October 16 - 18
14th EDITION 2015

Stroke Prevention In Non-Valvular AF
Efficacy vs Safety

Gianluca Botto, FESC
Elettrophysiology Unit , Dept. Medicine
Sant'Anna Hospital, Como - Italy

Friday 16 afternoon - Arazzi Room

12.30-14.00

Pfizer Luncheon Panel

The anticoagulation journey continues: the dilemma of thrombosis versus bleeding

Chairmen: **A. Raviele** / Venice-Mestre, Italy - **P. Simioni** / Padua, Italy

NOACs : pharmacological differences
A. Corsini / Milan, Italy

The clinical relevance of AMPLIFY programme
F. Dentali / Varese, Italy

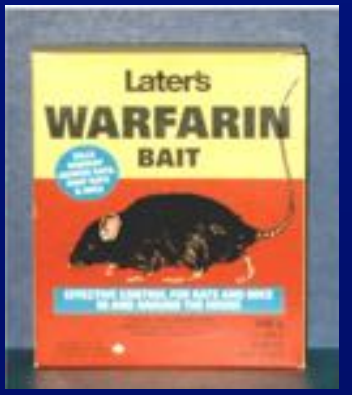
Stroke prevention in non valvular atrial fibrillation: efficacy vs safety
G.L. Botto / Como, Italy

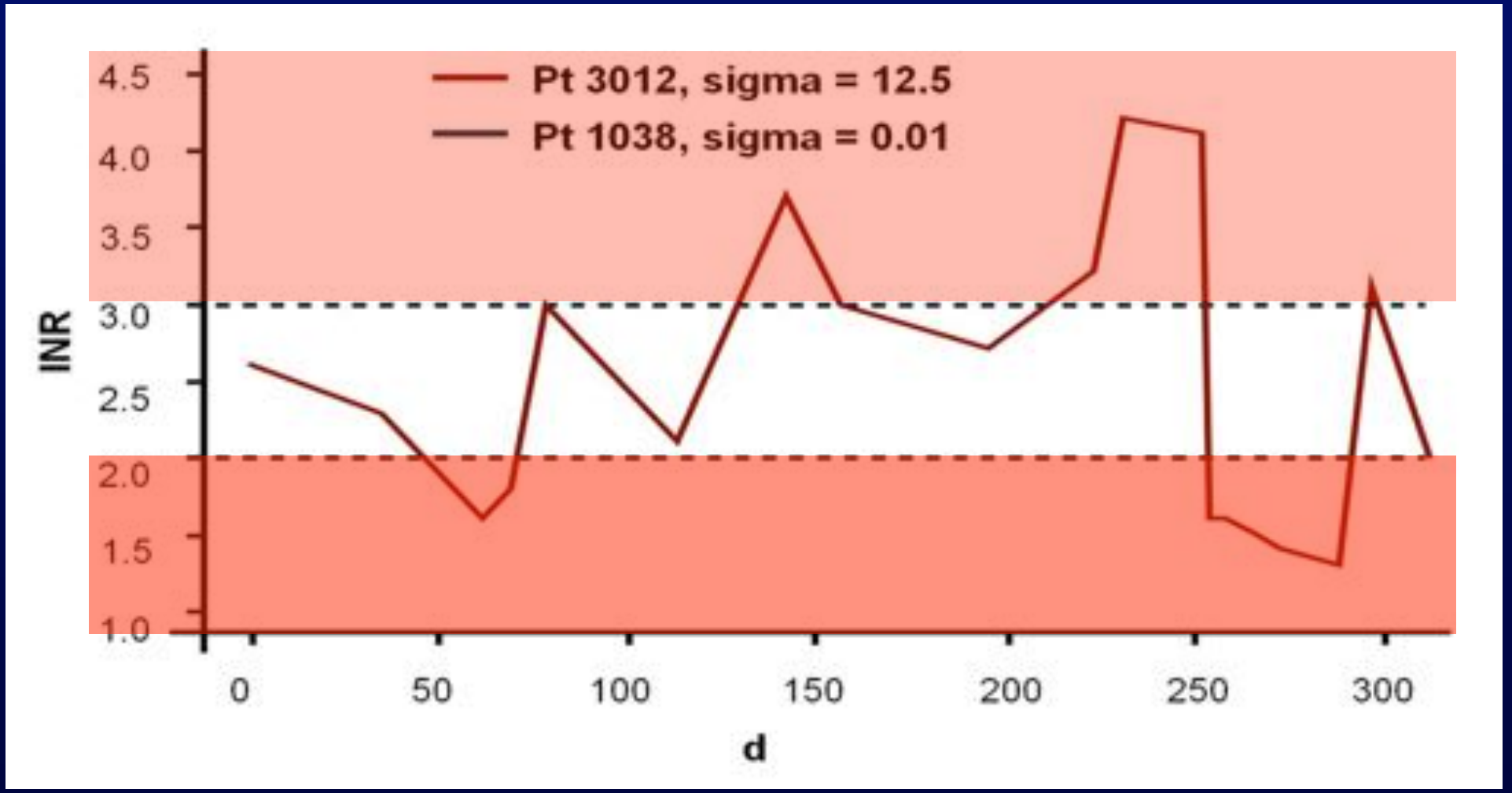
Challenging practical situations
A. Squizzato / Varese, Italy

Presenter Disclosure Information

- Research support:
  Boston Scientific, Medtronic; St. Jude Medical, Bayer Healthcare, Gilead, Sanofi
- Advisory Board:
  Biotronik, Medtronic; St. Jude Medical, Sorin Group, MSD, Bayer Healthcare, Boehringer, BMS/Pfizer, Sanofi
- Speaker Fees:
  Boston Scientific, Medtronic, St. Jude Medical, Sorin Group, Bayer Healthcare, Boehringer, BMS/Pfizer, Meda, MSD, Sanofi, Cardiome

Patient With High INR Variability



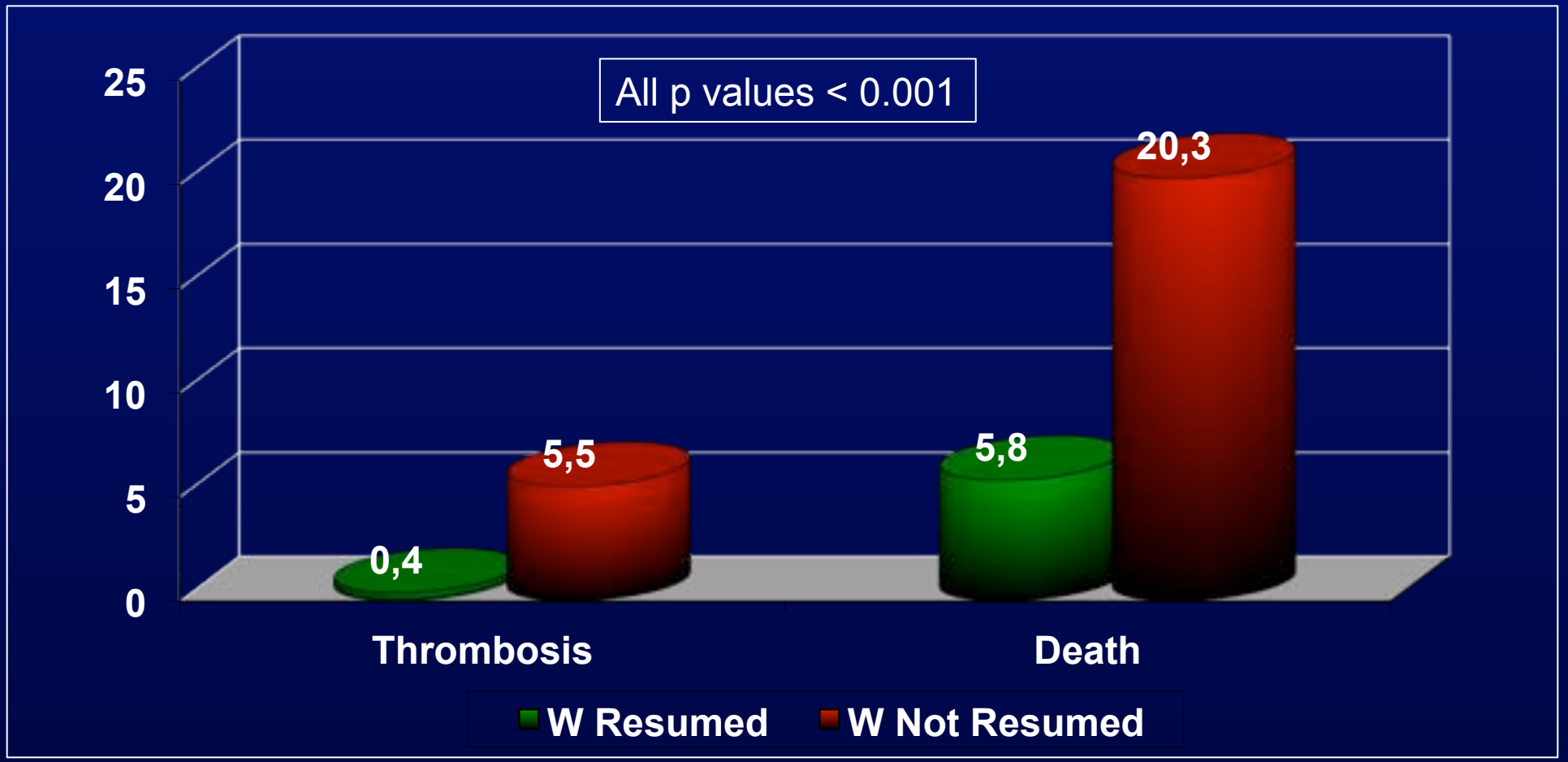


Hazards of Warfarin

Medication	Annual National Estimate of Hospitalizations (N = 99,628)		Proportion of Emergency Department Visits Resulting in Hospitalization
Most commonly implicated medications	no.	% (95% CI)	%
Warfarin	33,171	33.3 (28.0-38.5)	46.2
Insulins	13,854	13.9 (9.8-18.0)	40.6
Oral antiplatelet agents	13,263	13.3 (7.5-19.1)	41.5
Oral hypoglycemic agents	10,656	10.7 (8.1-13.3)	51.8
Opioid analgesics	4778	4.8 (3.5-6.1)	32.4
Antibiotics	4205	4.2 (2.9-5.5)	18.3

