La prévention primaire de l'AVC dans la fibrillation auriculaire

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Disclosures

Consultant	Bayer / Johnson & Johnson Boehringer-Ingelheim Pfizer / Bristol-Myers Squibb
Speaker Honoraria	Boehringer-Ingelheim Bayer / Johnson & Johnson Medtronic
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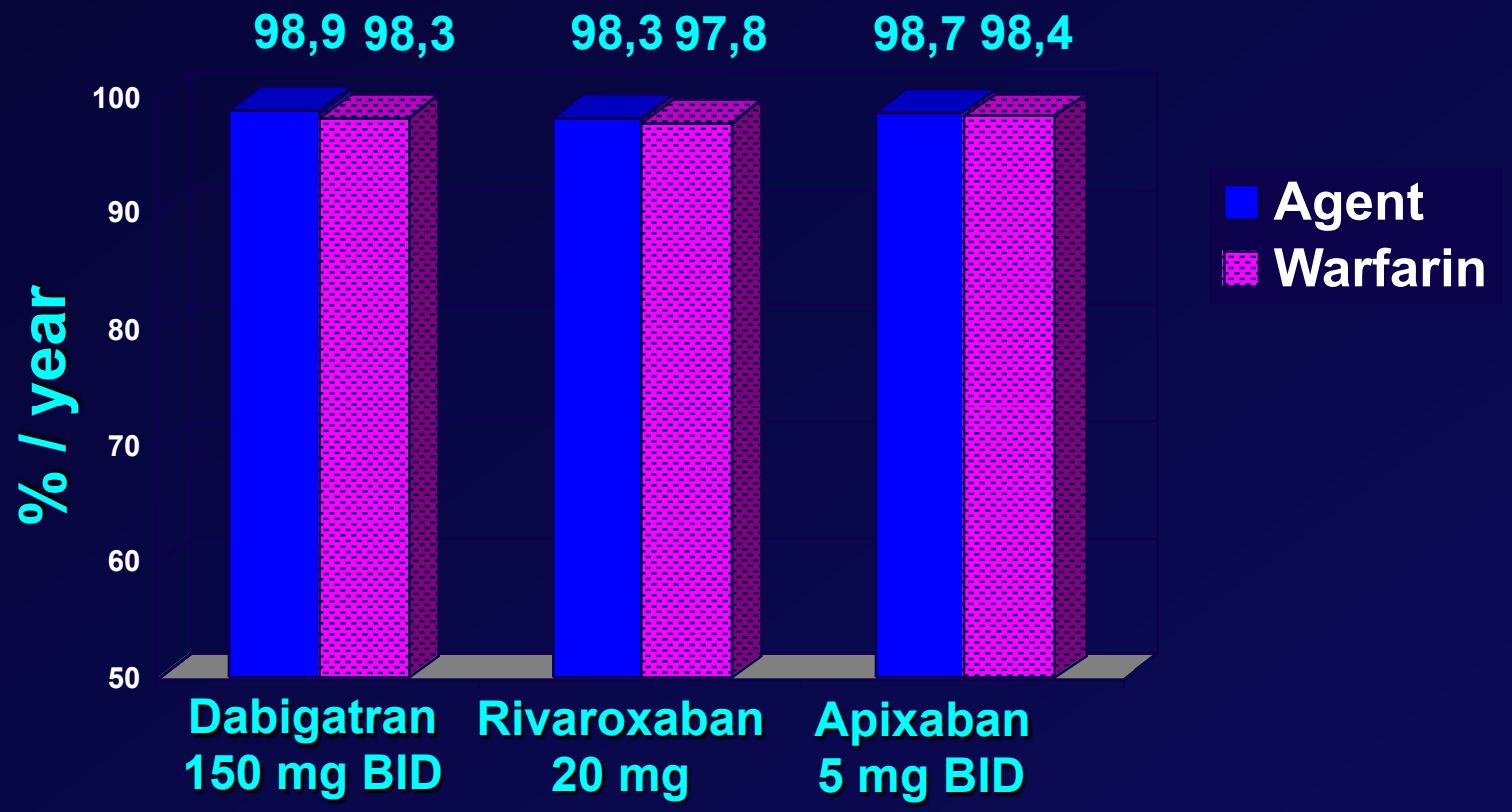
Objectifs

- Discuter des risques de l'AVC dans la FA
- Comprendre le rôle et les limitations de la warfarine et de l'AAS
- Gérer les nouveaux anticoagulants dans la prévention de l' AVC dans la fibrillation auriculaire

AVC ou embolie systémique	↓ 34 %
Hémorragie intracrânienne	↓ 33 %
Décès toutes causes	↓ 11 %

Dabigatran	AVC ou embolie systémique	↓ 34 %
Rivaroxaban	Hémorragie intracrânienne	↓ 33 %
Apixaban	Décès toutes causes	↓ 11 %

Patients without stroke or systemic embolism



Types de fibrillation auriculaire

- Fibrillation auriculaire avec valves mécaniques
- Fibrillation auriculaire non valvulaire
  - paroxystique
  - persistante
  - permanente

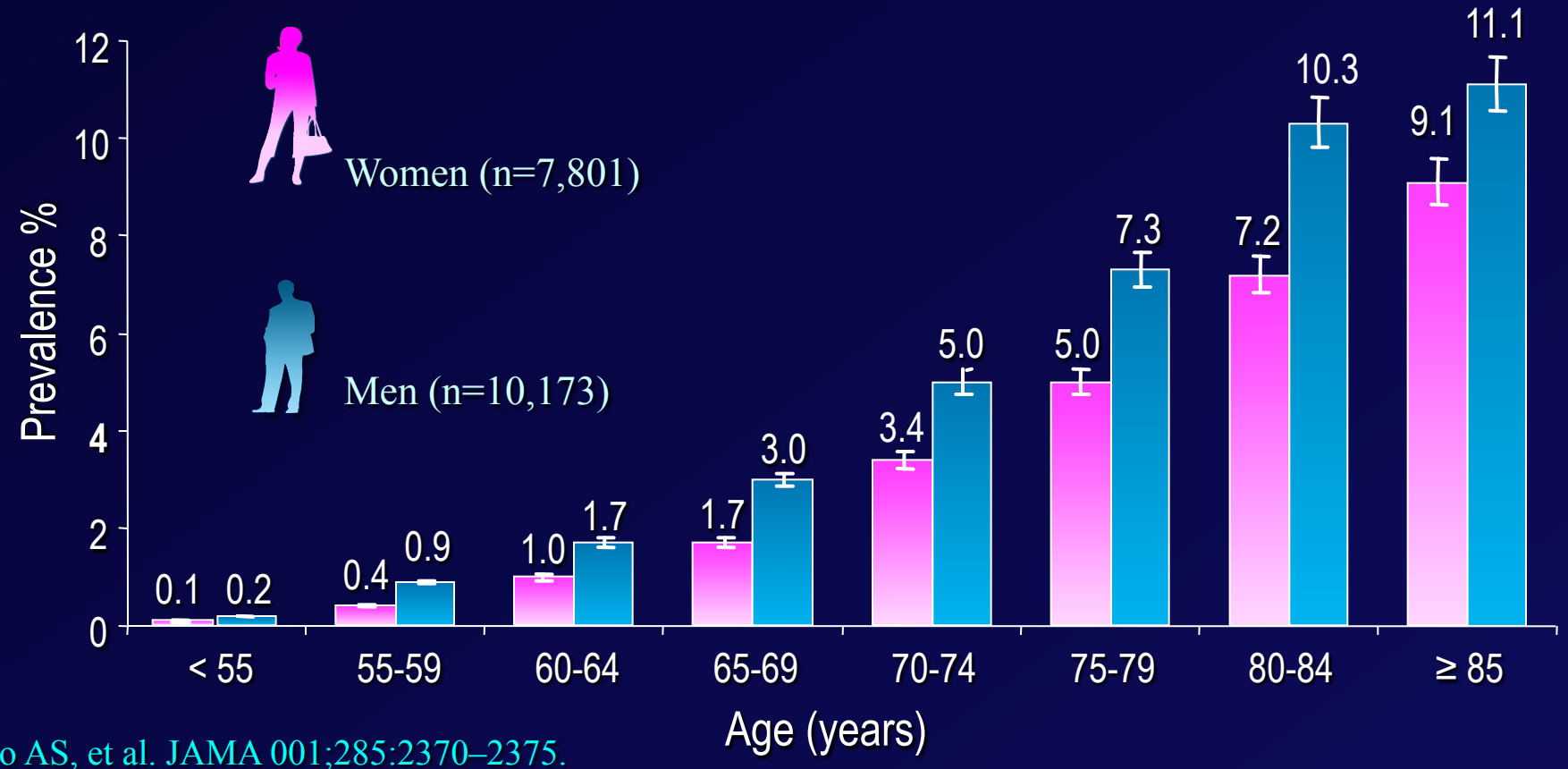
Strokes after Conversion to NSR Rate vs. Rhythm Control Trials

	n	Rate control	Rhythm control	RR (95% CI)	*p*
AFFIRM	4,917	5.7%	7.3%	1.28 (0.95-.72)	0.12
RACE	522	5.5%	7.9%	1.44 (0.75-.78)	0.44
STAF	266	1.0%	3.0%	3.01 (0.35-5.3)	0.52
PIAF	252	0.8%	0.8%	1.02 (0.73-.16)	0.49
Total	5,957	5.0%	6.5%	1.28 (0.98-.66)	0.08

Verheugt F, et al. *J Am Coll Cardiol* 2003;41(suppl):130A

AF Prevalence Increases with Age

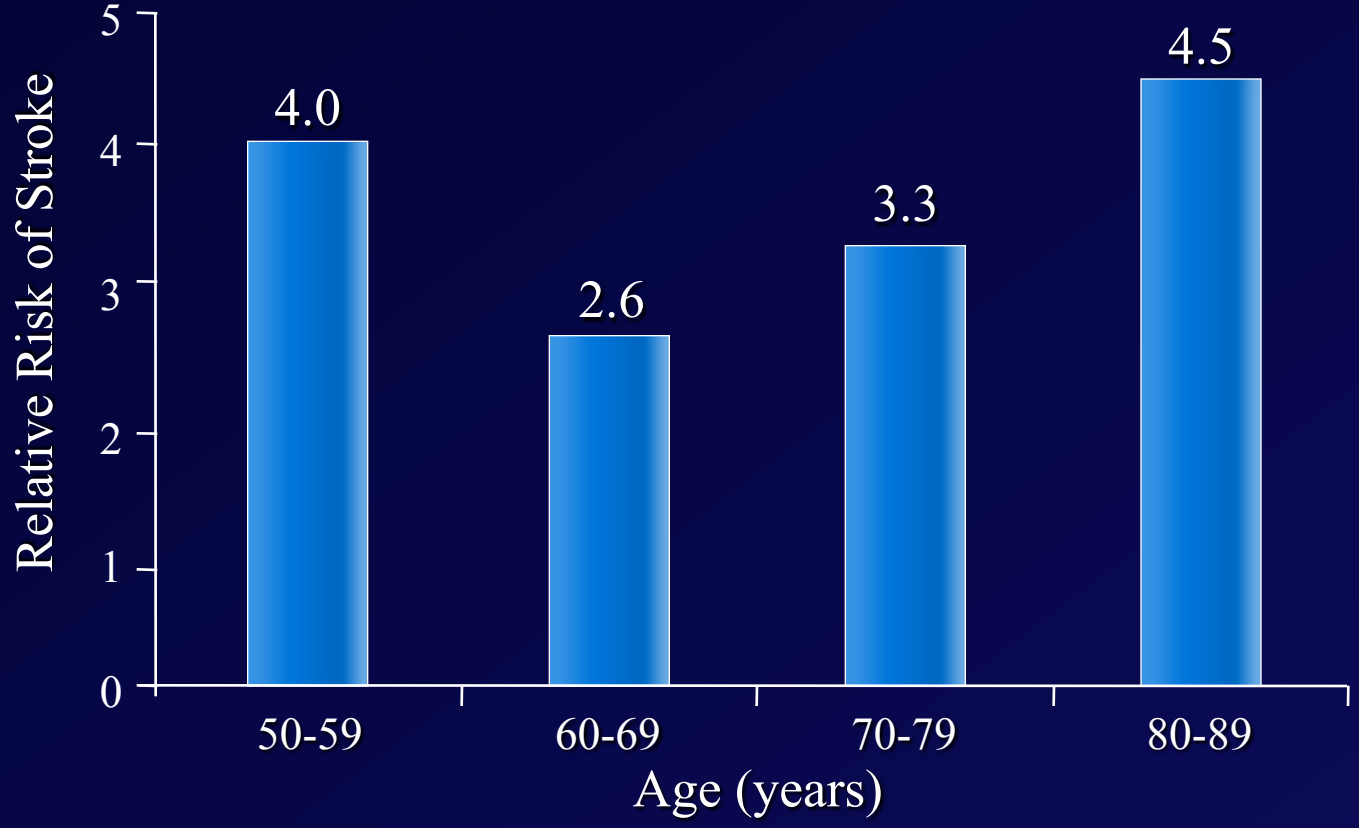
The ATRIA Study (the AnTicoagulation and Risk factors In Atrial fibrillation)



Go AS, et al. JAMA 001;285:2370–2375.

AF Increases the Risk of Stroke in All Age Groups

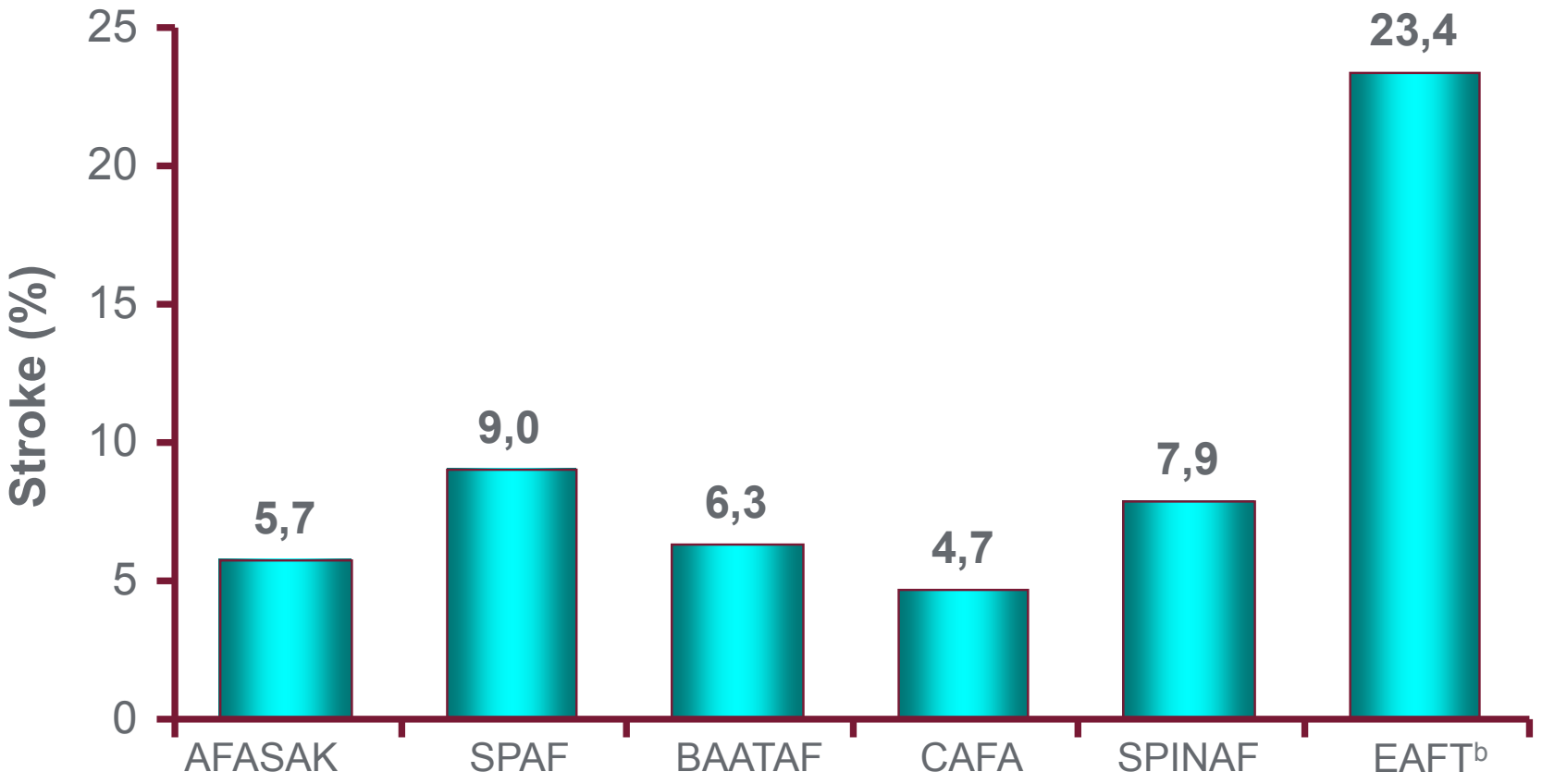
Framingham



Wolf et al. Stroke 1991;22:983-988.

p <0.001 vs non-AF patients

Stroke Rates in Placebo-Treated Patients With AF[a]



[a]Patients not anticoagulated; [b]Secondary prevention.

Hart et al. *Ann Intern Med. Ann Intern Med*. 2007;146:857-867.

$CHADS_2$ Risk Criteria	Score
Prior stroke or TIA	2
Age >75 y	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

Patients (N=1733)	Adjusted Stroke Rate (%/y)* (95% CI)	$CHADS_2$ Score
120	1.9 (1.2 to 3.0)	0
463	2.8 (2.0 to 3.8)	1
523	4.0 (3.1 to 5.1)	2
337	5.9 (4.6 to 7.3)	3
220	8.5 (6.3 to 11.1)	4
65	12.5 (8.2 to 17.5)	5
5	18.2 (10.5 to 27.4)	6

Approach to thromboprophylaxis in patients with AF

CCS Guidelines

Risk category	$CHADS_2$	Recommended antithrombotic therapy
Moderate risk	≥ 2	OAC
Low risk	1	OAC or aspirin OAC preferred
Very low risk	0	Aspirin (75 mg-325 mg)

Risk factors for stroke and thrombo-embolism in non-valvular AF

Major risk factors
Previous stroke
TIA or systemic embolism
Age ≥ 75 years

Clinically relevant non-major risk factors
CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ≤ 40%]
Hypertension
Diabetes mellitus
Age 65-74 years
Female sex
Vascular disease

AF= atrial fibrillation; EF = ejection fraction (as documented by echocardiography, radionuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left ventricular; TIA = transient ischaemic attack.

European Heart Journal (2010) 31, 2369-2429

Risk factor-based point-based scoring system - CHA_2DS_2-VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 ans	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65-74	1
Sex category [i.e. femal sex]	1
Maximum score	**9**

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

European Heart Journal (2010) 31, 2369-2429

Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n = 7329)	Adjusted stroke rate (%/y)
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

European Heart Journal (2010) 31, 2369-2429

Approach to thromboprophylaxis in patients with AF

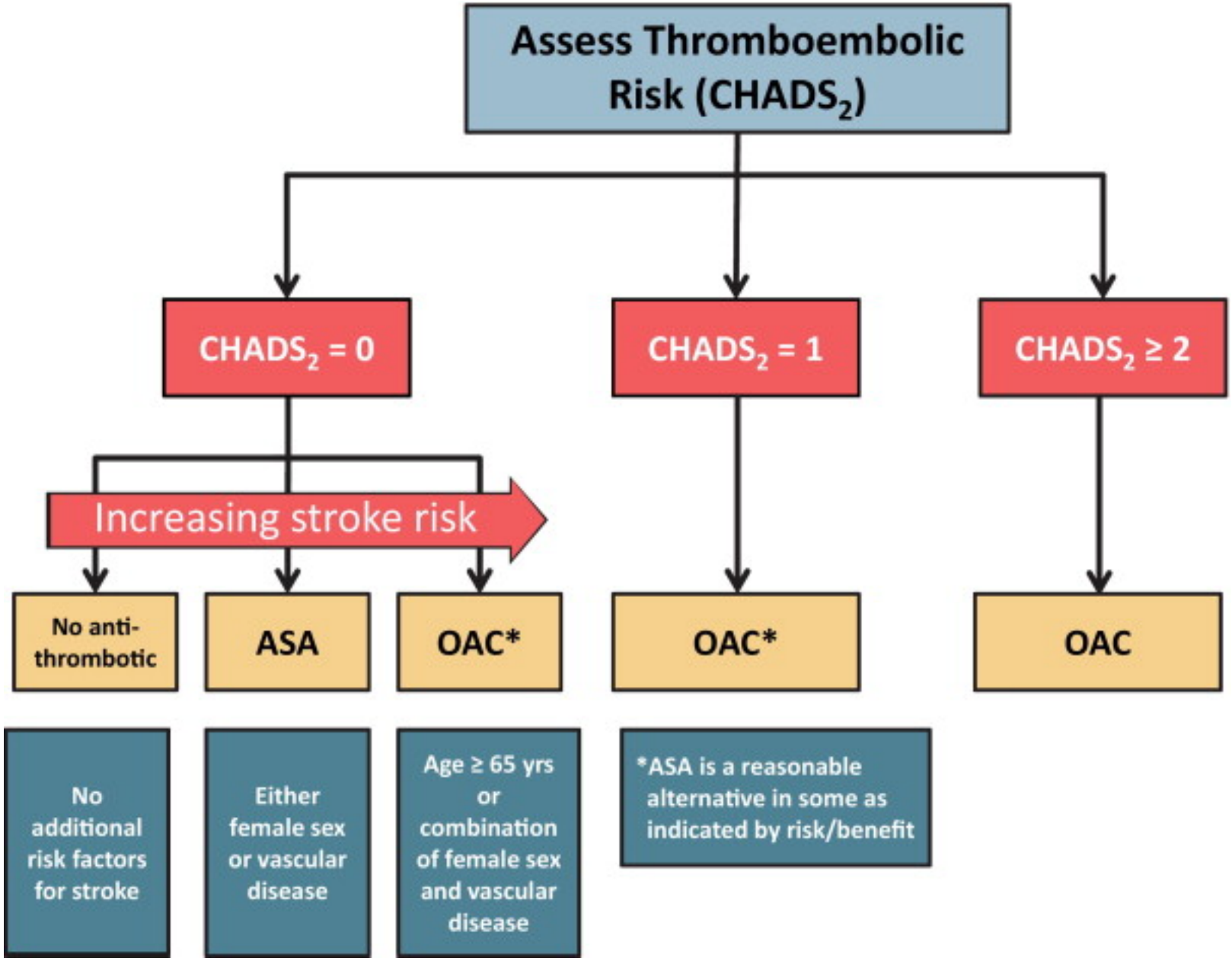
ESC Guidelines

Risk category	CHA_2DS-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors	≥ 2	OAC
One 'clinically relevant non-major' risk factor	1	Either OAC or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75-325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

