Aspetti innovativi della terapia anticoagulante per i pazienti con FA non valvolare

DAVIDE IMBERTI

MEDICINA INTERNA
CENTRO EMOSTASI E TROMBOSI
OSPEDALE GUGLIELMO DA SALICETO
PIACENZA

Rischio di ictus nei pazienti con fibrillazione atriale: si possono proteggere più pazienti ?

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Il *sottoscritto* *Imberti Davide*

dichiara

di aver avuto negli ultimi due anni rapporti di consulenza con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- ABBOTT
- ALFA WASSERMANN
- BAYER
- BAXTER
- BOHERINGER INGELHEIM
- DAIICHI-SANKYO
- GSK
- KEDRION
- IL
- SANOFI AVENTIS

La terapia anticoagulante nei pazienti con FA non-valvolare

- Evidenze della letteratura: la pratica clinica
- Evidenze delle letteratura: i nuovi anticoagulanti orali
- Cosa dicono le Linee Guida

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Stroke Risk Stratified by CHADS2

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

For patients with a CHADS2 Score of 4 the annual rate is about *8.5%*

Gage, JAMA, 2001

AF-RELATED STROKE IS PREVENTABLE

- Effective stroke prevention is a priority for patients with AF[1]
- Two-thirds of strokes due to AF are **preventable** with appropriate anticoagulant therapy
- A meta-analysis of 29 trials in 28,044 patients showed that the vitamin K antagonist (VKA) warfarin **reduces the risk of stroke and all-cause mortality**
  - **64% reduction in stroke and 24% reduction in all-cause mortality** compared with placebo
  - Aspirin also reduced the risk of stroke, but less effectively than warfarin (19% reduction compared with placebo)
- However, VKAs are associated with complications, such as increased bleeding risk

LIMITATIONS OF VKA THERAPY

Unpredictable response

Narrow therapeutic window (INR range 2.0–3.0)

Slow onset/ offset of action

VKA therapy has several limitations that make it difficult to use in practice

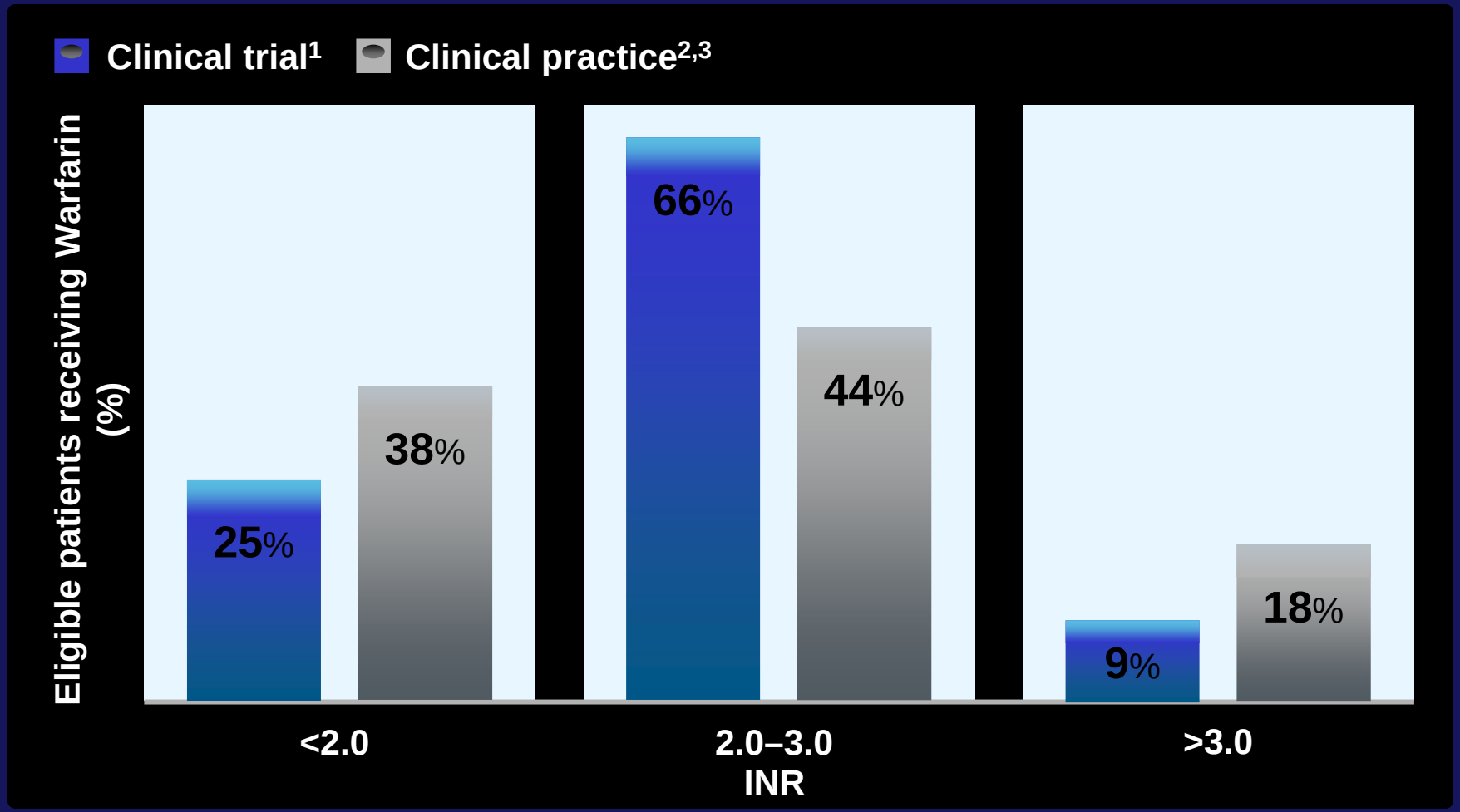
Numerous food–drug interactions

Numerous drug–drug interactions

Warfarin resistance

Routine coagulation monitoring → Frequent dose adjustments

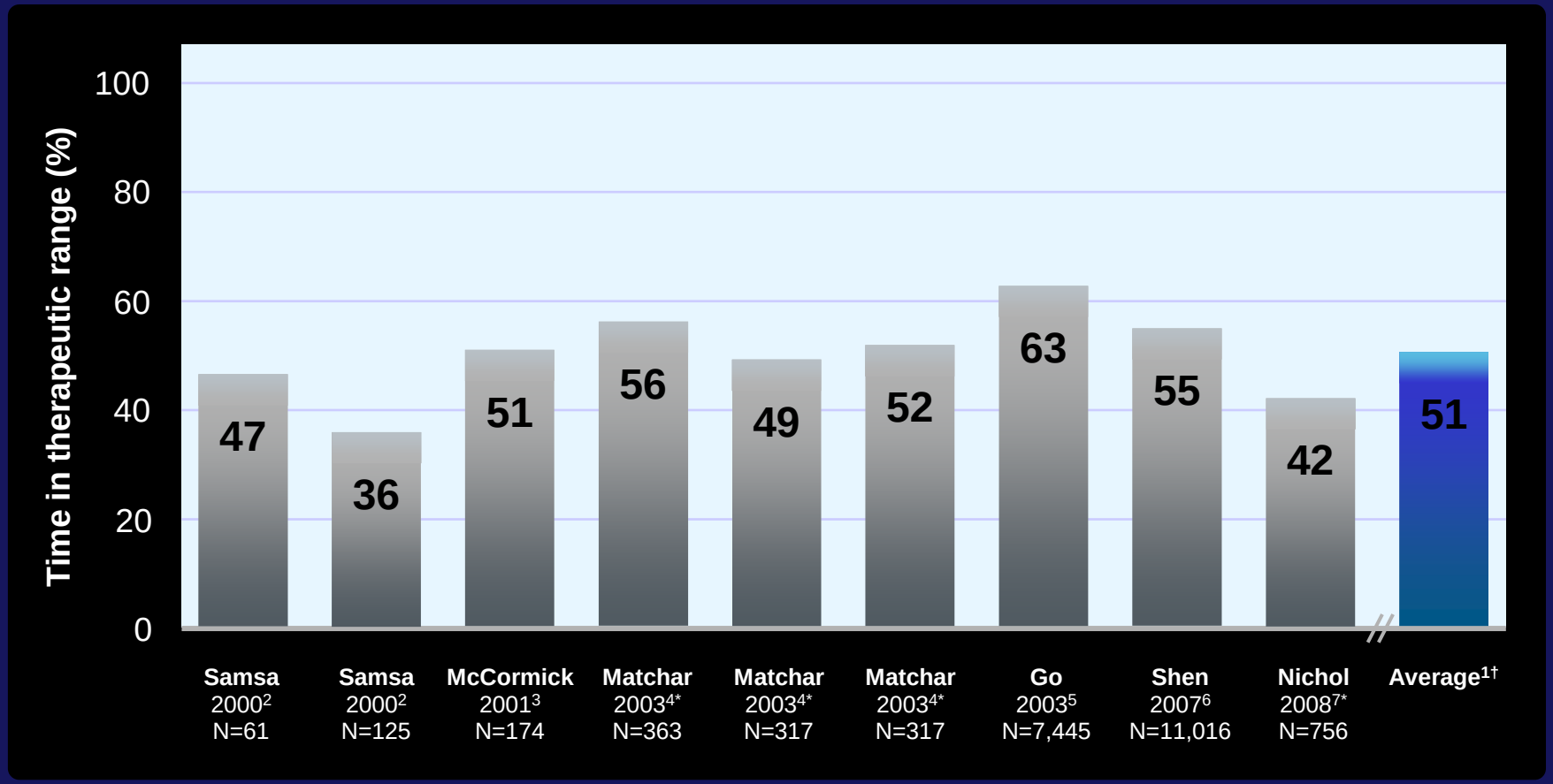
INR CONTROL: CLINICAL TRIALS VS. CLINICAL PRACTICE (TTR)



INR = international normalized ratio ; TTR = time-in-therapeutic-range (INR 2.0–3.0).

1. Kalra L, et al. *BMJ* 2000;320:1236-1239; *Pooled data: up to 83–71% in individualized trials.
2. Samsa GP, et al. *Arch Intern Med* 2000;160:967-973. 3. Matchar DB, et al. *Am J Med* 2002;113:42-51.

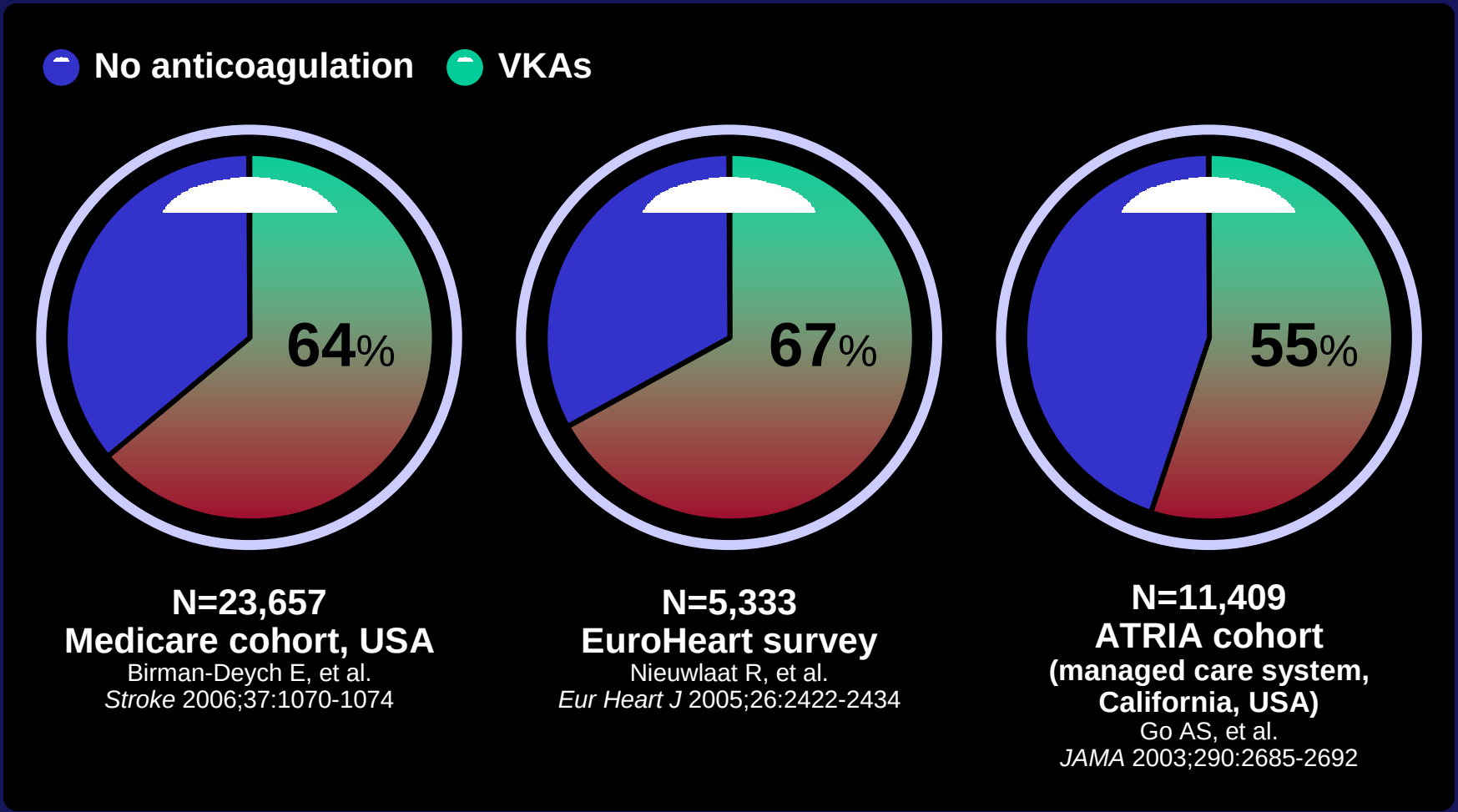
TIME-IN-THERAPEUTIC-RANGE WITH WARFARIN USE IN CLINICAL PRACTICE



* Linear interpolation method not used. † Overall effect = 0.55.

