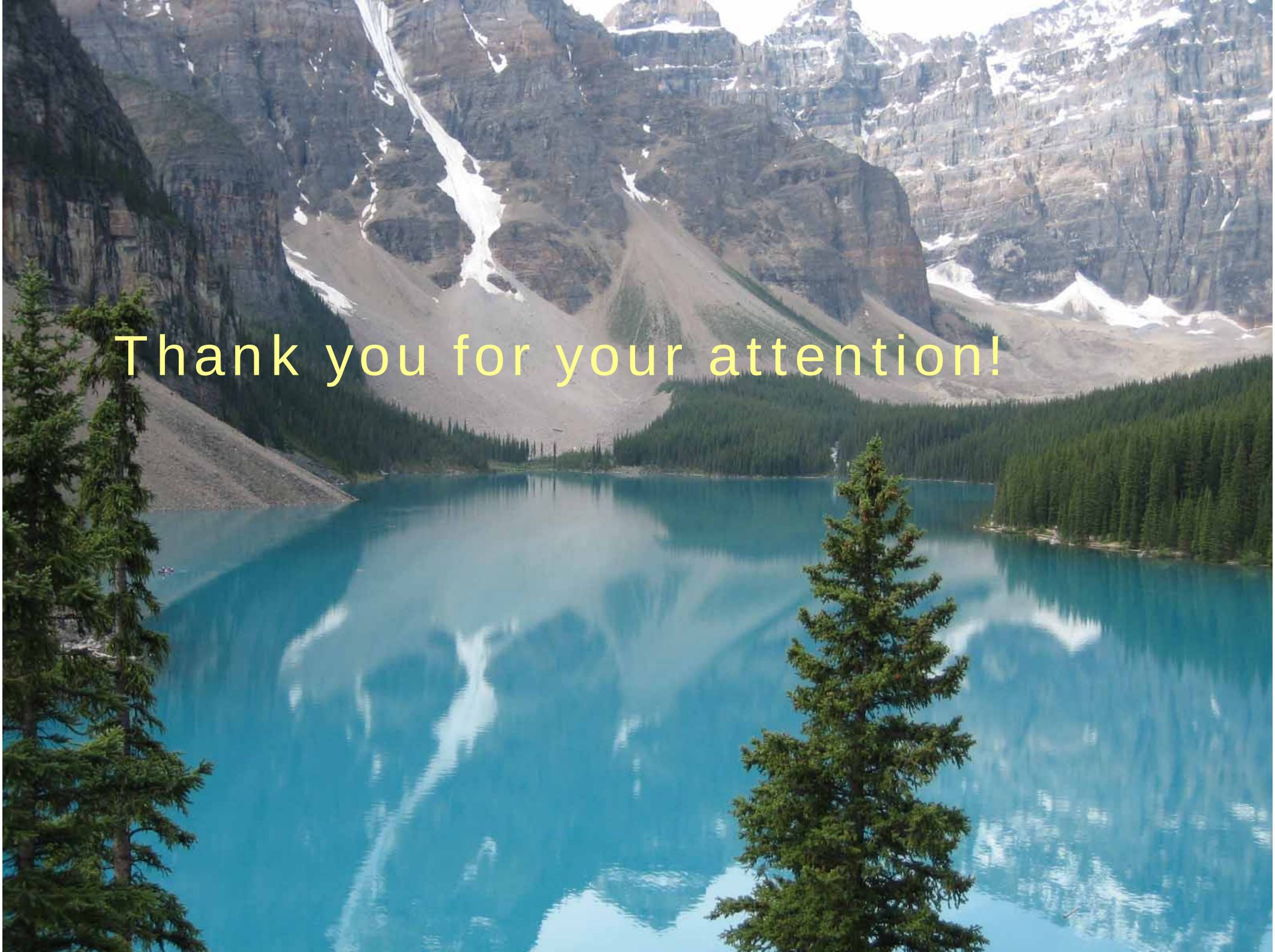
Percutaneous LAA occluder

- Alternative for very selective patients
- Safety concern for starter
- No comparison study with NOAC

- Still. . . .

Anticoagulation is irreplaceable!

- LAA occlusion is justified only in patients with high risk of stroke and high risk of bleeding or contraIx to oral


Thank you for your attention!