CCS Guidelines vs ESC Guidelines

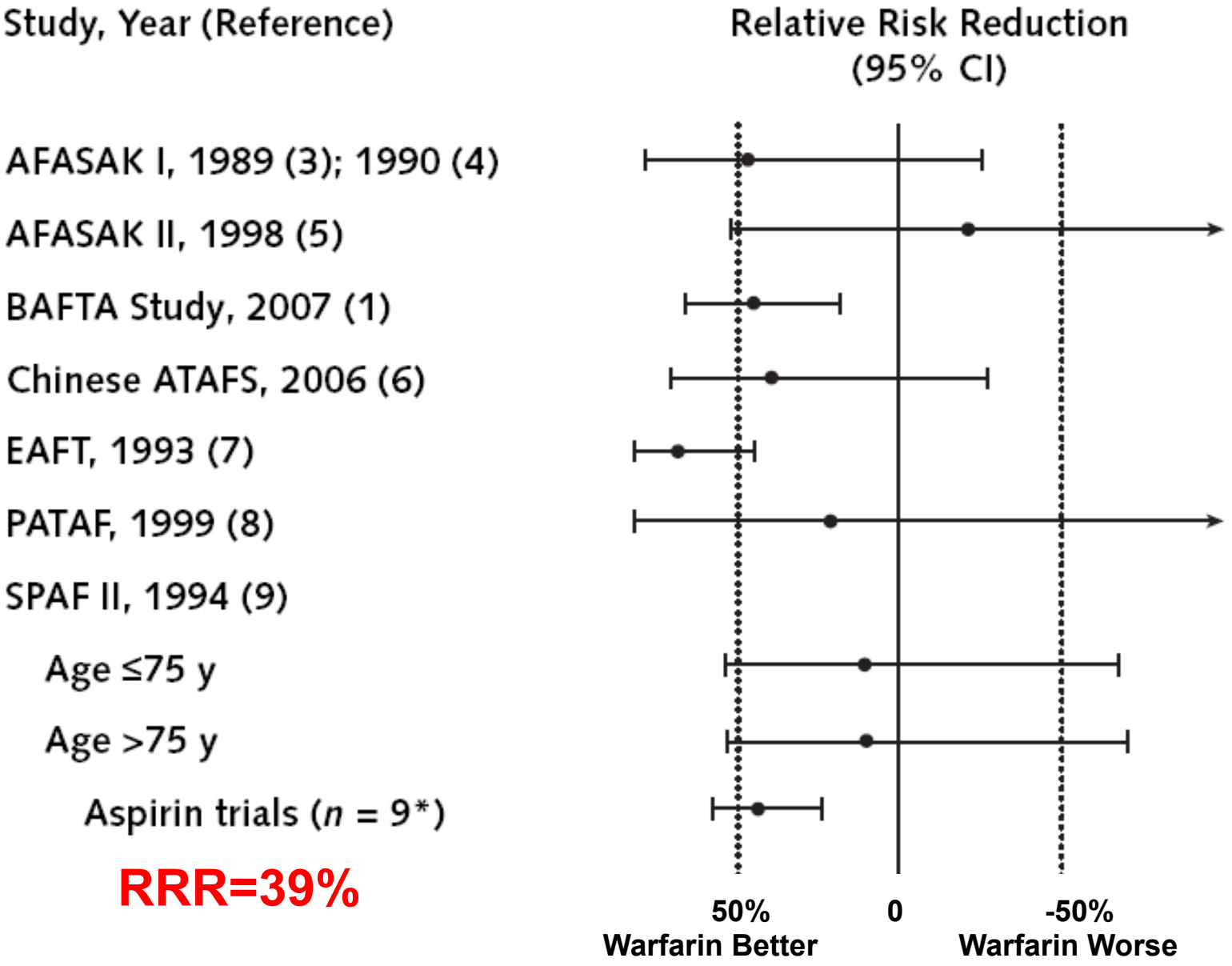
- Female patient
- 66 years old
- Vascular disease

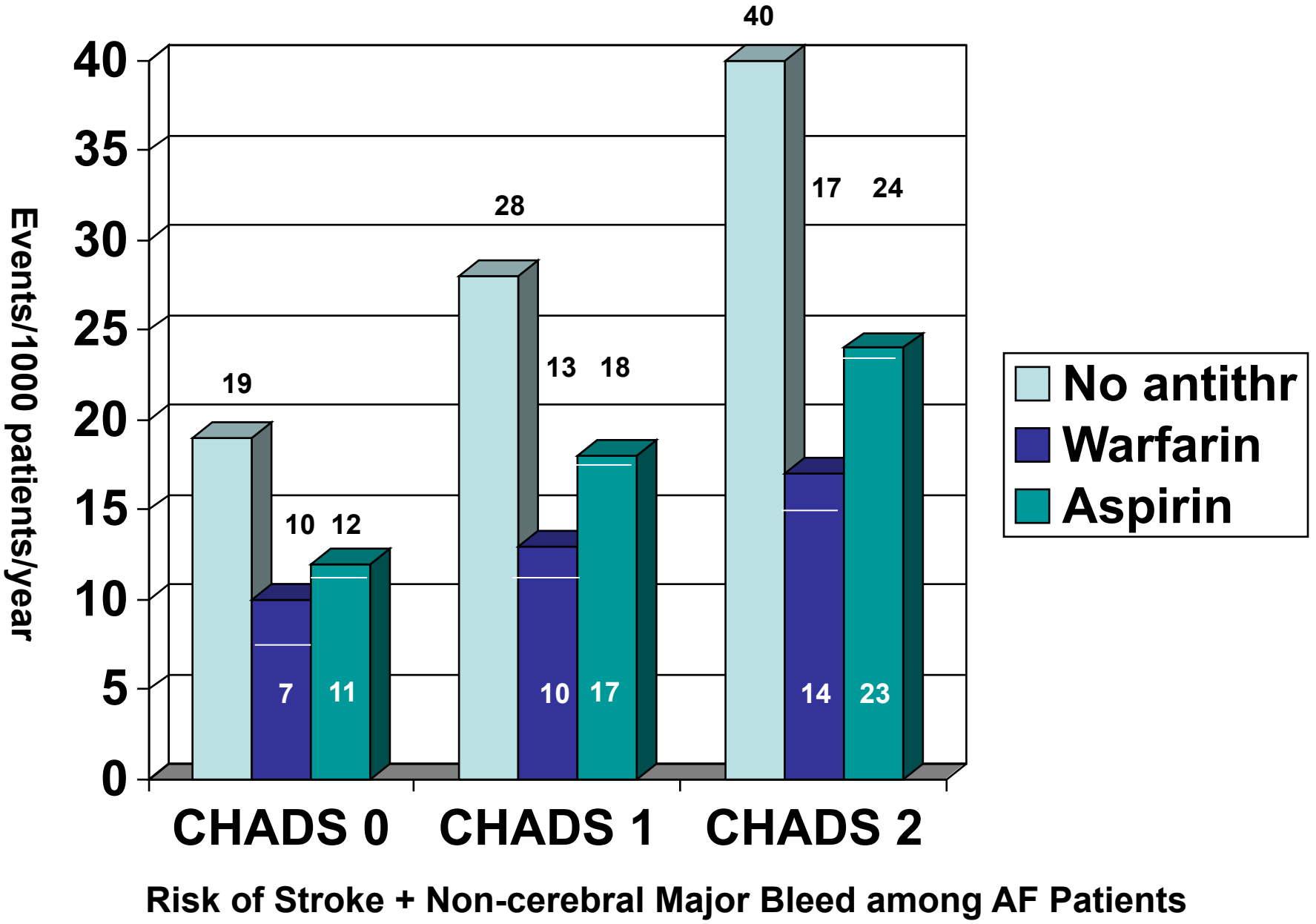
- $CHADS_2$ score $\rightarrow$ 0
- CHA_2DS_2–VASc score $\rightarrow$ 3


Assess Thromboembolic Risk ($CHADS_2$)
$CHADS_2 = 0$
$CHADS_2 = 1$
$CHADS_2 \geq 2$
Increasing stroke risk
No anti-thrombotic
ASA
OAC*
OAC*
OAC
No additional risk factors for stroke
Either female sex or vascular disease
Age ≥ 65 yrs or combination of female sex and vascular disease
*ASA is a reasonable alternative in some as indicated by risk/benefit

RCTs of Adjusted Dose Warfarin vs. Aspirin

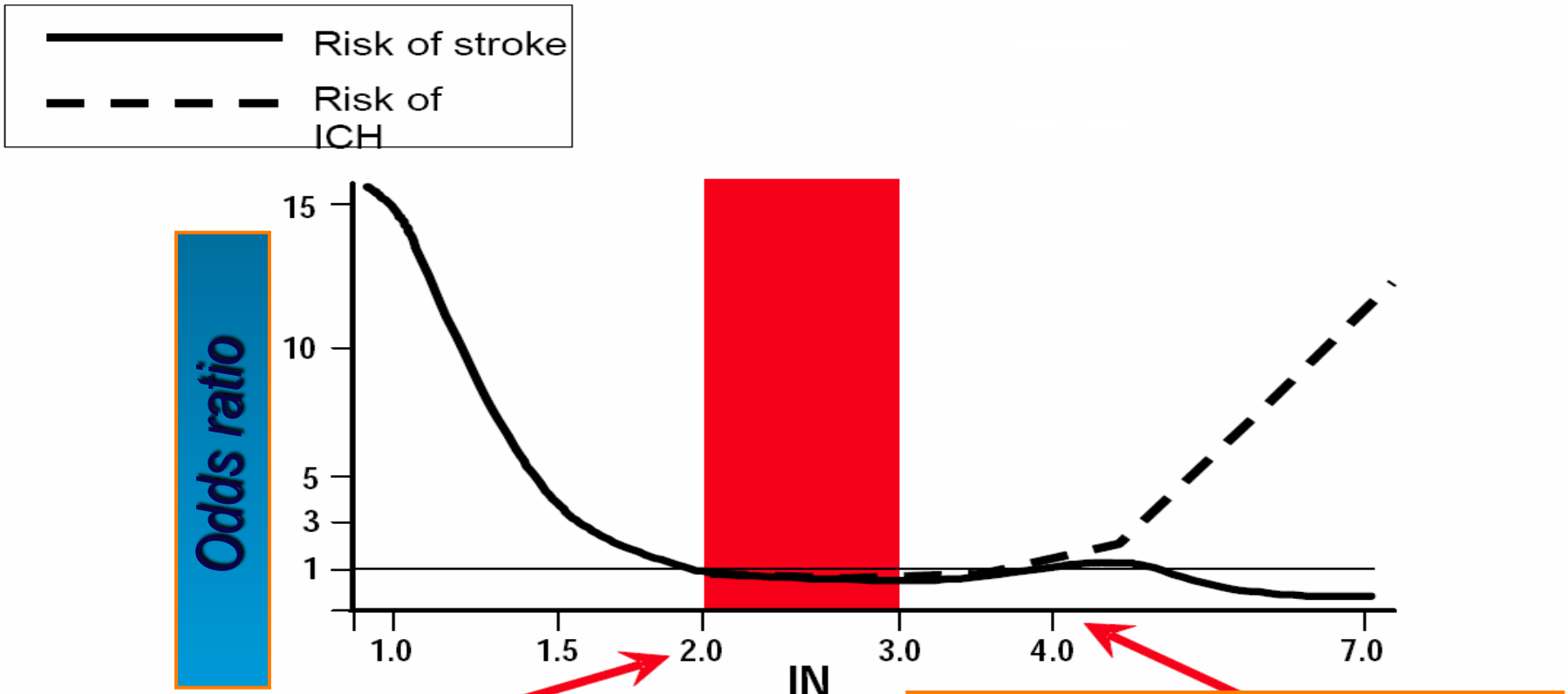
Hart. Ann Int Med 2007;147:590





Risk of Stroke + Non-cerebral Major Bleed among AF Patients

Oral anticoagulation has a narrow therapeutic window

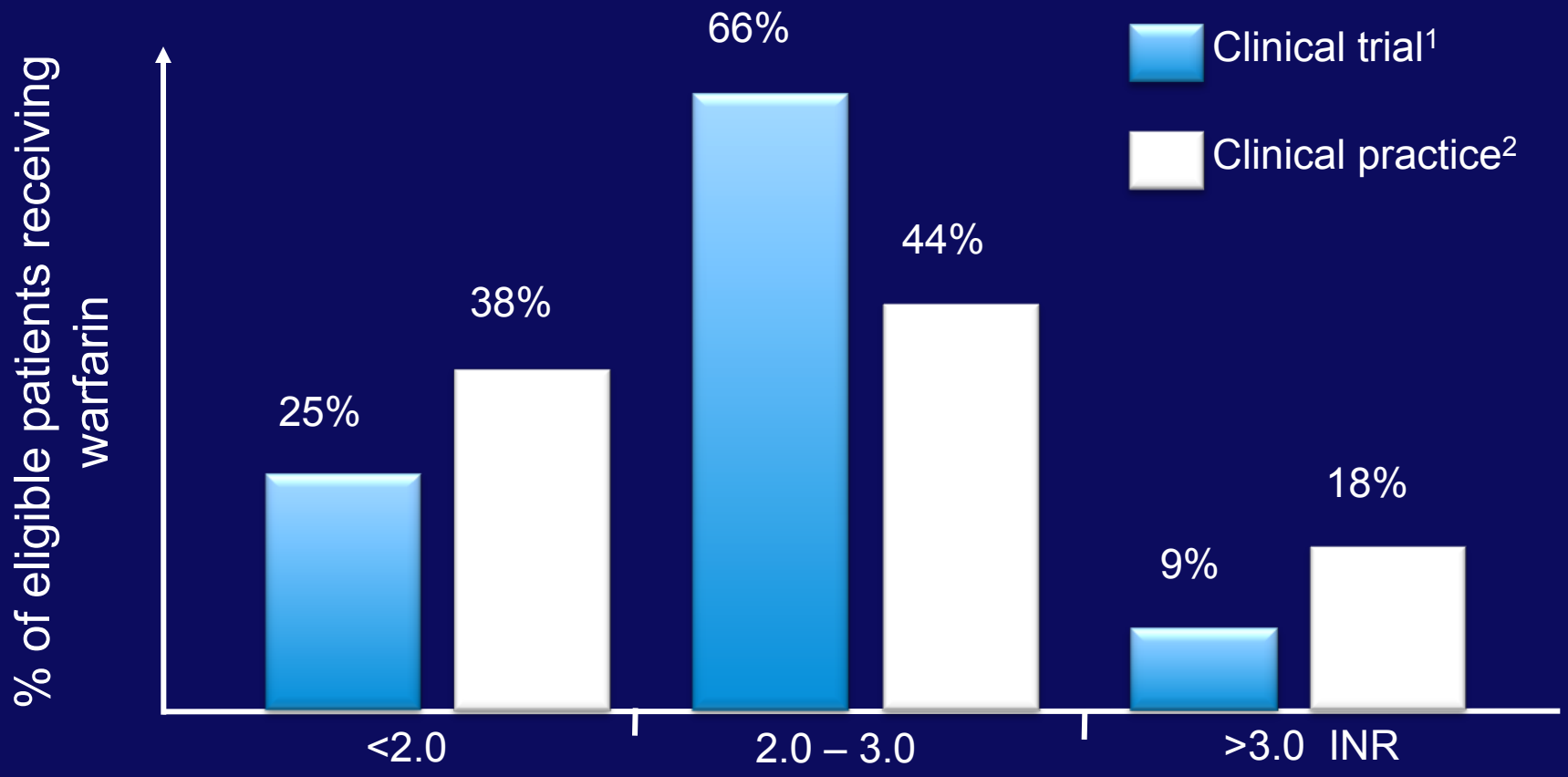


Hylek EM, et al. *N Engl J Med* 1996;335:540-546.

Hylek EM, and Singer DE. *Ann Intern Med* 1994;120:897-902

INR control: clinical trials v. clinical practice

INR* control in clinical trial versus clinical practice (TTR**)



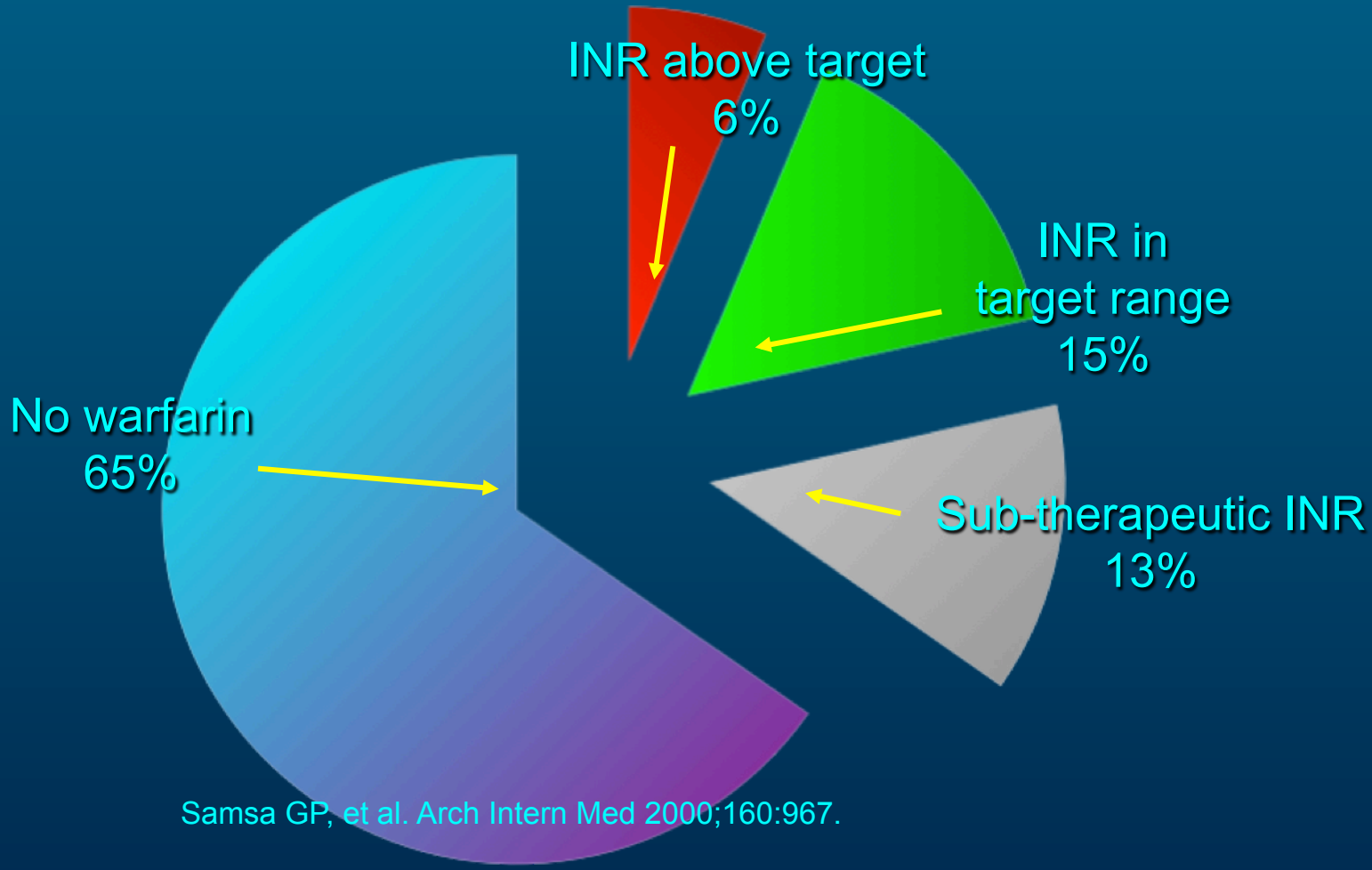
*INR = International normalized ratio

** TTR = Time in Therapeutic Range (INR2.0-3.0)

1. Kalra L, et al. *BMJ* 2000;320:1236-1239 * Pooled data: up to 83% to 71% in individualized trials; 2. Matchar DB, et al. *Am J Med* 2002; 113:42-51.