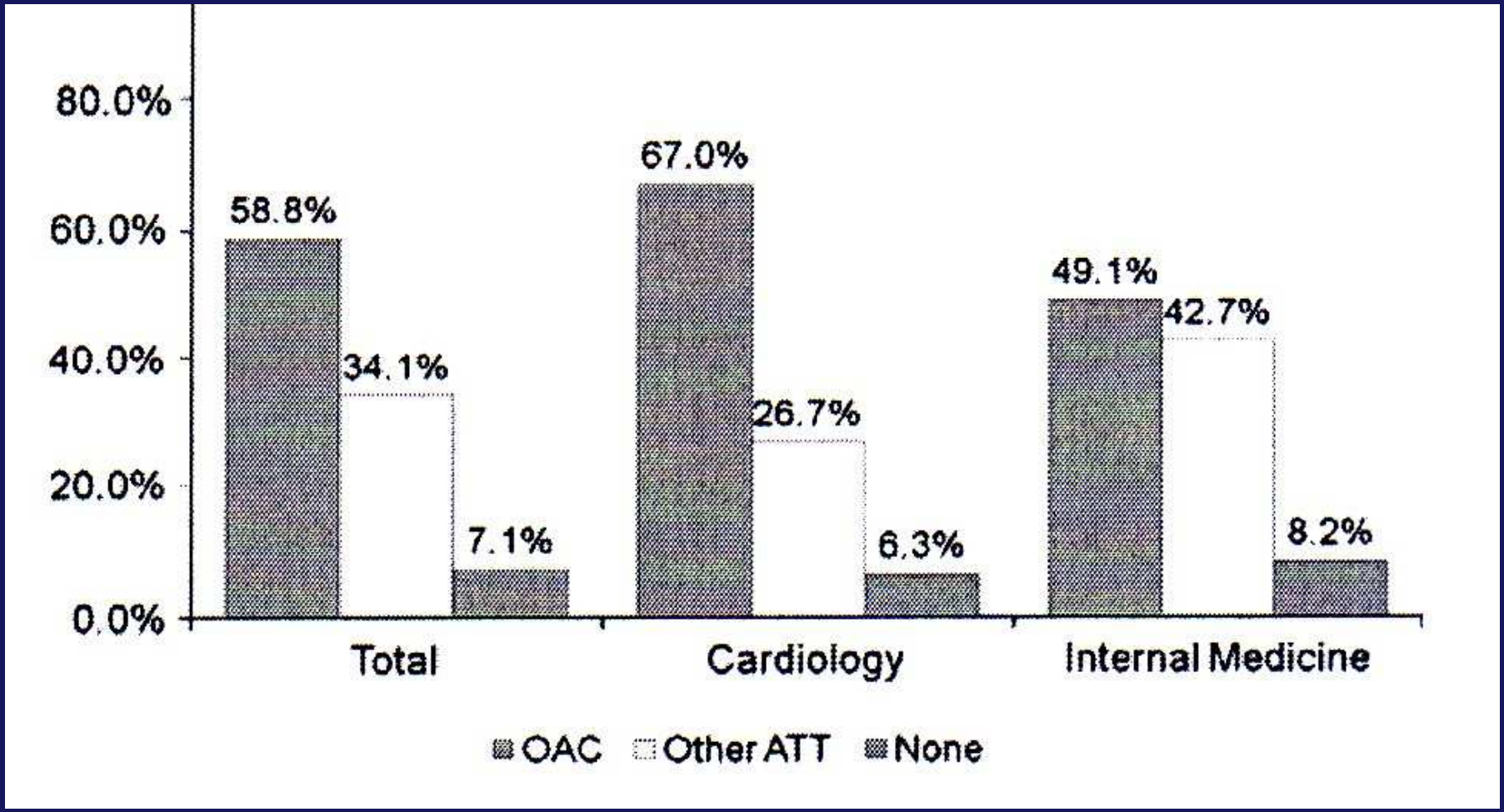
1. Baker WL, et al. *J Manag Care Pharm* 2009;15:244-252. 2. Samsa GP, et al. *Arch Intern Med* 2000;160:967-973.
3. McCormick D, et al. *Arch Intern Med* 2001;161:2458-2463. 4. Matchar DB. *Card Electrophysiol Rev* 2003;7:379-381.
5. Go AS, et al. *JAMA* 2003;290:2685-2692. 6. Shen AY, et al. *J Am Coll Cardiol* 2007;50:309-315.
7. Nichol MB, et al. *Ann Pharmacother* 2008;42:62-70.

MANAGEMENT OF AF IN CLINICAL PRACTICE: PRESCRIPTION OF VKAs



VKA = vitamin K antagonist.

Current presentation and management of 7148 patients with AF in cardiology and internal medicine hospital centers: the ATA AF study

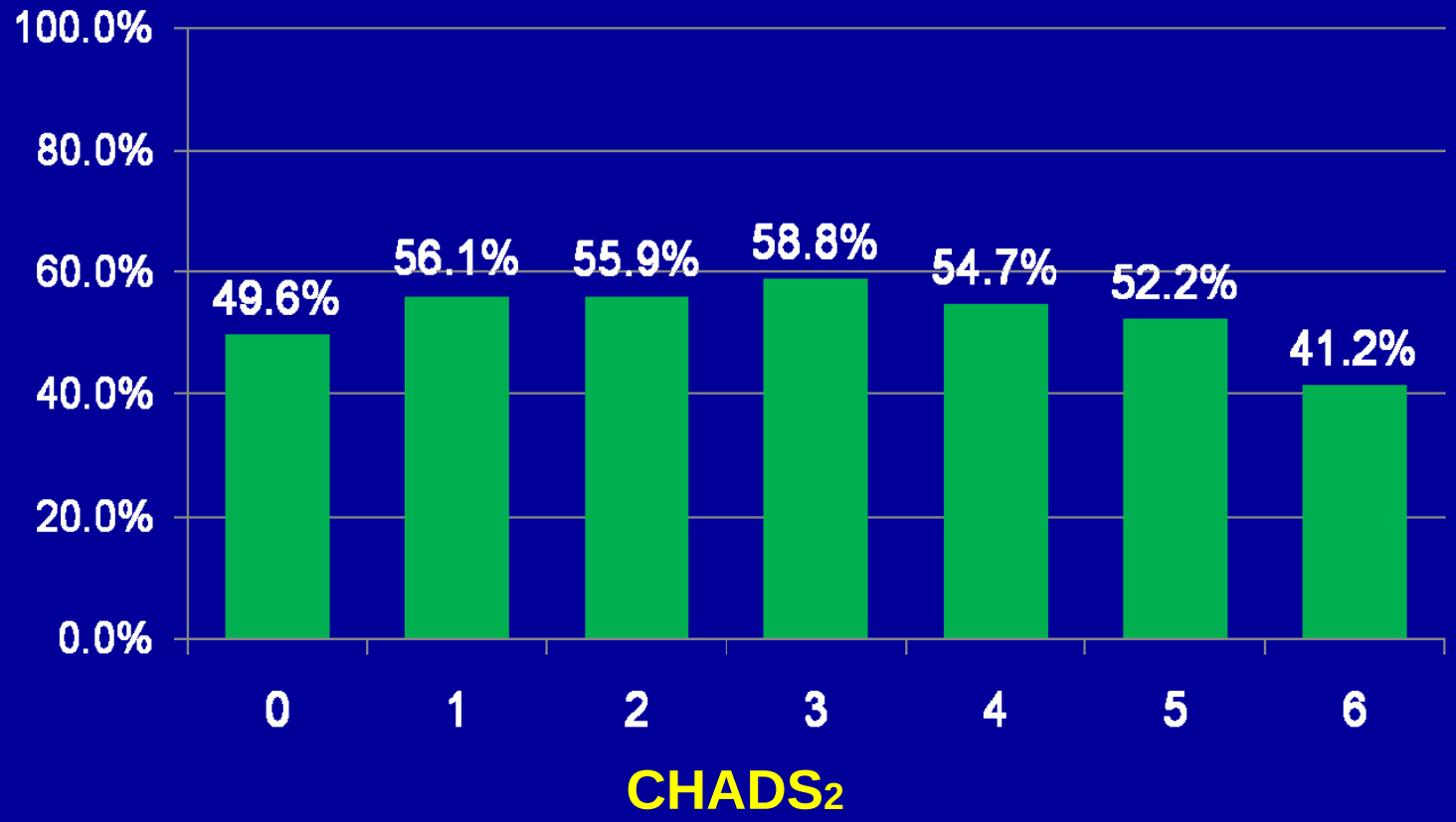


Di Pasquale, Int J Cardiol, 2012

Prescription of OAC by $CHADS_2$

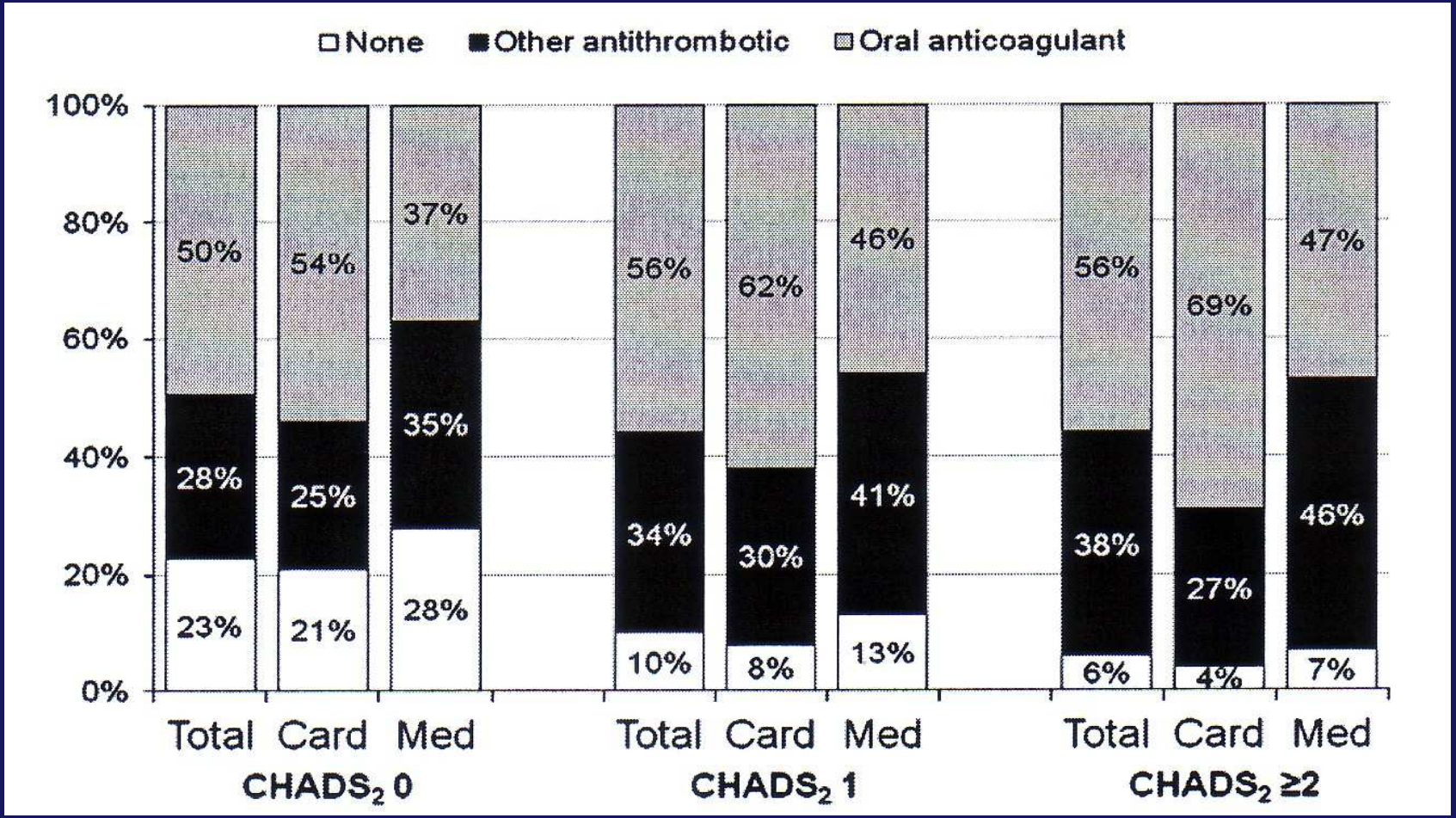
(non valvular AF, 4845 pts

p=0.024



Di Pasquale, Int J Cardiol, 2012

Antithrombotic treatment prescribed in cardiology and internal medicine according to the CHADS2 score



Di Pasquale, Int J Cardiol, 2012

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PK/PD of 5 Novel Oral Agents

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban (DU-176b)	Betrixaban (PRT054021)
Target	IIa (thrombin)	Xa	Xa	Xa	Xa
Hrs to Cmax	2	1-3	2-4	1-2	NR
Bioavailability	6.5%	50%	80%		
CYP Metabolism	None	15%	32%	NR	None
Half-Life	12-14h	8-15h	9-13h	8-10h	19-20h
Renal Elimination	80%	40%	33%	35%	<5%

Ruff CR and Giugliano RP. Hot Topics in Cardiology 2010;4:7-14
Ericksson BI et al. Clin Pharmacokinet 2009; 48: 1-22
Ruff CR et al. Am Heart J 2010; 160:635-41

CYP = cytochrome P450; NR = not reported

Challenges in the Interpretation and Comparison of Trials Involving Factor Xa and II Inhibition in Non Valvular Atrial Fibrillation

C. Michael Gibson, M.S., MD.

Challenges in the Interpretation and Comparison of Trials Involving Factor Xa and II Inhibition in Non Valvular Atrial Fibrillation

C. Michael Gibson, M.S., MD.

Profilo farmacologico apixaban vs rivaroxaban e dabigatran

	Apixaban	Rivaroxaban*	Dabigatran**
Meccanismo d'azione	FXa	FXa	DTI
Biodisponibilità orale	50 %	80 %	6.5 %
Via di somministrazione	Orale	Orale	Orale
Schema di somministrazione	BID	QD (TEVp, TEVt, FA) BID (SCA)	QD (TEVp) BID (TEVt, FA)
Pro-farmaco	No	No	Si
Interferenze cibo	No	No	No
Vie eliminazione	Renale ~ 27% Metabolica ~80 %	Renale ~33 % Metabolica – 46 %	Renale – 85 % Fecale – 6 %
Tempo di emivita medioT1/2	~ 12 h	7–11 h	14–17 h
Tmax	3 h	2–4 h	0.5–2 h
Interazioni farmacologiche	Inibitori CYP 3A4 e P-gp Induttori CYP 3A4	Inibitori CYP 3A4 e P-gp Induttori CYP 3A4	Inibitori P-gp Induttori P-gp Amiodarone

*Rivaroxaban EPAR at http://www.emea.europa.eu/humandocs/Humans/EPAR/xarelto/xarelto.htm

** Dabigatran Etexilate EPAR at http://www.emea.europa.eu/humandocs/Humans/EPAR/pradaxa/pradaxa.htm

Phase III AF Trials

	Re-LY	ROCKET-AF	ARISTO TLE	ENGAGE AF-TIMI 48
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose (mg) Freq	150, 110 BID	20 (15*) QD	5 (2.5*) BID	60*, 30* QD
N	18,113	14,266	18,206	>21,000
Design	PROBE	2x blind	2x blind	2x blind
AF criteria	AF x 1 < 6 mths	AF x 2 (≥1 in <30d)	AF or AFl x 2 <12 mths	AF x 1 < 12 mths
% VKA naive	50%	38%	43%	40% goal