Budnitz DS. M Engl J Med 2011; 365: 2002-2012

Thrombosis After Ceasing Warfarin
Following GI Bleed



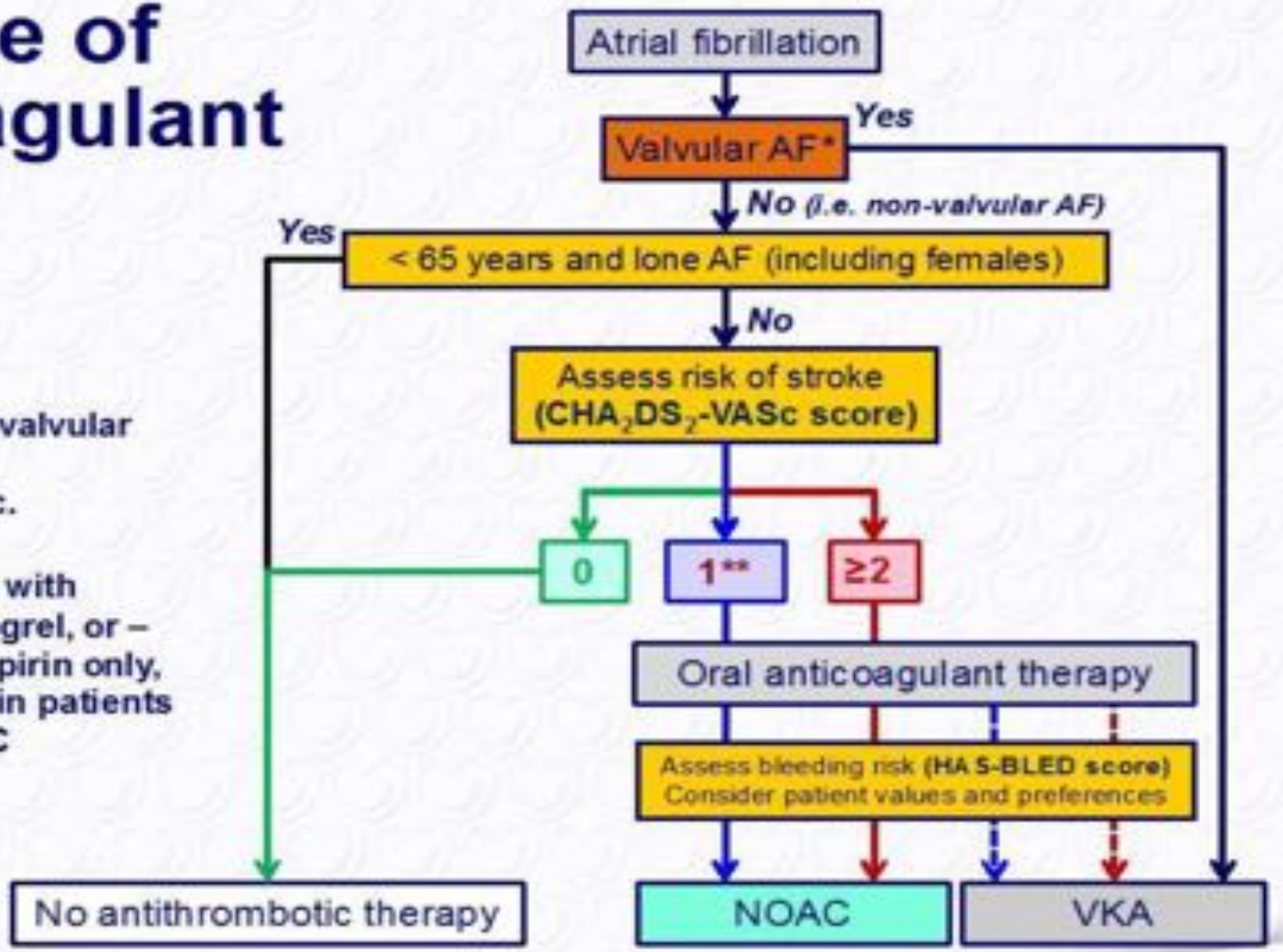
Witt DM. Arch Intern Med 2012; 172: 1484-91

Rationale of a Replacement for Warfarin in NV-AF

W is an effective agent for stroke prevention in NV-AF, however….

- Pts find frequent INR monitoring difficult
- Phisicians are reluctant to use W due to the increased risk for bleeds
- The potential for improvement in bleeding and possibly stroke prevention was seen with more targeted NOAC therapy

Choice of Anti-coagulant



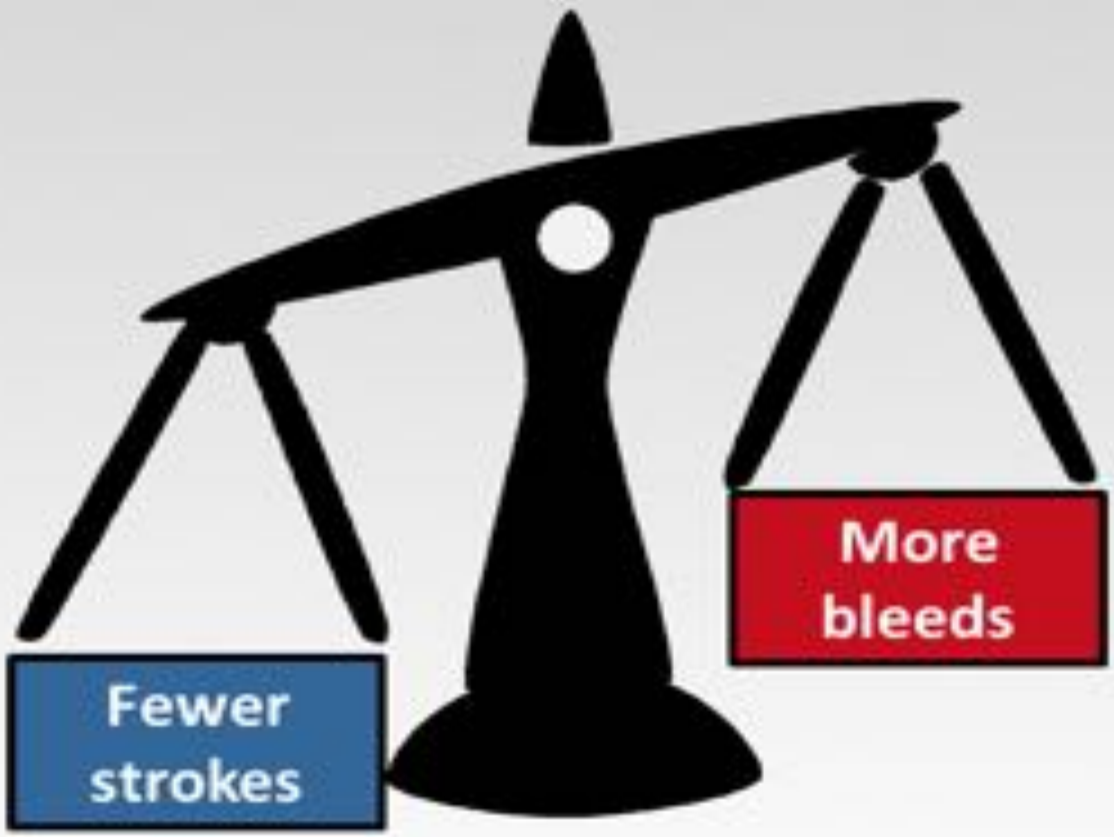
- Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

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

www.escardio.org/guidelines

European Heart Journal 2012;33:2719-2747 - doi:10.1093/eurheartj/ehs253

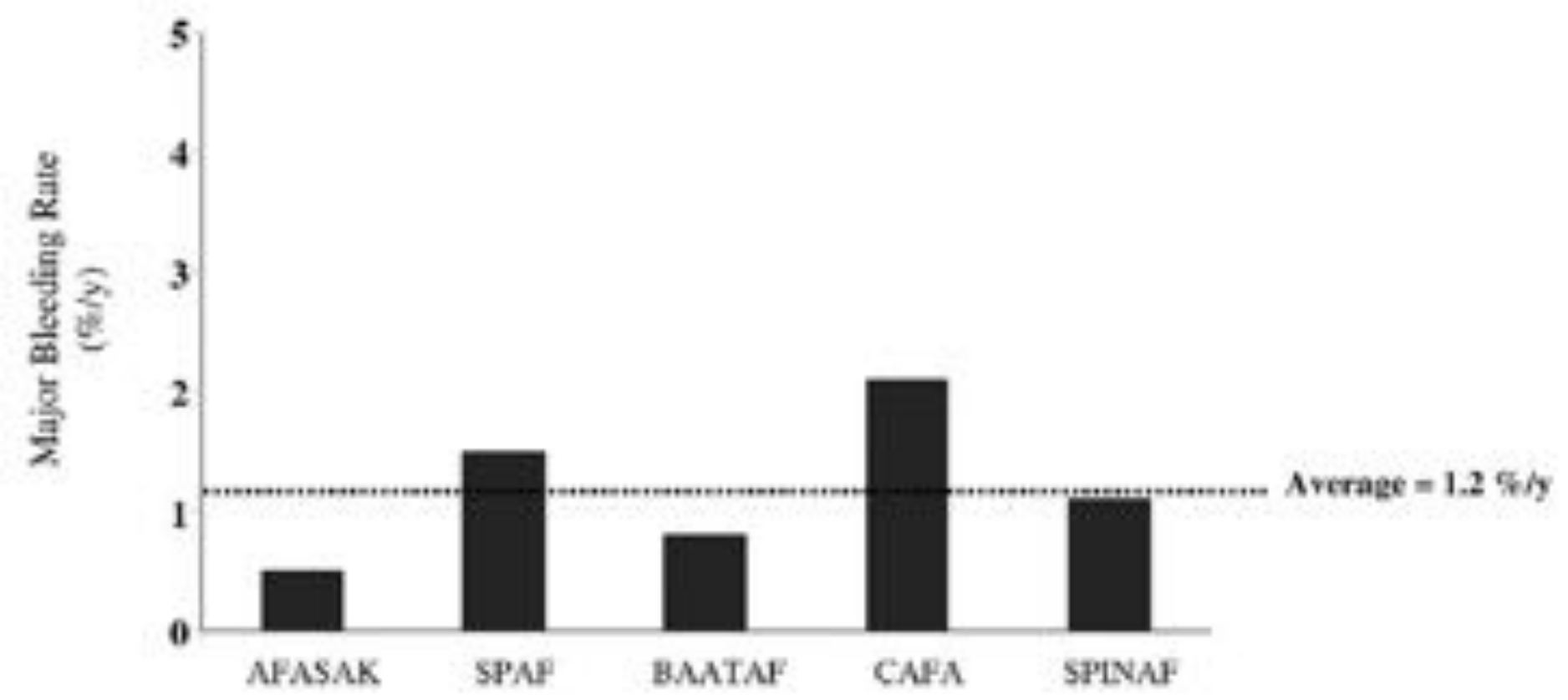
Optimizing Benefit and Reducing Risks



The net clinical benefit associated with a given therapeutic choice should guide this decision.

Anticoagulation In Pts With Non-Valvular AF

Annual Rates Of Major Hemorrhage with Warfarin



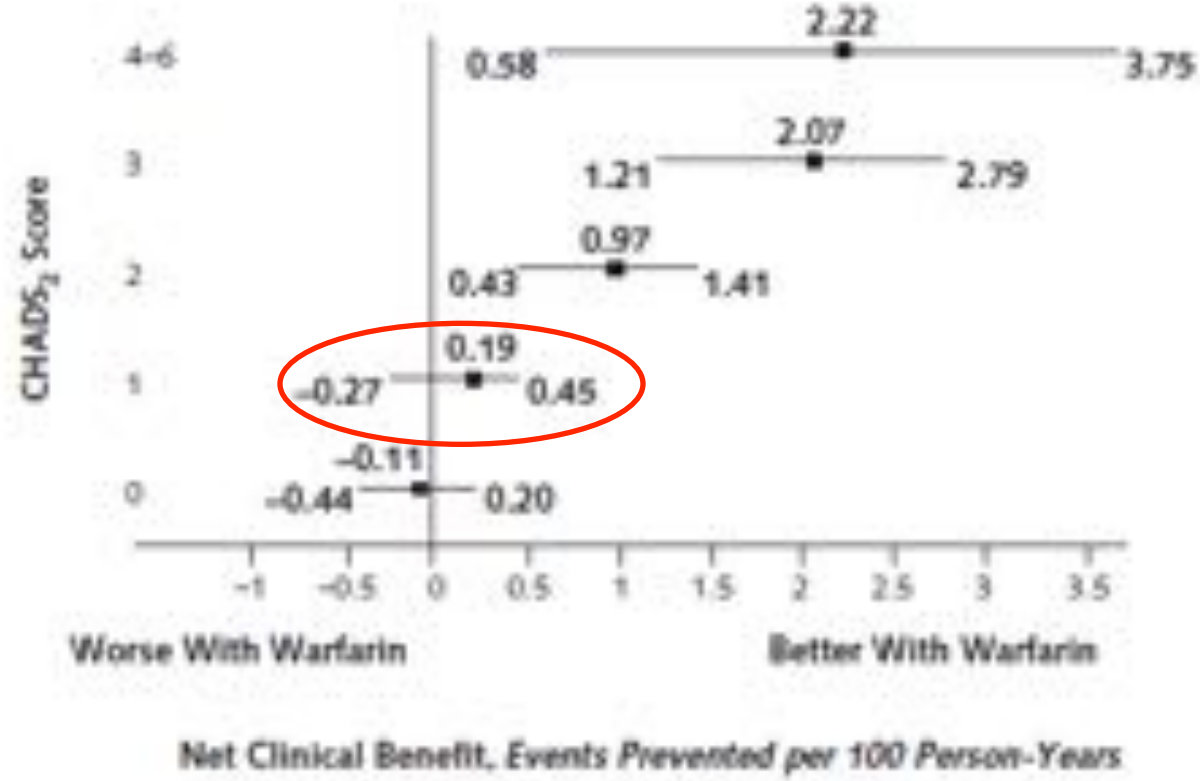
Fuster V. ACC/AHA/ESC Practice Guidelines 2006