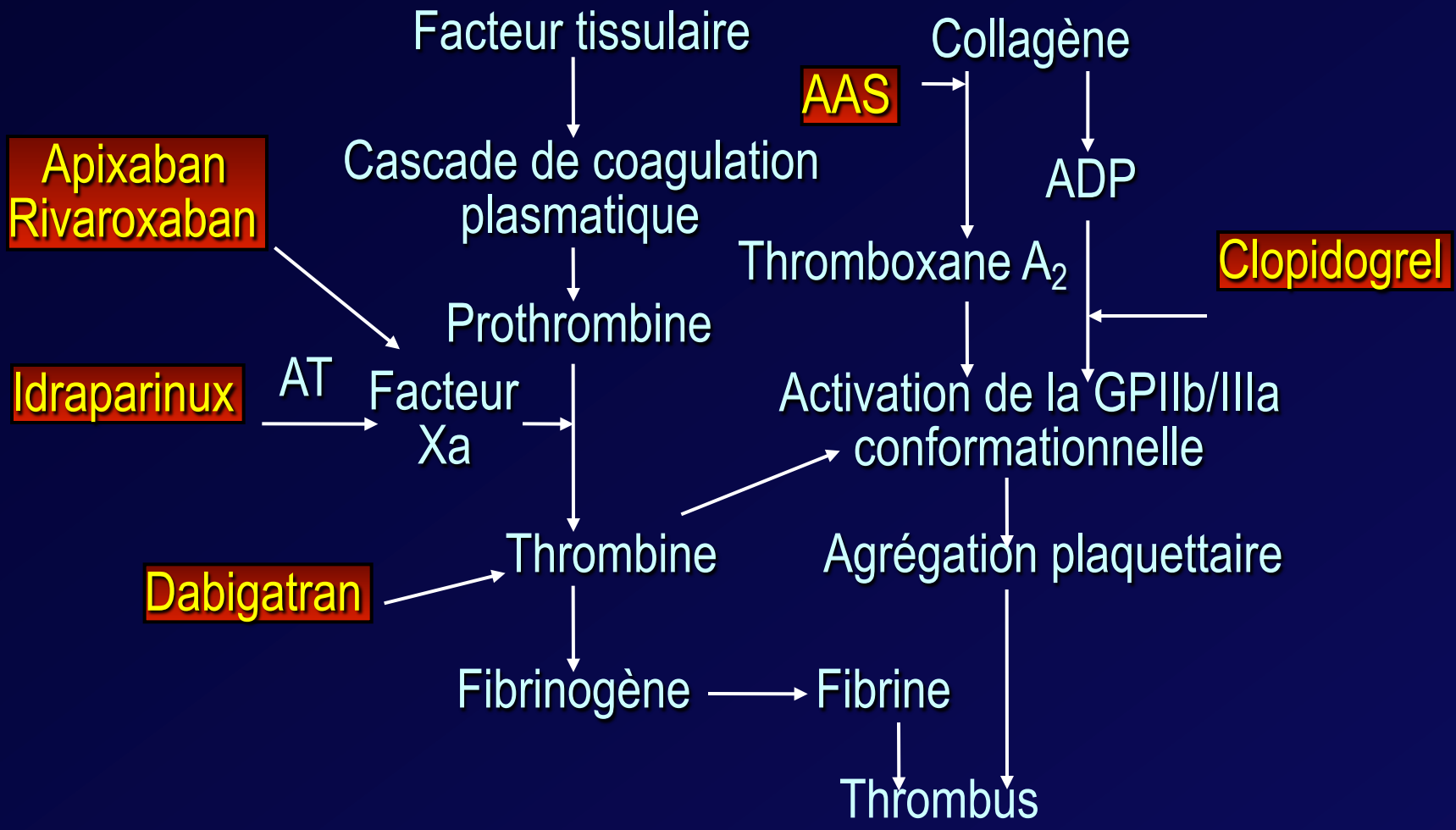
Inadequate VKA Treatment for AF

Adequacy of Anticoagulation in Patients with AF in Primary Care Practice



Samsa GP, et al. Arch Intern Med 2000;160:967.

Nouveaux agents antithrombotiques faisant l'objet d'études de Phase III pour la PACVFA



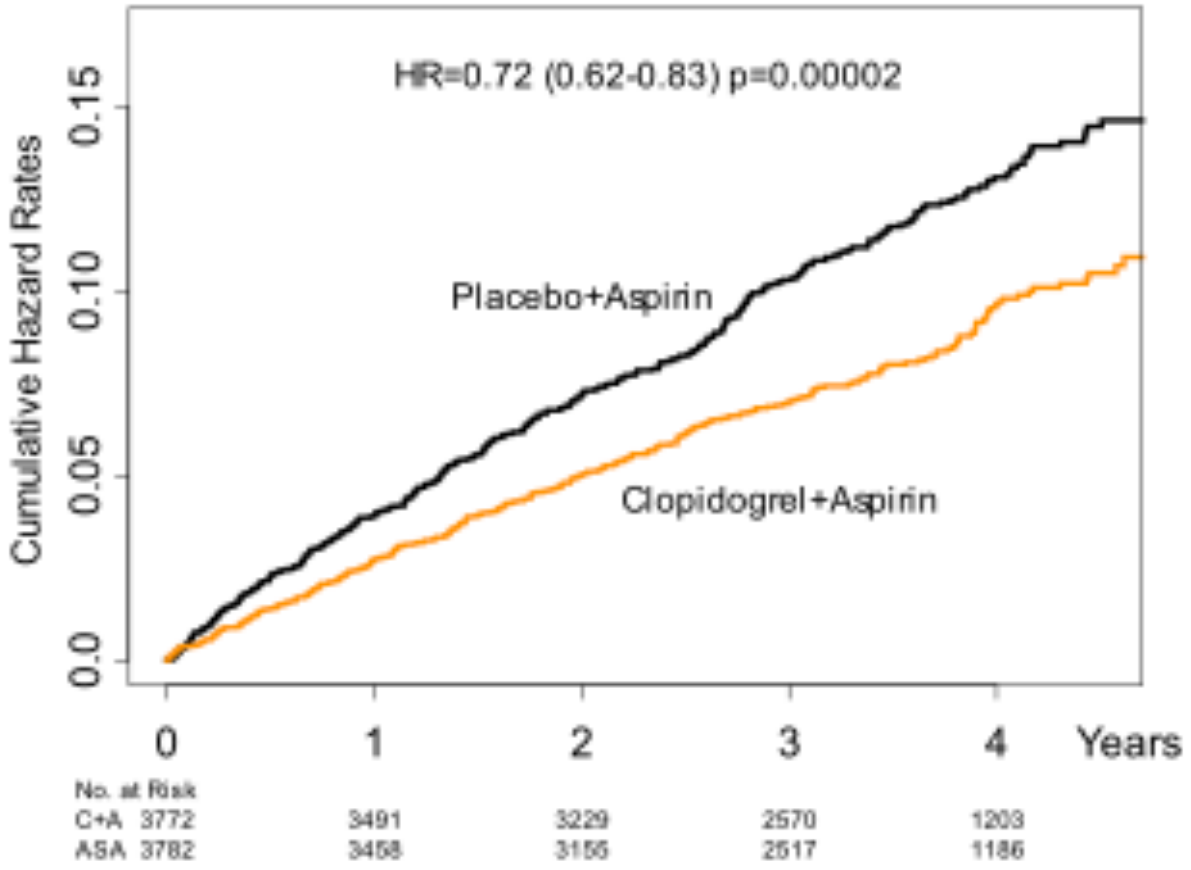
New Direct Thrombin Inhibitors and Factor Xa Inhibitors for AF

Medication	Action	Phase III Trial	Comparator	Design	n	n
Dabigatran	DTI	RE-LY	Warfarin	Non-inferiority	18 500	18 113
Apixaban	Anti Xa	AVERROES	Aspirin	Superiority	5 600	
		ARISTOLE	Warfarin	Non-inferiority	15 000	18 201
Rivaroxaban	Anti Xa	ROCKET AF	Warfarin	Non-inferiority	14 000	14 264
Edoxaban	Anti Xa	ENGAGE	Warfarin	Non-inferiority	16 500	± 22 000
Biotinylated Idraparinux	Anti Xa	BOREALIS-AF	Warfarin	Non-inferiority	9 600	

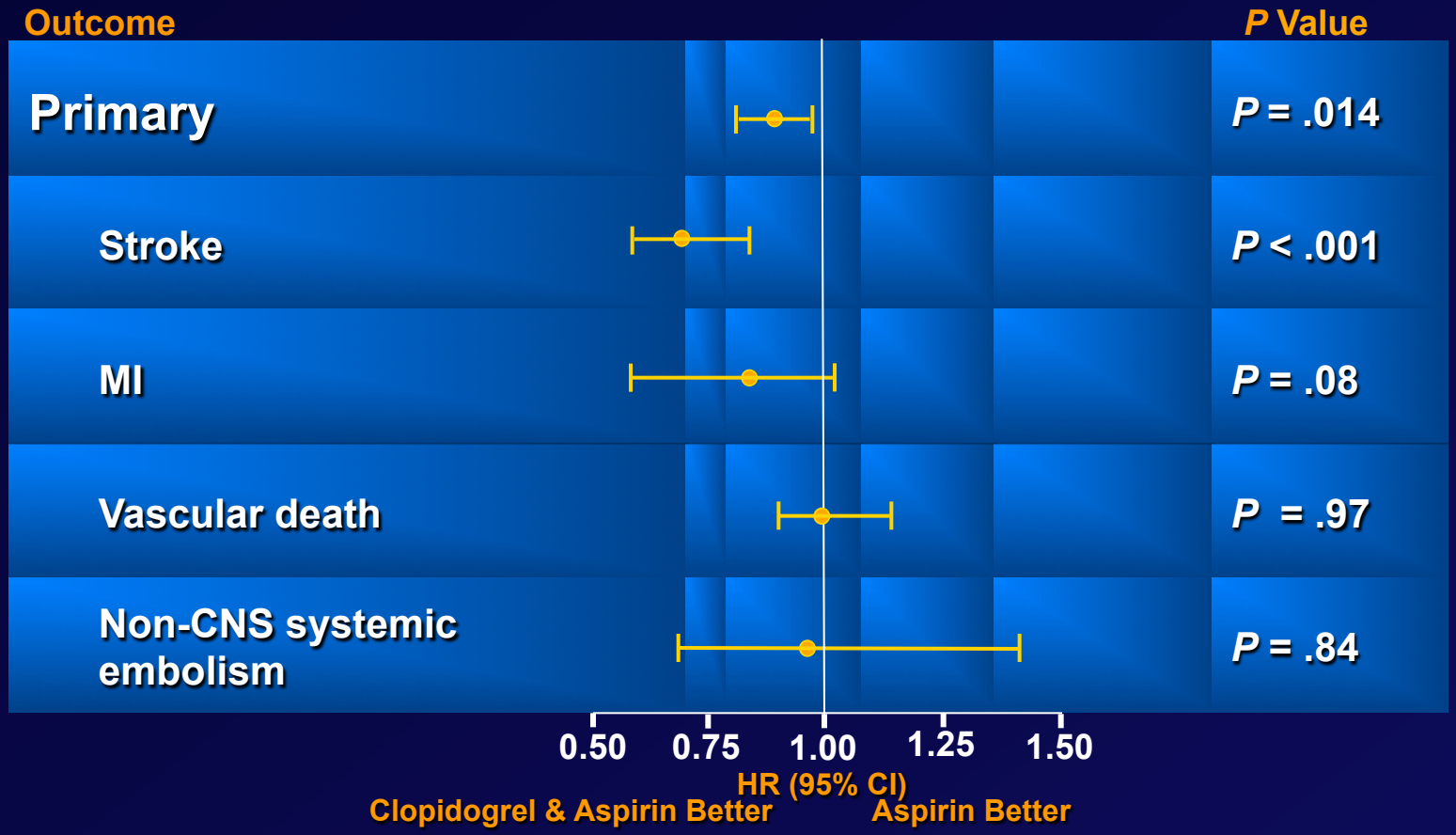
Others include: Betrixaban, LY 517717, YM 150

Unsuitable for warfarin

Stroke


HR=0.72 (0.62-0.83) p=0.00002
Placebo+Aspirin
Clopidogrel+Aspirin
Cumulative Hazard Rates
0.0
0.05
0.10
0.15
0
1
2
3
4
Years
No. at Risk
C+A 3772 3491 3229 2570 1203
ASA 3782 3458 3155 2517 1186

ACTIVE A
Components of the Primary Outcome



Connolly SJ, et al. Lancet. 2009;34:456-57

ACTIVE A Bleeding

Outcome	Clopidogrel + Aspirin		Aspirin		Clopidogrel + Aspirin versus Aspirin		
	#	rate/ year	#	rate/ year	RR	95% CI	P
Major	251	2.0	162	1.3	1.57	1.29-1.92	<0.001
Severe	190	1.5	122	1.0	1.57	1.25-1.98	<0.001
Fatal	42	0.3	27	0.2	1.56	0.96-2.53	0.07
Intra-cranial	54	0.4	29	0.2	1.87	1.19-1.94	0.006
Extra-cranial	200	1.6	134	1.1	1.51	1.21-1.88	<0.001

Benefits and Risks

1000 patients treated for 3 years

- Will prevent
  - 28 strokes (17 fatal or disabling)
  - 6 myocardial infarctions
- At a cost of 20 (non-stroke) major bleeds (3 fatal)

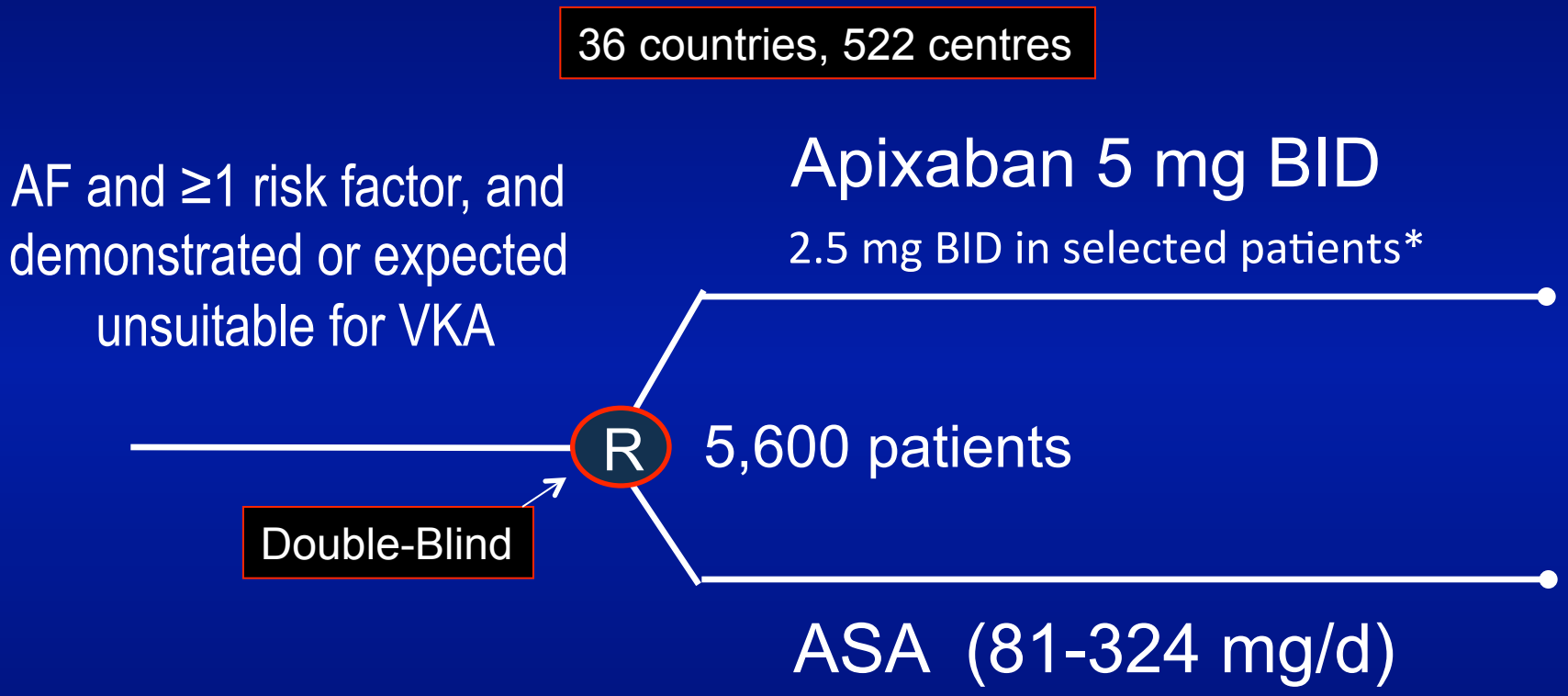
AVERROES
Apixaban vs acetylsalicylic acid to prevent strokes

- 5600 patients unsuitable for warfarin
- $CHADS_2$ score ≥ 1
- Follow-up 36 months

- Apixaban 2.5 mg BID
- Apixaban 5 mg BID
- ASA 80-325 mg Die

S. Connolly ESC 2010

AVERROES Design



Primary Outcome: Stroke or Systemic Embolic Event (SEE)

* Patients who met 2 of the following criteria: an age of 80 years or older, a body weight of 60kg or less, or a serum creatinine level of 1.5 mg per deciliter (133 μmol per liter) or higher

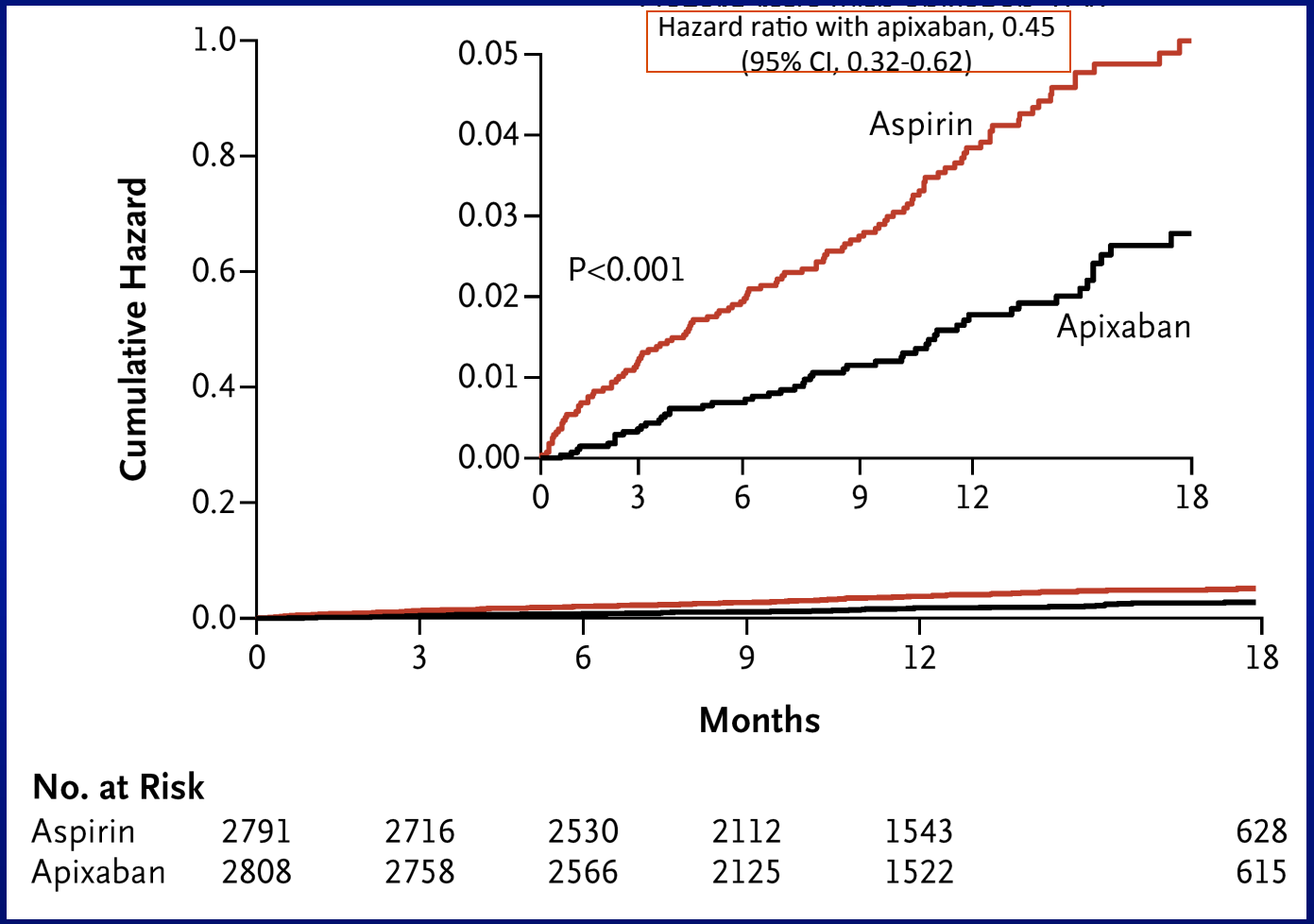
Connolly S.J. et al, 2011, NEJM.