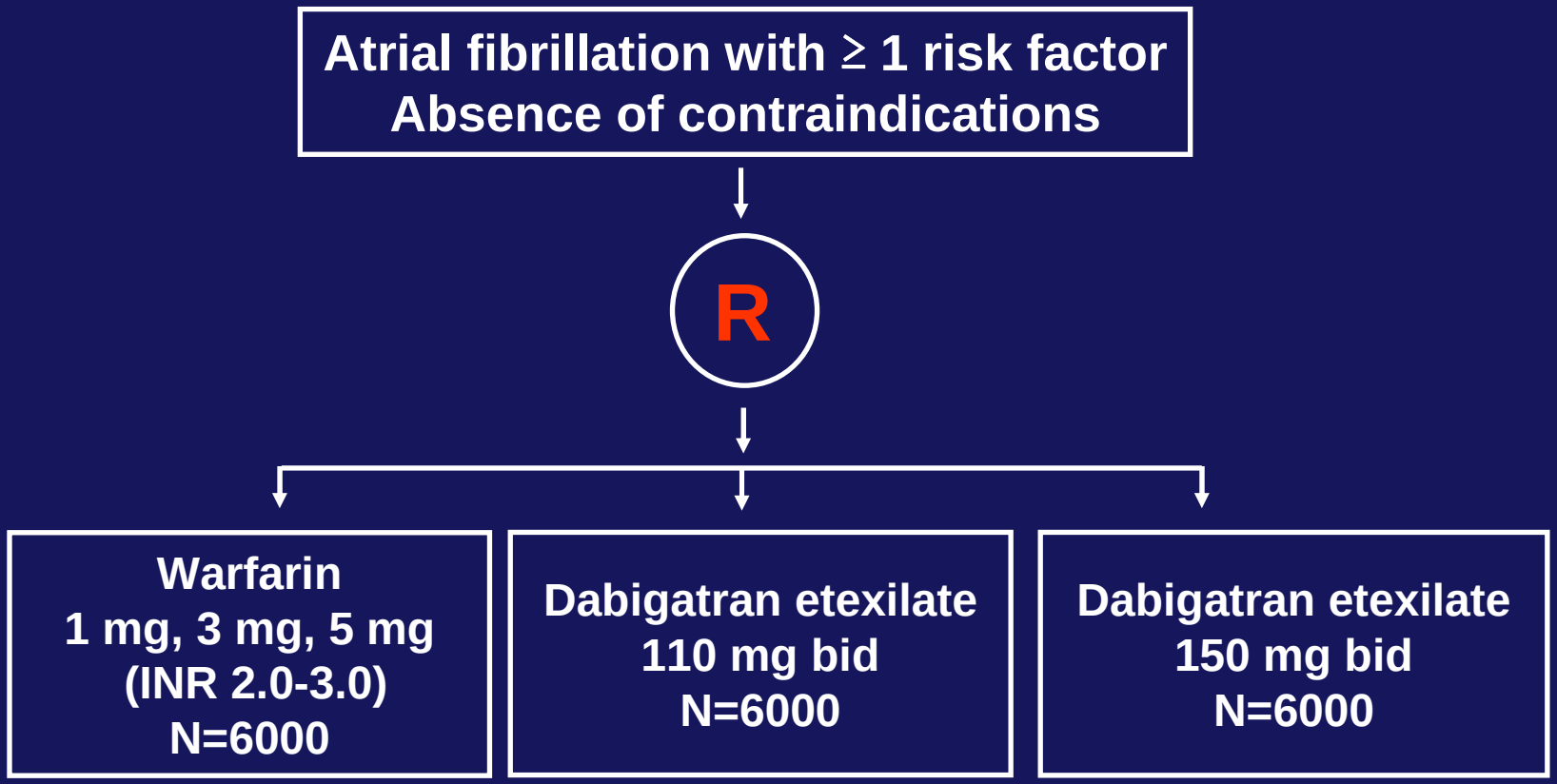
*Dose adjusted in patients with ↓ drug clearance.

**Max of 10% with CHADS-2 score = 2 and no stroke/TIA/SEE

PROBE = prospective, randomized, open-label, blinded end point evaluation

VKA = Vitamin K antagonist

RE-LY® – study design



- Primary objective: To establish the non-inferiority of dabigatran etexilate to warfarin
- Minimum 1 year follow-up, maximum of 3 years and mean of 2 years of follow-up

Connolly, NEJM, 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

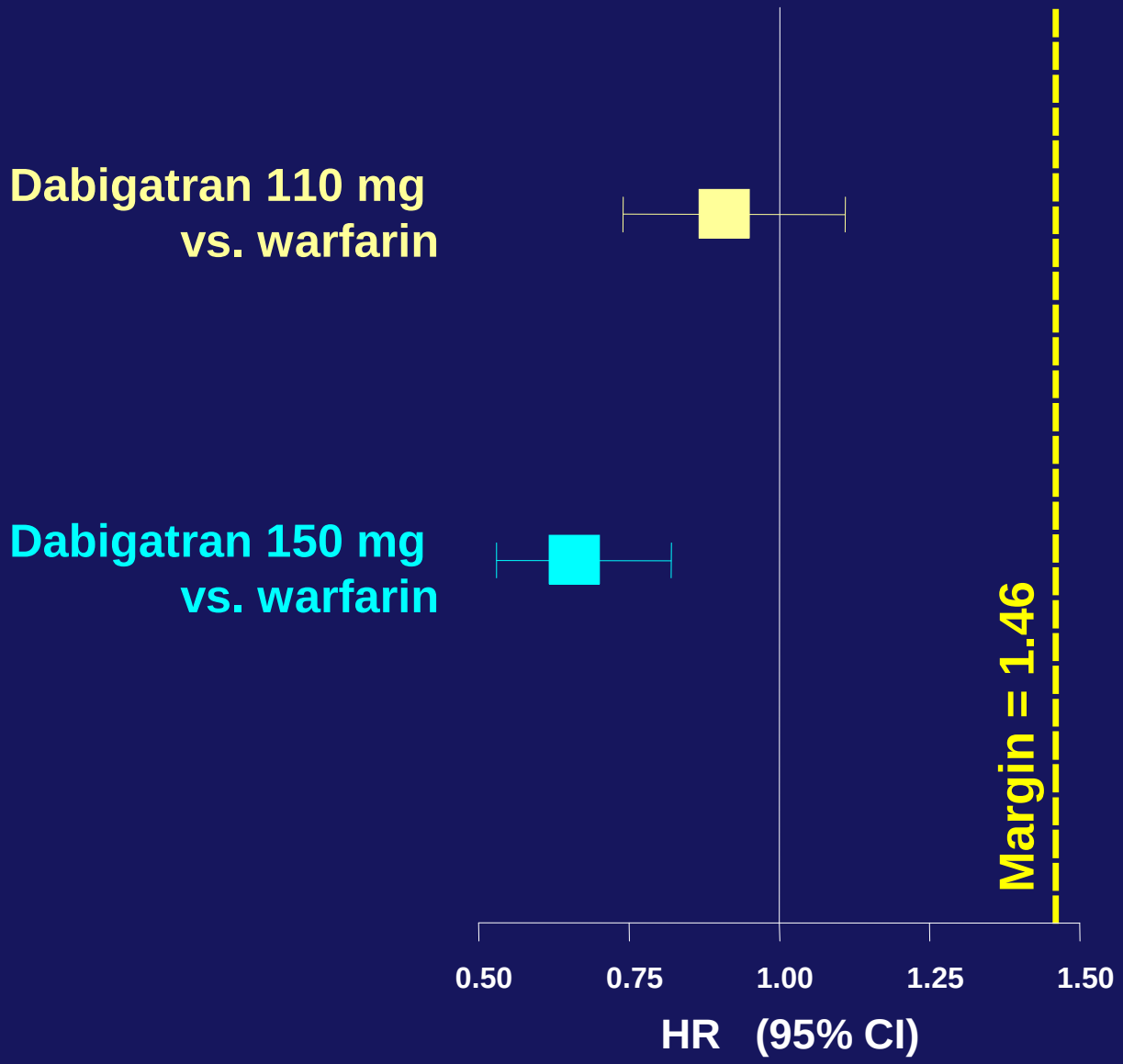
RE-LY® – outcome measures

Primary efficacy endpoint	Secondary efficacy endpoints	Safety criteria include
▶ All stroke (ischaemic + haemorrhagic) and systemic embolism	▶ All stroke (ischaemic + haemorrhagic) ▶ Systemic embolism ▶ All death	▶ Bleeding events (major and minor)
	▶ All stroke (ischaemic + haemorrhagic) ▶ Systemic embolism ▶ Pulmonary embolism ▶ Acute MI ▶ Vascular death (incl. deaths from bleeding)	▶ Intracranial haemorrhage ▶ Cerebral haemorrhage ▶ Subdural haematoma ▶ Subarachnoid haemorrhage
		▶ Elevations in liver enzymes or hepatic dysfunction

Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
DOI 10.1056/NEJMoa0905561

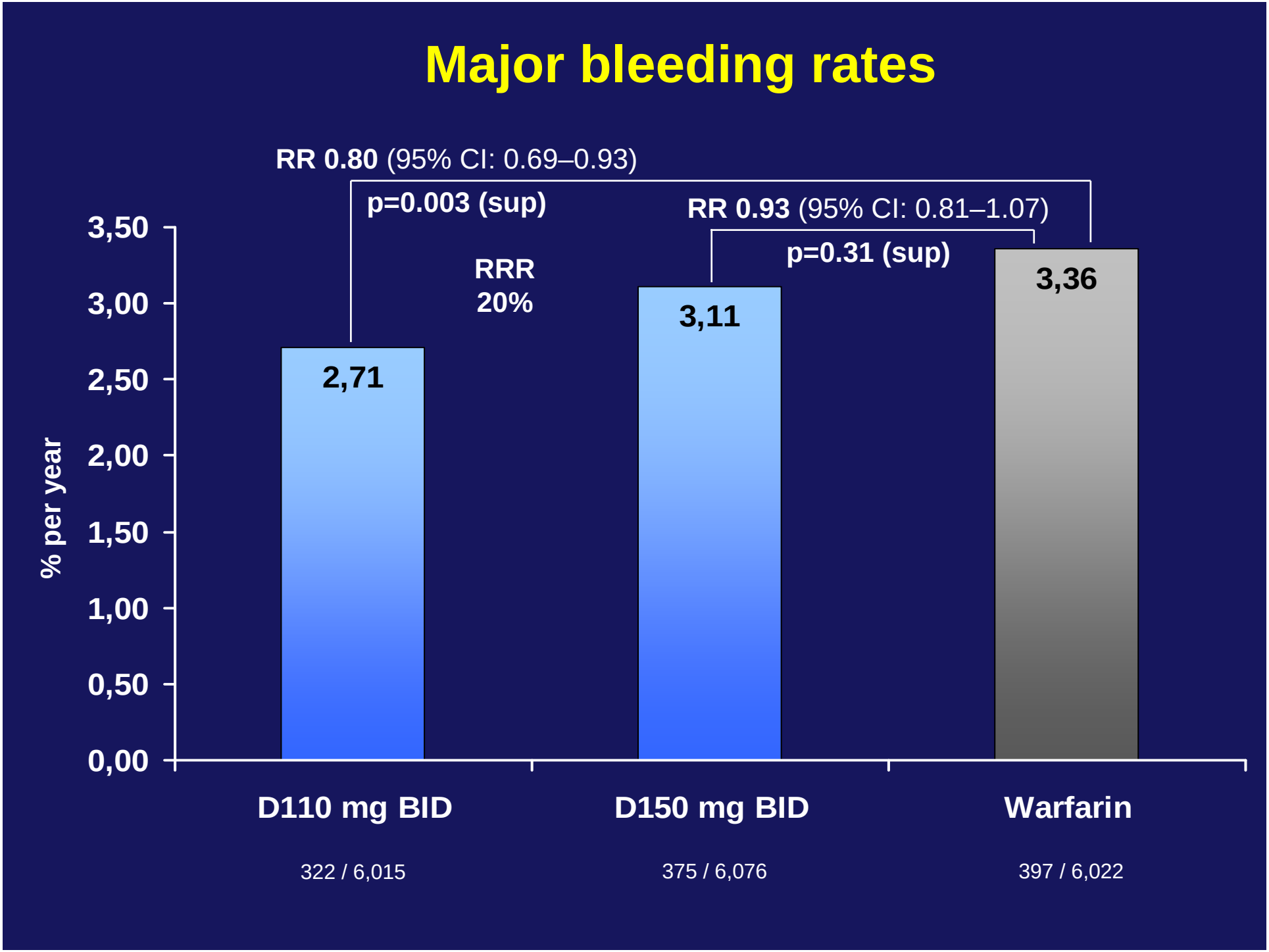
Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

Stroke or systemic embolism (SSE)

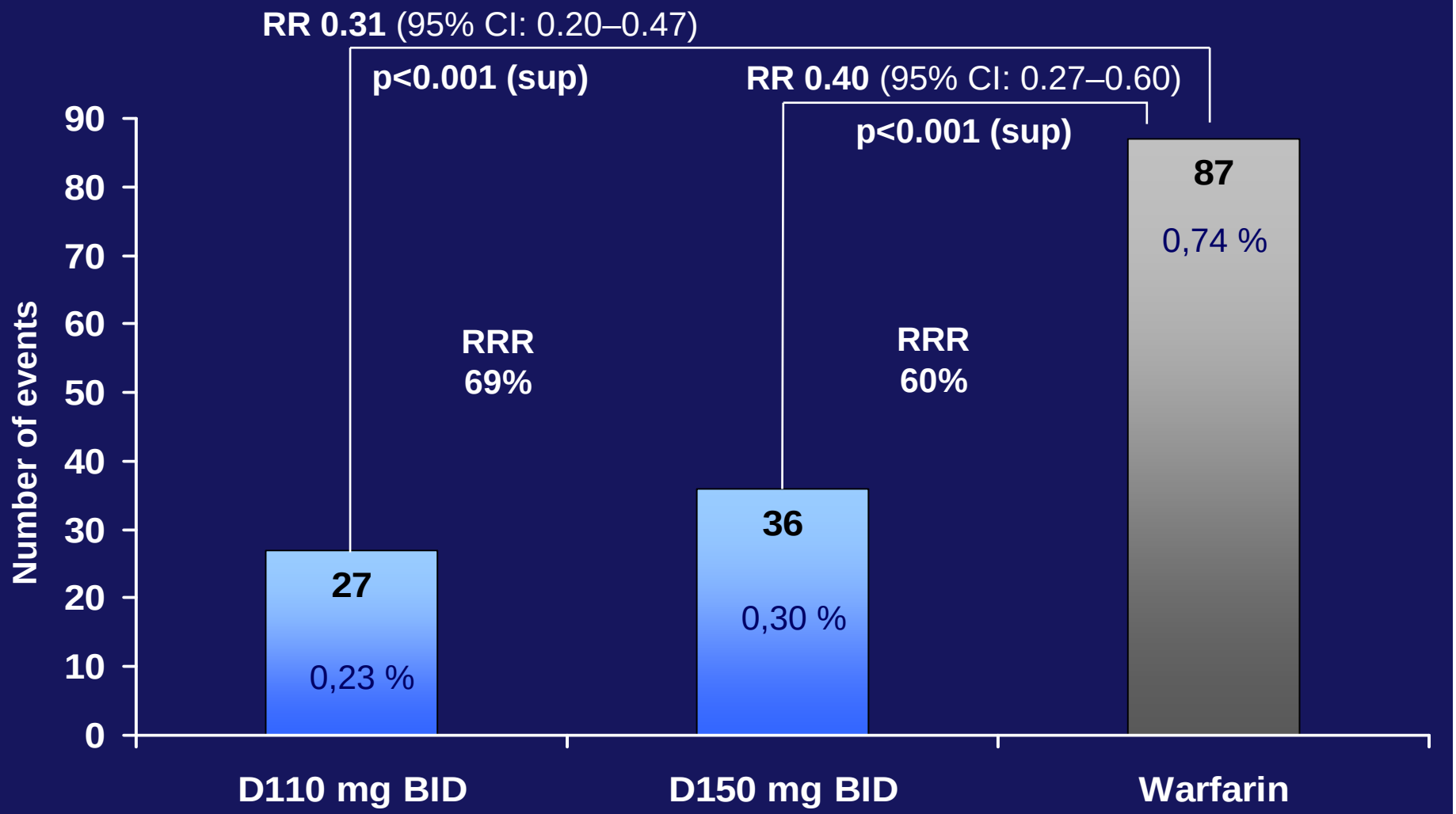


	Noninferiority p-value	Superiority p-value
Dabigatran 110 mg vs. warfarin	<0.001	0.34
Dabigatran 150 mg vs. warfarin	<0.001	<0.001