Annals of Internal Medicine | ARTICLE

The Net Clinical Benefit of Warfarin Anticoagulation in Atrial Fibrillation

Daniel E. Singer, MD; Yuchiao Chang, PhD; Margaret C. Fang, MD, MPH; Leila H. Borowsky, MPH; Niela K. Pomernacki, RD; Natalia Udaltsova, PhD; and Alan S. Go, MD

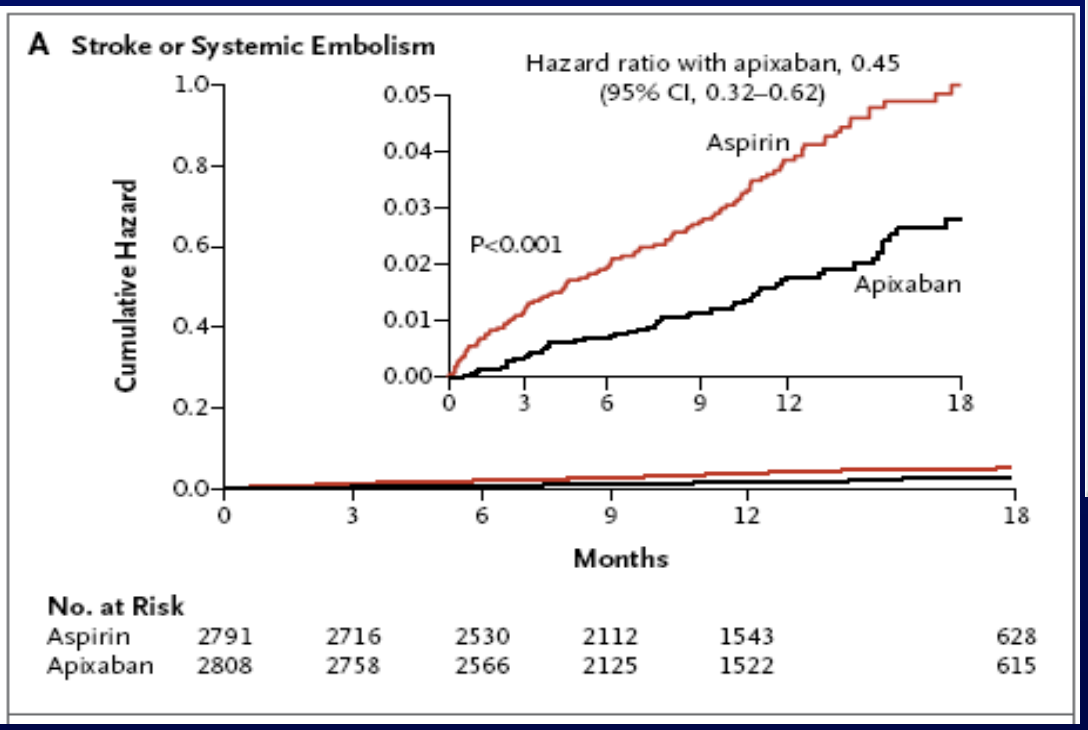
$CHADS_2$ annual stroke risk (%)	
4-6	≥8,5
3	5,9
2	4,0
1	2,8
0	1,9

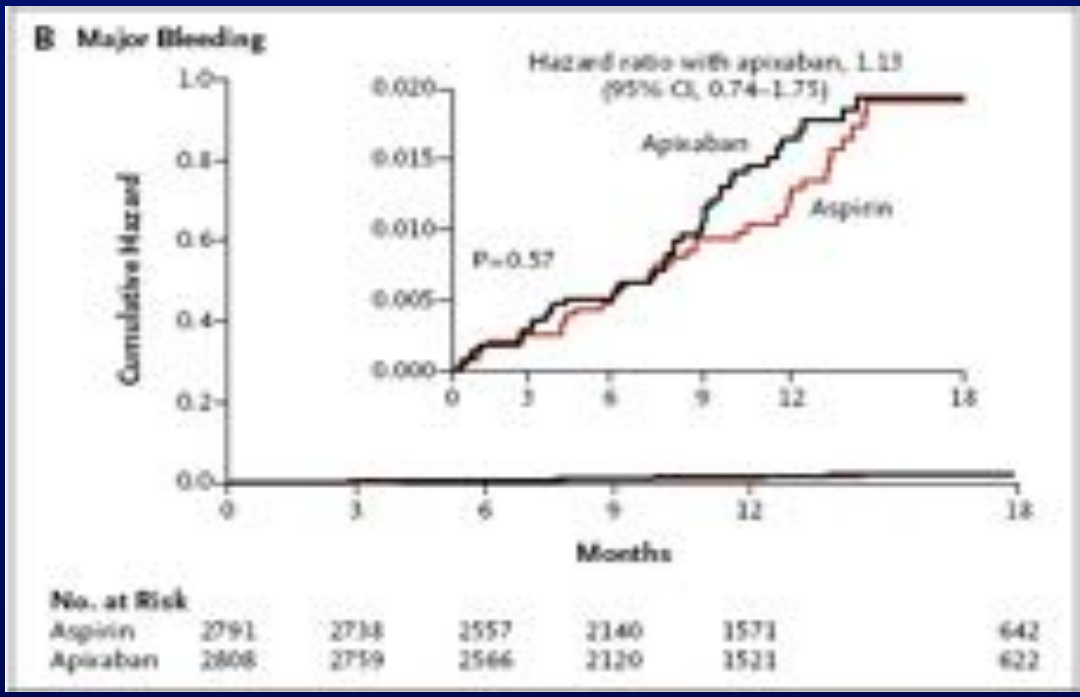


Ann Intern Med. 2009; 151: 297-305

AVERROES

Primary Efficacy and Safety Outcome





Connolly SJ. N Engl J Med 2011; 364: 806-17

Annals of Internal Medicine | ORIGINAL RESEARCH

Net Clinical Benefit of Adding Clopidogrel to Aspirin Therapy in Patients With Atrial Fibrillation for Whom Vitamin K Antagonists Are Unsuitable

Stuart J. Connolly, MD; John W. Eikelboom, MBBS; Jennifer Ng, MSc; Jack Hirsh, MD; Salim Yusuf, MD; Raffaele de Caterina, MD, PhD; Stefan Hohnloser, MD; and Robert G. Hart, MD, on behalf of the ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) Steering Committee and Investigators

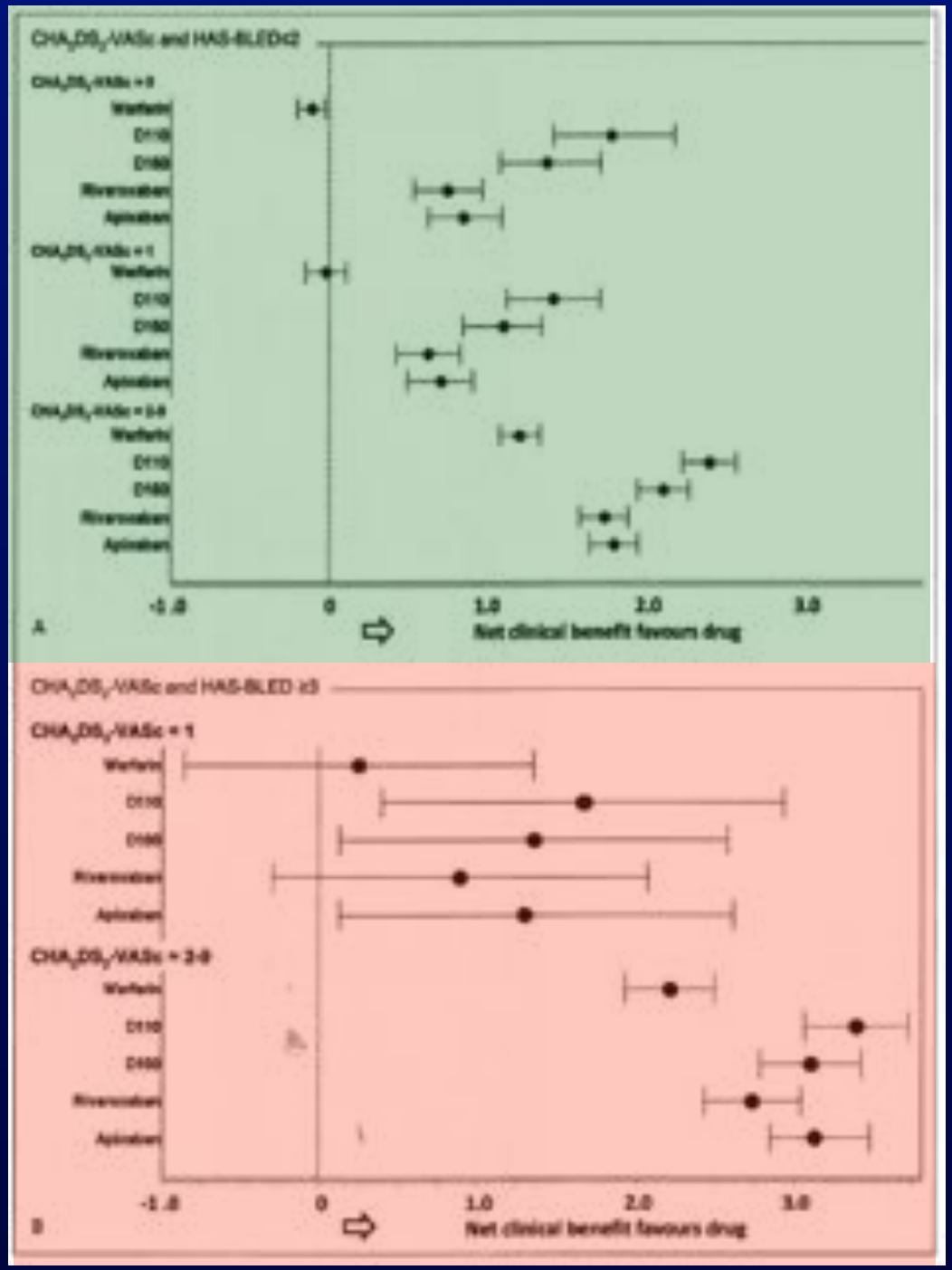
2011; 155: 579-586.

Endpoint	RR (95% CI)	P
All Strokes	0.72 (0.62-0.84)	< .001
Ischemic Stroke	0.68 (0.57-0.80)	< .001
Hemorrhagic Stroke	1.37 (0.79-2.37)	NS
Major Bleeding	1.57 (1.29-1.92)	< .001
Fatal Hemorrhage	1.56 (0.96-2.53)	.07

Net Clinical Benefit of Adding Clopidogrel to Aspirin Therapy in the ACTIVE A Trial, According to 3 Event-Weighting Systems and No Weighting*

Weighting System	Ischemic Stroke Equivalents (Rates per 100 Patient Years)		
	Aspirin Therapy Alone (95% CI)	Clopidogrel and Aspirin Therapy (95% CI)	Difference (95% CI)†
None‡	5.34 (4.86 to 5.77)	4.85 (4.47 to 5.31)	0.49 (−0.15 to 1.04)
Mortality	5.35 (4.66 to 6.06)	4.78 (4.00 to 5.65)	0.57 (−0.12 to 1.24)
Death or disability	5.04 (4.58 to 5.88)	4.37 (3.90 to 5.21)	0.67 (−0.03 to 1.18)
Singer and colleagues, 2009 (2)	3.50 (3.16 to 3.83)	2.76 (2.49 to 3.10)	0.74 (0.29 to 1.19)

Net Clinical Benefit for Warfarin and NOACs *by CHA_2DS_2-VASc and HAS-BLED Score*



Banerjee A.
Thrombosis Haemost
2012; 107: 584-589

Anticoagulation – General

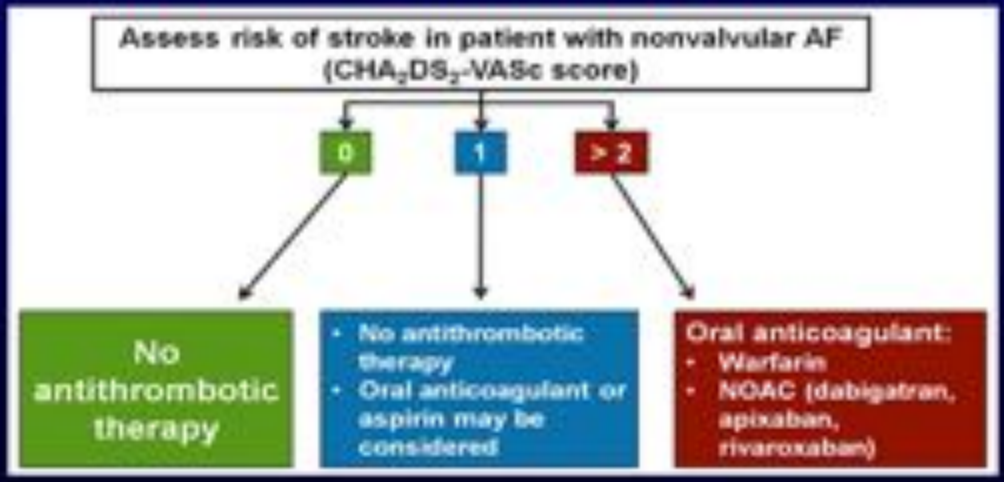
Recommendations	Class	Level
In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • 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)* ... should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A

* = pending EMA/FDA approval – prescribing information is awaited

European Heart Journal 2012;33:2719-2747 - doi:10.1093/eurheartj/ehs253

www.escardio.org/guidelines

2014 AHA/ACC/HRS Guidelines for the Management of Pts with AF



January CT. J Am Coll Cardiol 2014

Raccomandazioni AIAC Per La Terapia Antitrombotica Per La Riduzione Del Rischio Tromboembolico Nei Pazienti Con FA.