Most common reasons for unsuitability for VKA therapy

- Assessment that INR could not or was unlikely to be measured at requested intervals (43%)
- Patient's refusal to take VKA (37%)
- $CHADS_2$ score of 1 and VKA therapy not recommended by physician (21%)
- Uncertainty about patient's ability to adhere to instructions regarding VKA therapy (15%)

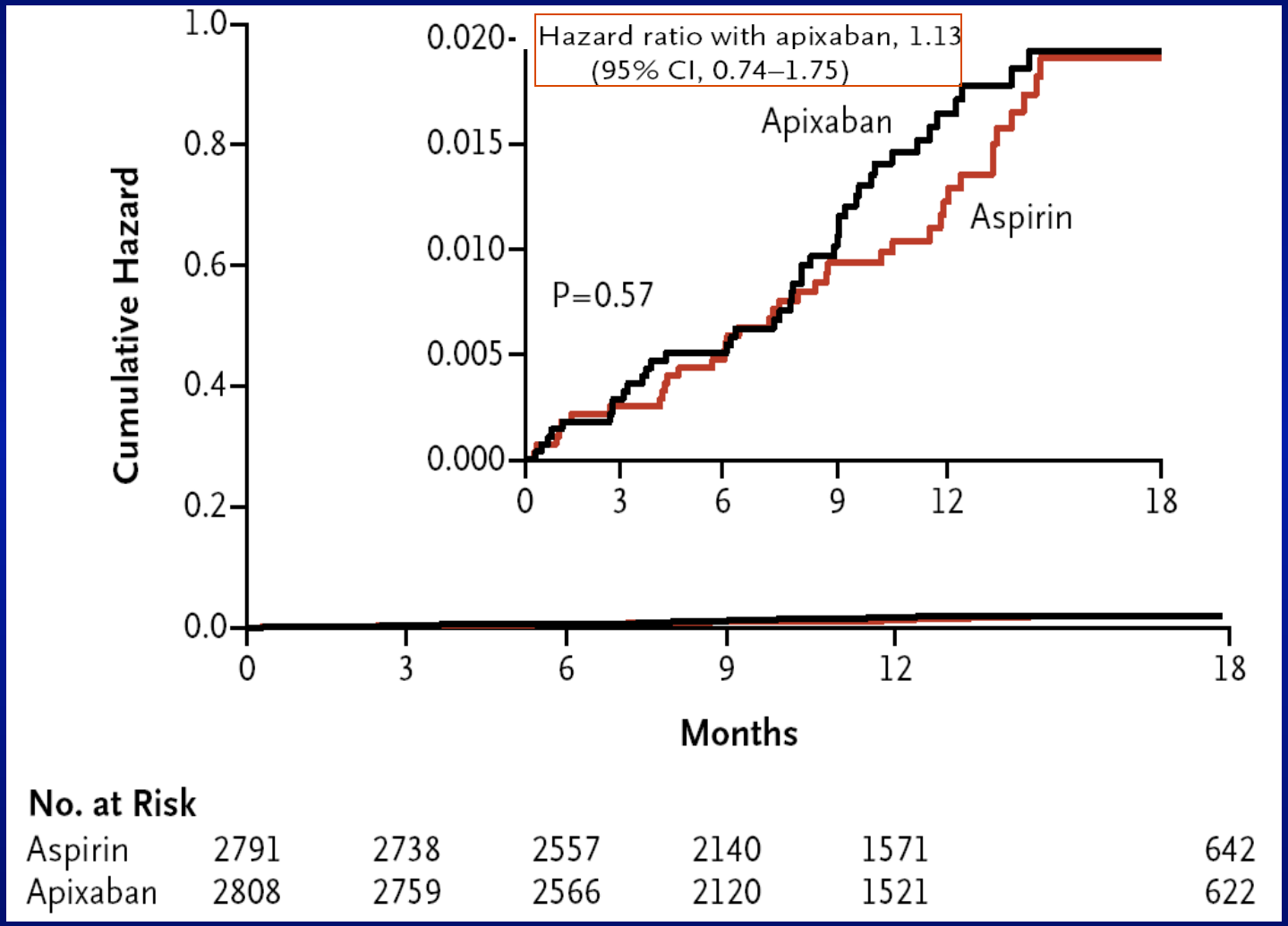
Connolly S.J. et al, 2011, NEJM.

Stroke or Systemic Embolism



Connolly S.J. et al, 2011, NEJM.

Major Bleeding



Connolly S.J. et al, 2011, NEJM.

AVERROES
Bleeding events

Outcomes	Apixaban (n = 2809)	Aspirin (n = 2791)	Relative risk (95% CI)
Major bleeding	1.4	1.2	1.14 (0.74-1.75)
Clinically relevant non major bleeding	5.0	2.6	1.18 (0.88-1.58)
Minor bleeding	5.2	4.1	1.27 (1.01-1.61)
Fatal bleeding	0.1	0.1	0.84 (0.26-2.75)
Intracranial bleeding	0.4	0.3	1.09 (0.50-2.39)

S. Connolly ESC 2010

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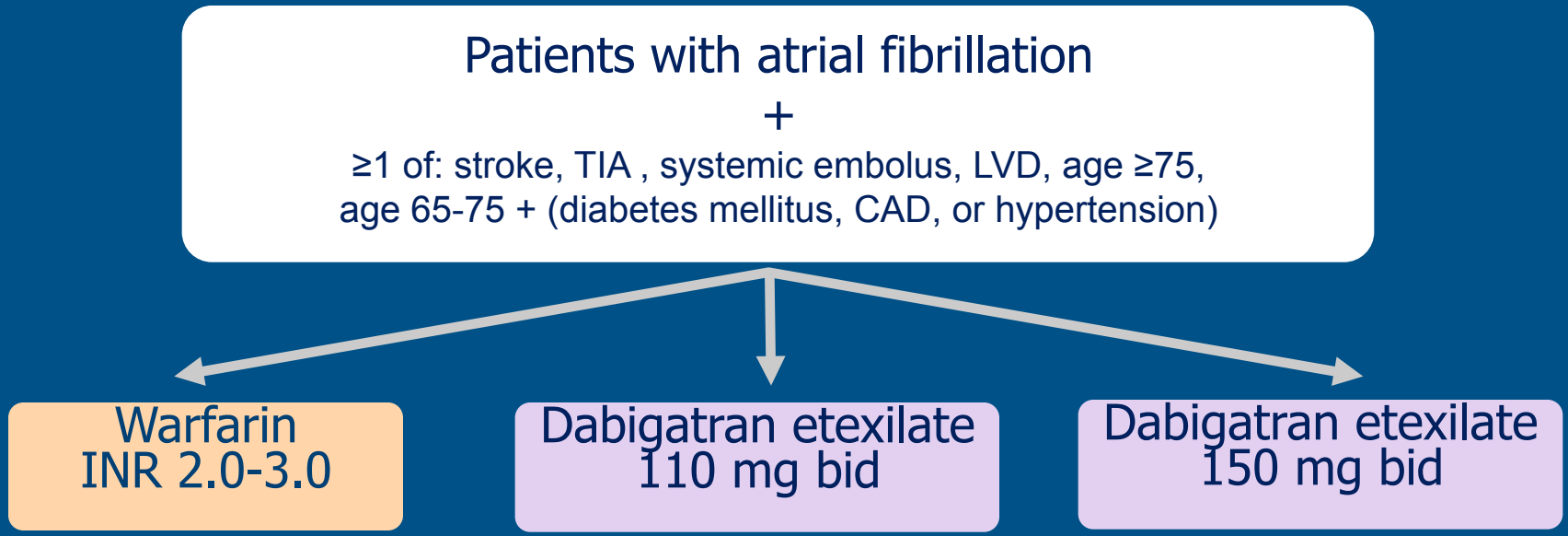
RE-LY Study Design



Treatment period 1-3 years
(median 2 years)

- Design: non-inferiority
- N = 18,113
- Dabigatran etexilate doses are blinded
- Primary outcome measures: Time to the first occurrence of stroke (including haemorrhagic) and systemic embolism; bleeding events during treatment

Ezekowitz MD et al. Am Heart J 2009

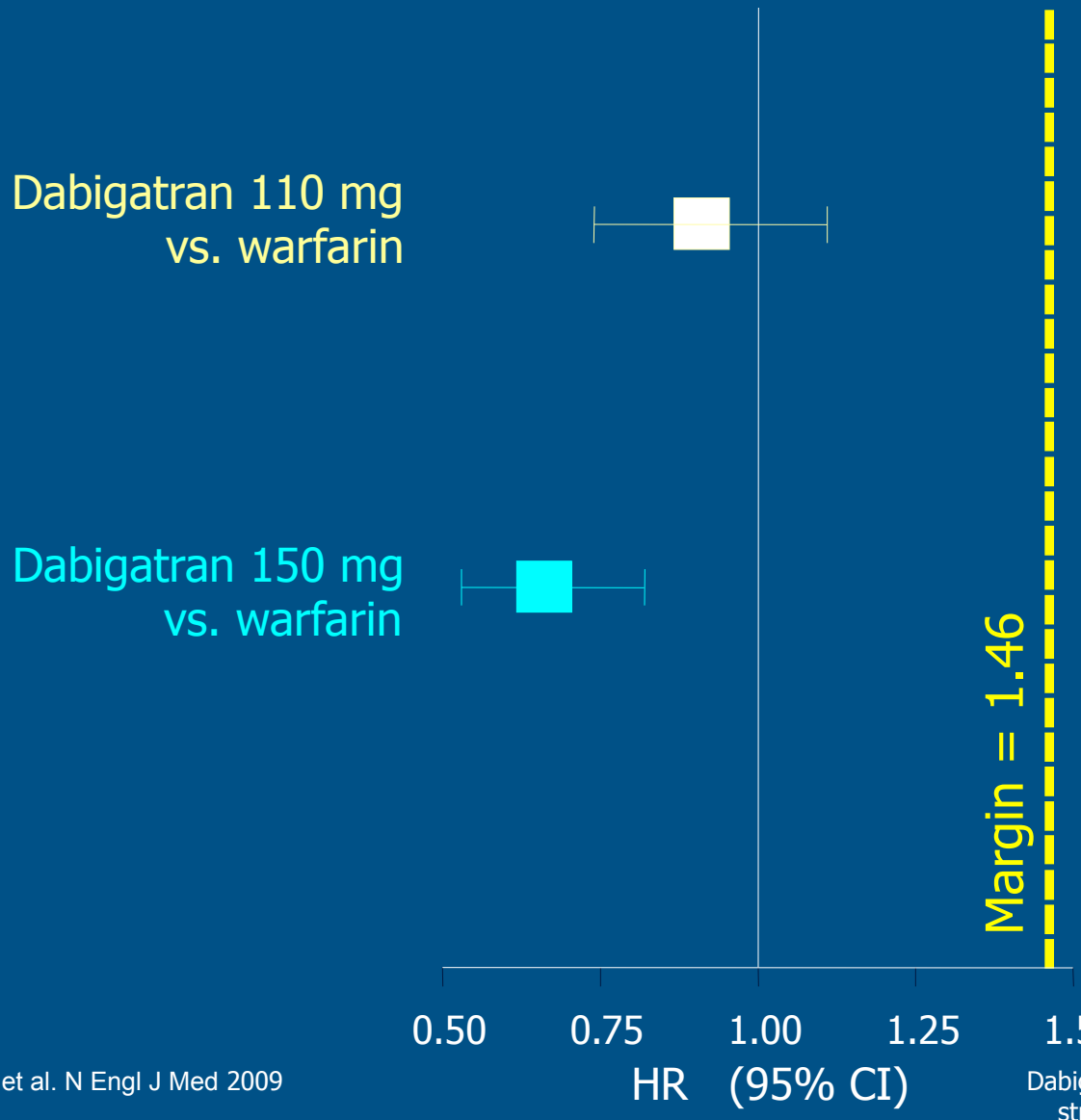
Baseline characteristics

Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomized	6015	6076	6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean) 0-1 (%) 2 (%) 3+ (%)	2.1 32.6 34.7 32.7	2.2 32.2 35.2 32.6	2.1 30.9 37.0 32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.3	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin naïve (%)	50.1	50.2	48.6

Connolly et al. N Engl J Med 2009

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

Stroke or systemic embolism (SSE)



	Noninferiority p-value	Superiority p-value
Dabigatran 110 mg vs. warfarin	<0.001	0.34
Dabigatran 150 mg vs. warfarin	<0.001	<0.001

Connolly et al. N Engl J Med 2009

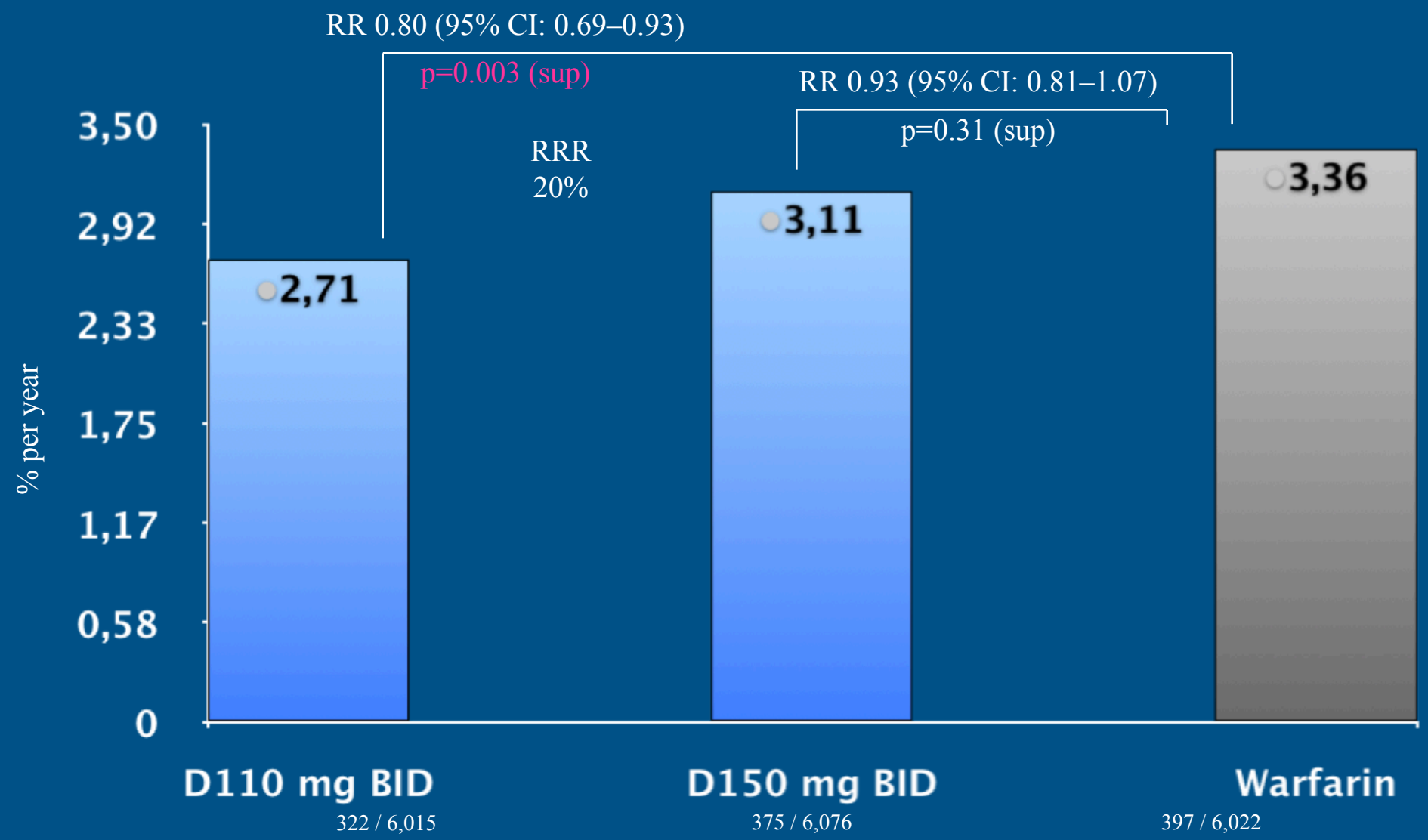
Dabigatran etexilate is not indicated for clinical use in stroke prevention for patients with atrial fibrillation

RE-LY
Efficacy Outcomes

	Dabigatran 110 mg Rate/ year	Dabigatran 150 mg Rate/ year	Warfarin Rate/ year	Dabigatran 110 mg vs warfarin RR (95% CI)	*P*	Dabigatran 150 mg vs warfarin RR (95% CI)	*P*	Dabigatran 150 mg vs 110 mg RR (95% CI)	*P*
n	6015	6076	6022						
Stroke or systemic embolism	1.53%	1.11%	1.69%	0.91 (0.74-1.11)	.34	0.66 (0.53-0.82)	<.001	0.73 (0.58-0.91)	.005
Death from any cause	3.75%	3.64%	4.13%	0.91 (0.80-1.03)	.13	0.88 (0.77-1.00)	.051	0.97 (0.85-1.11)	.66