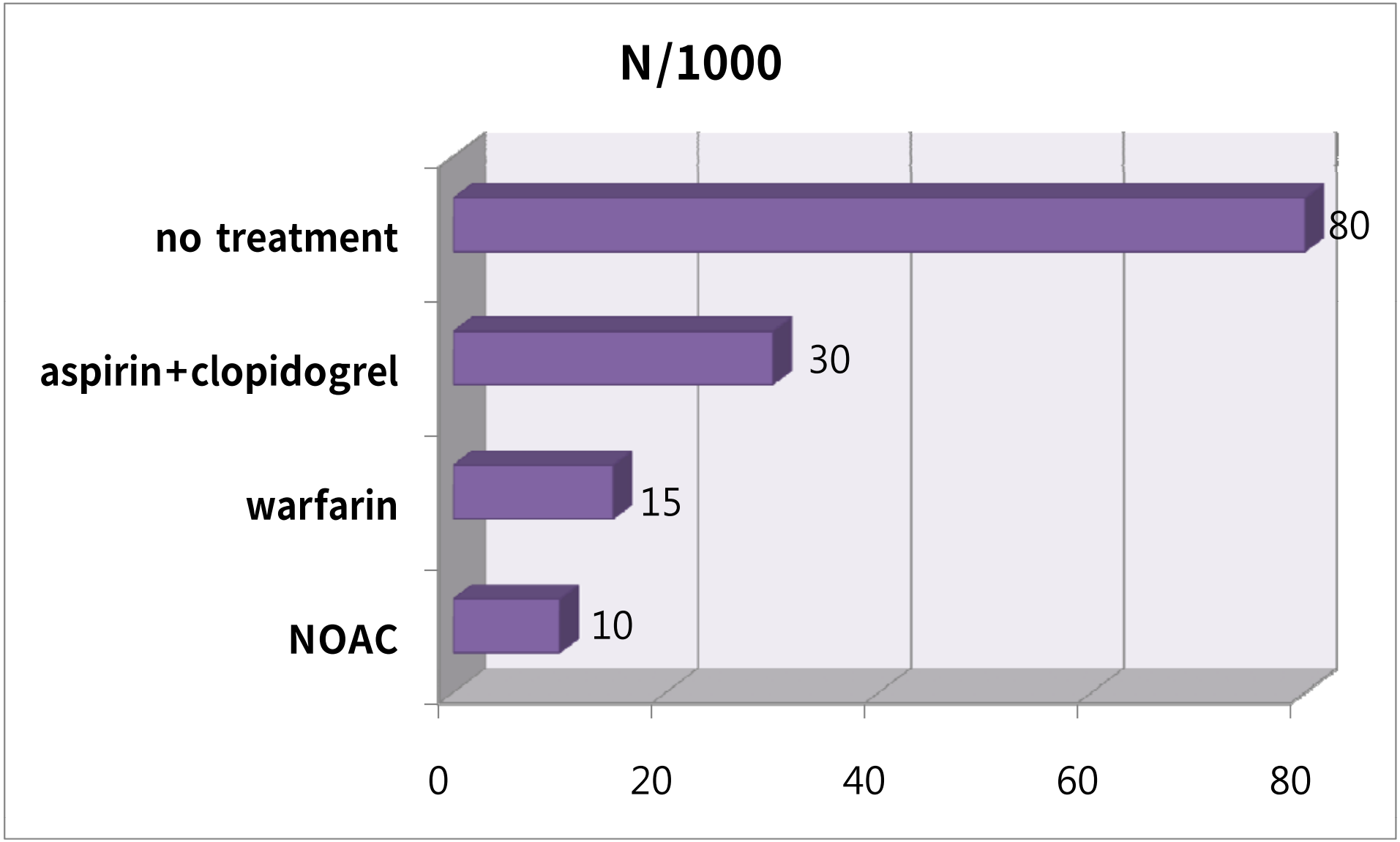
Limitations of traditional antithrombotic therapies for stroke prevention in AF

- With traditional agents, many patients with AF do not receive effective thromboprophylaxis
- VKAs – greater efficacy but challenging to use:[2,3]
  - Narrow therapeutic window
  - Variable and unpredictable PK/PD
  - Wide variety of drug–drug and drug–food interactions
  - Need for regular anticoagulation monitoring and dose adjustments
  - Slow onset and offset of action

PK/PD = pharmacokinetics/pharmacodynamics; VKAs = vitamin K antagonists

1. ACCF/AHA/HRS focused update guidelines: Fuster V et al. Circulation 2011;123:e269-367; Wann LS et al. Circulation 2011;123:104–23 & Circulation 2011;123:1144–50; **2**. Turpie AG. Eur Heart J 2008;29:155–65;
3. Khoo CW et al. Int J Clin Pract 2009;63:630–41