	Terapia antitrombotica raccomandata	Classe e livello di evidenza
CHA_2DS_2-VASc Score 0	Nessuna	I B
CHA_2DS_2-VASc Score 1	Warfarin (INR 2.0-3.0) o Dabigatran, Rivaroxaban, Apixaban	IIb B
CHA_2DS_2-VASc Score ≥2	Warfarin (INR 2.0-3.0) o Dabigatran, Rivaroxaban, Apixaban	I A

Linee Guida AIAC per la FA. Aggiornamento 2013. G Ital Cardiol 2013; 14: 215-40

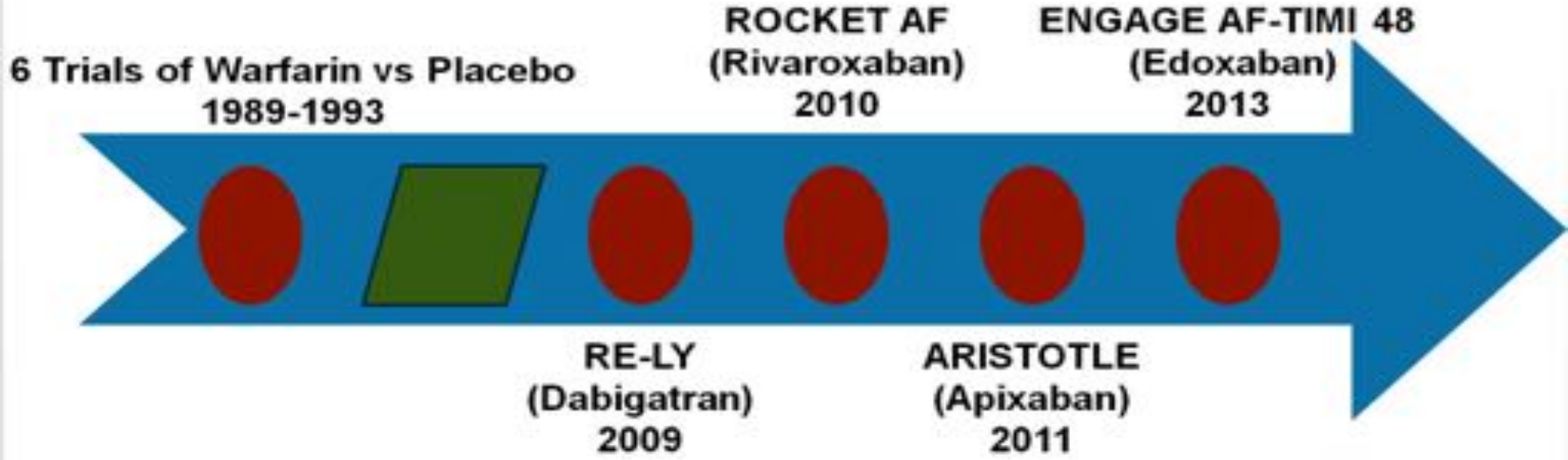
Although Stroke Is Generally More Feared By Patients, There Is A Strong Bias Among Physician Not To Cause Harm

Pivotal Warfarin-Controlled Trials
Stroke Prevention in AF

Warfarin vs Placebo
2,900 Patients

→

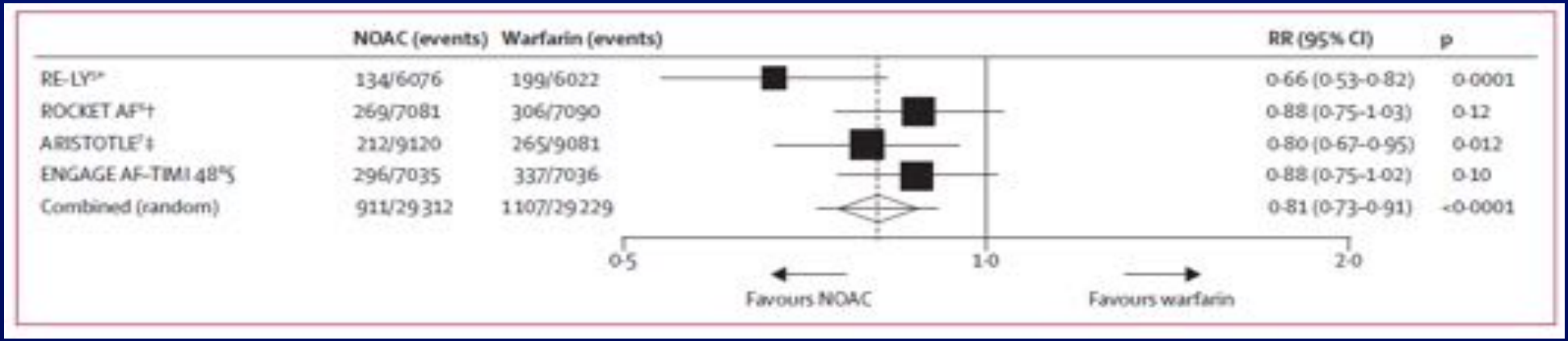
NOACs vs Warfarin
71,683 Patients



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

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

Published Online
December 4, 2013



- Allocation to a NOACs significantly *reduced the composite of stroke or systemic embolic events by 19% as compared to WRF*
- The overall beneficial effect was mainly driven by *a large reduction in haemorrhagic stroke*
  (RR on combined data: 0.49, 95%CI: 0.38-0.64, P<0.0001)
- *All-cause mortality was significantly reduced with NOACs vs. WRF*
  (RR: 0.90, 95%CI: 0.85-0.95, P=0.0003),
  while ischemic stroke and myocardial infarction were not

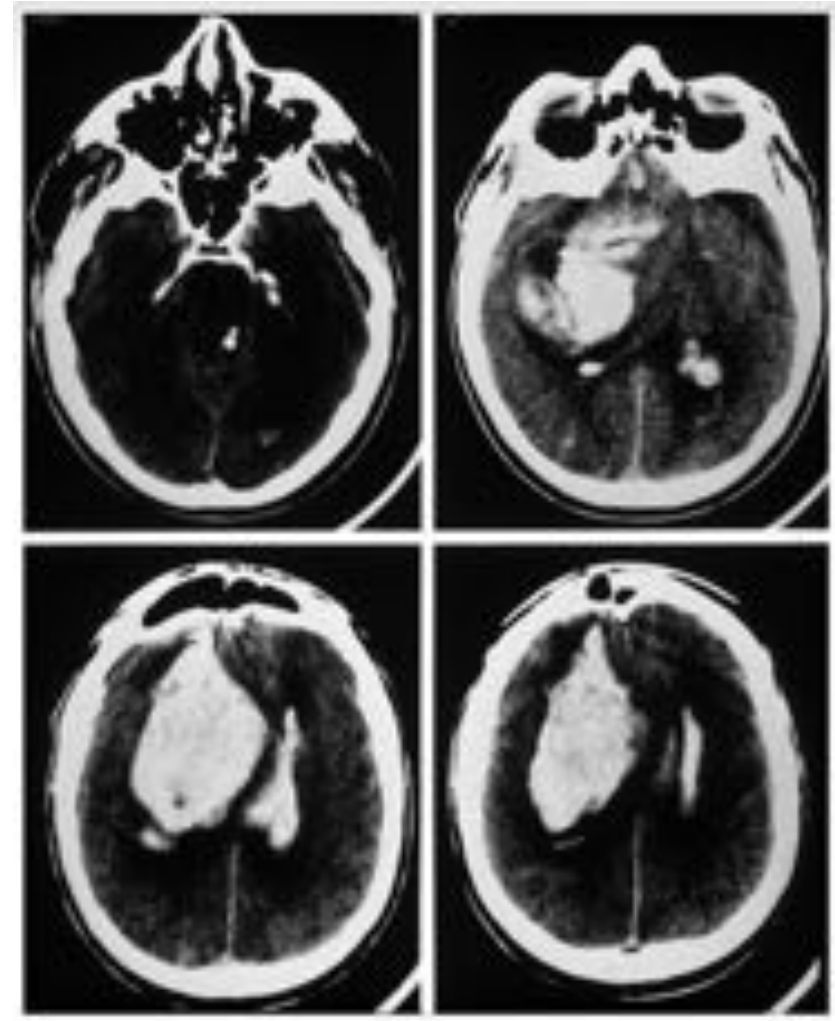
NOAC Intra-Cranial Haemorrage

Outcome vs Warfarin	RE-LY Dabigatran 150 mg BID HR (95% CI)	ROCKET-AF Rivaroxaban 20 mg OD HR (95% CI)	ARISTOTLE Apixaban 5 mg BID HR (95% CI)	ENGAGE-AF Edoxaban 60 mg OD HR (95% CI)
ICH	0.40 (0.27-0.60) P<0.001	0.87 (0.47-0.93) P<0.02	0.42 (0.30-0.58) P<0.001	0.47 (0.34-0.63) P<0.001

Stroke/Thromboembolism and Intracranial Hemorrhage in a Real-World AF Population

The Complications of Atrial Fibrillation in the Bologna Area (CAFBO) Study.