Connolly SJ, et al. N Engl J Med. 2009;361:1139-51

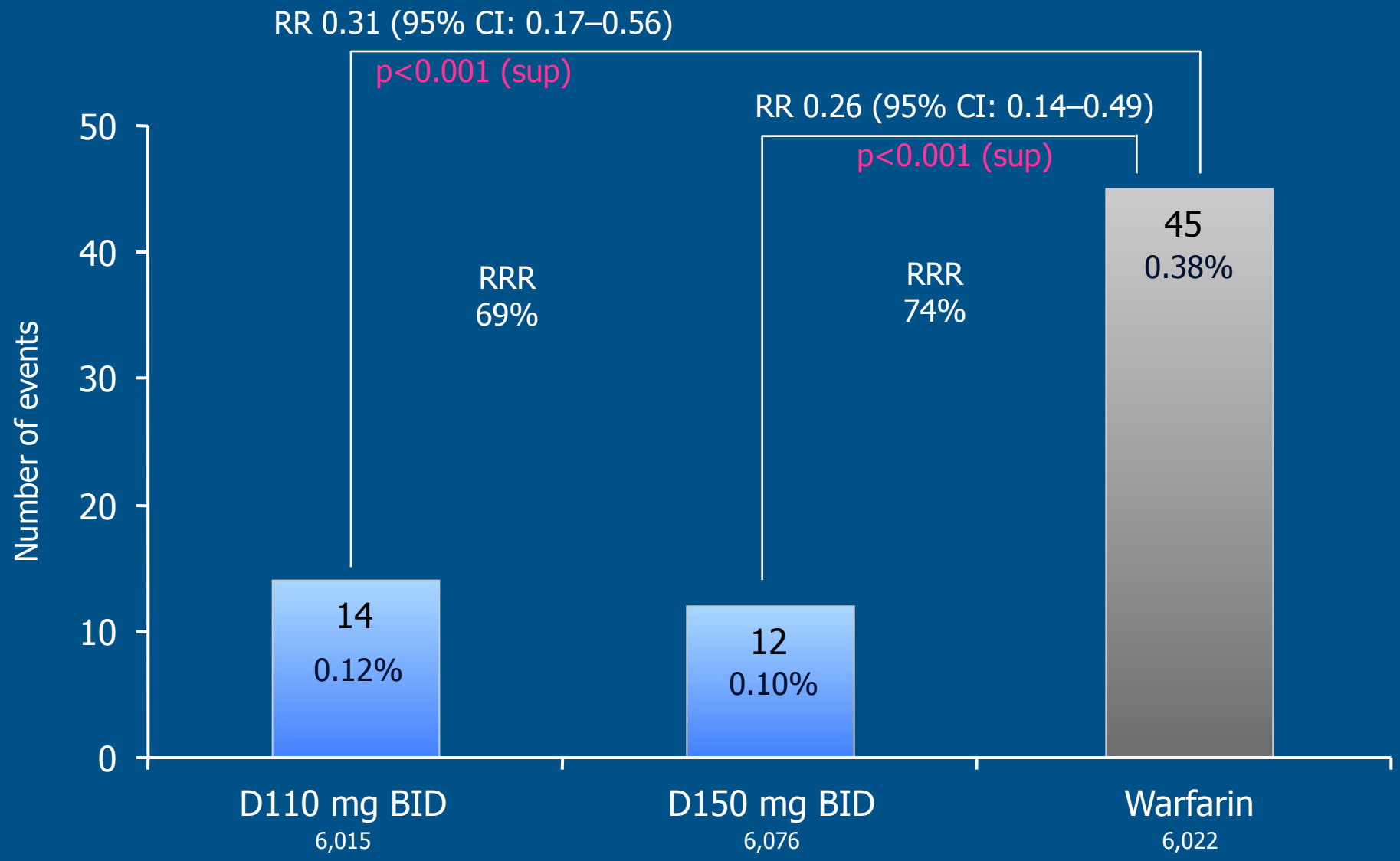
Major bleeding rates



Connolly et al. N Engl J Med 2009

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

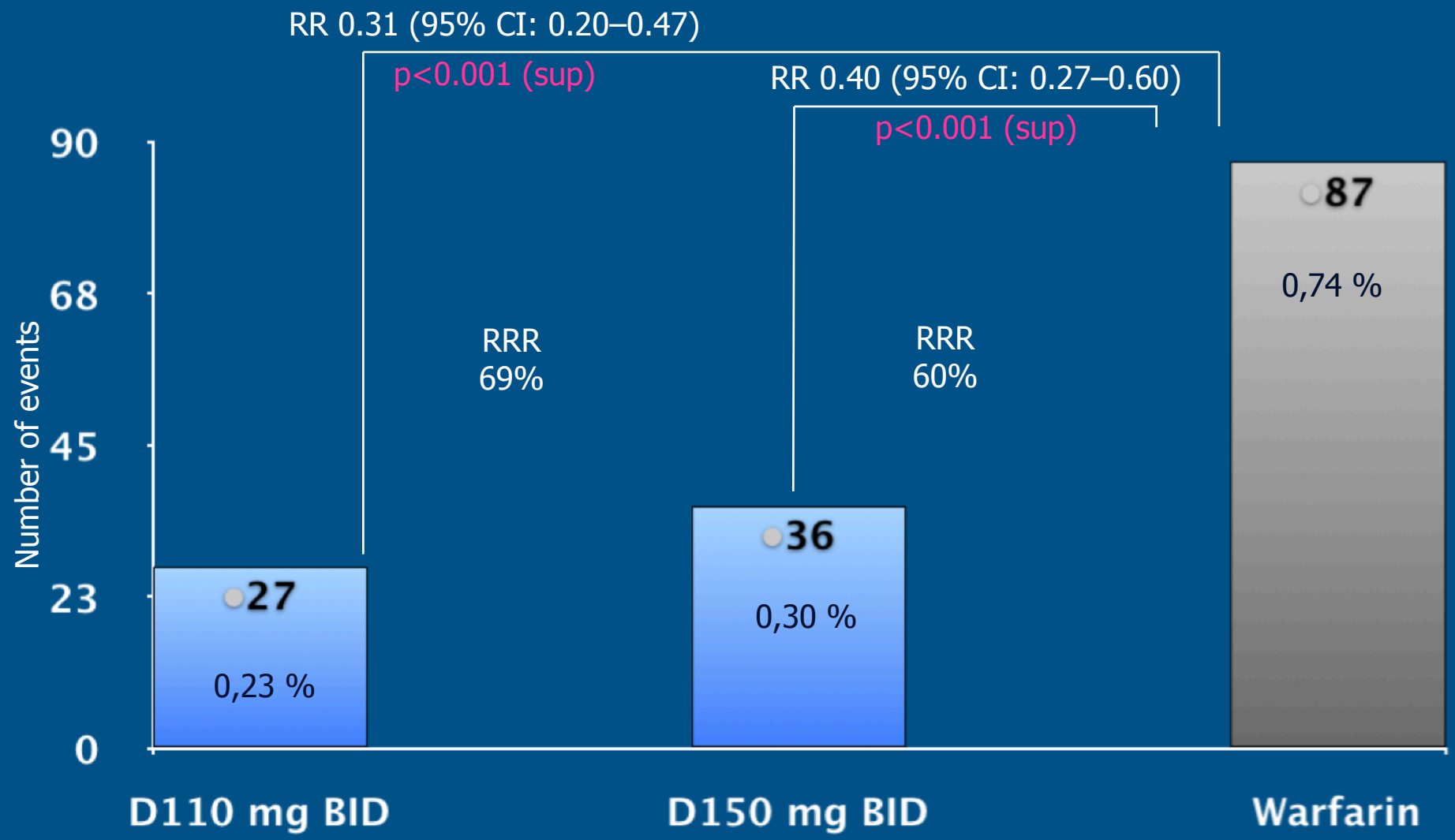
Hemorrhagic stroke



Connolly et al. N Engl J Med 2009

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

Intra-cranial bleeding rates

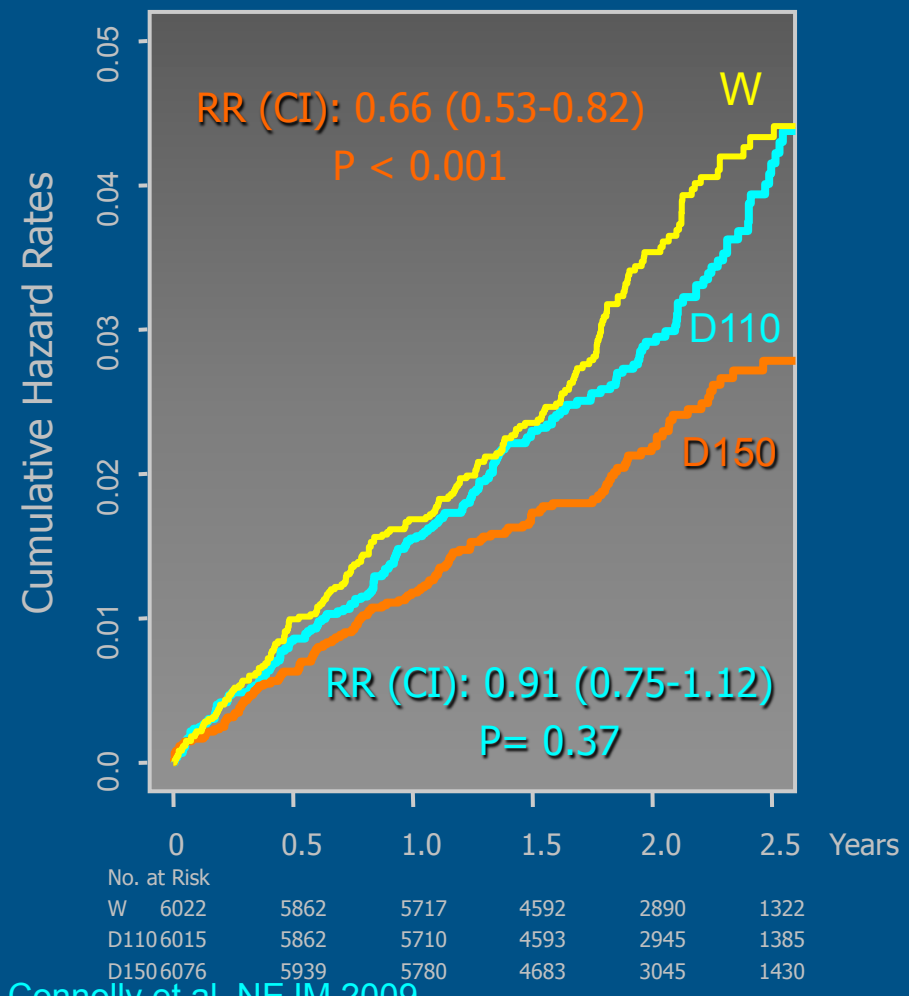


Connolly et al. N Engl J Med 2009

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

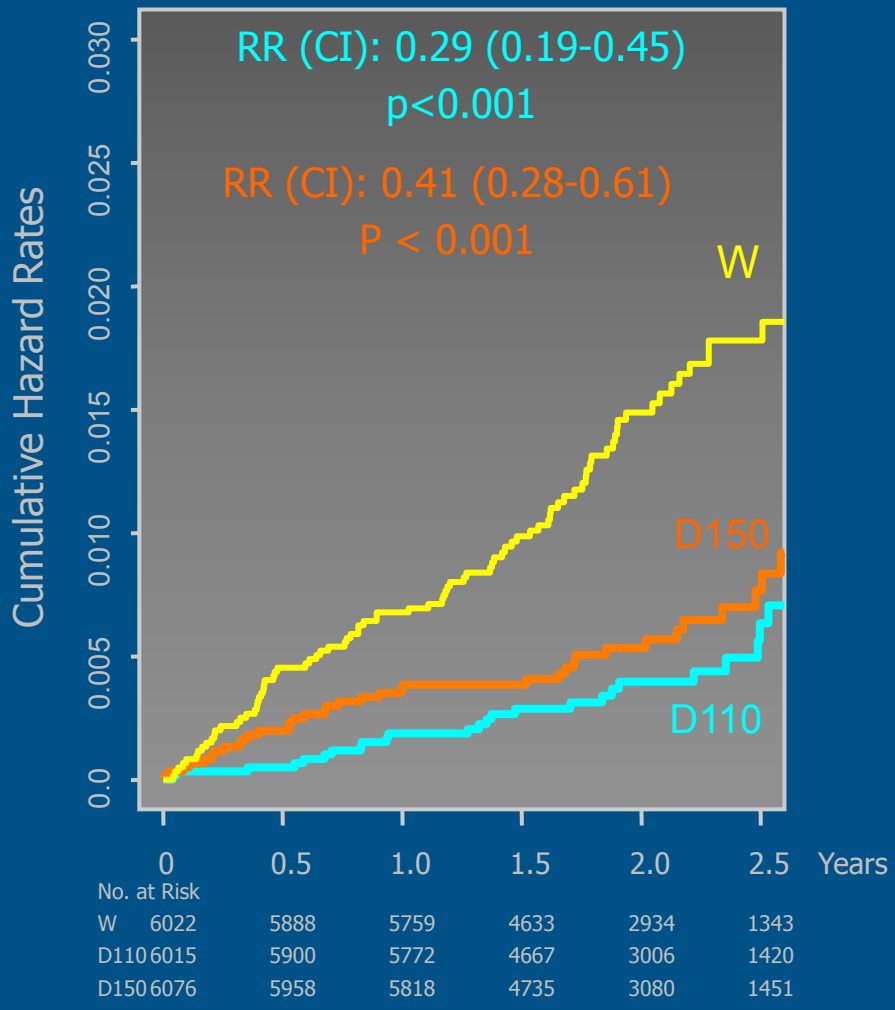
The RE-LY Trial

Primary Outcome

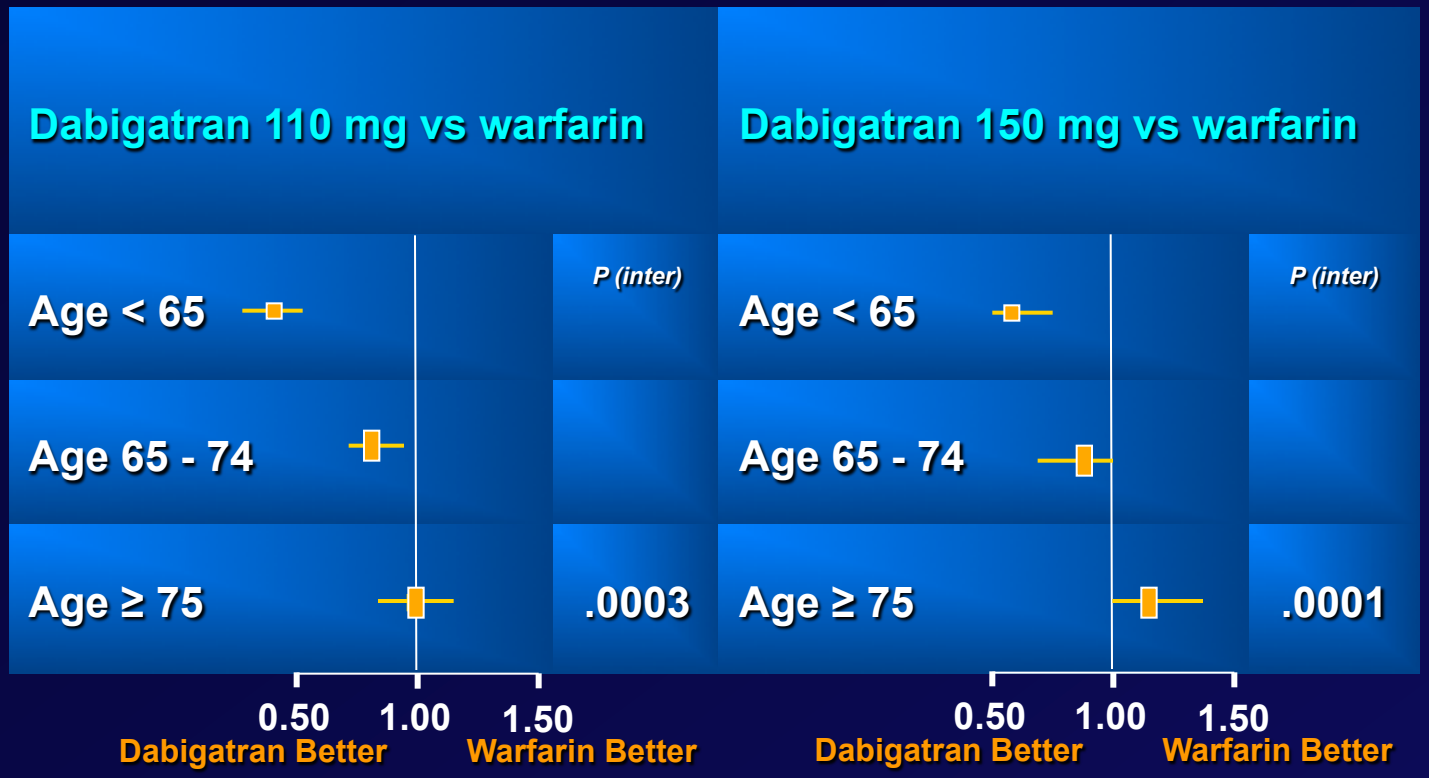


Connolly et al, NEJM 2009

Intracranial Haemorrhage



Risk of Major Bleeding in RE-LY Trial: Age



Eikelboom JW, et al. Circulation. 2011;123:2363-72

Recommendations - Antithrombotic

- 5. We suggest, that when OAC therapy is indicated, most patients should receive **dabigatran in preference to warfarin**. In general, the dose of dabigatran **150 mg po bid is preferable** to a dose of 110 mg po (exceptions discussed in text).

  (Conditional recommendation. High Quality Evidence).

ROCKET AF
Rivaroxaban vs Warfarin

- Primary endpoint — Stroke and non CNS systemic embolism
- 14264 patients
- $CHADS_2$ score — ≥ 2
- Follow-up — 2 years
- Rivaroxaban 20 mg die
- Rivaroxaban 15 mg die (Cr Cl 30-49)
- Warfarine

K. Mahaffey, AHA 2010

ROCKET AF – Study Design

Randomized, double-blind, double-dummy, event-driven

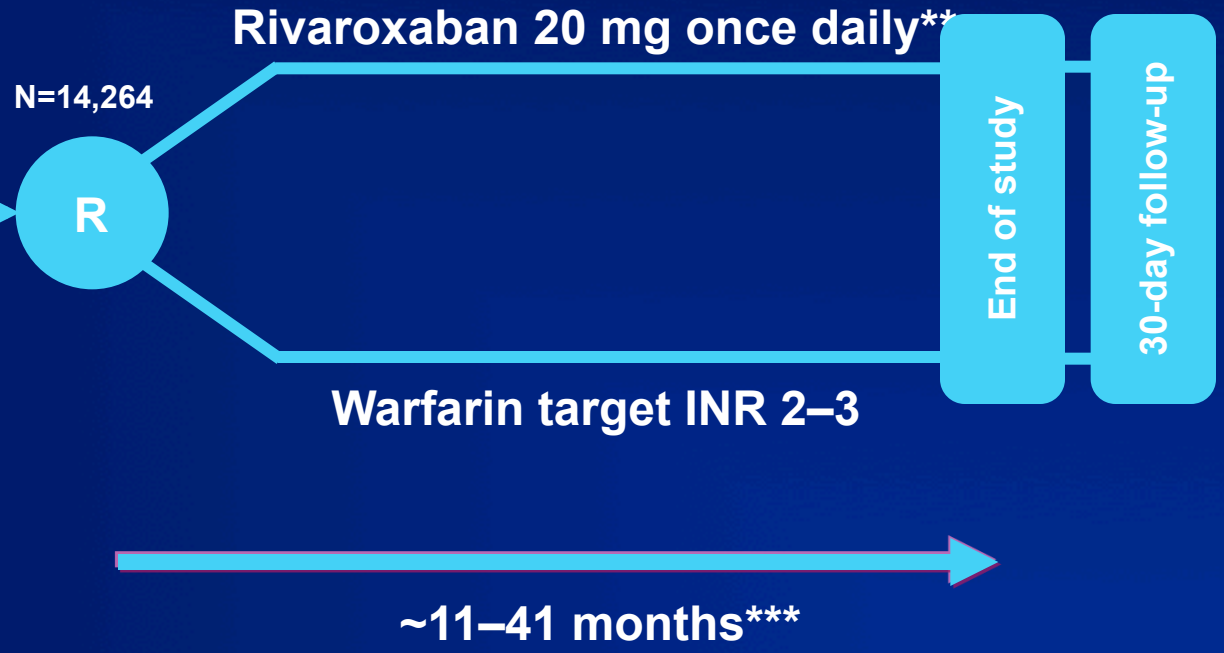
Non-valvular AF

- History of stroke, TIA or non-CNS SE

OR

≥2* of the following:

- CHF
- Hypertension
- Age ≥75 years
- Diabetes



*Enrollment of patients with ≤ 2 risk factors or without prior stroke/TIA or non-CNS SE was limited to 10%
**Patients with CrCl 30–49 ml/min: 15 mg rivaroxaban once daily
***Duration of therapy varied for each patient as study was event-driven

ROCKET AF Study Investigators. Am Heart J 2010; Patel *et al. NEJM* 2011, August 10th epub ahead of print

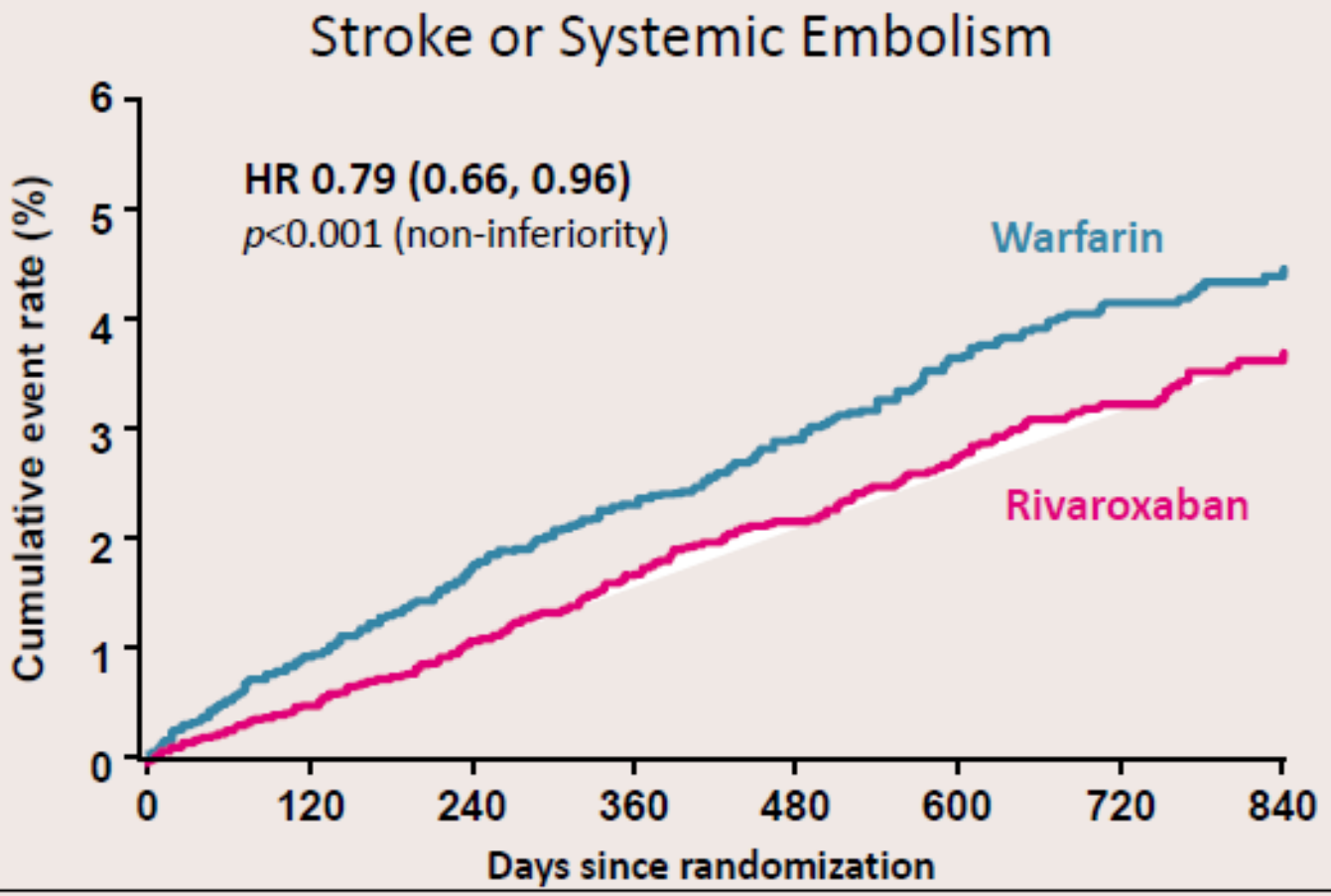
ROCKET AF – Baseline characteristics (2)

Characteristic	Rivaroxaban (N=7131)	Warfarin (N=7133)
$CHADS_2$ score, mean ± SD	3.48±0.94	3.46±0.95
2, n (%)	925 (13.0)	934 (13.1)
3, n (%)	3058 (42.9)	3158 (44.3)
4, n (%)	2092 (29.3)	1999 (28.0)
5, n (%)	932 (13.1)	881 (12.4)
6, n (%)	123 (1.7)	159 (2.2)
Coexisting condition, n (%)		
Previous stroke/TIA or SE	3916 (54.9)	3895 (54.6)
Congestive heart failure	4467 (62.6)	4441 (62.3)
Hypertension	6436 (90.3)	6474 (90.8)
Diabetes mellitus	2878 (40.4)	2817 (39.5)
Previous myocardial infarction	1182 (16.6)	1286 (18.0)
Peripheral vascular disease	401 (5.6)	438 (6.1)
Chronic obstructive pulmonary disease	754 (10.6)	743 (10.4)
CrCl, median (25th, 75th), ml/min	67 (52, 88)	67 (52, 86)

ITT population

Patel *et al. NEJM* 2011, August 10th epub ahead of print

Rocket AF met its primary efficacy endpoint



Number of subjects at risk								
Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538

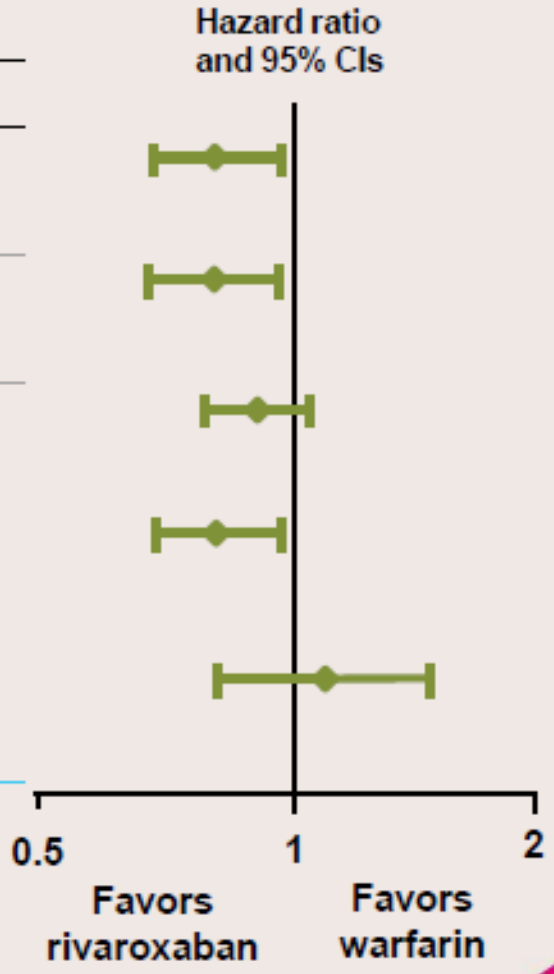
Per-protocol population – as treated population