Major bleeding rates



Intra-cranial bleeding rates



MAJOR BLEEDING AND COMPONENTS

Characteristic	Dabigatran 150 mg	Dabigatran 110 mg	Warfarin	P value D150 vs. W	P value D110 vs. W
Number of patients	6,076	6,015	6,022		
▶ **Life threatening**	1.49	1.24	1.85	0.03	<0.001
▶ **Non-life threatening**	2.06	1.83	1.92	0.39	0.65
▶ **Gastro-intestinal**	1.56	1.15	1.07	0.001	0.52

NET CLINICAL BENEFIT AND COMPONENTS

Characteristic	Dabigatran 150 mg	Dabigatran 110 mg	Warfarin	P value D150 vs. W	P value D110 vs. W
Number of patients	6,076	6,015	6,022		
▶ **Stroke or SSE**	1.11	1.54	1.71	<0.001(NI) **<0.001(sup)**	<0.001(NI) **0.30(sup)**
▶ **Death**	3.64	3.75	4.13	0.051	0.13
▶ **Major bleeding**	3.32	2.87	3.57	0.32	0.003
▶ **Pulmonary embolism**	0.15	0.12	0.10	0.30	0.71
▶ **Myocardial infarction**	0.81	0.82	0.64	0.12	0.09

MOST COMMON ADVERSE EVENTS

	Dabigatran 150 mg %	Dabigatran 110 mg %	Warfarin %
Dyspepsia*	11.3	11.8	5.8
Dyspnoea	9.5	9.3	9.7
Dizziness	8.3	8.1	9.4
Peripheral oedema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	6.2	5.2	5.9
Arthralgia	5.5	4.5	5.7
Back pain	5.2	5.3	5.6
Nasopharyngitis	5.4	5.6	5.6
Diarrhoea	6.5	6.3	5.7
Urinary tract infection	4.8	4.5	5.6
Upper respiratory tract infection	4.7	4.8	5.2

*** Occurred more commonly on dabigatran P <0.001**

ROCKET AF: Study Design

Atrial Fibrillation

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

At least 2 or 3 required*

OR
- Stroke, TIA or Systemic embolus

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomized Double Blind / Double Dummy (n ~ 14,000)

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

Patel, N Engl J Med, 2011

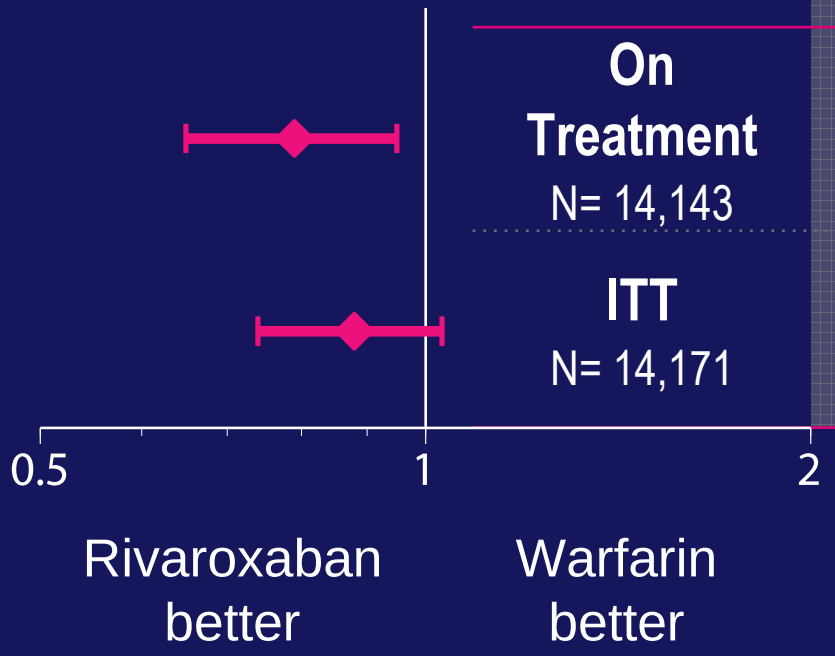
Baseline Demographics

	Rivaroxaban (N=7081)	Warfarin (N=7090)
→ $CHADS_2$ Score (mean)	3.48	3.46
2 (%)	13	13
3 (%)	43	44
4 (%)	29	28
5 (%)	13	12
6 (%)	2	2
→ Prior VKA Use (%)	62	63
Congestive Heart Failure (%)	63	62
Hypertension (%)	90	91
Diabetes Mellitus (%)	40	39
→ Prior Stroke/TIA/Embolism (%)	55	55
Prior Myocardial Infarction (%)	17	18

Based on Intention-to-Treat Population (for efficacy)

Primary Efficacy Outcome

Stroke and non-CNS Embolism



	Rivaroxaban Event Rate	Warfarin Event Rate	HR (95% CI)	P-value *
On Treatment N= 14,143	1.70	2.15	0.79 (0.65,0.95)	0.015
ITT N= 14,171	2.12	2.42	0.88 (0.74,1.03)	0.117

Event Rates are per 100 patient-years
Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations
Note: * p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.

Primary Safety Outcomes

	Rivaroxaban Event Rate	Warfarin Event Rate	HR (95% CI)	P-value
Major and non-major Clinically Relevant	14.91	14.52	1.03 (0.96, 1.11)	0.442
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
Non-major Clinically Relevant	11.80	11.37	1.04 (0.96, 1.13)	0.345

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

Primary Safety Outcomes

	Rivaroxaban Event Rate or N (Rate)	Warfarin Event Rate or N (Rate)	HR (95% CI)	P-value
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
≥2 g/dL Hgb drop	2.77	2.26	1.22 (1.03, 1.44)	0.019
Transfusion (> 2 units)	1.65	1.32	1.25 (1.01, 1.55)	0.044
→ Critical organ bleeding	0.82	1.18	0.69 (0.53, 0.91)	0.007
→ Bleeding causing death	0.24	0.48	0.50 (0.31, 0.79)	0.003
Intracranial Hemorrhage	55 (0.49)	84 (0.74)	0.67 (0.47, 0.94)	0.019 *
Intraparenchymal	37 (0.33)	56 (0.49)	0.67 (0.44, 1.02)	0.060
Intraventricular	2 (0.02)	4 (0.04)		
Subdural	14 (0.13)	27 (0.27)	0.53 (0.28, 1.00)	0.051
Subarachnoid	4 (0.04)	1 (0.01)		

* P = 0.019

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

ROCKET AF: events during and after discontinuation of treatment

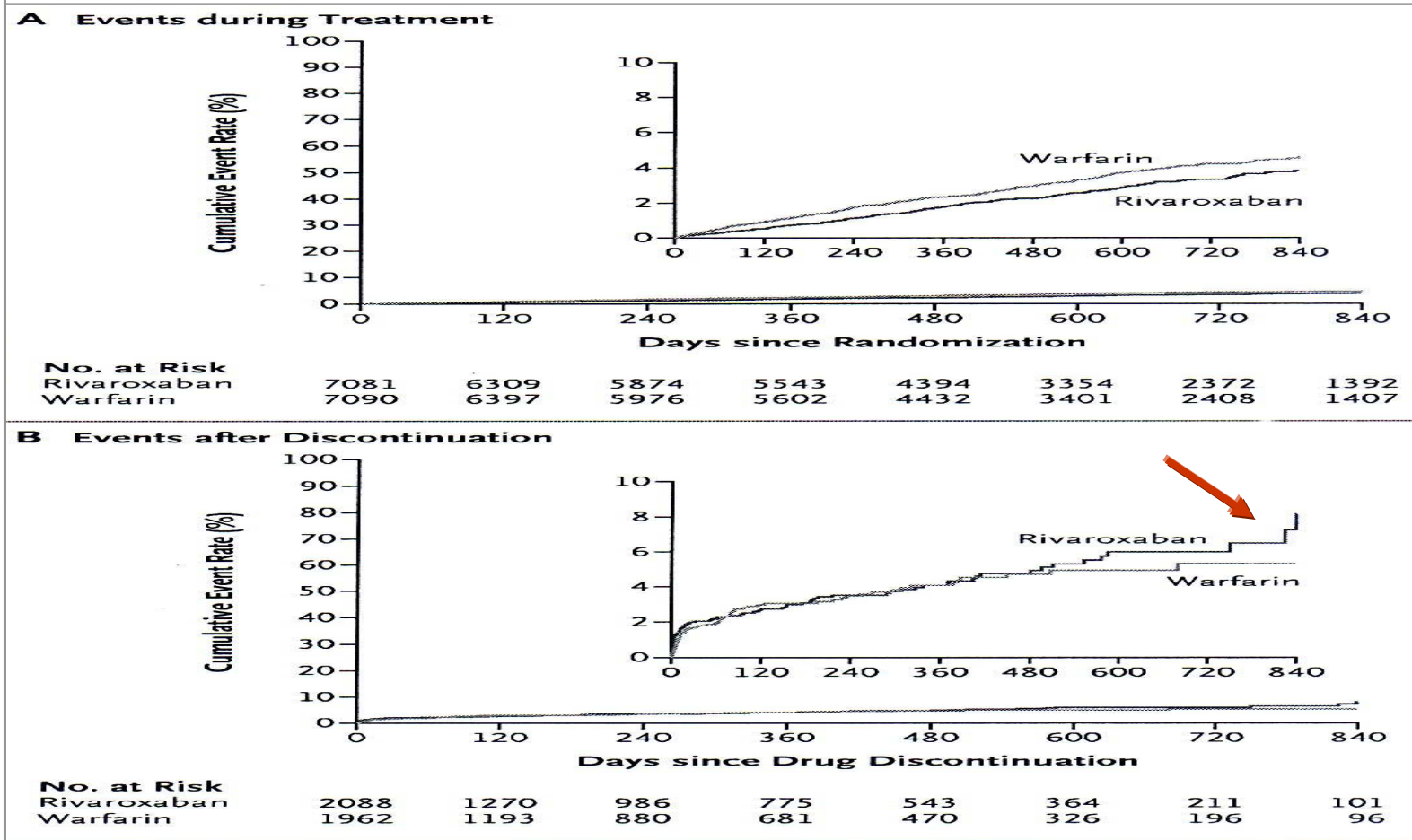
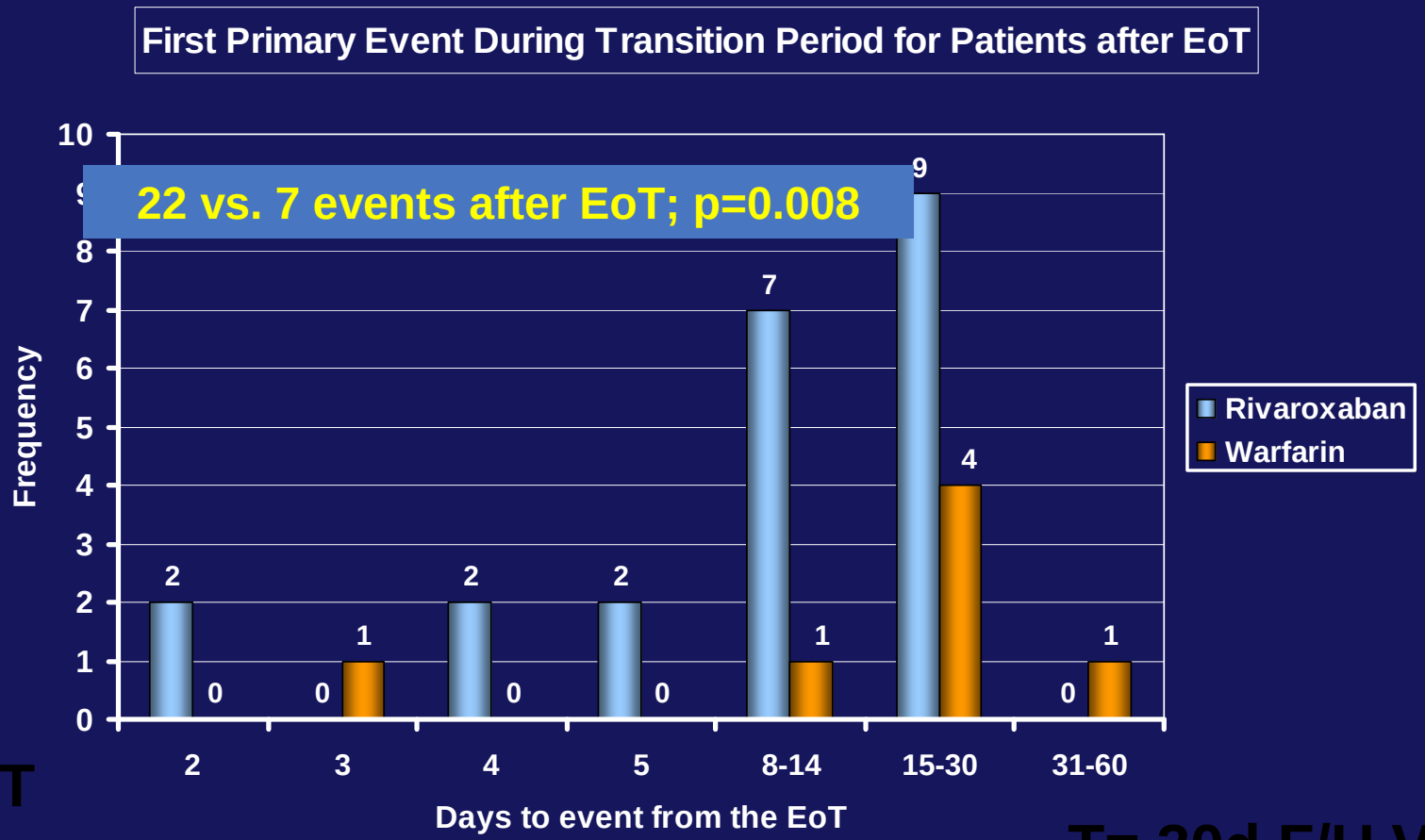


Figure 2. Cumulative Rates of the Primary End Point during Treatment and after Discontinuation in the Intention-to-Treat Population.

Patel, N Engl J Med, 2011

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



T=EoT

R

T= 30d F/U Visit

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

ARISTOTLE: Study Design

AF with at Least One Additional Risk Factor for Stroke

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

Randomized
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)
(≥ 80 years, weight ≤ 60 kg or creatinine > 1,5 mg/dL)
(n. 9.120)

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

Granger, NEJM, 2011

Objectives

Primary objective

- To determine whether apixaban is non-inferior to warfarin at reducing stroke (ischemic or hemorrhagic) or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke.