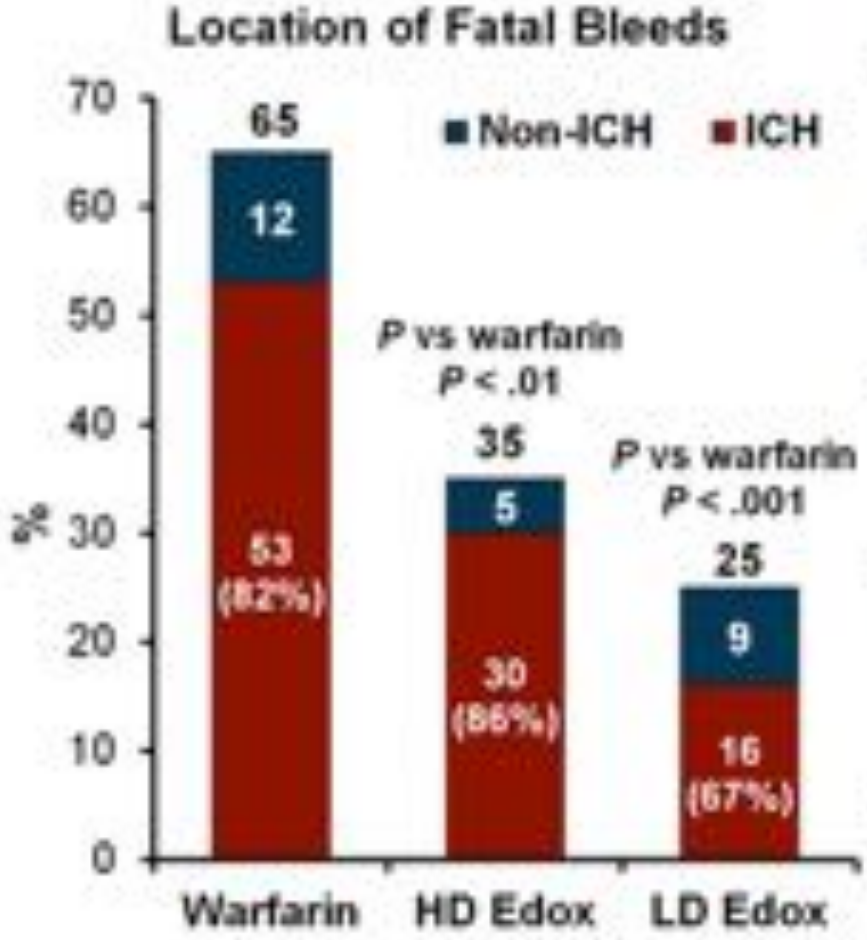
- 20 pts with ICH
  median age 82 ys
- W 65%, ASA 30%
- 95% in pts > 70 yrs
- **85% occur with an INR in 2.0-3.0 range**
- 45% in-H mortality
- 17% major deficit



Palareti G. CHEST 2014

ENGAGE-AF

Fatal Bleeding



- Intracranial hemorrhages
  - 73% Primary hem stroke
  - 16% Sub/epidural bleeds
- Both significantly ↑ warfarin

- Extracranial hemorrhages
  - 65% GI bleeds
  - 27% Retroperitoneal
- No differences by treatment

Time from Fatal Bleed to Death, d

	Warfarin	HD Edox	LD Edox
Median (IQR)	3 (2-5)	2 (1-7)	**5 (1-13)**

Giuliano RP. ESC Annual Meeting, Barcelona 2014 (abstract)

Intracerebral/Hemorragic Stroke and Mortality in SPAF

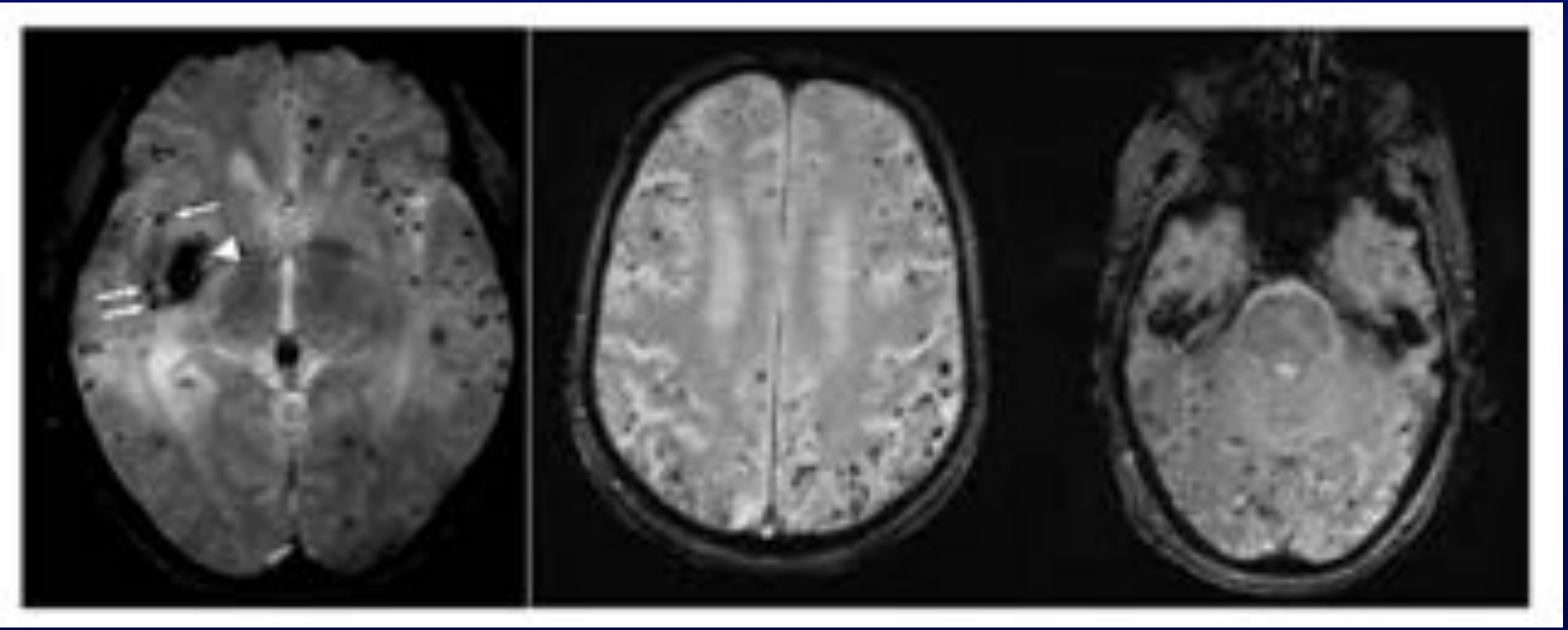
- ICH has a mortality rate of 40-50%
- Much worse than ischemic stroke, MI, GI bleed

NNT to prevent ICH vs Warfarin

Drug	NNT vs Warfarin (Median)
Dabigatran, 110 mg	29.32
Dabigatran, 150 mg	34.53
Rivaroxaban 20 mg	59.11
Apixaban 5 mg	35.07
Aspirin	39.60

Chatterrjee S. JAMA Neurol 2013; 70: 1486-90

Risk of ICH in Pts with Chonic Cerebral Microbleeds on Gradient Echo MRI



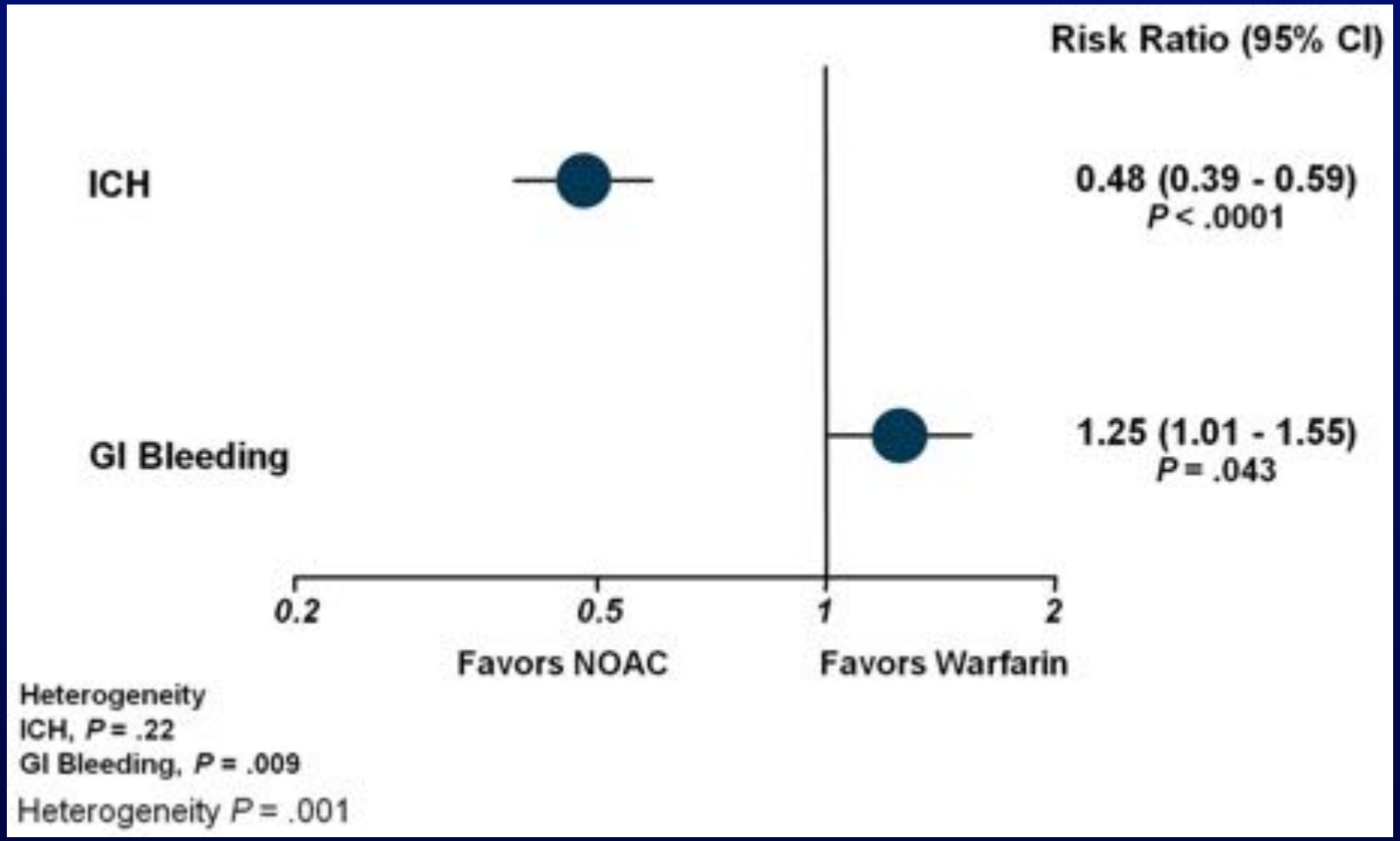
- 68% of spontaneous ICH
- Microbleeds increase the risk of Warfarin-associated ICH 12 fold

Van Etten ES. Stroke 2014: 45; 2280-2285

Reducing the Risk for ICH in SPAF Pts Receiving Anticoagulation Rx

- Assesses risk factors
- Aggressive risk factor reduction
- Do not add AP to anticoagulant unless pts has recently had a coronary stent deployed
- Switch from an AVK to a NAOC

Secondary Safety Outcomes



Ruff CT Lancet dec 2013 early on line pub modif

Safety With NOACs

What Does It Really Mean ?

- Ischemic stroke in AF is serious and devasting with a 24% 30-day mortality and severe disabling
- Intracranial haemorrage is even worse with a 30-day mortality as high as 46% in pts on WRF
- Mortality associated with GI bleeding is lower
  - *upper GI* *2,7%*
  - *lower GI* *2,9%*
  - *unspecifed* *3,6%*

Fang MC Stroke 2012; 43: 1795-99
El Tawil AM. Worl J Gastroenterl 2012; 18: 1154-58

Efficacy and Safety of the Novel Oral Anticoagulants in Atrial Fibrillation

A Systematic Review and Meta-Analysis of the Literature

Francesco Dentali, MD; Nicoletta Riva, MD; Mark Crowther, MD; Alexander G.G. Turpie, MD; Gregory Y.H. Lip, MD; Walter Ageno, MD

-Poor outcome

(30-day mortality = 48.6%)

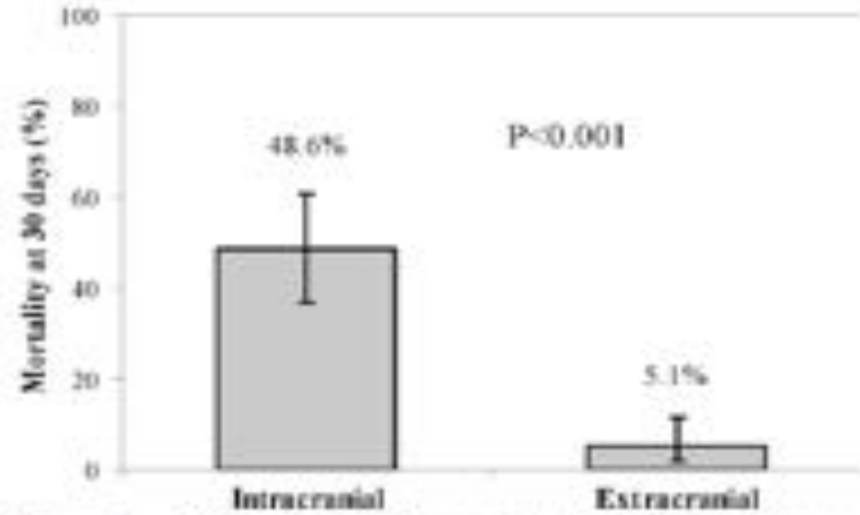


Figure 1 Risk of death 30 days after hospitalization for warfarin-associated intracranial hemorrhage versus major extracranial hemorrhage; 95% confidence intervals (CIs) (*vertical bars*). *P* value refers to the chi-square comparison of mortality rate of intracranial versus extracranial hemorrhage.