Patel *et al*. N Engl J Med. 2011 Sep 8;365(10):883-91

ROCKET AF – Primary Efficacy Endpoint On- and Off-Treatment

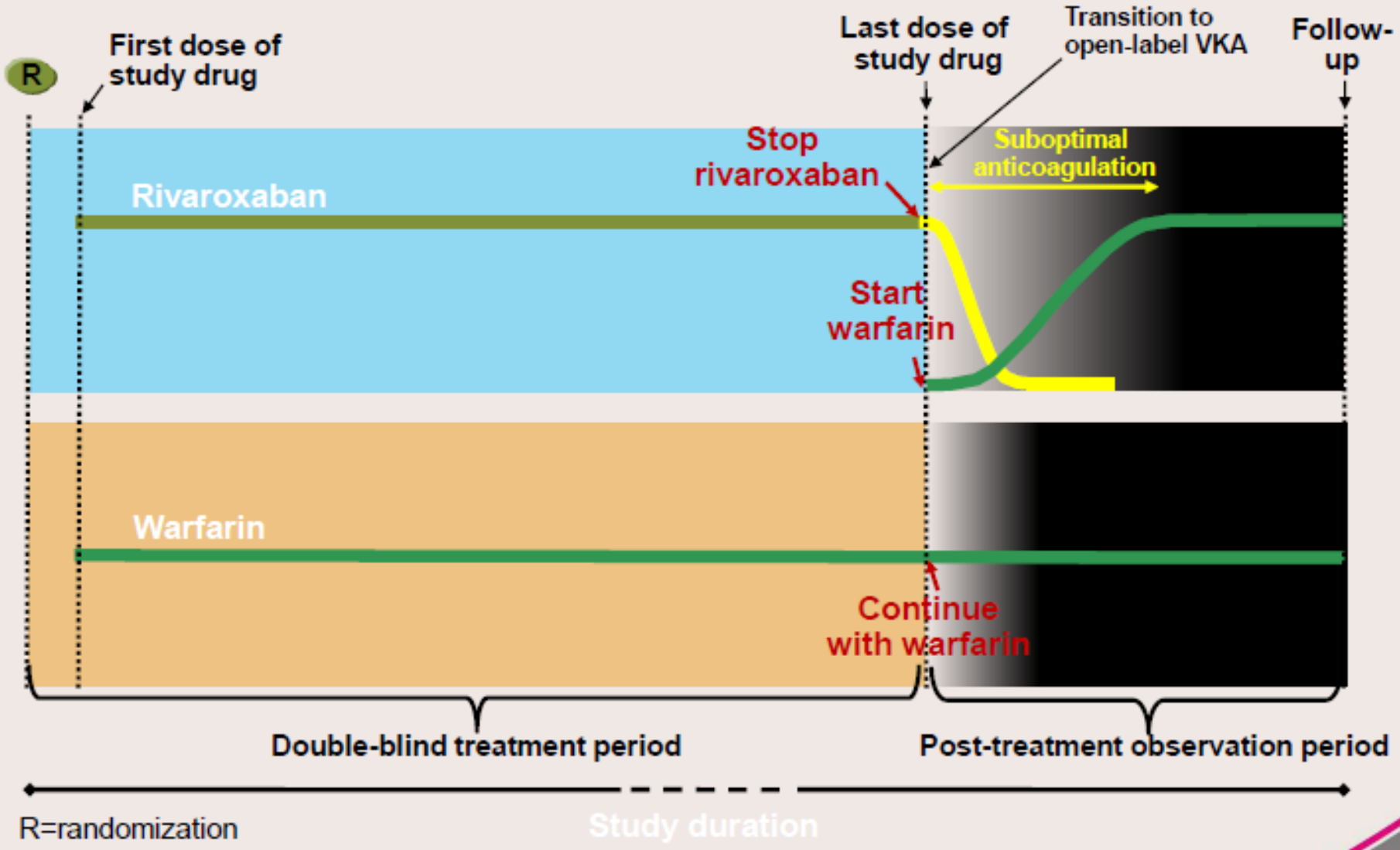
	Rivaroxaban n/N (% per year)	Warfarin n/N (% per year)	Hazard ratio (95% CI)	*p*-value	
				Non-inf.	Sup.
Per-protocol, as-treated	188/6958 (1.7)	241/7004 (2.2)	0.79 (0.66,0.96)	<0.001	
Safety, as-treated	189/7061 (1.7)	243 /7082 (2.2)	0.79 (0.65,0.95)		0.02
ITT	269/7081 (2.1)	306/7090 (2.4)	0.88 (0.75,1.03)	<0.001	0.12
ITT, during treatment	188 (1.7)	240 (2.2)	0.79 (0.66,0.96)		0.02
ITT, after discontinuation	81 (4.7)	66 (4.3)	1.10 (0.79,1.52)		0.58

Primary efficacy endpoint: stroke or systemic embolism
ITT during treatment, after discontinuation: *post hoc* analyses

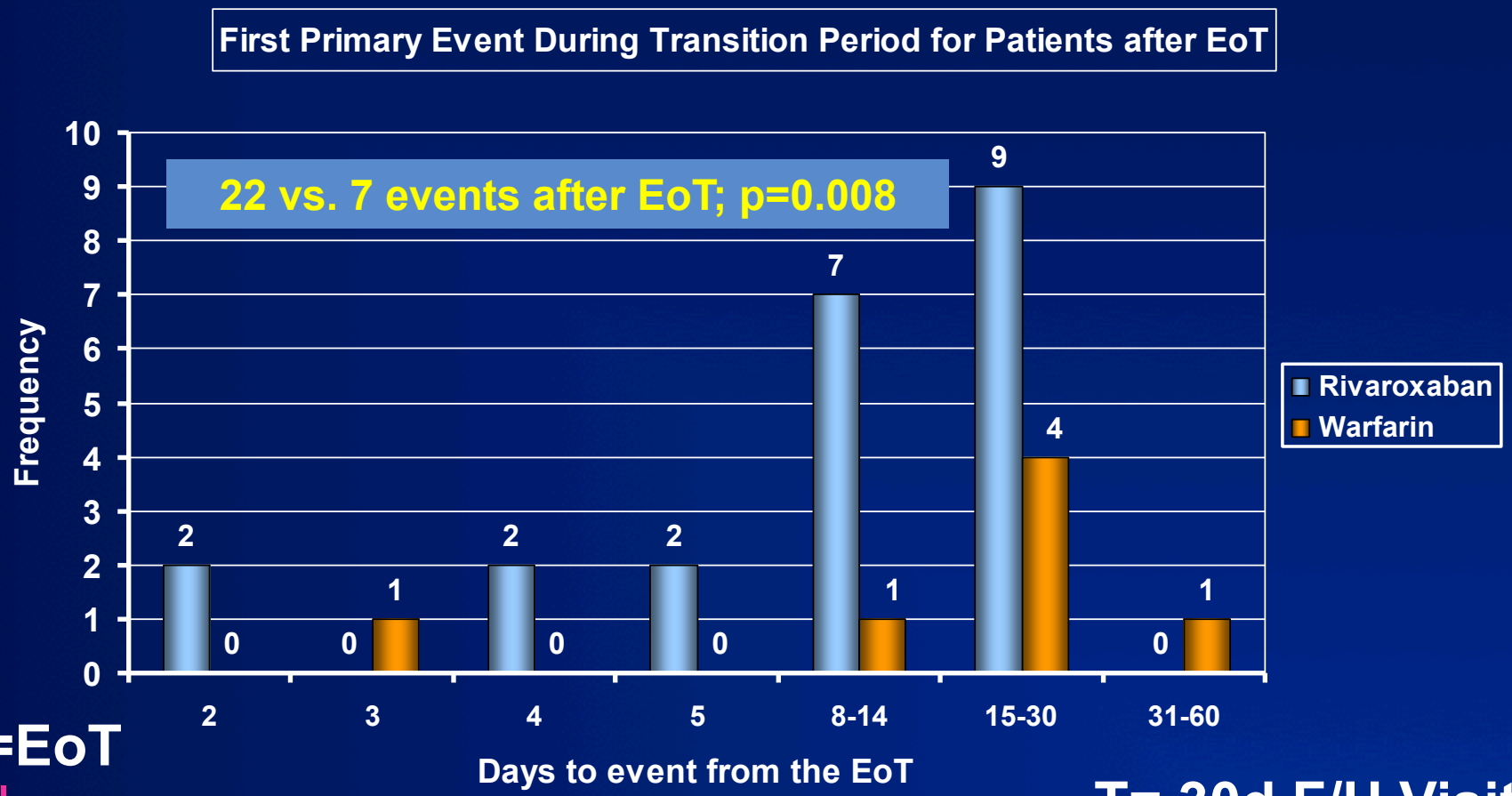


Patel *et al*. N Engl J Med. 2011 Sep 8;365(10):883-91

ROCKET AF – Difficulties in transitioning to Open-Label VKA (Study Completers)



Differential Event Rates & TTR INR for the 60d Transition after EoT to F/U



T=EoT

T= 30d F/U Visit

R

Median time to TTR INR 13d / 365 d x avg. annual risk 8.5% x 7131 = 21.6

W

Median time to TTR INR 3 / 365 d x avg. annual risk 8.5% x 7133 = 4.98

ROCKET AF – Secondary Endpoints

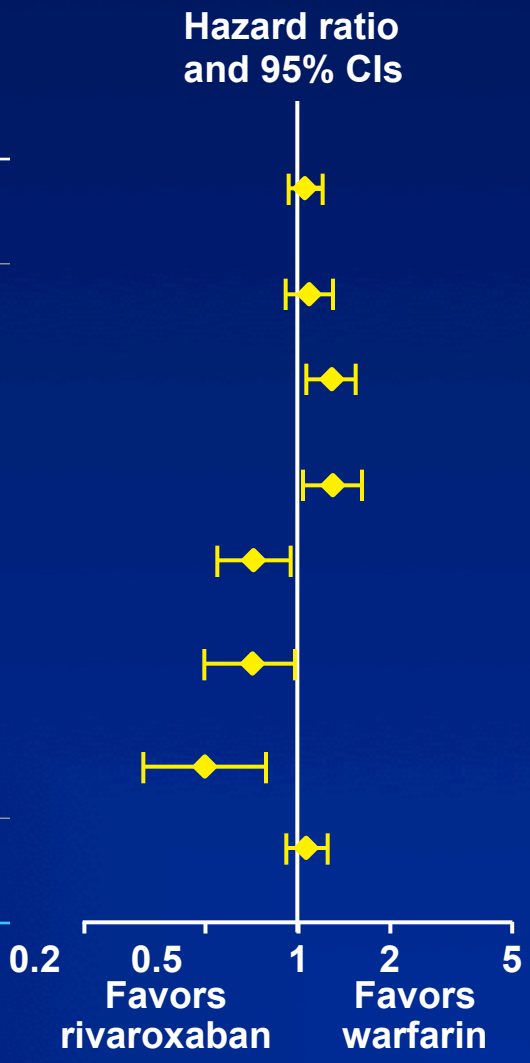
Endpoints	Rivaroxaban (N=7061) n (% per year)	Warfarin (N=7082) n (% per year)	Hazard ratio (95% CI)
Composite of stroke, non-CNS SE, and vascular death	346 (3.1)	410 (3.6)	0.86 (0.74, 0.99)*
Composite of stroke, non-CNS SE, vascular death, and MI	433 (3.9)	519 (4.6)	0.85 (0.74, 0.96)*
Components of major secondary endpoints			
All-cause stroke	184 (1.7)	221 (2.0)	0.85 (0.70, 1.03)
Non-CNS SE	5 (0.04)	22 (0.2)	0.23 (0.09, 0.61)*
MI	101 (0.9)	126 (1.1)	0.81 (0.63, 1.06)
Vascular death	170 (1.5)	193 (1.7)	0.89 (0.73, 1.10)
All-cause mortality	208 (1.9)	250 (2.2)	0.85 (0.70, 1.02)

Safety population – on-treatment analysis
*Statistically significant

Patel et al. NEJM 2011, August 10th epub ahead of print

ROCKET AF – Bleeding Analysis

Parameter	Rivaroxaban (N=7111) n (% per year)	Warfarin (N=7125) n (% per year)	Hazard ratio (95% CI)
Principal safety endpoint	1475 (14.9)	1449 (14.5)	1.03 (0.96,1.11)
Major bleeding	395 (3.6)	386 (3.4)	1.04 (0.90,1.20)
Hemoglobin drop (≥2 g/dl)	305 (2.8)	254 (2.3)	1.22 (1.03,1.44)*
Transfusion	183 (1.6)	149 (1.3)	1.25 (1.01,1.55)*
Critical organ bleeding	91 (0.8)	133 (1.2)	0.69 (0.53,0.91)*
Intracranial hemorrhage	55 (0.5)	84 (0.7)	0.67 (0.47,0.93)*
Fatal bleeding	27 (0.2)	55 (0.5)	0.50 (0.31,0.79)*
Non-major clinically relevant bleeding	1185 (11.8)	1151 (11.4)	1.04 (0.96,1.13)



Major bleeding from gastrointestinal site (upper, lower and rectal): rivaroxaban = 224 events (3.2%); warfarin = 154 events (2.2%); $p<0.001$*

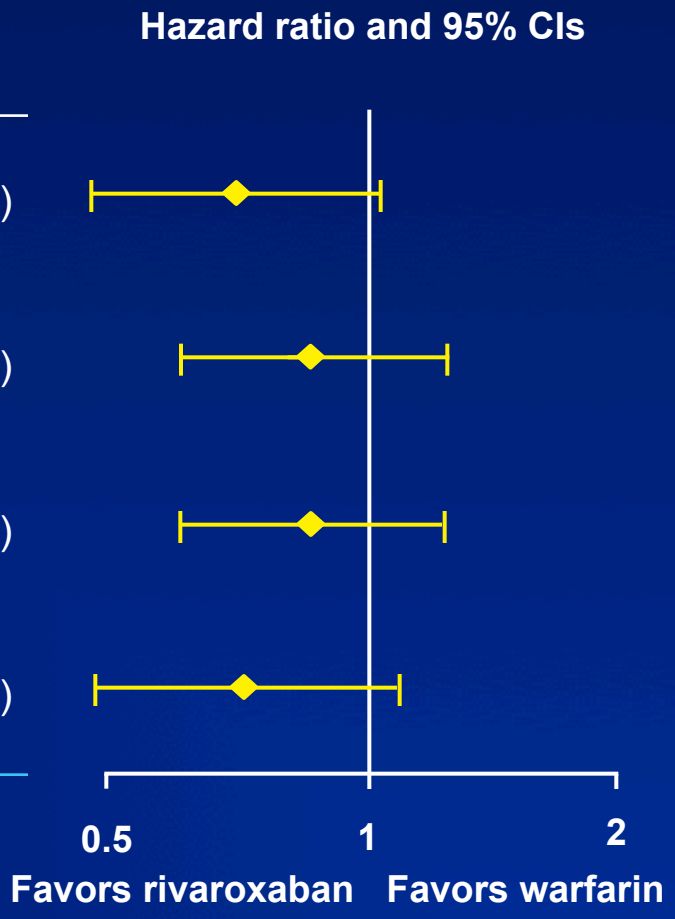
Safety population – as-treated analysis; *statistically significant

Patel *et al. NEJM* 2011, August 10th epub ahead of print

ROCKET AF – Primary Efficacy Endpoint
Center-Based INR Control ¥*

cTTR	Rivaroxaban (% per year)	Warfarin (% per year)	Hazard ratio (95% CI)
0.0–50.6%	1.8	2.5	0.70 (0.48,1.03)
50.7–58.5%	1.9	2.2	0.89 (0.62,1.29)
58.6–65.7%	1.9	2.1	0.89 (0.62,1.28)
65.7–100.0%	1.3	1.8	0.74 (0.49,1.12)

Better INR control



¥ cTTR, center-based time in therapeutic range
Based on Rosendaal method with all INR values included
**p*-value for interaction = 0.74

Safety population (N=7061 [rivaroxaban], N=7082 [warfarin])

Patel *et al. NEJM* 2011, August 10th epub ahead of print

ARISTOTLE
Apixaban vs Warfarin

- **Primary endpoint** — Determine if apixaban is non-inferior to warfarin in prevention of stroke and systemic embolic events for patients with non-valvular atrial fibrillation
- **15000 patients**
- **$CHADS_2$ score** — ≥ 1
- **Follow-up** — 3-4 years

- Apixaban 5 mg BID
- Apixaban 2.5 mg BID (age 80 years, < 60 kg, Cr ≥ 133)
- Warfarin
- Closed 1-2011

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

ARISTOTLE

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

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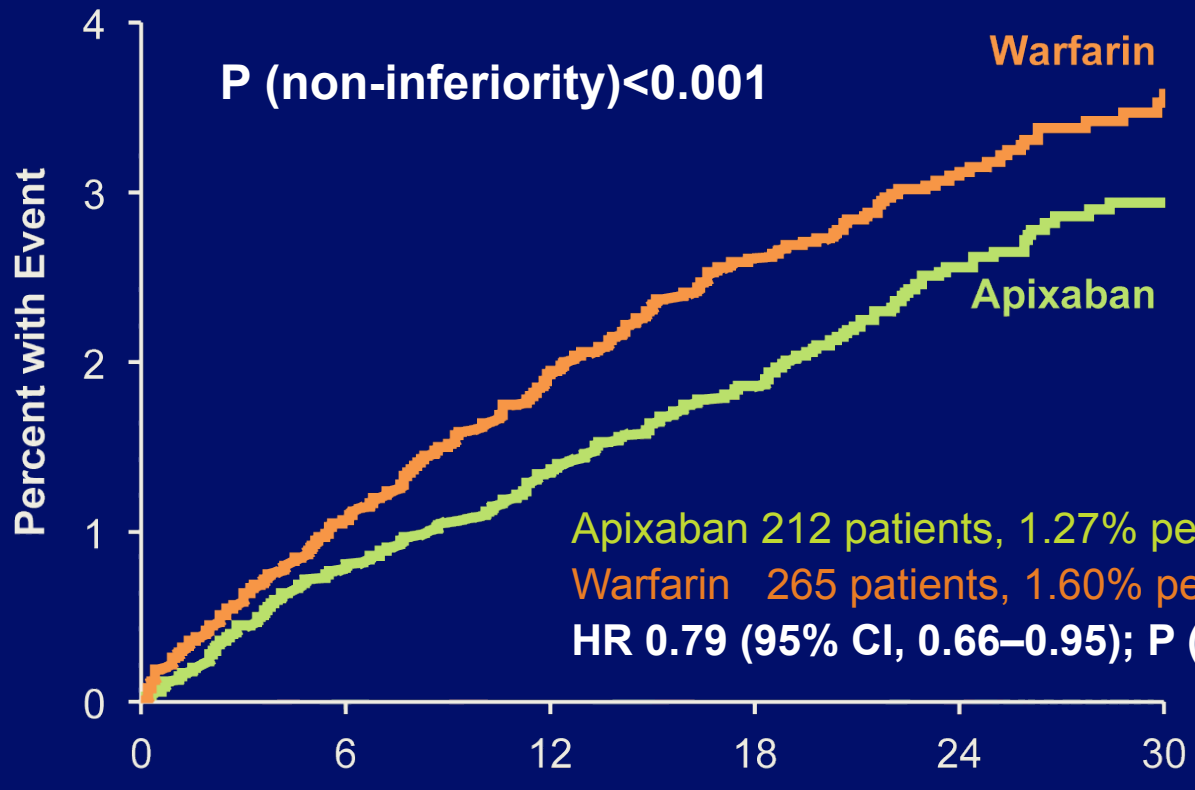
Baseline Characteristics

ARISTOTLE

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Age, years, median (25th, 75th %ile)	70 (63, 76)	70 (63, 76)
Women, %	35	35
Region, %		
North America	25	25
Latin America	19	19
Europe	40	40
Asia/Pacific	16	16
Warfarin naïve, %	43	43
CHADS score, mean (+/- SD)	2.1 (+/- 1.1)	2.1 (+/- 1.1)
1, %	34	34
2, %	36	36
≥ 3, %	30	30

Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

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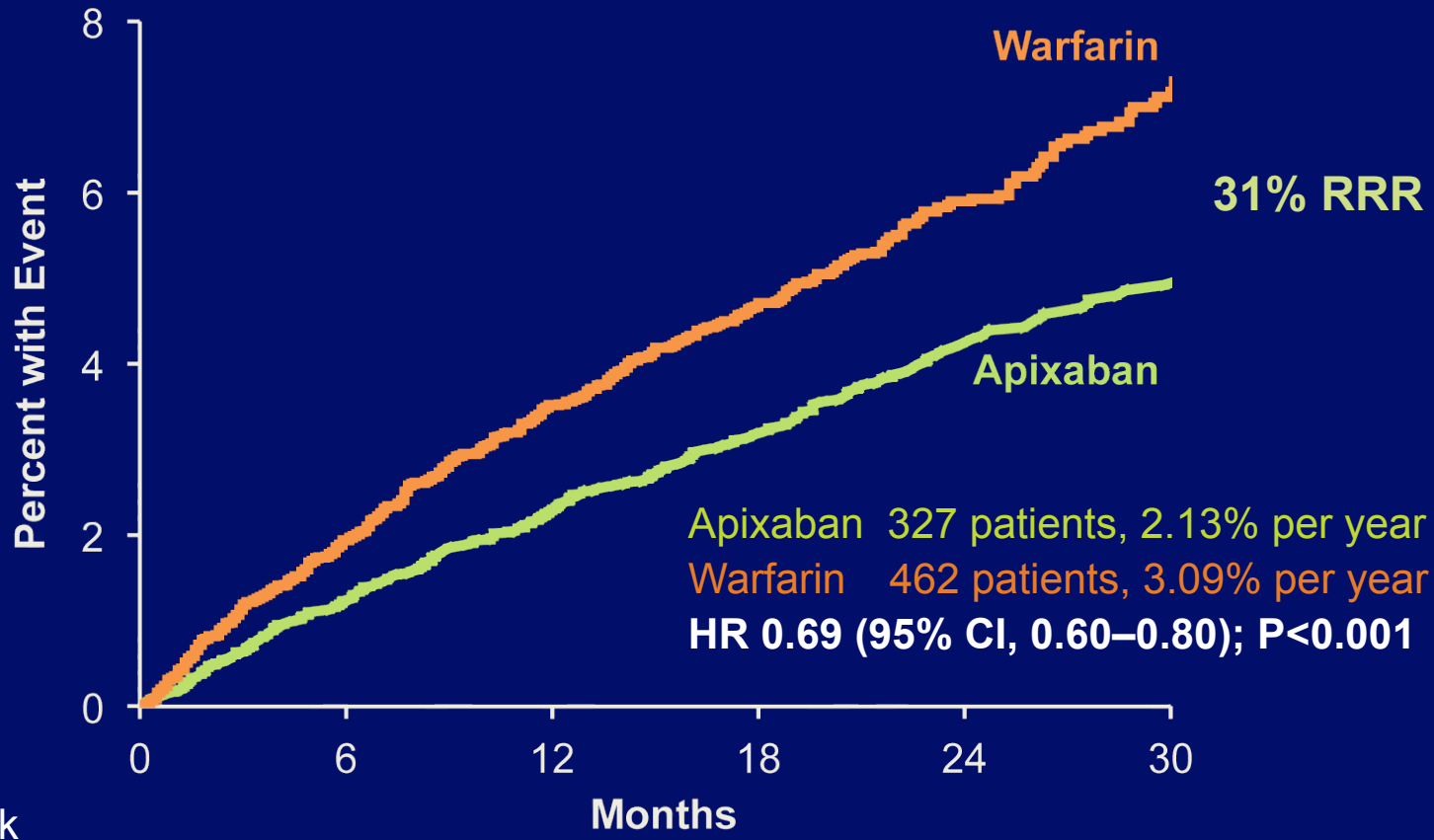
Major Bleeding
ISTH definition