Primary safety outcome

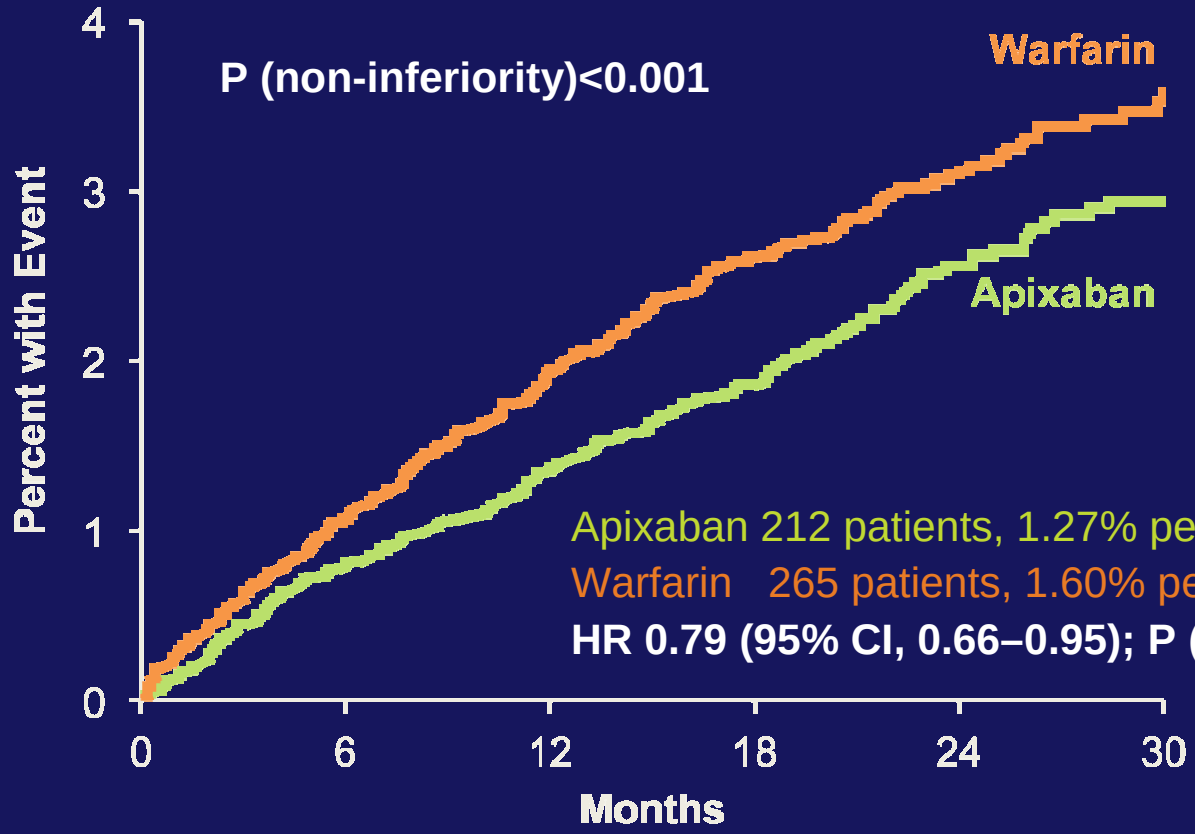
- Major bleeding according to the International Society of Thrombosis and Hemostasis (ISTH) definition.

Baseline Characteristics

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Qualifying risk factors, %		
Age ≥75 yrs	31	31
Prior stroke, TIA, or SE	19	20
Heart failure or reduced LV EF	35	36
Diabetes	25	25
Hypertension	87	88
Renal function (Cl_{Cr} ml/min), %		
Normal (>80)	41	41
Mild impairment (>50 – 80)	42	42
Moderate impairment (>30 – 50)	15	15
Severe impairment (≤ 30)	1.5	1.5

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

Bleeding Outcomes

Outcome	Apixaban (N=9088) Event Rate (%/yr)	Warfarin (N=9052) Event Rate (%/yr)	HR (95% CI)	P Value
Primary safety outcome: ISTH major bleeding*	2.13	3.09	0.69 (0.60, 0.80)	<0.001
Intracranial	0.33	0.80	0.42 (0.30, 0.58)	<0.001
Gastrointestinal	0.76	0.86	0.89 (0.70, 1.15)	0.37
Major or clinically relevant non-major bleeding	4.07	6.01	0.68 (0.61, 0.75)	<0.001
GUSTO severe bleeding	0.52	1.13	0.46 (0.35, 0.60)	<0.001
TIMI major bleeding	0.96	1.69	0.57 (0.46, 0.70)	<0.001
Any bleeding	18.1	25.8	0.71 (0.68, 0.75)	<0.001

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

RELY	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
$CHADS_2$ Mean	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1

ROCKET AF	Rivaroxaban	Warfarin
$CHADS_2$ Mean	3.5	3.5
2 (%)	13	13
3 (%)	43	44
4 (%)	29	28
5 (%)	13	12
6 (%)	2	2

3+ 87%

ARISTOTLE	Rivaroxaban	Warfarin
$CHADS_2$ Mean	2.1	2.1
0-1 (%)	34	34
2 (%)	35.8	35.8
3+ (%)	30.2	30.2

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Comparison of Trial Metrics

	RE-LY	ROCKET AF	ARISTOTLE
Time in Therapeutic Range (TTR)	64% **67% warfarin-experienced** 61% warfarin-naïve	Mean 55% Median 58%	Mean 62% Median 66%

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Primary Endpoint of Stroke or Systemic Embolism: Non-inferiority Analysis

			Non Inferiorirty p vs warfarin
RE-LY			ITT Analysis
Dabigatran 110 mg	1.53% per year	HR = 0.91	p<0.001
Dabigatran 150 mg	1.11% per year	HR = 0.66	p<0.001
Warfarin	1.69% per year		
ROCKET AF			Modified ITT
Rivaroxaban 20mg	1.7% per year	HR = 0.79	p<0.001
Warfarin	2.2% per year		
ARISTOTLE			ITT Analysis
Apixaban 5 mg	1.27% per year	HR = 0.79	p<0.001
Warfarin	1.60% per year		

No ITT analysis is available for non-inferiority in Rocket AF. An on treatment or per-protocol analysis is generally performed in the assessment of non-inferiority. If numerous patients come off of study drug, this biases the trial towards a non-inferior result in an ITT analysis. This is the basis for performing a per-protocol analysis in a non-inferiority assessment.

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Hemorrhagic Stroke

		ITT HR	ITT P-value
RELY			
Dabigatran 110 mg	0.12% / yr	0.31	<0.001
Dabigatran 150 mg	0.10% / yr	0.26	<0.001
Warfarin	0.38% / yr		
ROCKET			
Rivaroxaban 20 mg	0.26% / yr	0.59	0.012*
Warfarin	0.44% / yr		
ARISTOTLE			
Apixaban 5 mg	0.24% / yr	0.51	<0.001
Warfarin	0.47% / yr		

*In an on treatment analysis in Rocket AF Hemorrhagic Stoke rates were 0.26% / yr for rivaroxaban and 0.44% / yr for warfarin, p=0.024. No on treatment analysis is available from RE-LY.

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Ischemic Stroke

		HR	ITT P-value
RELY			
Dabigatran 110 mg	1.34% / yr	1.20	0.35
Dabigatran 150 mg	0.92% / yr	0.76	0.03
Warfarin	1.20% / yr		
ROCKET			
Rivaroxaban 20 mg	1.62% / yr	0.99	0.92*
Warfarin	1.64% / yr		
ARISTOTLE			
Apixaban 5 mg	0.97% / yr	0.92	0.42
Warfarin	1.05% / yr		

*In an on treatment analysis in Rocket AF Ischemic Stoke rates were 1.34% / yr for rivaroxaban and 1.42% / yr for warfarin, p=0.58. No on treatment analysis is available from RE-LY.

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Major Bleeding

RE-LY

		HR	ITT P-value
Dabigatran 110 mg	2.71% / yr	0.8	0.003
Dabigatran 150 mg	3.11% / yr	0.93	0.31
Warfarin	3.36		

150 mg Dabigatran vs 110 mg Dabigatran = HR of 1.16 (1.00–1.34) p = 0.052

ROCKET

		On Treatment P-value
Rivaroxaban 20 mg	3.60% / yr	0.92	0.58*
Warfarin	3.45% / yr	2 g drop	

*There is no ITT analysis of safety in Rocket AF. There is no on treatment analysis of safety from RE-LY.

ARISTOTLE

		P-value
Apixaban 5 mg	2.13% / yr	0.69	<0.001
Warfarin	3.09% / yr	2 g drop in 24 hours	

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

All Cause Mortality

		HR	ITT p-value
RELY			
Dabigatran 110 mg	3.75% / yr	0.91	0.35
Dabigatran 150 mg	3.64% / yr	0.88	0.051
Warfarin	4.13% / yr		
ROCKET			
Rivaroxaban 20 mg	4.52% / yr	0.92	0.152*
Warfarin	4.91% / yr		
ARISTOTLE			
Apixaban 5 mg	3.52% / yr	0.89	0.01
Warfarin	3.94% / yr	95% CI 0.89 (0.80, 0.998) N=448 events planned, 480 in trial	

*In an on treatment analysis in Rocket AF mortality rates were 1.87% / yr for rivaroxaban and 2.21% / yr for warfarin, p=0.073. No on treatment analysis is available from RE-LY.

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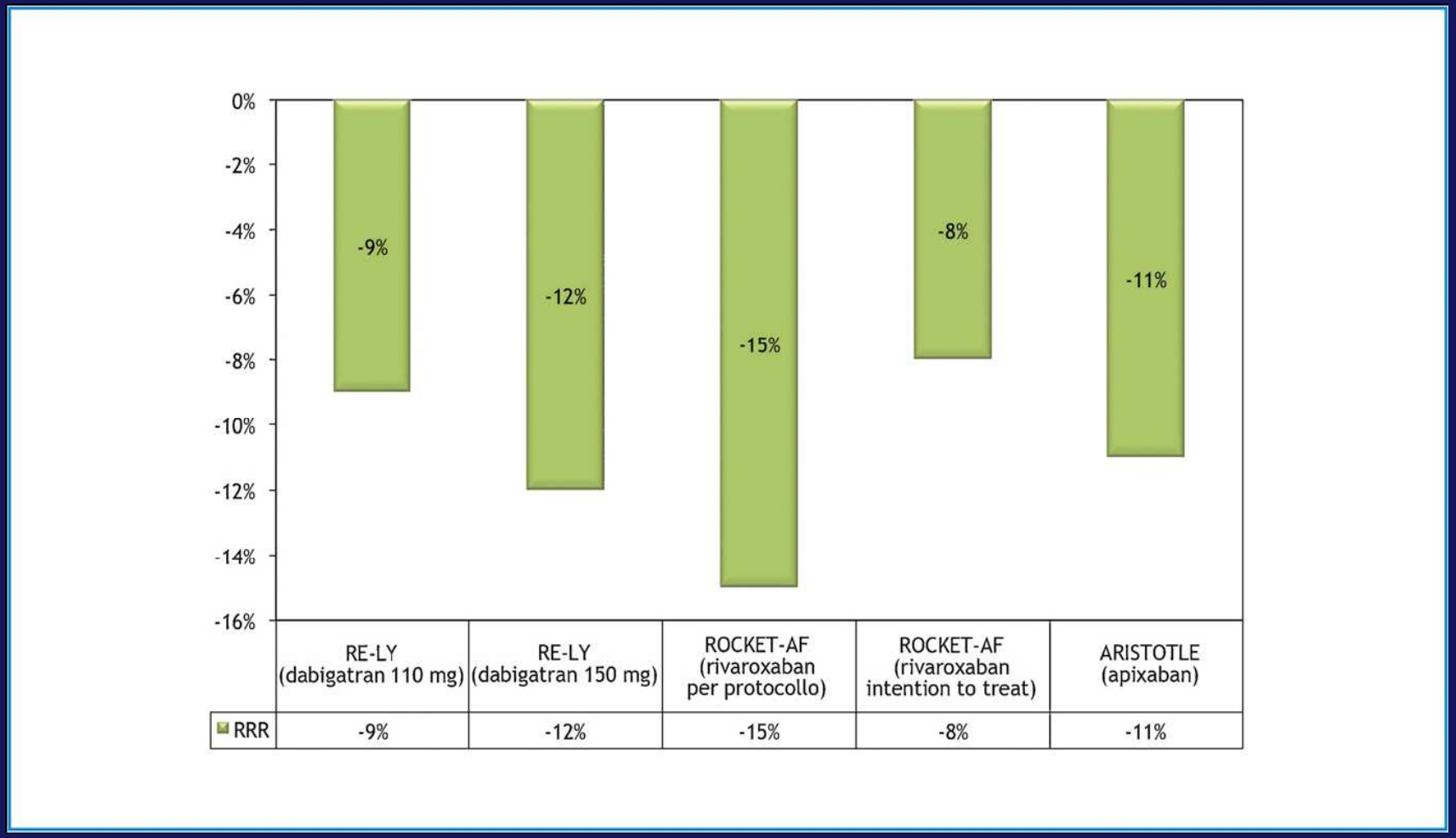
Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Efficacy and safety of new oral anticoagulants compared with warfarin in cardioembolic prophylaxis of patients with non valvular atrial fibrillation. More lights than shadows

Luca Masotti, Mario Di Napoli, Walter Ageno, Davide Imberti , Daniel Godoy, Grazia Panigada, Niccolo` Napoli , Giancarlo Landini , Roberto Cappelli, Ido Iori, Domenico Prisco, Giancarlo Agnelli

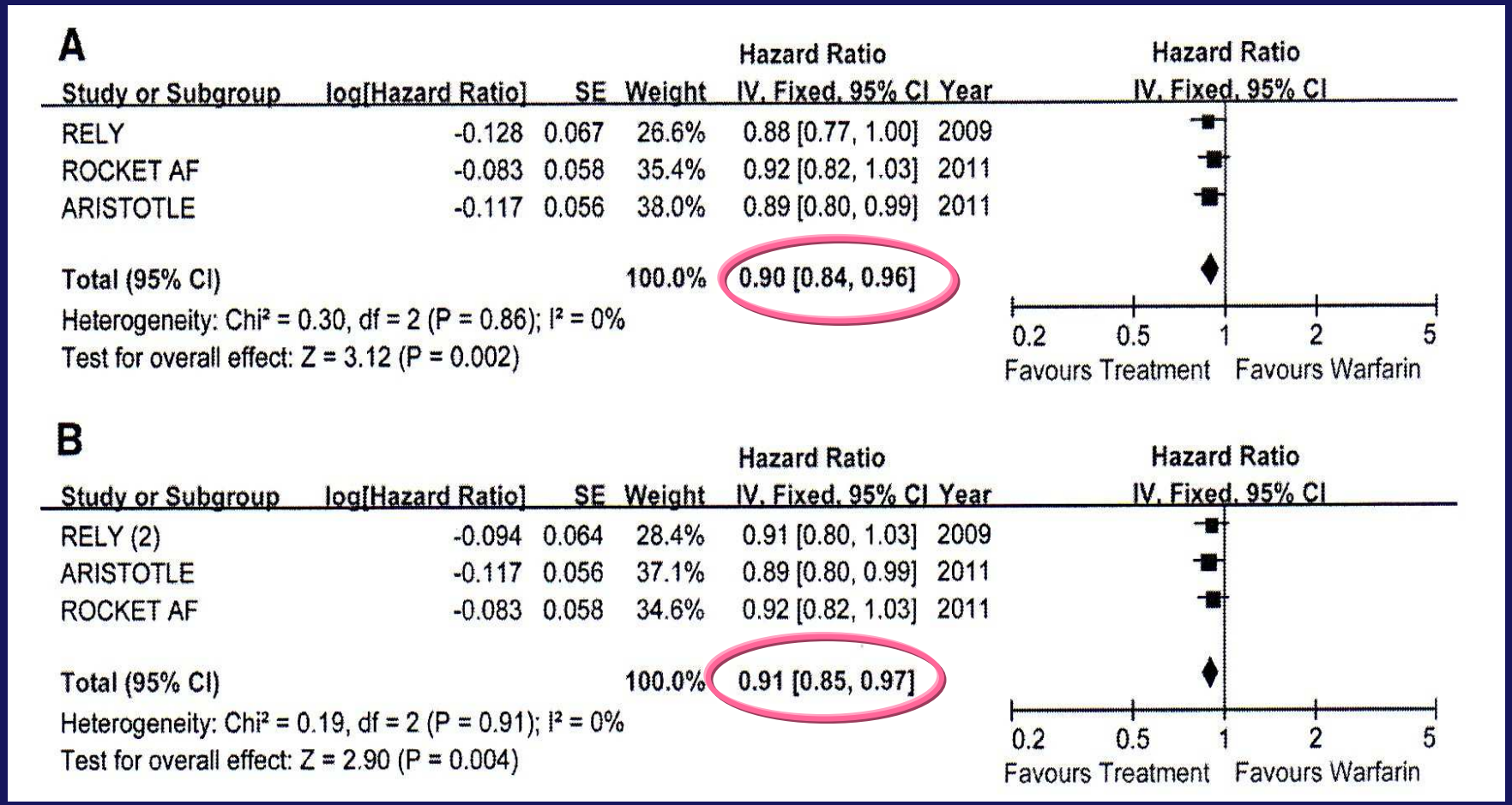
Masotti, Internal J Med, 2012

RRR della mortalità per tutte le cause rispetto al warfarin



Masotti, Internal J Med, 2012

Survival benefit of new anticoagulants compared witf warfarin in patients with AF: a meta-analysis