TABLE 4: Adjusted total incremental cost of ischemic stroke, intracranial hemorrhage, and other major bleeding events (2011 USD).

Matching characteristics	Ischemic stroke[1] Adjusted cost (95% CI)	Major bleeding events: ICH[2] Adjusted cost (95% CI)	Major bleeding events: Other major bleeds[2] Adjusted cost (95% CI)
Acute and annual costs			
Acute (quarter of event)	$22,204 ($21,699–$22,808)	$33,887 ($31,692–$36,868)	$16,437 ($16,056–$16,853)
Year 1	$34,772 ($33,691–$35,870)	$49,216 ($45,490–$53,431)	$25,442 ($24,700–$26,190)
Year 2	$6,186 ($4,964–$7,450)	$8,572 ($5,207–$12,206)	$7,193 ($6,342–$8,038)
Year 3	$4,504 ($3,383–$5,617)	$3,150 ($475–$5,764)	$5,852 ($5,010–$6,671)

ICH: intracranial hemorrhage; CI: confidence interval.

Note: multivariate adjusted costs were estimated using generalized estimating equation (GEE) models with a gamma distribution and log link function. Year 1 costs include acute costs incurred during the quarter of the event.

-High cost

(30% more than ischemic stroke)

(*Circulation*. 2012;126:2381-2391.)

NOACs Bleeding

Outcome vs Warfarin	RE-LY Dabigatran 150 mg BID HR (95% CI)	ROCKET-AF Rivaroxaban 20 mg OD HR (95% CI)	ARISTOTLE Apixaban 5 mg BID HR (95% CI)	ENGAGE-AF Edoxaban 60 mg OD HR (95% CI)
GI Bleeding	1.50 (1.19-1.89)	1.39 (1.19-1.61)	0.89 (0.70-1.15)	1.23 (1.02-1.50)
Major Bleeding	0.93 (0.81-1-07)	1.04 (0.90-1.20)	0.69 (0.60-0.80)	0.80 (0.71-0.91)

NOACs in Clinical Practice

Identifyng Pts with Increased Bleeding Risk

- Patient-related factors
  - *advanced age (≥80 ys)*
  - *low body weight (≤60 Kg)*
  - *renal impairment / fluctuation in renal function*
  - *GI-related comorbidities*
- Clinical Considerations
  - *examine creatinine clearance rates (not just serum creatinine)*
  - *use of antiplatelet Rx*

EHRA Practical GL. Europace 2013; 15: 625-651

Factors Linked to Raised Plama Concentrations of NOACs

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Other factors:					
Age ≥ 80 years	Increased plasma level		#	%	
Age ≥75 years	Increased plasma level			%	
Weight ≤ 60 kg	Increased plasma level		#		
Renal function	Increased plasma level	See Table 8			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs: NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Heidbuchel H. Europace 2015

EHRA Practical Guide Update Out Now !

EHRA PRACTICAL GUIDE

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

EUROPEAN Heart Rhythm ASSOCIATION

	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp competition	+12-60%	no PK data	+40%	minor effect (caution if CrCl 15-50 ml/min)
Digoxin	P-gp competition	no effect	no data yet	no effect	no effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	no effect	+40%	no data yet	minor effect (caution if CrCl 15-50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70-140% (do not co-administer)	no clear PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%	no data yet	+77% (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180% (reduce NOAC dose and take simultaneously)	no PK data	+53% (SR) (No dose reduction required by label)	minor effect (use with caution if CrCl 15-50 ml/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%	no data yet	no effect	no effect

Heidbuchel H. Europace 2015

NOAC Dose Reduction

RE-LY[a] Dabigatran	ROCKET AF[b] Rivaroxaban	ARISTOTLE[c] Apixaban	ENGAGE-AF[d] Edoxaban *
• None – US Regulators • CrCl 15-30 mL/min: 75 mg BID • Age > 80 years • CrCl 30-50 mL/min + P-gp inhibitor, dronedarone, or ketoconazole	• 20 → 15 mg OD for – Creatinine clearance < 30-49 mL/min	• 5 → 2.5 mg BID for ANY TWO of –Age ≥ 80 years –Body weight ≤ 60 kg –Serum creatinine ≥ 15 mg/dL • US Regulators – Strong dual inhibitors of CYP3A4 and P-gp	•60 → 30 mg OD or 30 → 15 mg OD for – Creatinine clearance 30-50 mL/min – Body weight ≤ 60 kg – Use of quinidine, verapamil, or dronedarone

BID = twice daily; OD = once daily
* not approved as of November 2014

a. Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151[4]; b. Patel MR, et al. *N Engl J Med*. 2011;365:883-891[5]; c. Granger CB, et al. *N Engl J Med*. 2011;365:981-992[6]; d. Giuliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.[7]

Dose Selection in Aristotle

Results

ARISTOTLE

	5 mg BID vs. Warfarin	2.5 mg BID vs. Warfarin
No dose-reduction criteria	13,356 (73.9	
One dose-reduction criterion	3,966 (	
• Creatinine only	90	
• Weight only		
• Age only	.1%)	
Two dose-reduction criteria		733 (4.1%)
• Weight, creatinine		51 (0.3%)
• Age, creatinine		225 (1.2%)
• Age, weight		457 (2.5%)
Three dose-reductio ria		18 (0.1%)
• Age, weight, creatinine		

Bleeding in ARISTOTLE was NOT really driven by a low-dose group

Duke Clinical Research Institute

Alexander JH. ESC Meeting, London 2015

UCR

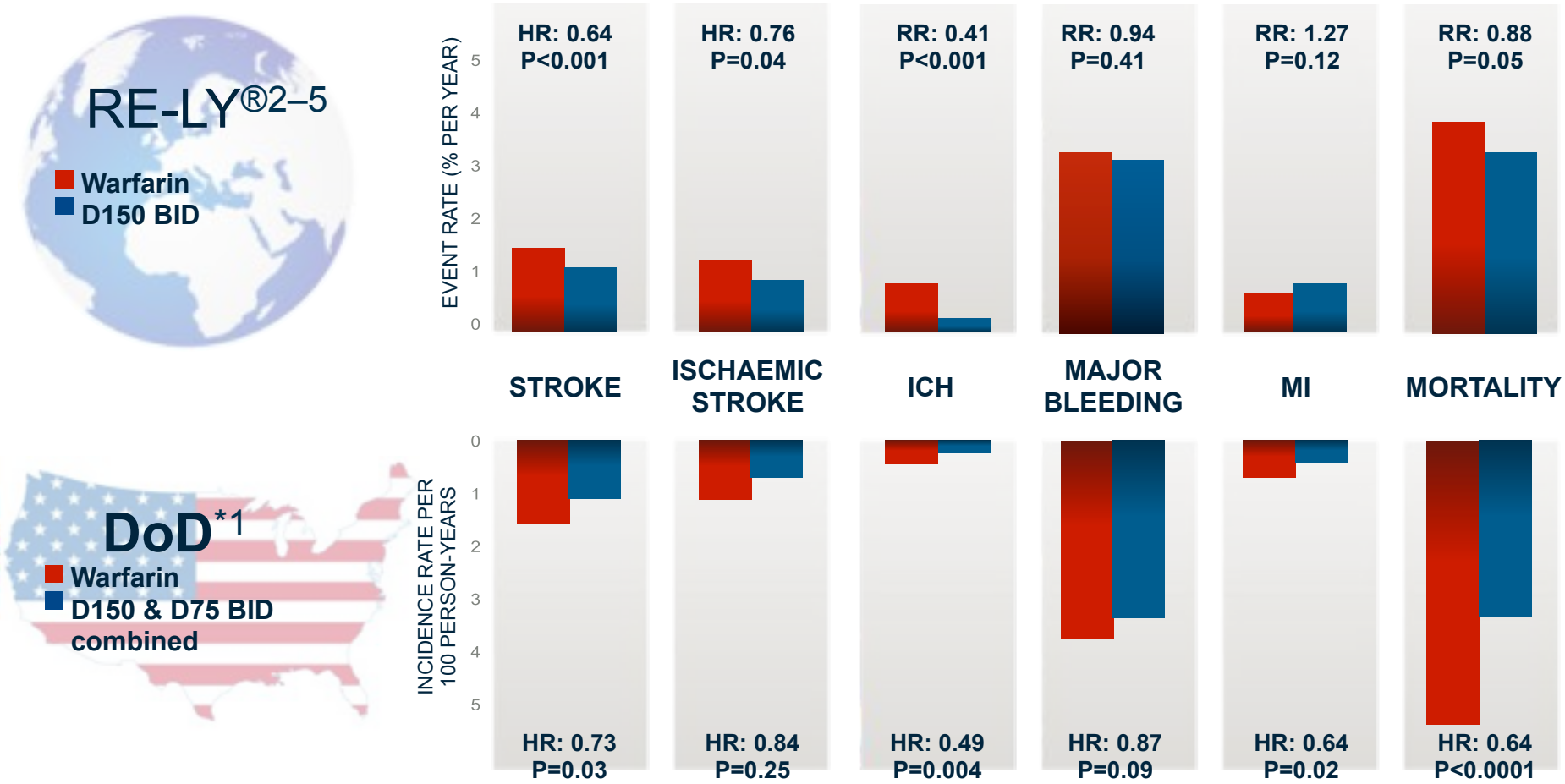
NOAC Real-Life Prescription Data

An Unexpectedly High Proportion Of Prescriptions For Lower Dosages

	Apixaban		Rivaroxaban			Dabigatran		
	Q4 2014		Q4 2014			Q4 2014		
Country	2.5mg	5mg	10mg	15mg	20mg	75mg	110mg	150mg
UNITED STATES	24%	76%	6%	21%	73%	16%	0%	84%
JAPAN	58%	42%	55%	45%	0%	40%	60%	0%
GERMANY	41%	59%	4%	34%	61%	2%	61%	37%
CANADA	38%	62%	6%	26%	68%	1%	52%	47%
AUSTRALIA	39%	61%	2%	30%	68%	0%	63%	37%
UNITED KINGDOM	42%	58%	6%	22%	71%	3%	51%	46%
SPAIN	37%	63%	5%	33%	63%	3%	60%	38%
FRANCE	46%	54%	0%	0%	0%	0%	0%	0%
BELGIUM	30%	70%	2%	42%	56%	0%	60%	40%
ITALY	35%	65%	2%	37%	61%	0%	63%	36%

Alexander JH. Poster presentation at ESC Aug/Sept 2015; London, UK

US Department of Defense database **mirrors** the favourable dabigatran profile seen in RE-LY® and FDA Medicare data