ARISTOTLE



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

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Efficacy Outcomes

ARISTOTLE

Outcome	Apixaban (N=9120) Event Rate (%/yr)	Warfarin (N=9081) Event Rate (%/yr)	HR (95% CI)	P Value
Stroke or systemic embolism*	1.27	1.60	0.79 (0.66, 0.95)	0.011
Stroke	1.19	1.51	0.79 (0.65, 0.95)	0.012
Ischemic or uncertain	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
Systemic embolism (SE)	0.09	0.10	0.87 (0.44, 1.75)	0.70
All-cause death*	3.52	3.94	0.89 (0.80, 0.998)	0.047
Stroke, SE, or all-cause death	4.49	5.04	0.89 (0.81, 0.98)	0.019
Myocardial infarction	0.53	0.61	0.88 (0.66, 1.17)	0.37

* Part of sequential testing sequence preserving the overall type I error

Stroke and Systemic Embolism (primary outcome) in Relation to Centers' TTR

ARISTOTLE

	Apixaban		Warfarin			
Center TTR (%)	E	Rate/100 person yrs	E	Rate/100 person yrs	HR (95% CI)	Adjusted Interaction
< 58.0	70	1.75	88	2.28	0.77 (0.56, 1.06)	0.29
58.0–65.7	54	1.30	68	1.61	0.80 (0.56, 1.15)	
65.7–72.2	51	1.21	65	1.55	0.79 (0.54, 1.13)	
> 72.2	36	0.83	44	1.02	0.81 (0.52, 1.26)	

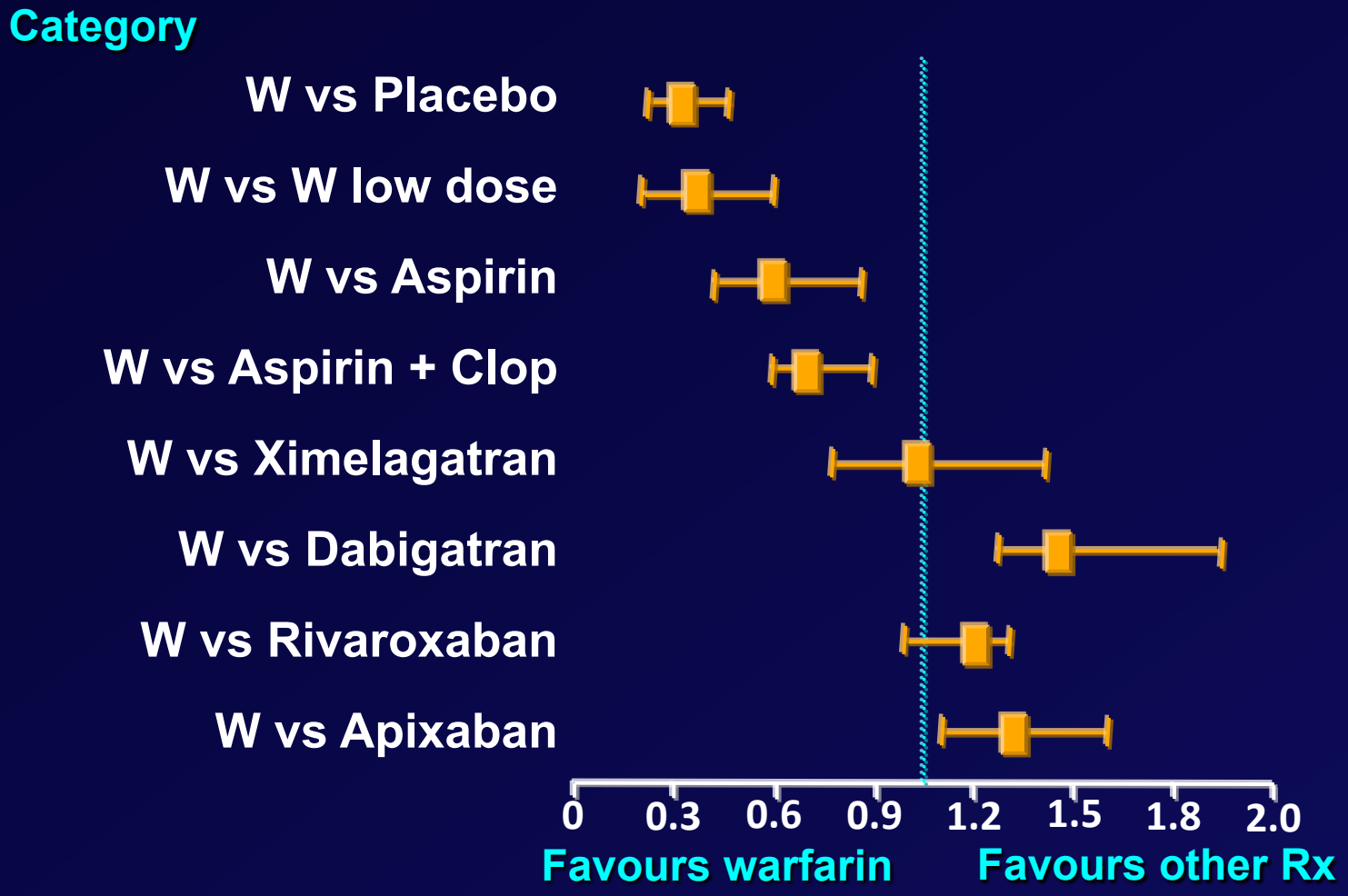
Quel est le meilleur antithrombotique pour la prévention des AVC dans la F.A. non valvulaire ?

Different drug
Different population
Different study

Head-to-head comparison?

Stroke Prevention in Atrial Fibrillation

Meta-analysis of Ischaemic Stroke or Systemic Embolism



Agent	Dabigatran	Apixaban		Rivaroxaban
Action	Anti-II	Anti-X_a		Anti X_a
Demie vie	14 à 17 hres	12 hres		5 à 13 hres
Administration	BID	BID		Die
Élimination	Rénale 80%	Rénale 25% Hépatique 75%		Rénale 1/3 Hépatique 2/3
Essai	RE-LY	Averroes	Aristotle	Rocket-AF
Comparateur	Warfarine	Aspirine	Warfarine	Warfarine
Dessin	Ouvert	Ouvert	Double aveugle	Double aveugle

Risk factors in the ROCKET-AF ARISTOTLE and RE-LY population

	Age	Stroke or TIA	HBP	Heart failure	Diabetes	$CHADS_2$ Score
ROCKET-AF (n=14264)	73	55%	91%	62%	39%	3.5
RE-LY (n=18113)	72	20%	79%	32%	23%	2.1
ARISTOTLE (n=18201)	70	19%	87%	35%	25%	2.1

Patel M, et al. N Engl J Med 2010;365:883-91; Granger CB, et al. N Engl J Med 2011;365:981-92; Connolly SJ, et al. N Engl J Med 2009:Aug 30 [Epub]

Baseline Patient Demographics Comparison of Previous VKA-controlled Trials

$CHADS_2$	ROCKET-AF Score %	RE-LY Score %	ACTIVE W Score %	ARISTOTLE Score %	AMADEUS Score %	SPORTIF V Score %
0 - 1	< 1	32	N/A	34	41	25
2	13	36	N/A	36	32	31
≥ 3	86	32	N/A	30	27	44
Median $CHADS_2$ Score	3.5	2.1	2	2.1	2	2

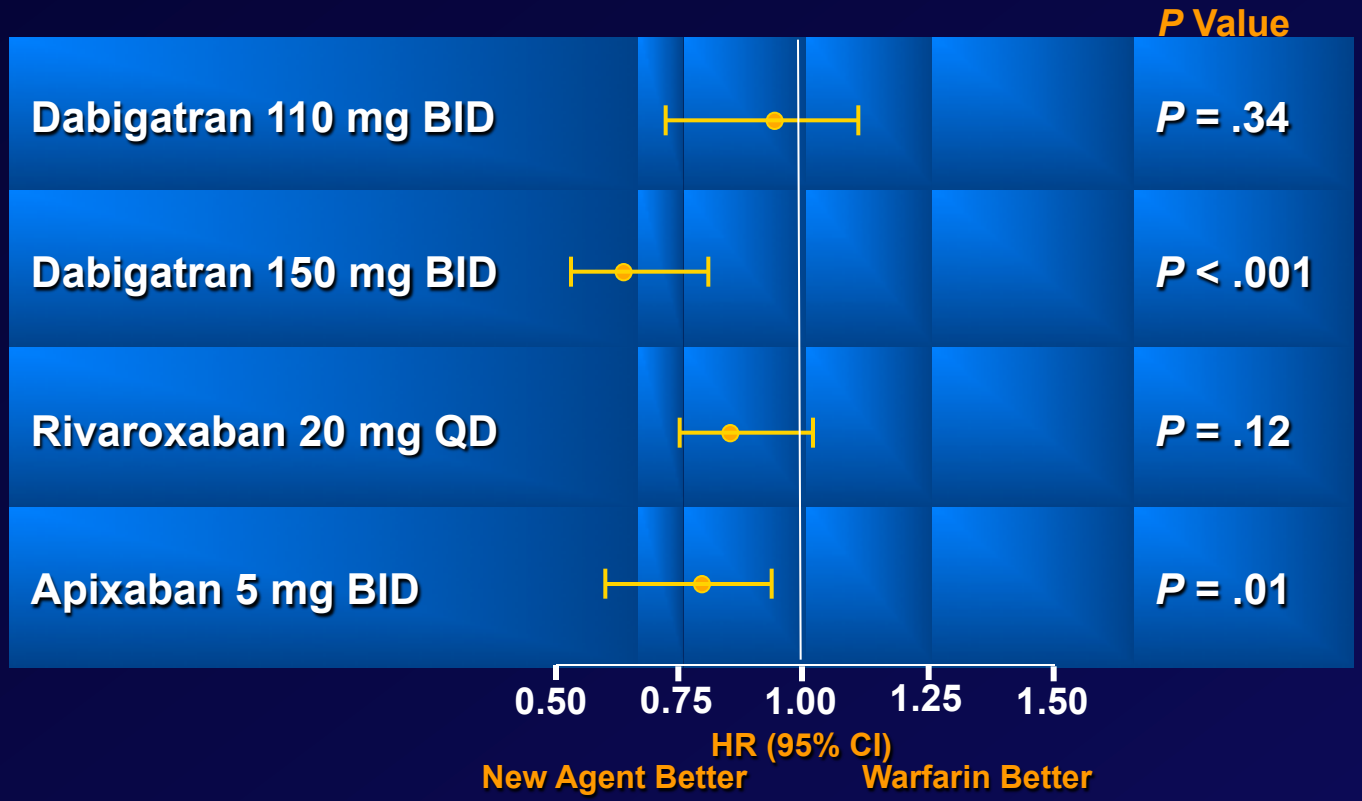
Exclusion Criteria

	RE-LY	Rocket-AF	Aristotle
Severe stroke	6 months	3 months	
Any stroke	14 days	14 days	7 days
Major surgery	1 month	1 month	1 month
Previous intracranial hemorrhage	+	+	+
Cl Creatinine	≤ 30 ml/min	< 30 ml/min	< 25 ml/min

Complexity of Dosage

Dabigatran	110 mg BID	CrCl 30-50 ml/min , age > 75
	150 mg BID	
Rivaroxaban	20 mg Die	
	15 mg Die	CrCl 30-50 ml/min
Apixaban	5 mg BID	
	2.5 mg BID	2 factors • age ≥ 80 • weight ≤ 60 kg • creat. ≥ 133

Recent Oral Anticoagulation Trials Stroke or Systemic Embolism



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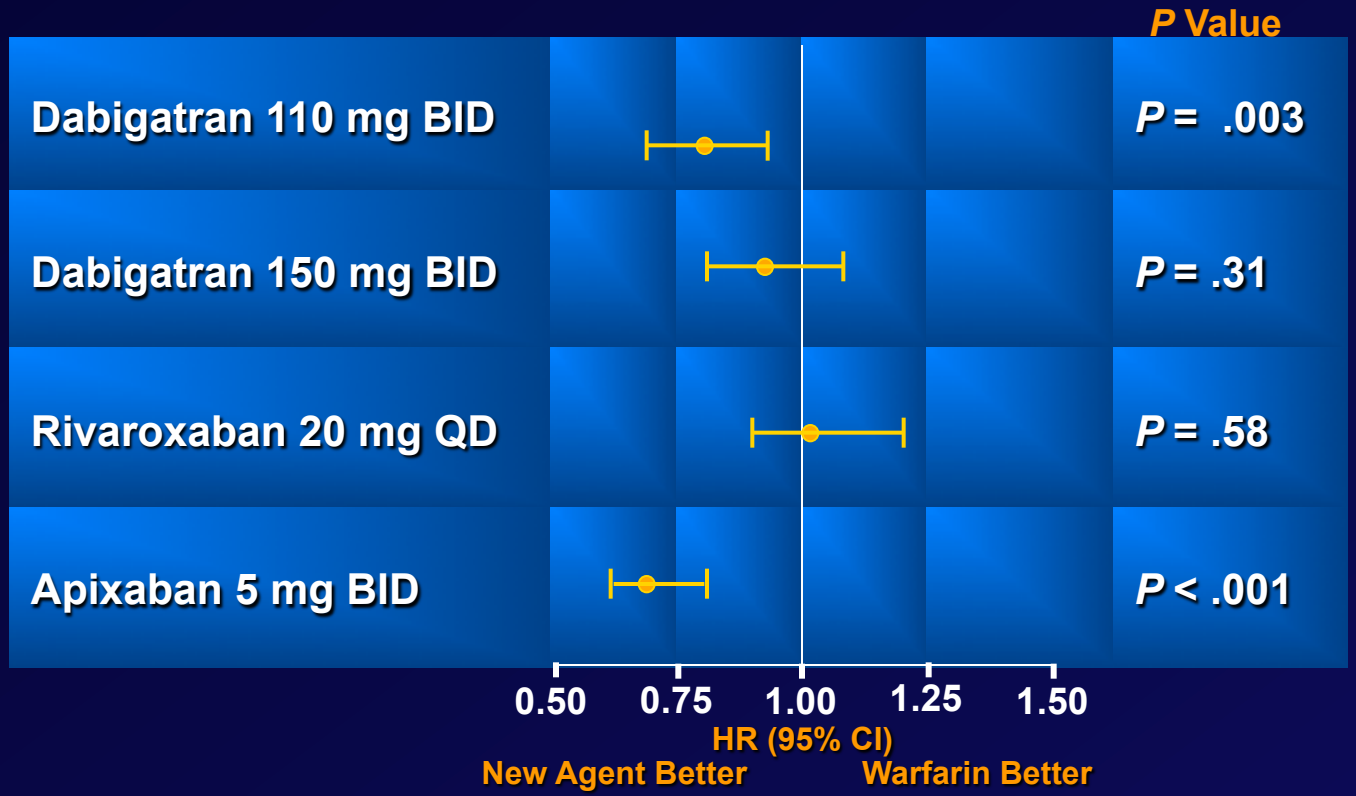
Patel MR, et al. N Engl J Med. 2011;365-883-91
Granger C, et al. N Engl J Med. 2011;365:981-92

Recent Oral Anticoagulation Trials
Major Bleeding



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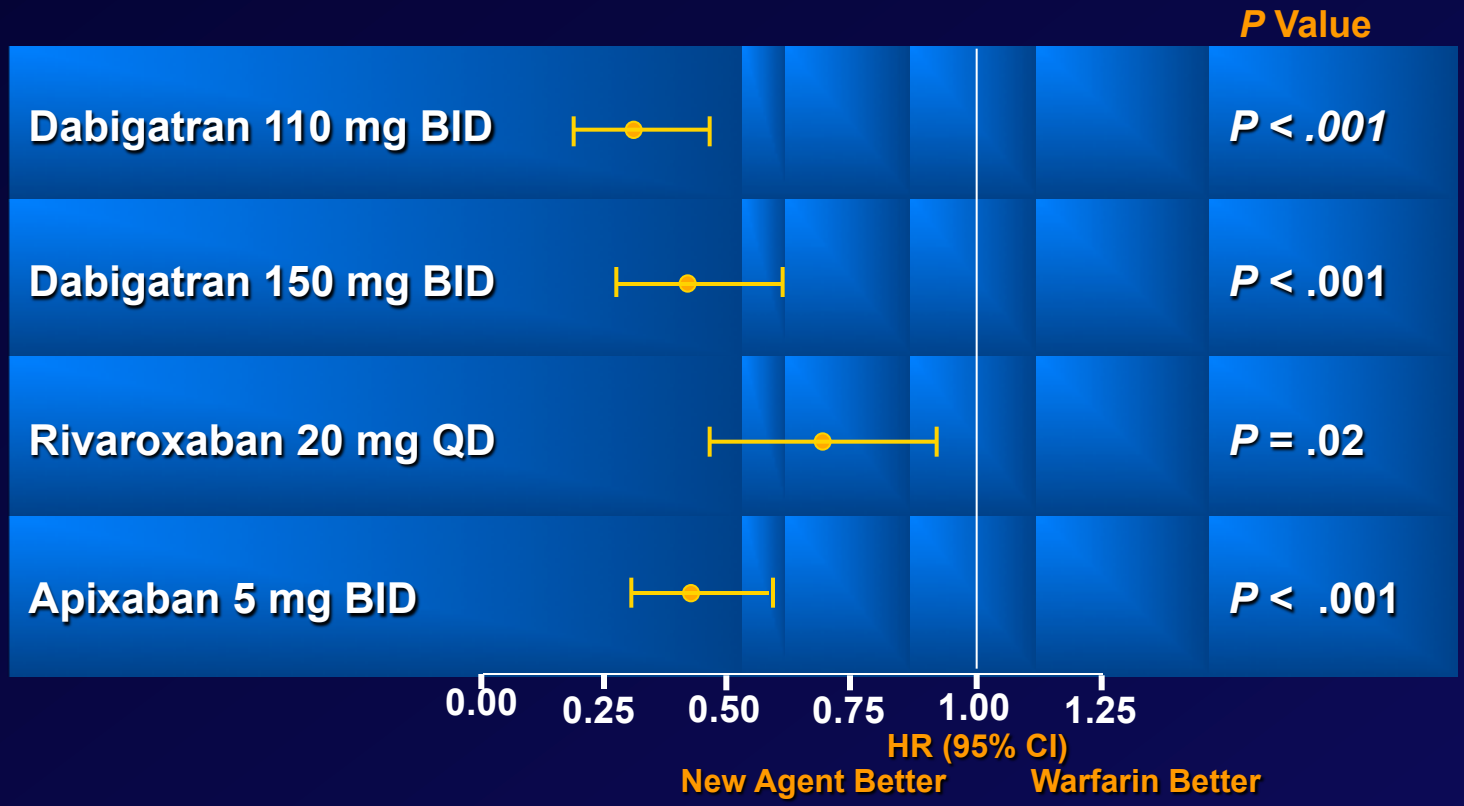
Recent Oral Anticoagulation Trials Intracranial Hemorrhage



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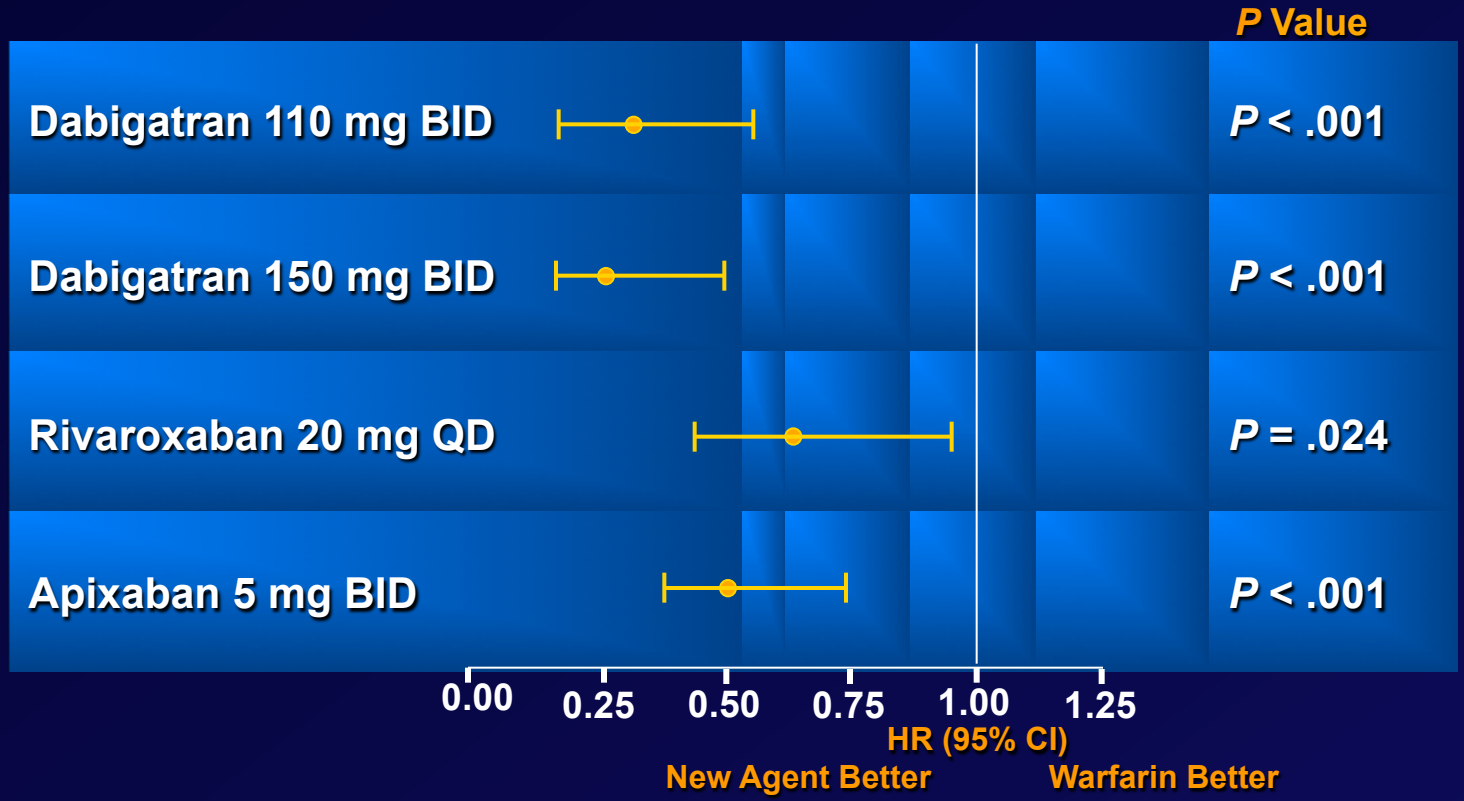
Granger C, et al. N Engl J Med. 2011;365:981-92