Liu, Int J Cardiol, 2012

Incidenza di emorragie digestive maggiori negli studi registrativi della FA con i NAO

	Emorragie gastrointestinali maggiori (% paz./anno)
Warfarin vs Dabigatran 110 mg/die	1.02 vs 1.12
Warfarin vs Dabigatran 150 mg/die	1.02 vs 1.51*
Warfarin vs Rivaroxaban	1.34 vs 2.04*
Warfarin vs Apixaban	0,86 vs 0,76

*P<0.001vs warfarin

Conclusions

Class Effects:

- **All three novel anticoagulants are non-inferior to warfarin in reducing the risk of stroke and systemic embolization.**
- **All three agents reduce the risk of bleeding (fatal for Rivaroxaban, major for Apixaban, major at 110 mg for Dabigatran) and intracranial hemorrhage.**
- **The directionality and magnitude of the mortality reduction is consistent and approximates a RRR of 10% / year**

Differentiators:

- **Dabigatran at a dose of 150 mg was associated with a reduction in ischemic stroke**
- **Rivaroxaban is a once a day drug associated with a lower rate of fatal bleeding**
- **Apixaban was associated with a reduction in all cause but not CV mortality**

ROCKET was a Higher Risk Patient Population

- **Whereas 30%-34% of patients in RE-LY / ARISTOTLE were low risk CHADS 0-1 patients, there were *none of these patients in Rocket AF***

- **Whereas 32% of RELY and 30% of ARISTOTLE patients had CHADS score of 3 or more, *87% of Rocket AF patients had a CHADS score of 3 or more***

- **Prior stroke TIA embolism was about 19-20% in RE-LY / ARISTOTLE and was 55% in ROCKET**

Variability in Trial Designs

- Blinding
- Risk of Patients (CHADS Score, prior stroke, age, % Vitamin K antagonist naïve)
- Interpretation of TTR data given variability in risk
- Varying application of ITT and modified ITT
- Timing of ascertainment of endpoint in relation to trial termination and drug discontinuation

CHADS Scores Differ Between Trials and Care Should be Taken in Comparing Them

- The CHADS Score is a nominal variable (like a name or a category) not an ordinal variable (in this case a CHADS score of 6 would be 6 times worse than a CHADS score of 1)
- Mean and Median CHADS scores should not be compared
- There are some trials where there are *no patients* in certain CHADS score categories and a mean or median value conceals this information

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Interpreting TTR Data

Cross Trial Comparisons of TTR are hampered by variations in:

- **CHADS Score:** Higher the CHADS score, lower the TTR. Sicker patients may have reduced access to frequent testing.
- **Age:** Older patients may have reduced access to frequent testing
- **CHF:** Varying drug clearance and distribution (CHF: 63% in ROCKET, 32% RELY, 35% ARISTOTLE)
- **Country:** Highest in Scandanavia, lowest in developing countries
  - What is the TTR in ROCKET AF in those countries who conducted RE-LY and vice versa (adjusting for the number of sites in each country)?
  - Should trials only be conducted in countries with a high TTR or should sponsors conduct real world trials throughout the world?

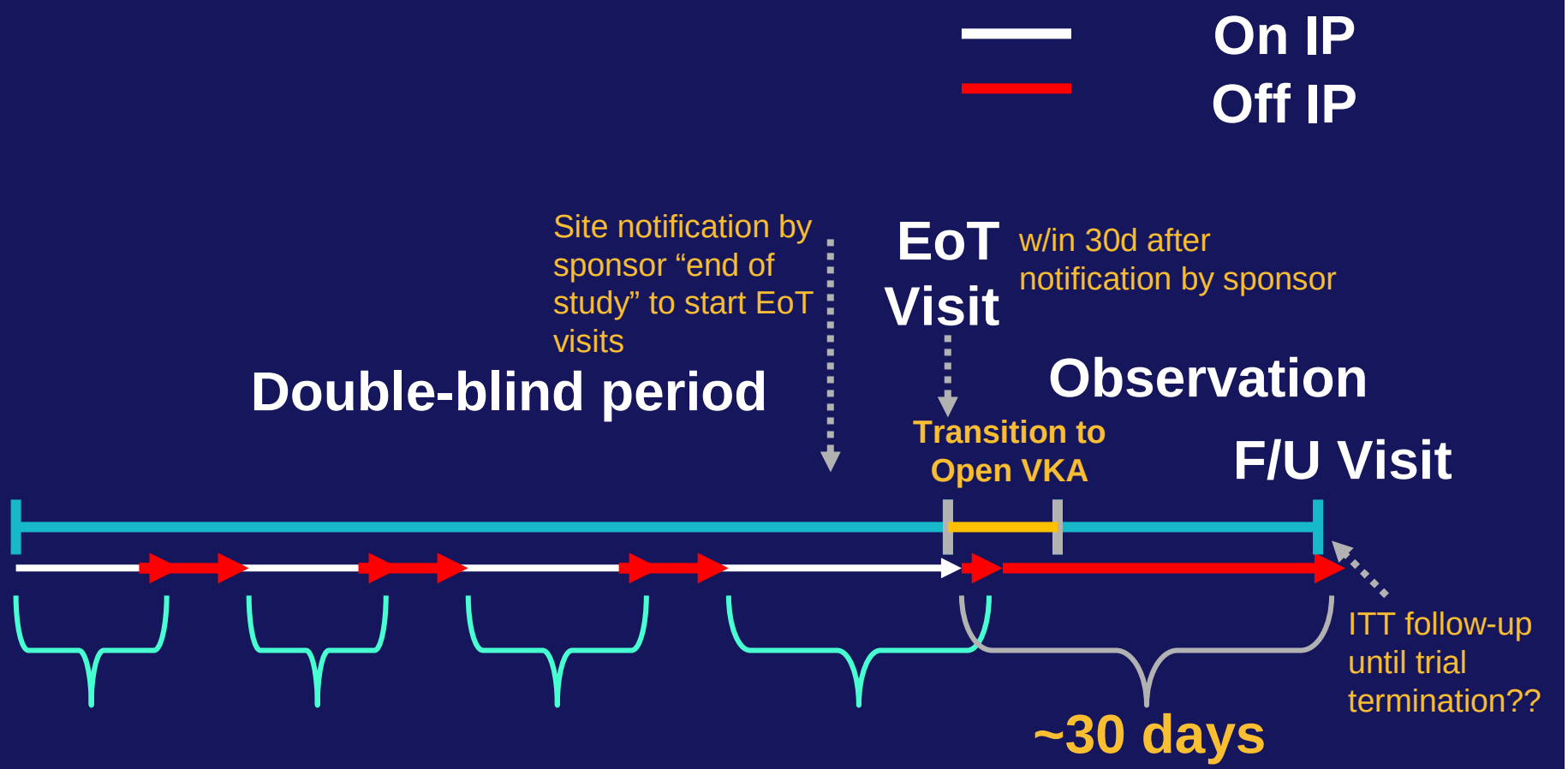
Baseline Characteristics and Centers' TTR

Center TTR	<58.0	58.0–65.7	65.7–72.2	≥72.2	P-value
Randomized	4538	4535	4533	4538	
TTR with warfarin	50.7%	62.5%	69.3	76.7	
Warfarin naive	57.4%	50.3%	35.4%	28.4%	<0.0001
Age (years, median)	68.0	69.0	71.0	72.0	<0.0001
Male	61.8%	61.8%	65.4%	70.1%	<0.0001
Weight (kg, median)	76.3	81.0	83.3	87.0	<0.0001
CHADS2 Score Mean	2.2	2.2	2.1	2.0	<0.0001
CHADS2 Score 3-6	32.6%	31.1%	30.0%	27.0%	<0.0001
Age ≥ 75 yr	24.0%	28.1%	33.1%	39.5%	<0.0001
Prior stroke	13.4%	12.0%	11.5%	9.8%	<0.0001
Heart failure	41.8%	36.5%	27.2%	16.4%	<0.0001
Diabetes mellitus	23.8%	23.9%	25.1%	27.0%	0.0011
Hypertension	86.2%	89.8%	88.1%	85.7%	<0.0001
Prior MI	12.6%	15.3%	13.0%	15.9%	<0.0001

Interpreting TTR Data: *Continued*

- **Prior Vitamin K Antagonism Increases TTR**: Vitamin K naïve 61% in TTR, vs 67% for prior vitamin K (RE-LY)
- **Open Label Design:** In an open design, MDs can make adjustments more frequently as there is no device required to perform the testing, patient may undertake testing closer to home and may undertake it more frequently
- **Was an algorithm used to adjust dose** or was this left to the discretion of the treating physician as in the "Real World"

Study Flow Diagram: Comparison of "On Treatment" vs. ITT



ROCKET: TTR included time on and off drug
ARISTOTLE and RELY included time on drug only

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

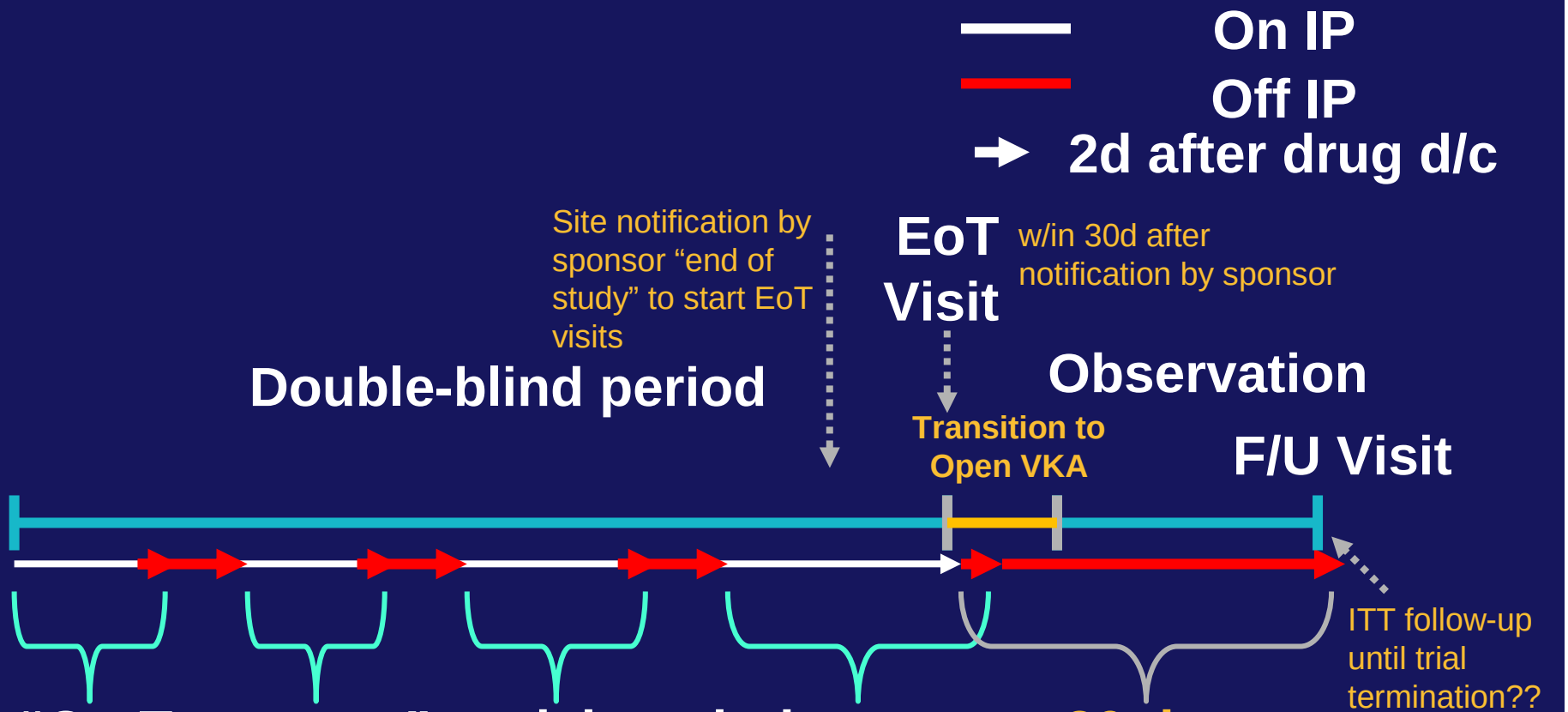
	Apixaban		Warfarin			
Center TTR (%)	E	Rate/100 person yrs	E	Rate/100 person yrs	HR (95% CI)	Adjusted Interaction
< 58.0	70	1.75	88	2.28	0.77 (0.56, 1.06)	0.29
58.0–65.7	54	1.30	68	1.61	0.80 (0.56, 1.15)	
65.7–72.2	51	1.21	65	1.55	0.79 (0.54, 1.13)	
> 72.2	36	0.83	44	1.02	0.81 (0.52, 1.26)	

What Are The Components of an ITT Analysis?

- Who is included in the Analysis: The ITT analysis includes all patients randomized to a therapy irrespective of protocol deviations, discontinuation of study drug, drug administration errors, cross-over to another strategy, or withdrawal from the study by the subject.

- How long were they followed for in the analysis? Were patients who discontinued drug followed through completion of the trial, or where they censored at the time of or shortly after drug discontinuation? What proportion of patients withdrew consent, and was their status imputed to the end of the trial (last observation forward) or were they censored at the time of consent withdrawal?

Study Flow Diagram: Comparison of "On Treatment" vs. ITT



Standardizing “ITT”

- Data should be provided to allow comparisons of trials that end using either a “Common Trial Censoring Date”, versus 2 days after the last dose, versus 30 days after last dose, versus the status at the last visit of the patient etc.
- There should be consistency in how data is handled for patients who discontinue study drug (should they be censored on the date of discontinuation, 2 days later, 30 days later, or should the last observation carried forward or should their status be ascertained at end of the study along with patients who remain on drug?)