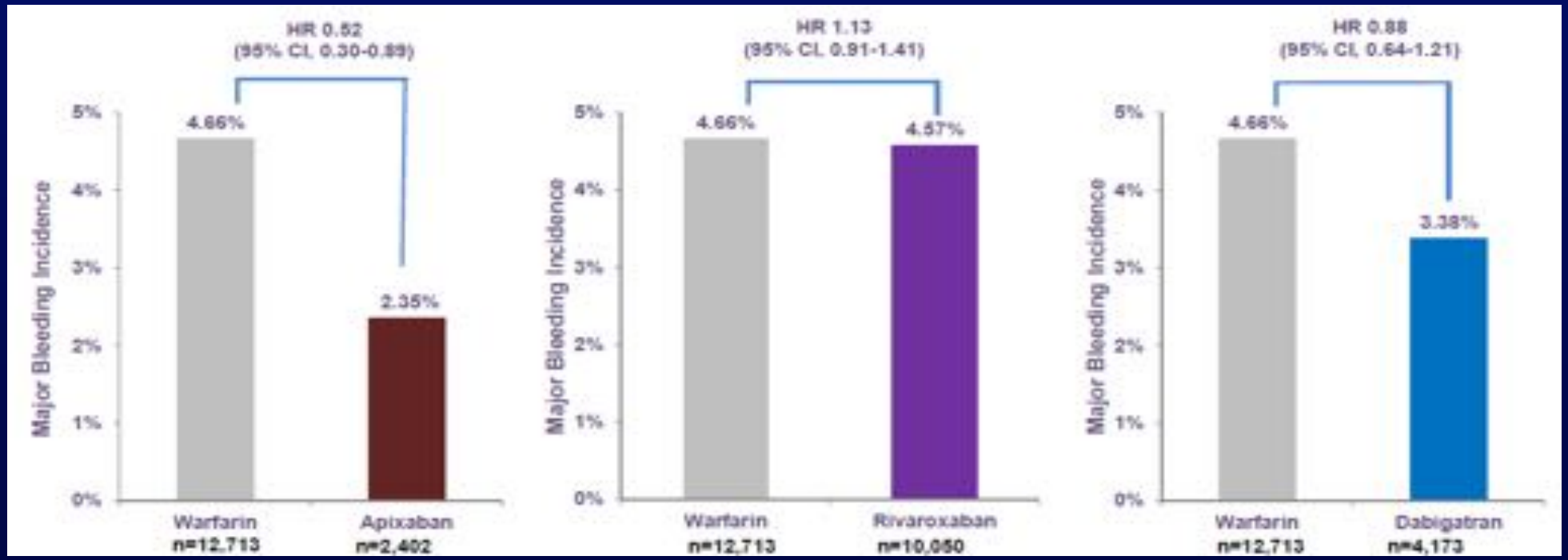
In the USA, the licensed doses for Pradaxa® are: 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with NVAF. In the EU, dabigatran 110 mg BID is indicated for certain patients, and was shown to be as effective vs VKA for prevention of stroke/SE. RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study

*Primary findings for dabigatran are based on analysis of both 75 mg and150 mg together without stratification by dose. **1.** Villines et al. Presented at AHA 2014; **2.** Connolly et al. NEJM 2009; **3.** Connolly et al. NEJM 2010; **4.** Pradaxa®: EU SPC, 2014; **5.** Connolly et al. NEJM 2014

Major Bleeding Risk Among NVAF Pts Newly Initiated On Apixaban, Dabigatran, Rivaroxaban Or Warfarin

A Real World Comparison

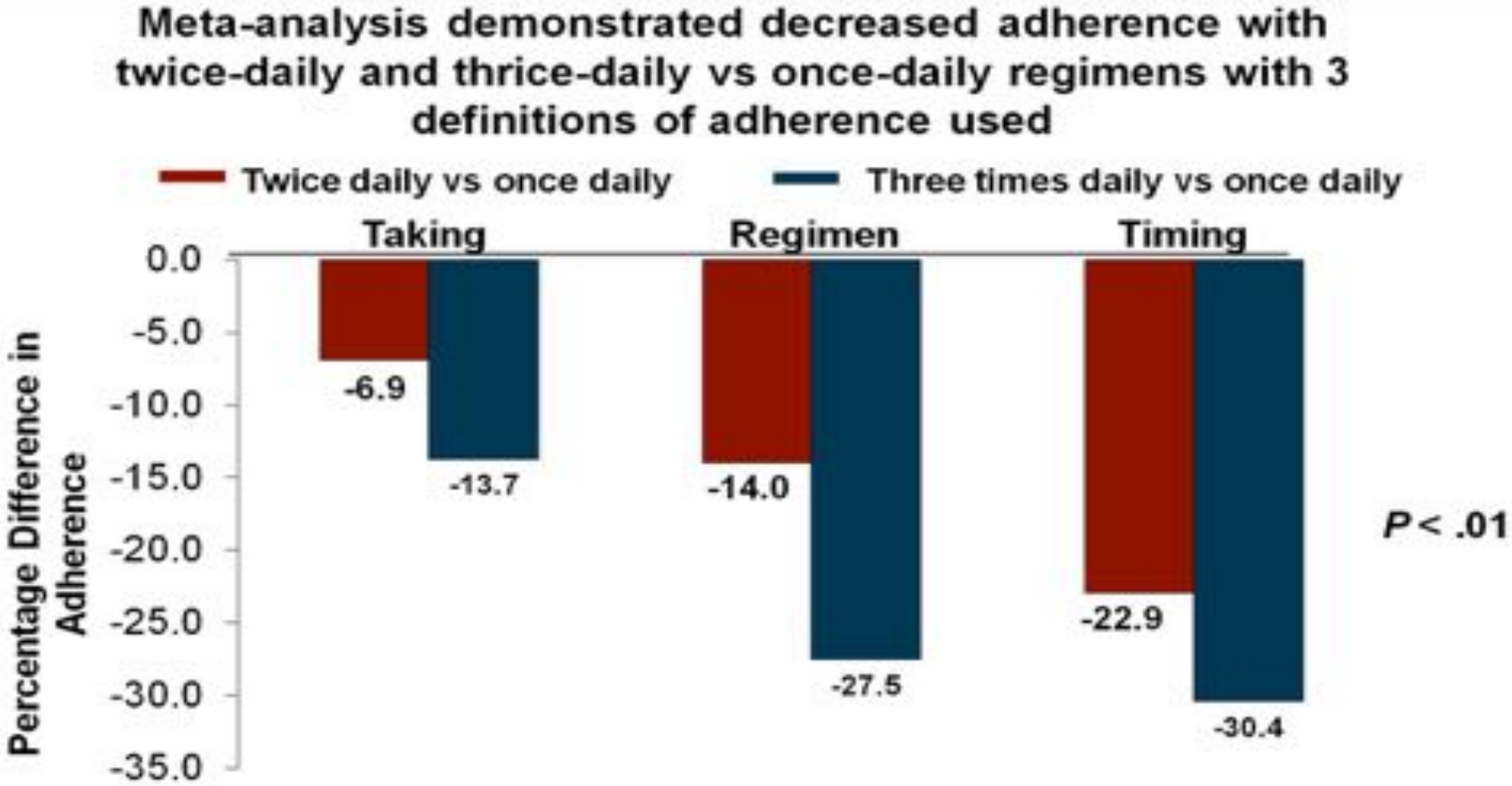
Retrospective analisys of Truven Marketscan Commercial and Medicare DB
29.338 pts enrollmed from jan 01 to dec 31, 2013
Adjusted for baseline differences in the treatment population



Lip G.Y.H. ESC Meeting 2015; London, UK

ESC CONGRESS LONDON 2015

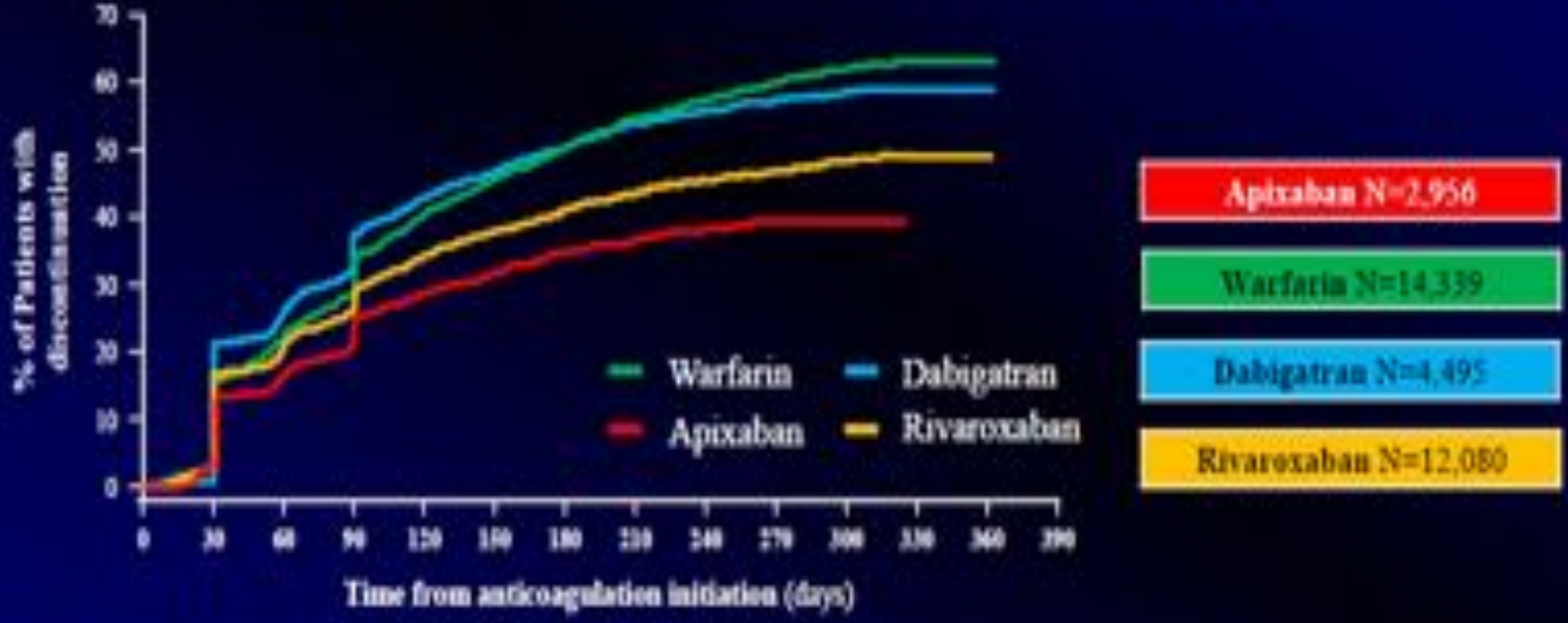
Chronic Cardiovascular Medication Adherence



Coleman CI. Curr Med Res Opin 2012; 28: 669-680

Discontinuation rates in USA NVAF patients new to anticoagulation (Jan 2013 – Dec 2013)

Warfarin vs. Apixaban:	Adjusted HR: 1.638 (95% CI: 1.514–1.772) P<0.001
Rivaroxaban vs. Apixaban:	Adjusted HR: 1.215 (95%CI: 1.121 –1.317) P<0.001
Dabigatran vs. Apixaban:	Adjusted HR: 1.581(95% CI: 1.451–1.721) P<0.001



Analysis controlled for other variables including age, gender, onset of embolic or primary ischemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of TIA or stroke and history of bleeding

Presentation by Pan X et al at ESC 2014 and BMS/Pfizer, data on file

Summary

- Appropriate AC is required to prevent TE events in pts with NV-AF while minimizing the risk for bleeding
- NOACs provide a similar level of protection from ischemic stroke as VKAs but are associated with a significant lower rate of intracranial bleeding
- Consider the advantage of NOACs when pts are appropriate, particularly recognizing the advantage with respect to reduction in brain hemorrhage and major bleeding

Comparison Between Annualized Thromboembolic Risk Stratified by $CHADS_2$ Risk Score and CHA_2DS_2-VASc Risk Score

		$CHADS_2$ Score	$CHADS_2$ Score	Stroke Risk, %	CHA_2DS_2 -VASc Score	CHA_2DS_2 -VASc Score	Stroke Risk, %
C	Congestive heart failure	1	0	1.9	1	0	0
H	Hypertension	1	1	2.8	1	1	1.3
A	Age ≥ 75 years	1	2	4.0	2	2	2.2
D	Diabetes mellitus	1	3	5.9	1	3	3.2
S	Stroke (or transient ischemic attack)	2	4	8.5	2	4	4.0
V	Vascular disease		5	12.5	1	5	6.7
A	Age 66-74 years		6	18.2	1	6	9.8
Sc	Sex category (female)				1	7	9.6
						8	?
						9	15.2