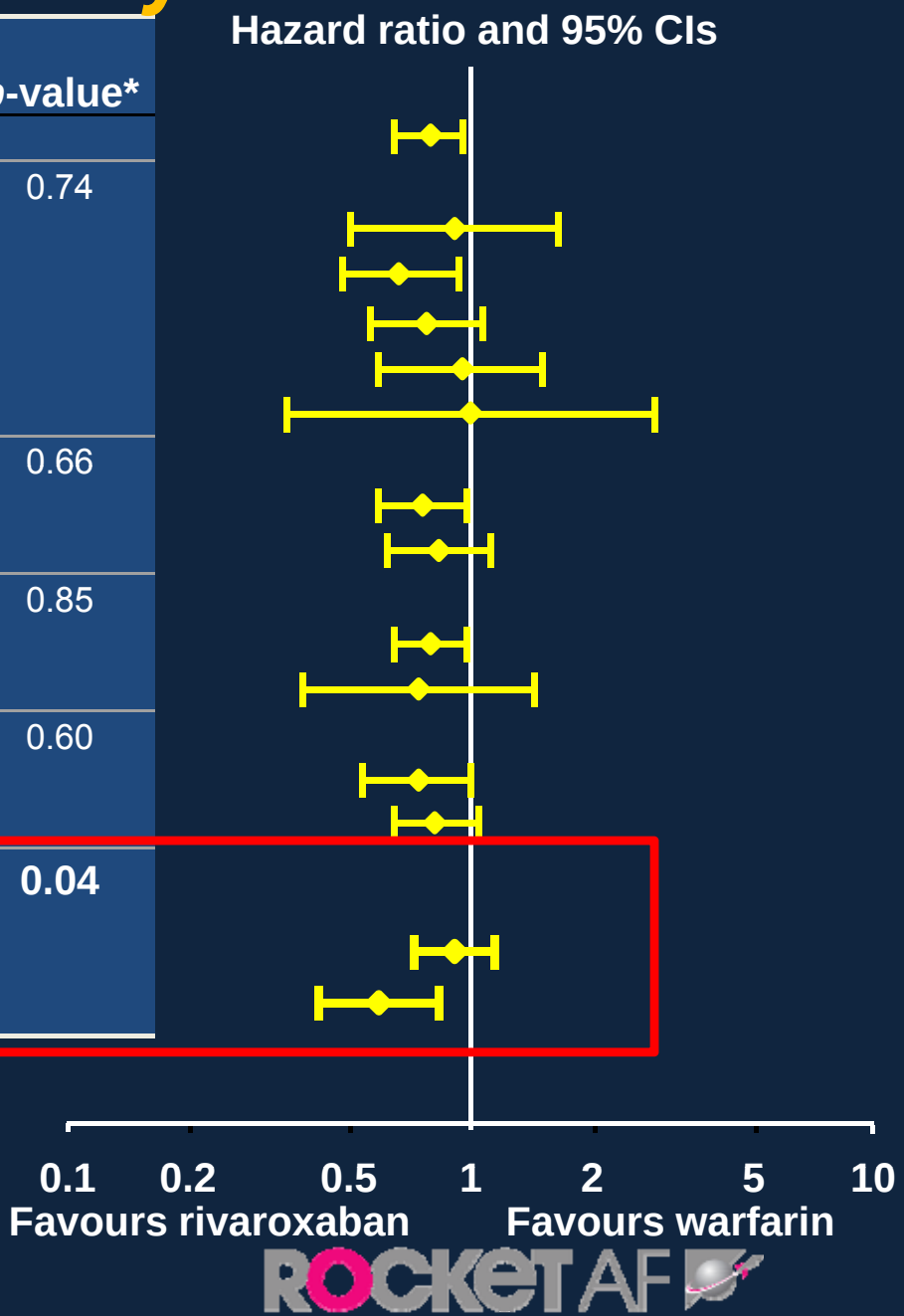
Stroke rate (per year)



Arch Intern Med 2012;172:623-631
JAMA 2003;290:2685-2692

ROCKET AF – primary efficacy endpoint subgroup analysis#

	Rivaroxaban n/N	(%)	Warfarin n/N	(%)	*p*-value*
Overall	189/7,061	2.7	243/7,082	3.4	
$CHADS_2$					0.74
2	21/922	2.3	24/931	2.6	
3	56/3,025	1.9	87/3,131	2.8	
4	71/2,073	3.4	88/1,988	4.4	
5	35/918	3.8	36/875	4.1	
6	6/122	4.9	8/155	5.2	
Congestive heart failure					0.66
Yes	106/4,428	2.4	141/4,409	3.2	
No	83/2,632	3.2	102/2,672	3.8	
Hypertension					0.85
Yes	174/6,372	2.7	223/6,429	3.5	
No	15/689	2.2	20/653	3.1	
Diabetes					0.60
Yes	70/2,842	2.5	94/2,793	3.4	
No	119/4,219	2.8	149/4,289	3.5	
Previous stroke/TIA/Non-CNS SE					**0.04**
Yes	**136/3,881**	**3.5**	**151/3,869**	**3.9**	
No	**53/3,180**	**1.7**	**92/3,213**	**2.9**	



Safety population – on-treatment analysis
*p-value for interaction
#Stroke or systemic embolism

Patel MR *et al. N Engl J Med* 2011;365:883–891