Following Study Drug Discontinuation: Are There "Rebound" Events *or* a "Resumption" of Events?

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Questions for Future Trials

- Will investigators be willing to include patients in a Warfarin controlled trial when newer/better products become widley available?
- When will novel anticoagulants become the control arm?

What Will Be The Role of Factor II and Xa Reversal Agents?

Deaths Prompt Dabigatran Safety Advisory in Japan

August 17, 2011 Tokyo, Japan **-** The Japanese Ministry of Health, Labor, and Welfare has issued a safety advisory in that country warning of the potential for adverse events with dabigatran (Prazaxa in Japan; Pradaxa elsewhere, Boehringer Ingelheim), following the deaths of five patients. The advisory notes that there have been 81 cases of serious side effects, including gastrointestinal bleeding, since the launch of dabigatran;

The role (if any) of factor II and Xa reversal agents in reversing or minimizing is unclear

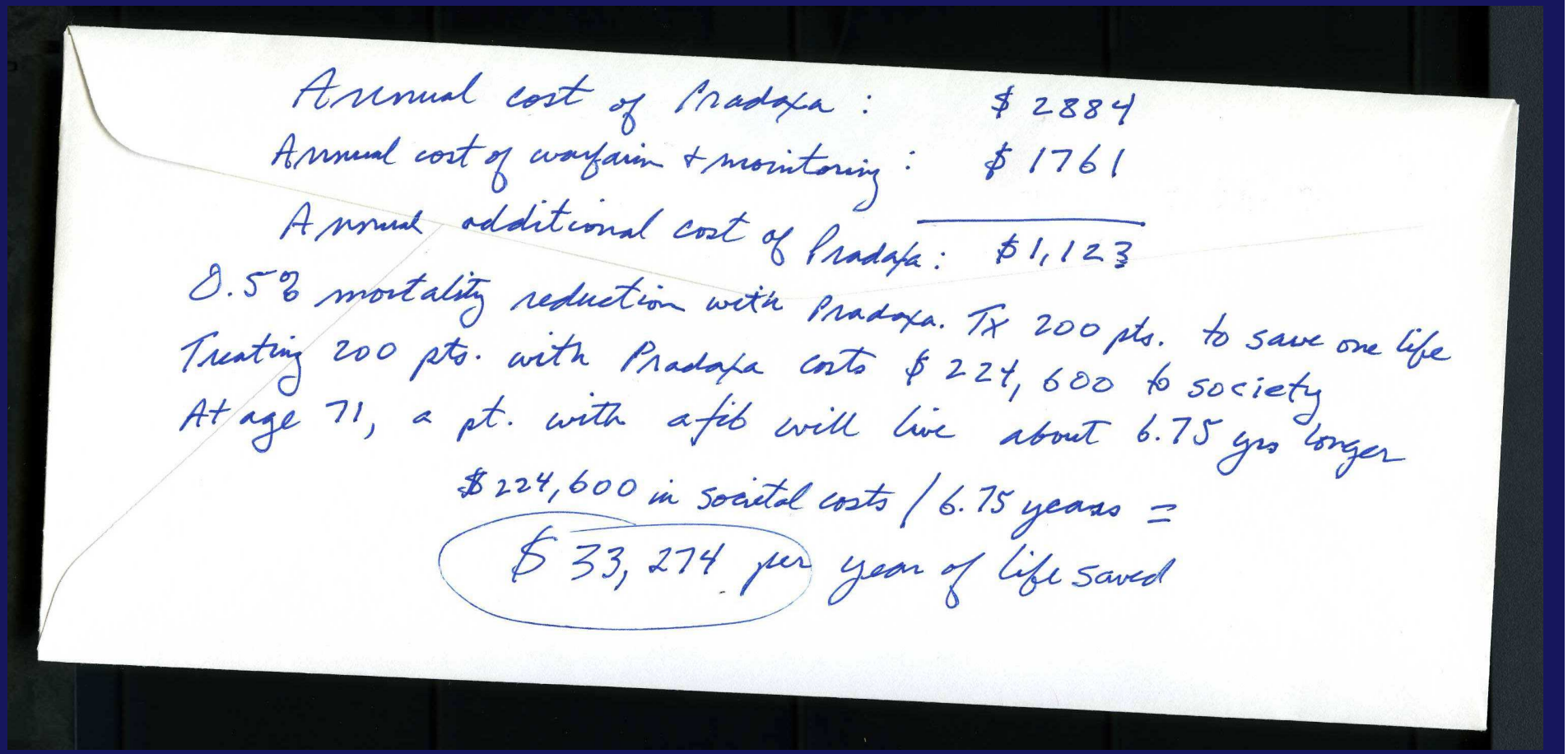
Regulatory approval will likely require a reduction in bleeding events rather than a reduction in bleeding biomarkers, and will require supportive data separately for each agent

NICE Guidance on Dabigatran Emphasizes Need for Cost-Effectiveness Data

Appraisal Committee's preliminary recommendations
1.1 The Committee is minded not to recommend the use of dabigatran etexilate for the prevention of stroke and systemic embolism in people with atrial fibrillation.

The manufacturer of dabigatran etexilate should provide the following for the second Appraisal Committee meeting:
A cost-effectiveness analysis of the sequential regimen outlined above, comparing dabigatran etexilate with warfarin using relative risks from the whole RE-LY trial population rather than from the post hoc subgroup analysis. The analysis should include sensitivity analyses using a range of assumptions of international normalised ratio (INR) monitoring costs such as those used by the Evidence Review Group (ERG) (£279.36, £241.54 and £115.14) in addition to the cost stated in the manufacturer's submission (£414.90).

A “Back of the Envelope” Assessment of the Potential Cost Effectiveness of Dabigatran (Pradaxa) in Non- Valvular Atrial Fibrillation



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. Cost-Effectiveness of Dabigatran Compared With Warfarin for Stroke Prevention in Atrial Fibrillation.

- The incremental cost-effectiveness ratios compared with warfarin was $45,372 per QALY for high-dose dabigatran.

Freeman JV et al. Cost-Effectiveness of Dabigatran Compared With Warfarin for Stroke Prevention in Atrial Fibrillation. Ann Intern Med. 2011 Jan 4;154(1):1-11. Epub 2010 Nov 1.

What Variables Were Used to Calculate the Cost of INR Monitoring?

- Variables included in estimating the cost of INR monitoring were:
  - The actual number of annual visits was used (average 16 visits)
  - The cost in an RNs time and a GPs time were calculated in each case
  - The cost of home testing was included (which was more expensive than office testing)
  - The cost of a patient who did not show up for an appointment was included
  - The cost of the laboratory staff in taking the blood sample
  - The cost of analyzing the sample
  - The sample transportation costs

  - Limitations:
  - Based on 2003 costs
  - Does not reflect costs of INR performed elsewhere outside of GP office
  - *Does not include patient transportation costs, or the societal costs of a patient's time off from work!*

Björholt et al, *BMC Family Practice* 2007, 8:6doi:10.1186/1471-2296-8-6. http://www.biomedcentral.com/1471-2296/8/6/

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How Much Is A Year of Life Worth?


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The Value of a Human Life: $129,000

By KATHLEEN KINGSBURY Tuesday, May. 20, 2008

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In theory, a year of human life is priceless. In reality, it's worth $50,000.

While estimates of what governments are willing to pay for are generally about $50,000 per year of life saved, hemodialysis costs approximately $129,000 per year of life saved.

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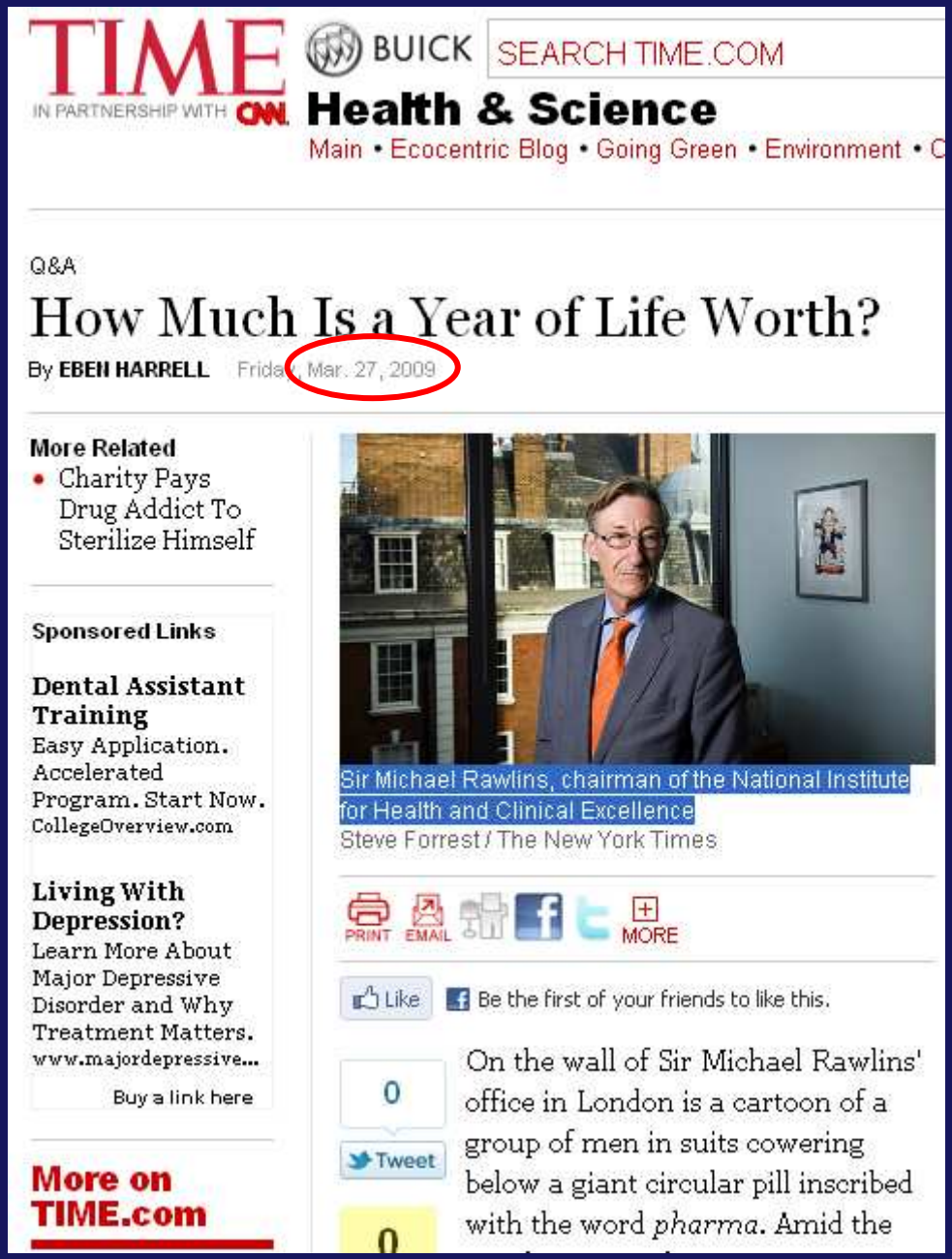
http://www.time.com/time/health/article/0,8599,1808049,00.html



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Q&A

How Much Is a Year of Life Worth?

By EBEN HARRELL Friday, Mar. 27, 2009

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On the wall of Sir Michael Rawlins' office in London is a cartoon of a group of men in suits cowering below a giant circular pill inscribed with the word *pharma*. Amid the

How Much Is A Year of Life Worth?

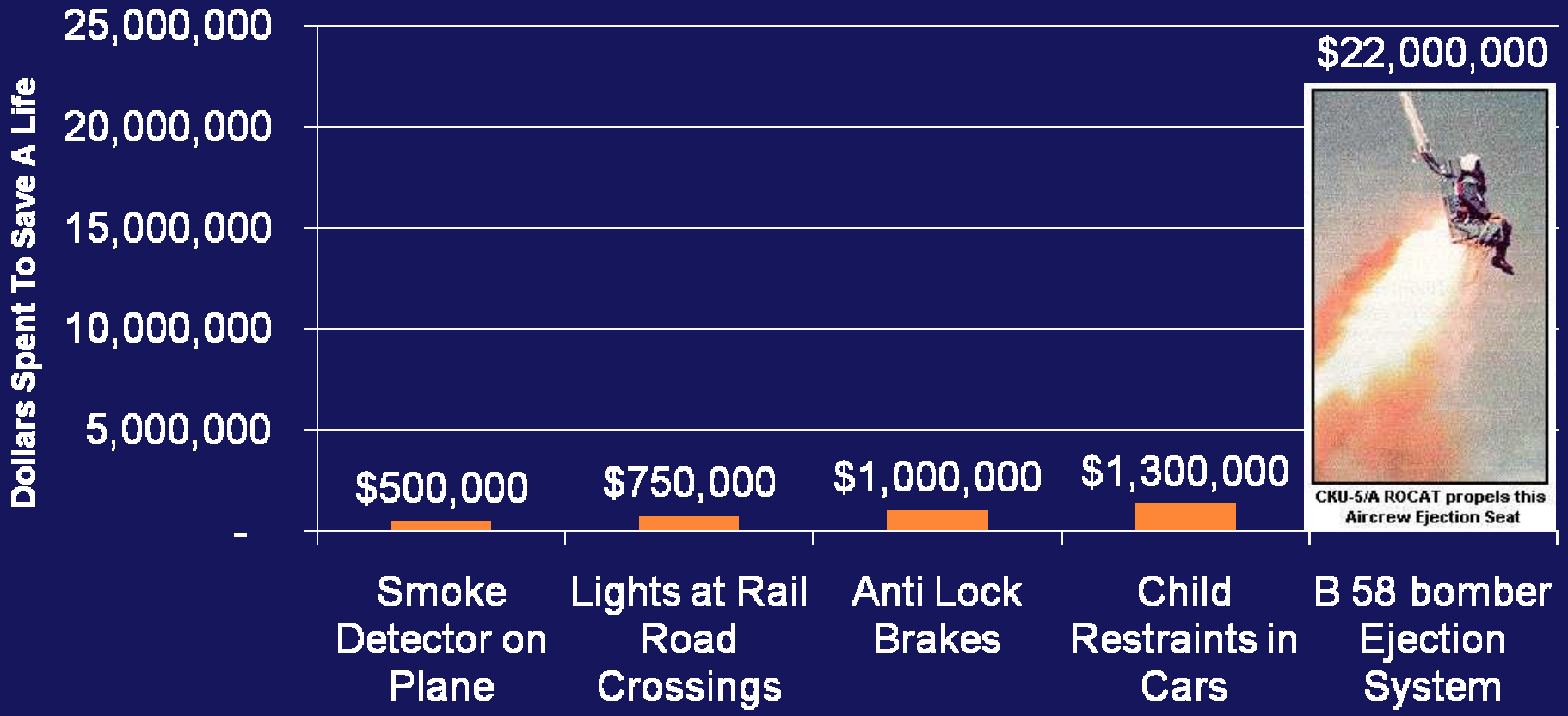
"Our Department of Transport, for instance, has a cost-per-life-saved threshold for new road schemes of about 1.5 million GBP per life, or around 30,000 GBP per life year gained. The judgment of our health economists is that somewhere in the region of 20,000-30,000 GBP ($31,600 USD to $47,400 USD) per quality-adjusted life year is the [threshold], but it's not a strict limit."