Recent Oral Anticoagulation Trials Hemorrhagic Stroke



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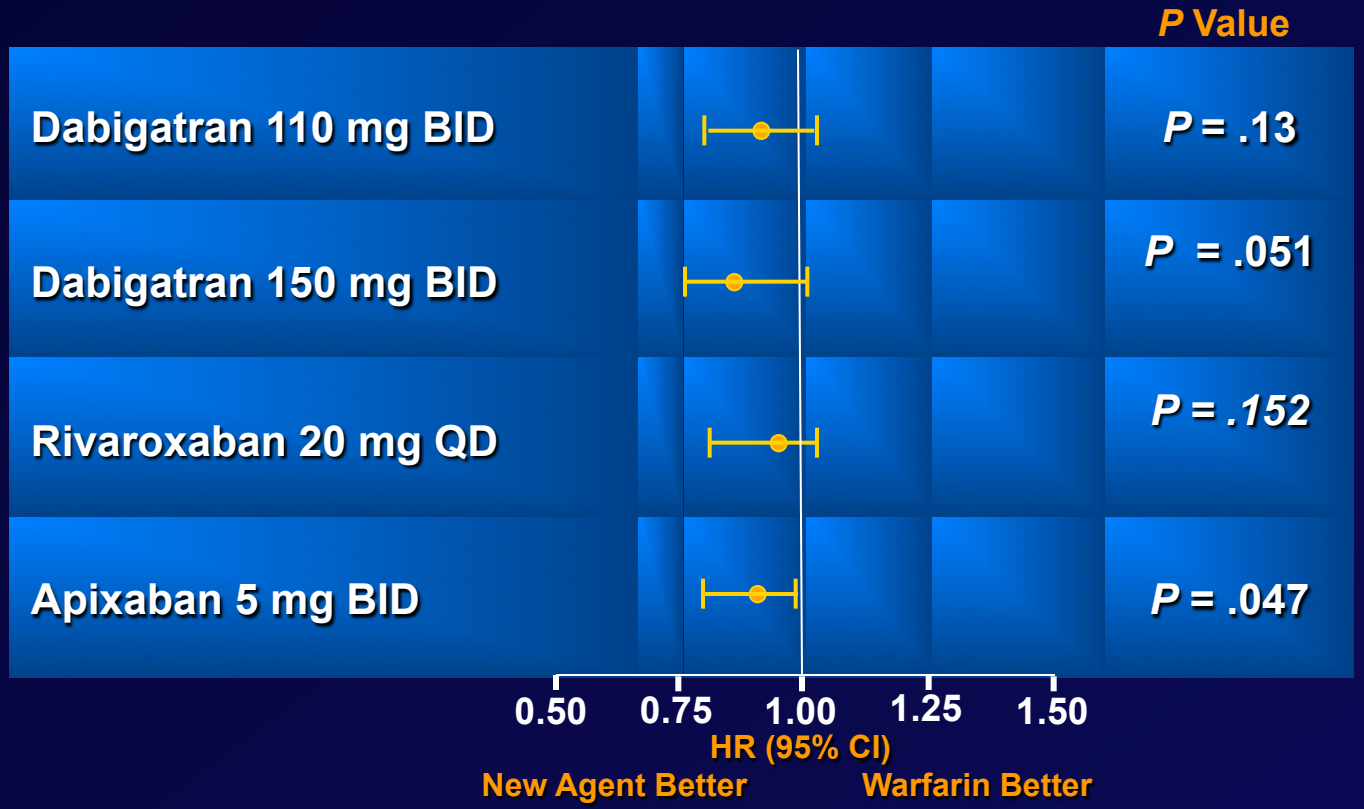
Granger C, et al. N Engl J Med. 2011;365:981-92

Recent Oral Anticoagulation Trials
All Deaths



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Patel MR, et al. N Engl J Med. 2011;365-883-91
Granger C, et al. N Engl J Med. 2011;365:981-92

Recommendations for risk stratification and choice of antithrombotic (cont'd)

2010
We suggest, that when OAC therapy is indicated, most patients should receive dabigatran in preference to warfarin. In general, the dose of dabigatran 150 mg po bid is preferable to a dose of 110 mg po bid (exceptions discussed in text). (Conditional recommendation. High Quality Evidence).

Values and preferences: This recommendation places a relatively high value on the greater efficacy of dabigatran over a relatively short time of follow-up, particularly among patients who have not previously received an oral anticoagulant, the lower incidence of intracranial hemorrhage and its ease of use, and less value on the long safety experience with warfarin.

2012
We suggest, that when OAC therapy is indicated, most patients should receive dabigatran or rivaroxaban* or apixaban* in preference to warfarin. (Conditional recommendation. High Quality Evidence).
•Once approved by Health Canada.

Values and preferences: This recommendation places a relatively high value on comparisons to warfarin showing dabigatran, rivaroxaban and apixaban are much simpler to use; dabigatran and apixaban have greater efficacy for stroke prevention; dabigatran, reivaroxaban and apixaban have less intracranial haemorrhage; and apixaban has less all-cause mortality and less major bleeding. The recommendation places less value on the long safety experience with warfarin.

DRAFT

Circulation

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Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation

Shimoli V. Shah and Brian F. Gage

Circulation 2011, 123:2562-2570: originally published online May 23, 2011
doi: 10.1161/CIRCULATIONAHA.110.985655
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Cost-Effectiveness

CHADS2 Score 0	Only Aspirin may be cost-effective.
$CHADS_2$ Score 1-2	Warfarin is cost-effective (unless risk of hemorrhage is high or INR control poor TTR < 57%)
$CHADS_2$ Score ≥ 3	Dabigatran 150 mg BID is cost-effective (unless INR control excellent TTR > 72%)

Drug Cost

Warfarin	**$ 545 / year** **including 14 INR tests**
Clopidogrel	**$ 1 847 / year ($ 5.06 / day)**
Dabigatran 150 mg BID	**$ 3 240 / year ($ 9.00 / day)**

↓

At $ 2 000 / year would be cost-effective regardless of risk of stroke or hemorrhage

Circulation

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The Relative Cost-Effectiveness of Anticoagulants : Obvious, Except for the Cost and the Effectiveness

Jerry Avorn

Circulation 2011, 123:2519-2521: originally published online May 23, 2011
doi: 10.1161/CIRCULATIONAHA.111.030148
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 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Cost-Effective ≠ Cost-Saving

Efficacy ≠ Effectiveness

Efficacy → randomized trial

Effectiveness → everyday practice

Efficacy ≠ Effectiveness

- Dabigatran is BID, short half-life
- Poor adherence because of cost
- Level of anticoagulation can be detected for Warfarin (INR) not for Dabigatran
- Antidote for Warfarine not for Dabigatran
- No experience facing emergency procedure and trauma
- In RE-LY, INR TTR 65%
  > $ 2 000 / year per patient for INR

Efficacy ≠ Effectiveness

- More experience is needed to evaluate the cost-effectiveness
- Assiduous post-marketing surveillance is required
- May be beneficial for some patients but for a stable patient with very good INR …

Dabigatran Bleeding Warnings

- **August 2011** Japan issues a bleeding warning
- **October 2011** Australia issues a bleeding warning
- **Letter to the Editor** B.A. Cotton NEJM 2011:365;21:2039-40

  « We strongly urge that hemorrhagic complications and death resulting from trauma be included as part of routine surveillance of all newly approved oral anticoagulants. »

March 2012

New Zealand issues a bleeding warning

- 78 Bleeding episodes with 1 death
- 5 factors
  - Prescription error 25%
  - Renal impairment 58%
  - Patient age > 80 60%
  - Patient weight < 60 kg 50%
  - Lack of reversal agent

Harper P. Bleeding risk with dabigatran in the frail Elderly. NEJM Letter to the Editor, 366; 9:864-66

ARISTOTLE

↓ 21% AVC ou embolies systémiques

↓ 31% saignements majeurs

↓ 11% mortalité

1 000 patients traités pendant 1,8 an prévient

- 6 AVC (4 AVC hémorragiques)
- 15 saignements majeurs
- 8 décès

ARISTOTLE

100 patients traités pendant 1 an prévient

- **0,33 AVC**
- **0,88 saignements majeurs**
- **0,44 décès**

Stroke	ARR	NNT
Warfarin vs Control	2.7% / year	37
Dabigatran vs Warfarin	0.58% / year	172
Apixaban vs Warfarin	0.33% / year	303

Intracranial Haemorrhage	ARR	NNT
Dabigatran vs Warfarin	0.44% / year	303
Rivaroxaban vs Warfarin	0.2% / year	500
Apixaban vs Warfarin	0.47% / year	213

AAR Absolute Risk Reduction
NNT Number Needed to Treat

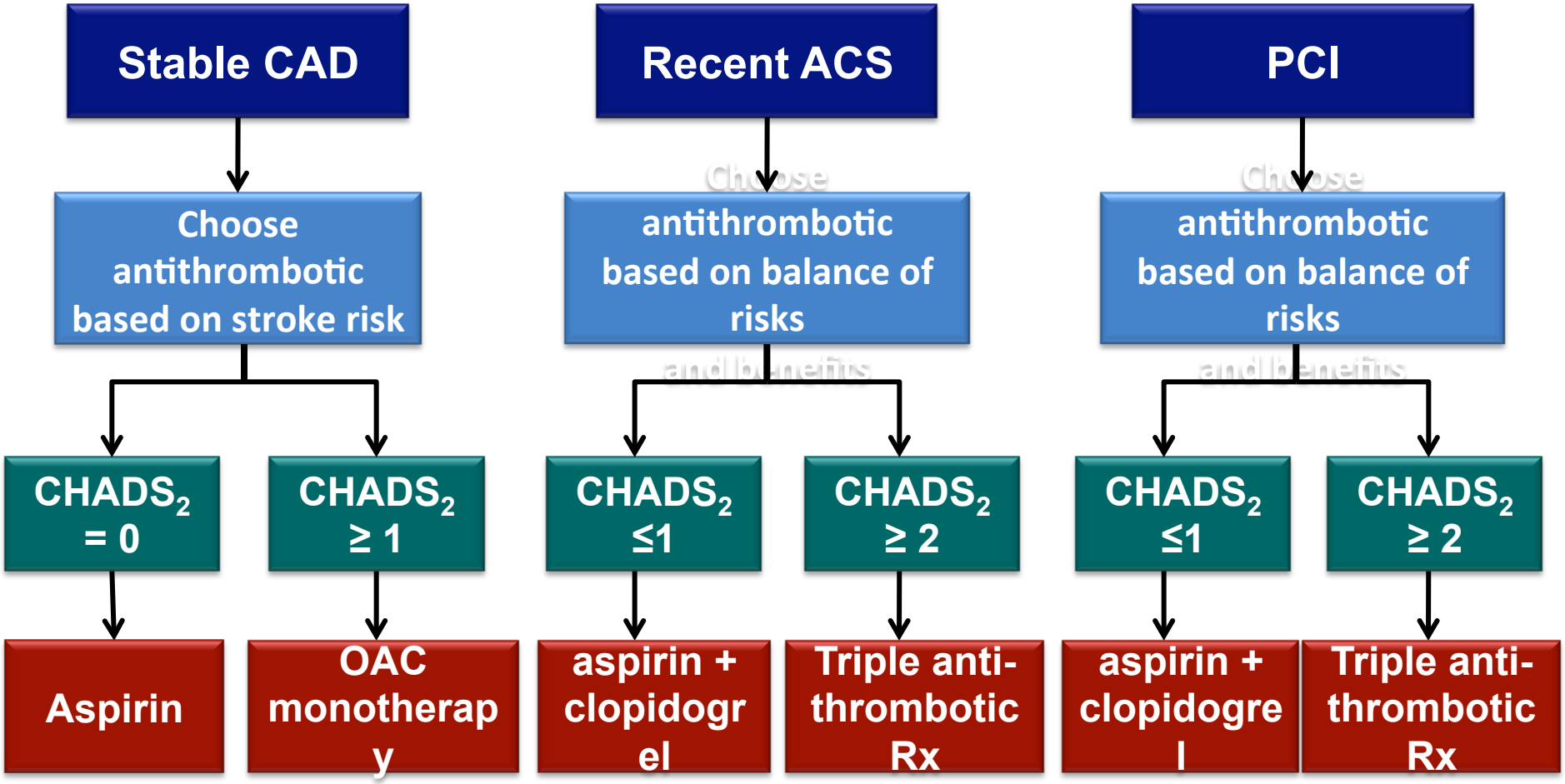
New OAC drugs

- New OAC are the drugs of choice for low-medium-high risk patients
- New OAC are there to stay
- Dabigatran, rivaroxaban, apixaban
- Edoxaban, betrixaban
- “Head to Head study”
- Different drugs / Different populations / Different Studies

New OAC Drugs

- Unsuitable for warfarin
- Stable patient on warfarin
- Guidelines are guidelines
- Coronary artery disease
  - Adding ASA to warfarin does not reduce the risk of stroke but increases the risk of bleeding
  - New agents

Antithrombotic Management of AF/AFL in CAD



Will Warfarin Remain?

- Severe renal insufficiency
- Mechanical heart valves
- Non-believers
  - No antidote
  - Measurement of anticoagulation effect challenging

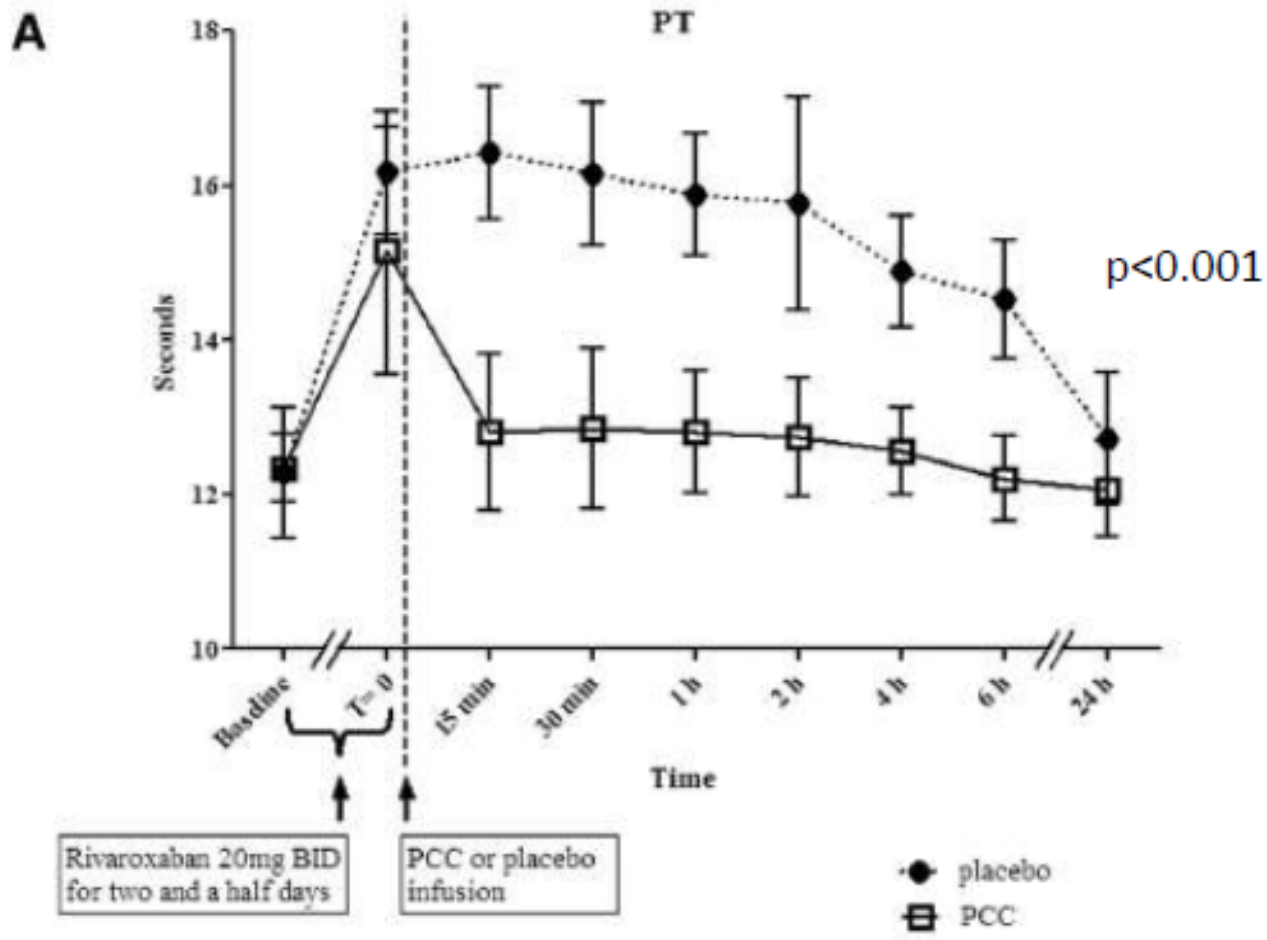
Circulation 2011

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

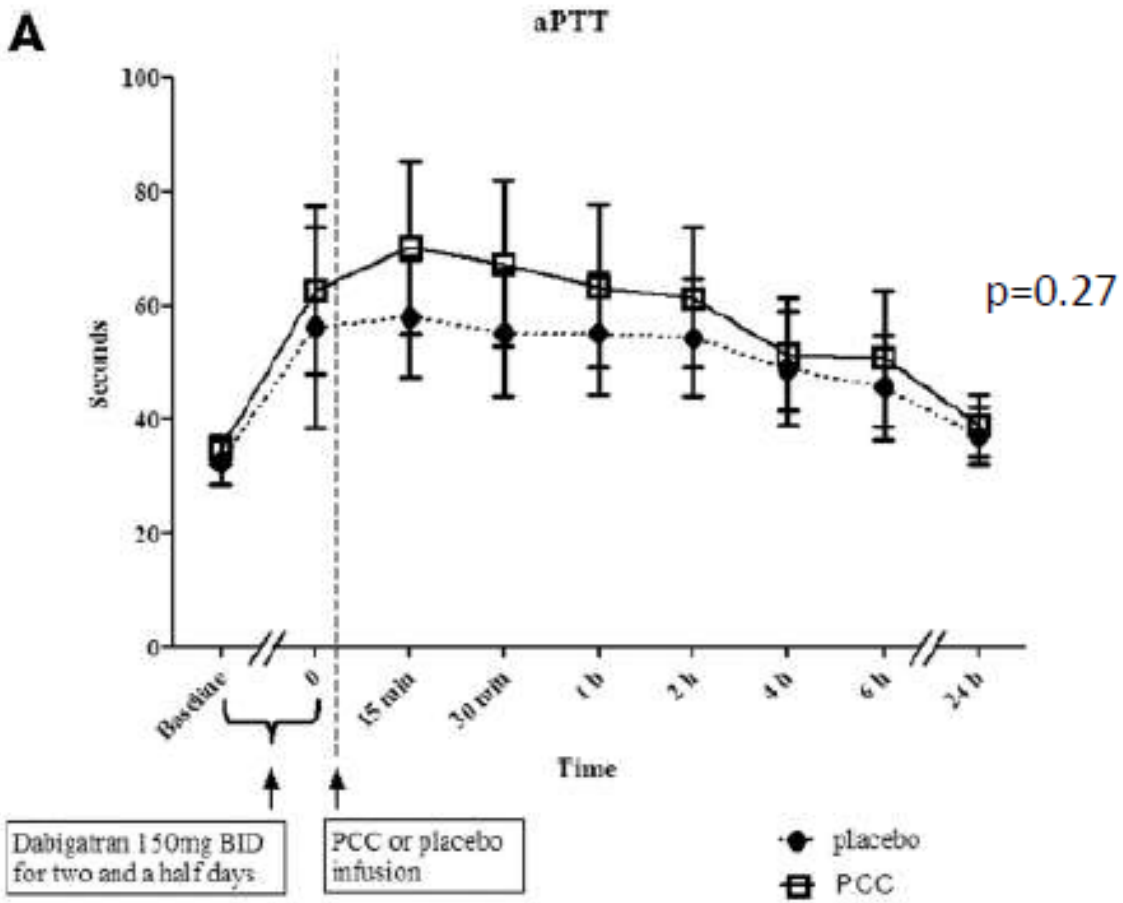
A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc; Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

PCC Reverses Rivaroxaban



PCC Does Not Completely Reverse Dabigatran



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