Sir Michael Rawlins

Chairman of the UK's NICE (National Institute for Health and Clinical Excellence)

http://www.time.com/time/health/article/0,8599,1888006,00.html#ixzz13Z0tUMuG

What Do We Spend In Society To Save A Life?



New York Times, **January 29, 1995, p. F3.**

http://www.cbe.wwu.edu/Krieg/Econ.%20Documents/how_much_for_a_life.htm

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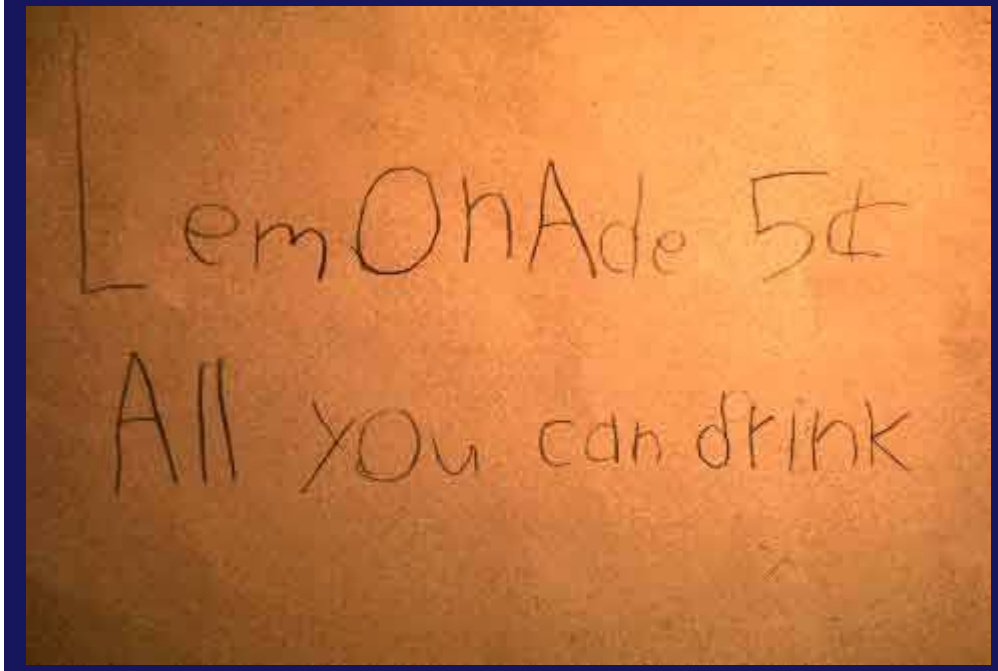
Cost Effectiveness: A Lesson From My Son's Lemonade Stand



Dad: I think I will have a glass of lemonade.
Son: Here you go.
Dad: That was good! I think I will have another one.
Son: You can't have another one.
Dad: But the sign says "all you can drink"
Son: That is what I am saying dad, that is all you can drink!

Let's make sure we have a clear societal understanding of "All you can drink"

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AVERROES: Factor Xa Versus Placebo in the Management of Atrial Fibrillation

RELY and ROCKET compared the safety and efficacy of novel agents to a Vitamin K antagonist

However, many patients are not suitable candidates for or are unwilling to receive vitamin K antagonist therapy, and these patients have a high risk of stroke.

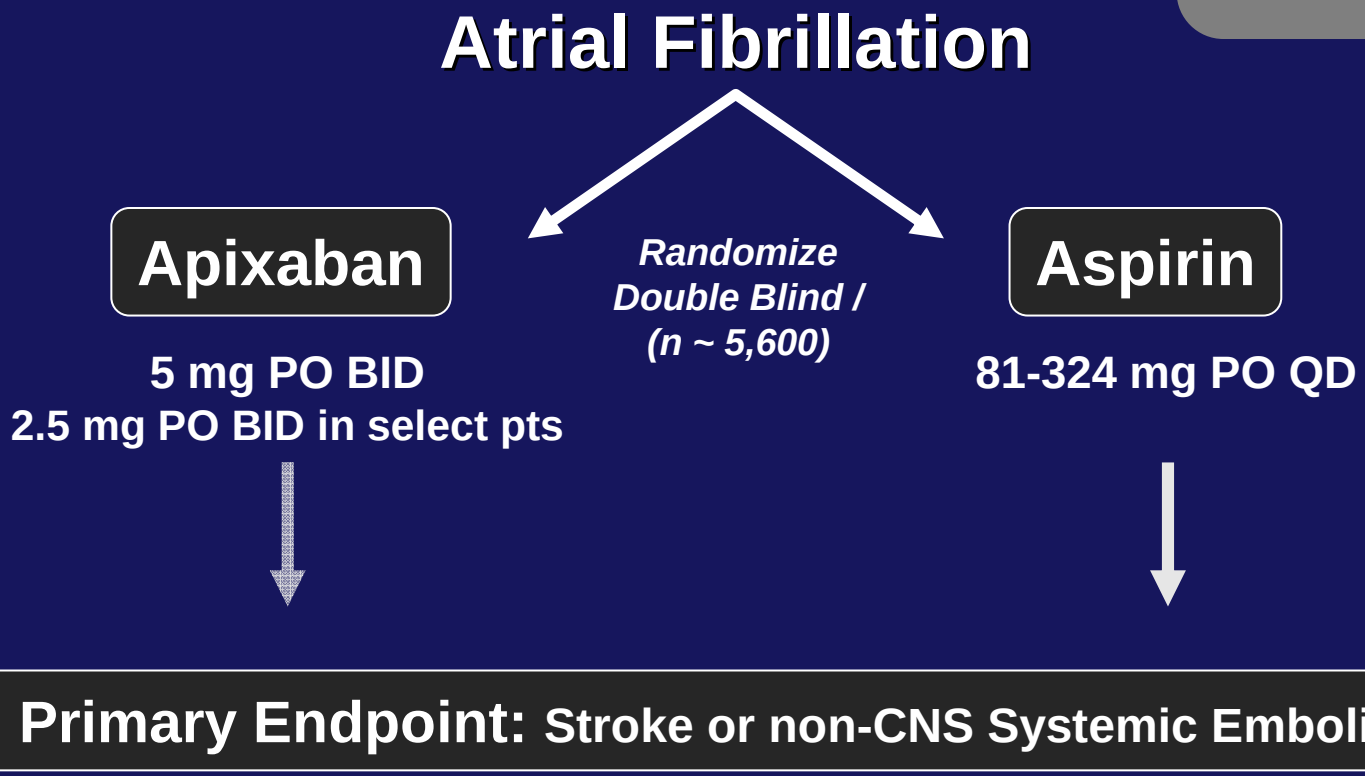
Apixaban, a novel factor Xa inhibitor, may be an alternative treatment for such patients.

Connolly SJ et al, N Engl J Med 2011; 364:806-817

AVERROES Study Design

≥ 1 Risk Factors

Expected or documented intolerance to warfarin



Connolly SJ et al, N Engl J Med 2011; 364:806-817

AVERROES: Baseline Characteristics

Characteristic	Apixaban	ASA
Randomized	2809	2791
Mean age (years)	70.0	70.0
Male (%)	59%	58%
CHADS2 score (mean) 0-1 (%) 2 (%) 3+ (%)	**2.1** **36%** **37%** **27%**	**2.1** **37%** **34%** **29%**
Prior stroke/TIA (%)	14%	13%
CHF (%)	40%	38%
Baseline ASA (%)	76%	74%
Unsuitable for VKA (%) VKA used and Dc'd VKA expected unsuitable	39% 61%	40% 60%

Connolly SJ et al, N Engl J Med 2011; 364:806-817

AVERROES: Primary Endpoint of Stroke or Systemic Embolism: Superiority Analysis

AVERROES		Superiority p vs ASA
		ITT Analysis
Apixaban 5 mg BID	1.6% per year	p<0.001
ASA 81-324 mg QD	3.7% per year	HR =0.45

AVERROES: Secondary Endpoint of Death: Superiority Analysis

AVERROES		Superiority p vs ASA
		ITT Analysis
Apixaban 5 mg BID	3.5% per year	p=0.07
ASA 81-324 mg QD	4.4% per year	HR =0.79

Connolly SJ et al, N Engl J Med 2011; 364:806-817

AVERROES: Safety Endpoint of Major Bleeding

		p vs ASA
AVERROES		
Apixaban 5 mg BID	1.4% per year	p<0.57
ASA 81-324 mg QD	1.2% per year	HR =1.13

AVERROES: Secondary Safety Endpoint of Intracranial Bleeding

		p vs ASA
AVERROES		ITT Analysis
Apixaban 5 mg BID	11 cases	p=NS
ASA 81-324 mg QD	13 cases	

Connolly SJ et al, N Engl J Med 2011; 364:806-817

AVERROES: Limitations

Only 7% of patients were treated with 324 mg of ASA

There is, however, no clear dose response curve for ASA in stroke prevention

ASA was the comparator in this trial; Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) compares Apixaban at a dose of 5 mg BID to Warfarin

Connolly SJ et al, N Engl J Med 2011; 364:806-817

AVERROES: Limitations

Among patients who cannot tolerate warfarin, and who are largely treated with aspirin doses < 324 mg, twice a day dosing of apixaban aspirinOnly 7% of patients were treated with 324 mg of ASA

There is, however, no clear dose response curve for ASA in stroke prevention

ASA was the comparator in this trial; Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) compares Apixaban at a dose of 5 mg BID to Warfarin

Disclosures

I would like to thank Dr. David Cohen and Matt Reynolds for critiquing the cost-effectiveness slides

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Consultant and Speaking Engagements
Angel Medical Systems; Atrium Medical Corporation; Bayer Corporation; Boehringer Ingelheim; ICON Medical Imaging; Johnson & Johnson Corporation; Merck; Portola Pharmaceuticals, Inc.; Sanofi-Aventis Pharmaceuticals; St. Jude Medical; The Medicines Company

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DABIGATRAN

- Evidenze della letteratura
- Cosa dicono le Linee Guida
- Aspetti pratici

Nuovi anticoagulanti: pratica clinica

- Monitoraggio laboratoristico
- Compliance
- “Reverse” dell’effetto anticoagulante
- Gestione complicanze emorragiche
- Gestione perioperatoria

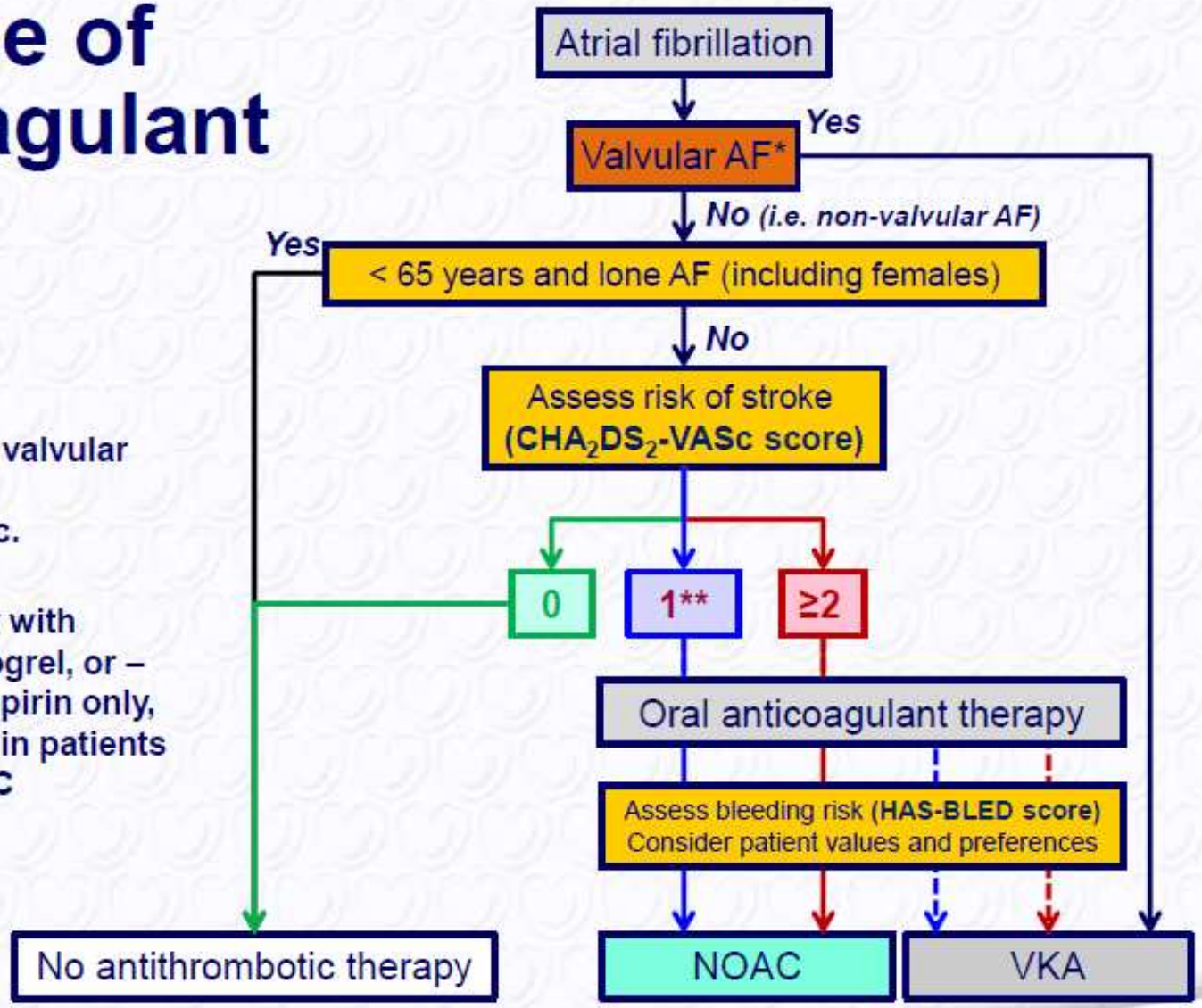
Indicazioni (e controindicazioni) al trattamento: a cosa fare attenzione

- Chi trattare (piani terapeutici?)
- Controindicazioni ufficiali
- Attenzione per età > 80 anni
- Affidabilità personale (compliance)
- Storia emorragica pregressa (con/senza AVK)
- Farmaci associati
- Funzione renale

La terapia anticoagulante nei pazienti con FA non-valvolare

- Evidenze della letteratura: la pratica clinica
- Evidenze delle letteratura: i nuovi anticoagulanti orali
- Cosa dicono le Linee Guida

Choice of Anti-coagulant



- Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or – less effectively – aspirin only, may be considered in patients who refuse any OAC

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Anticoagulation - General

Recommendations for prevention of thromboembolism in non-valvular AF - general		
Recommendations	**Class**	**Level**
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications.	I	A
The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.	I	A
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A

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Recommendations	Class	Level
In patients with a CHA2DS2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban …. is recommended, unless contraindicated.	I	A
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] …. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A

[d] = pending EMA/FDA approval – prescribing information is awaited

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Anticoagulation - General

Recommendations for prevention of thromboembolism in non-valvular AF - general		
Recommendations	**Class**	**Level**
When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or – less effectively – aspirin 75–325 mg daily.	**IIa**	**B**

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Anticoagulation - NOACs

Recommendations for prevention of thromboembolism in non-valvular AF - NOACs		
Recommendations	**Class**	**Level**
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)d … is recommended.	I	B
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)d … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A

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