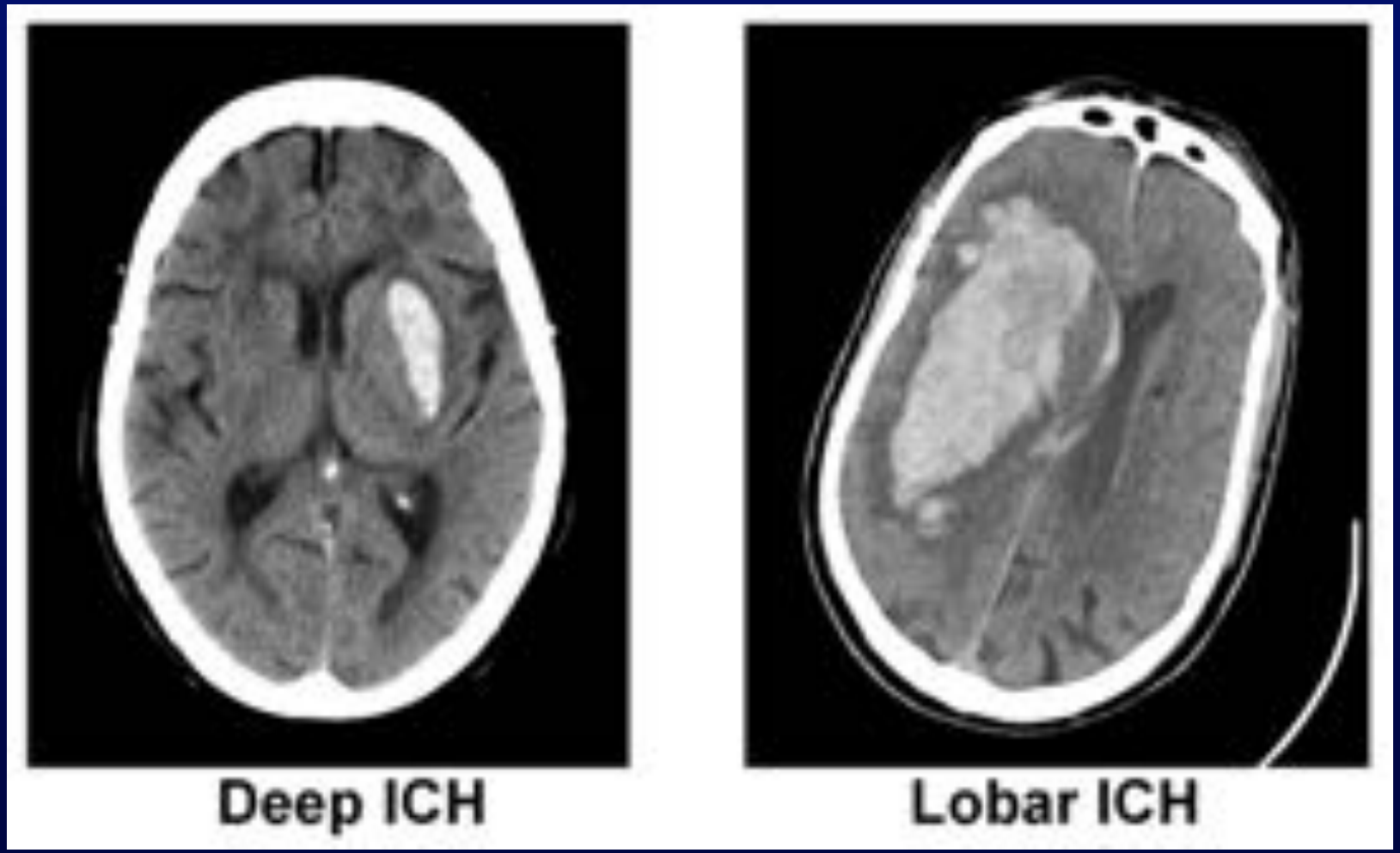
Atrial Fibrillation

HAS-BLED Bleeding Risk Score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

A score ≥ 3 indicates “High Risk” and cautions and regular review of the pt is needed

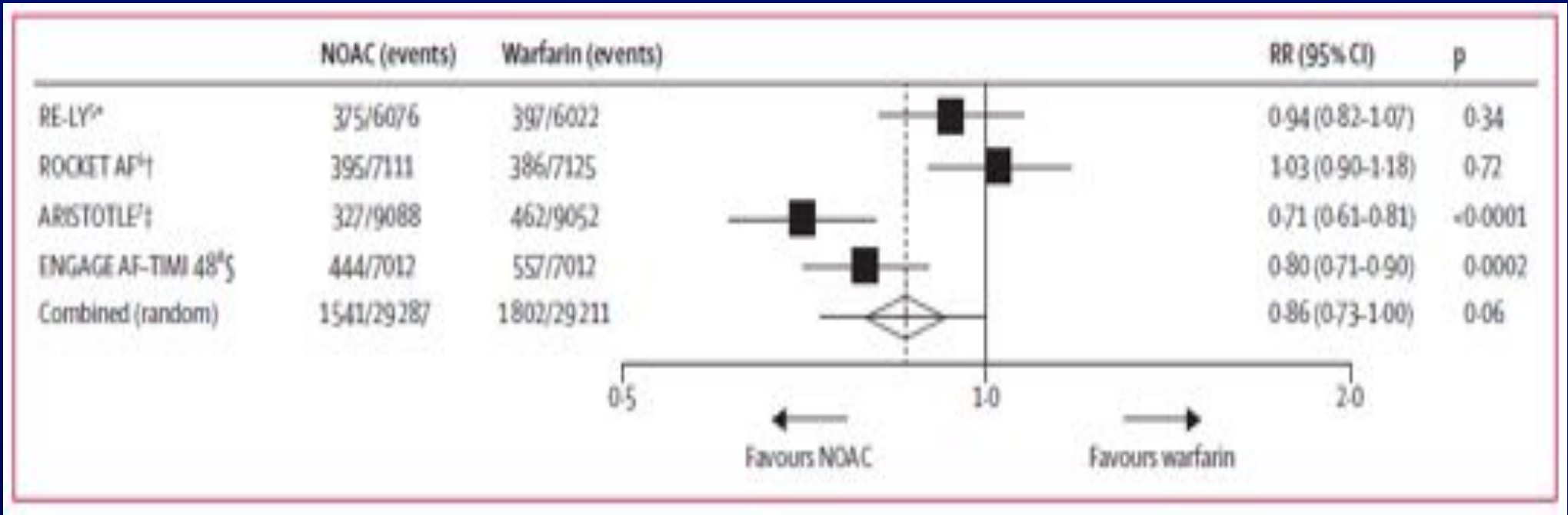
Intracranial Hemorrage



NOACs Are Associated with Significant Fewer Intracranial Bleeds than Warfarin

RE-LY[4]	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	HR (95% CI) 110 mg	HR (95% CI) 150 mg	P
Intracranial Bleed %/Y	0.23	0.30	0.76	0.31 (0.20-0.47)	0.40 (0.27-0.60)	< .001
Hemorrhagic Stroke %/Y	0.12	0.10	0.38	0.31 (0.17-0.56)	0.26 (0.14-0.49)	< .001
ROCKET AF[5]	Rivaroxaban		Warfarin	HR (95% CI)		P
Intracranial Bleed %/Y	0.8		1.2	0.67 (0.47-0.93)		.02
Hemorrhagic Stroke %/Y	0.41		0.71	0.59 (0.37-0.93)		.024
ARISTOTLE[3]	Apixaban		Warfarin	HR (95% CI)		P
Intracranial Bleed %/Y	0.33		0.80	0.42 (0.30-0.58)		< .001
Hemorrhagic Stroke %/Y	0.24		0.47	0.51 (0.35-0.75)		< .001
ENGAGE AF[6]	Edoxaban[a] Low (15/30 mg)	Edoxaban[a] High (30/60 mg)	Warfarin	HR (95% CI) Low (15/30 mg)	HR (95% CI) High (30/60 mg)	P
Intracranial Bleed %/Y	0.26	0.39	0.85	0.30 (0.21-0.43)	0.47 (0.34-0.63)	< .001
Hemorrhagic Stroke %/Y	0.16	0.26	0.47	0.33 (0.22-0.50)	0.54 (0.38-0.77)	< .001

Major Bleeding in the NOACs SPAF Trial



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

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

Published Online
December 4, 2013

Major GI Bleeding in the NOAC SPAF Trials

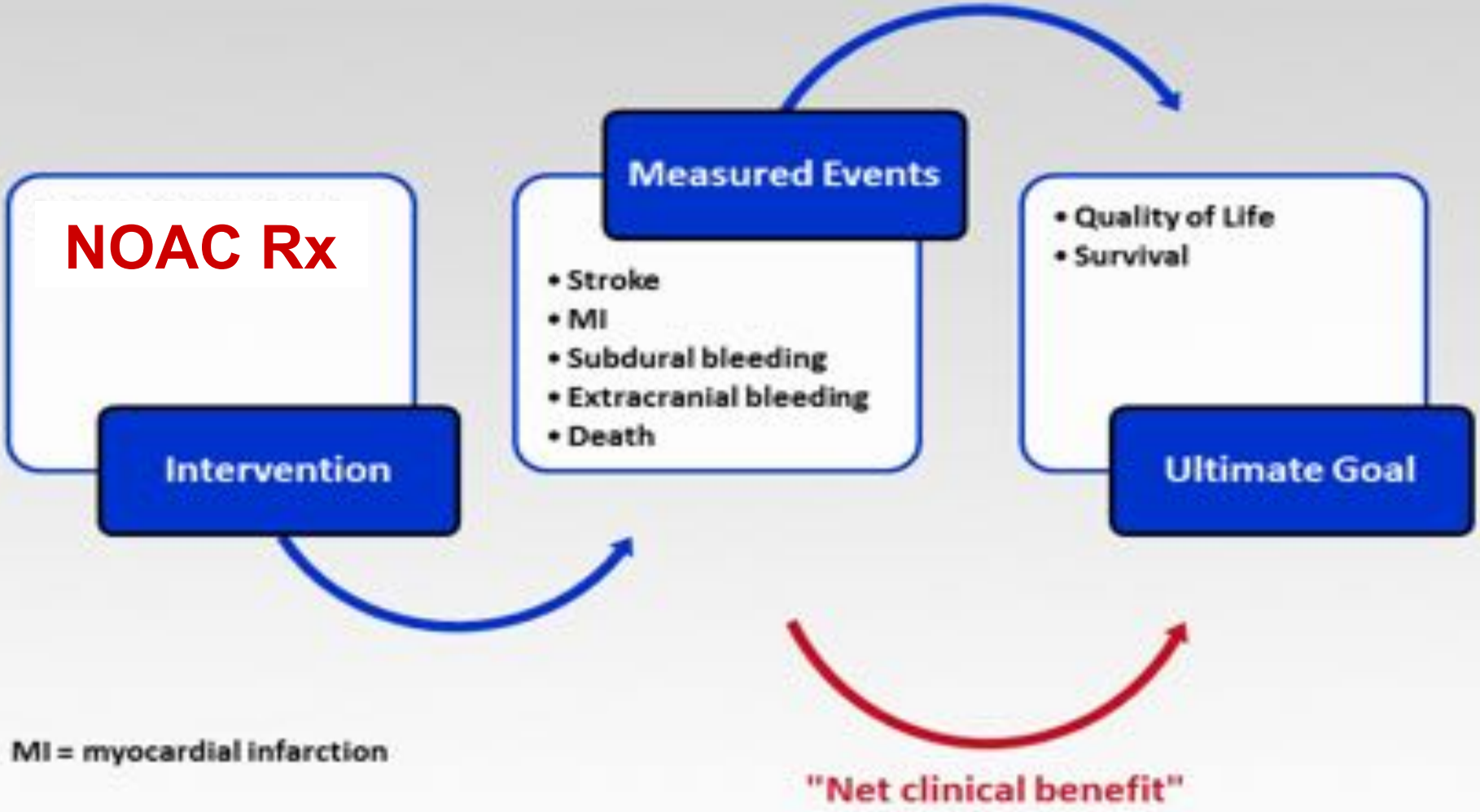
RE-LY[14]	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	*P* (110 mg)	*P* (150 mg)
Major GI Bleed %/Y	1.12	1.51	1.02	.043	< .001

ROCKET AF[15]	Rivaroxaban	Warfarin	*P*
Major GI Bleed %/Y	3.2	2.2	< .001

ARISTOTLE[13]	Apixaban	Warfarin	*P*
Major GI Bleed %/Y	0.76	0.86	.37

ENGAGE AF[16]	Edoxaban* Low (15/30 mg)	Edoxaban* High (30/60 mg)	Warfarin	*P* Low (15/30 mg)	*P* High (30/60 mg)
Major GI Bleed %/Y	0.82	1.51	1.23	< .001	.03

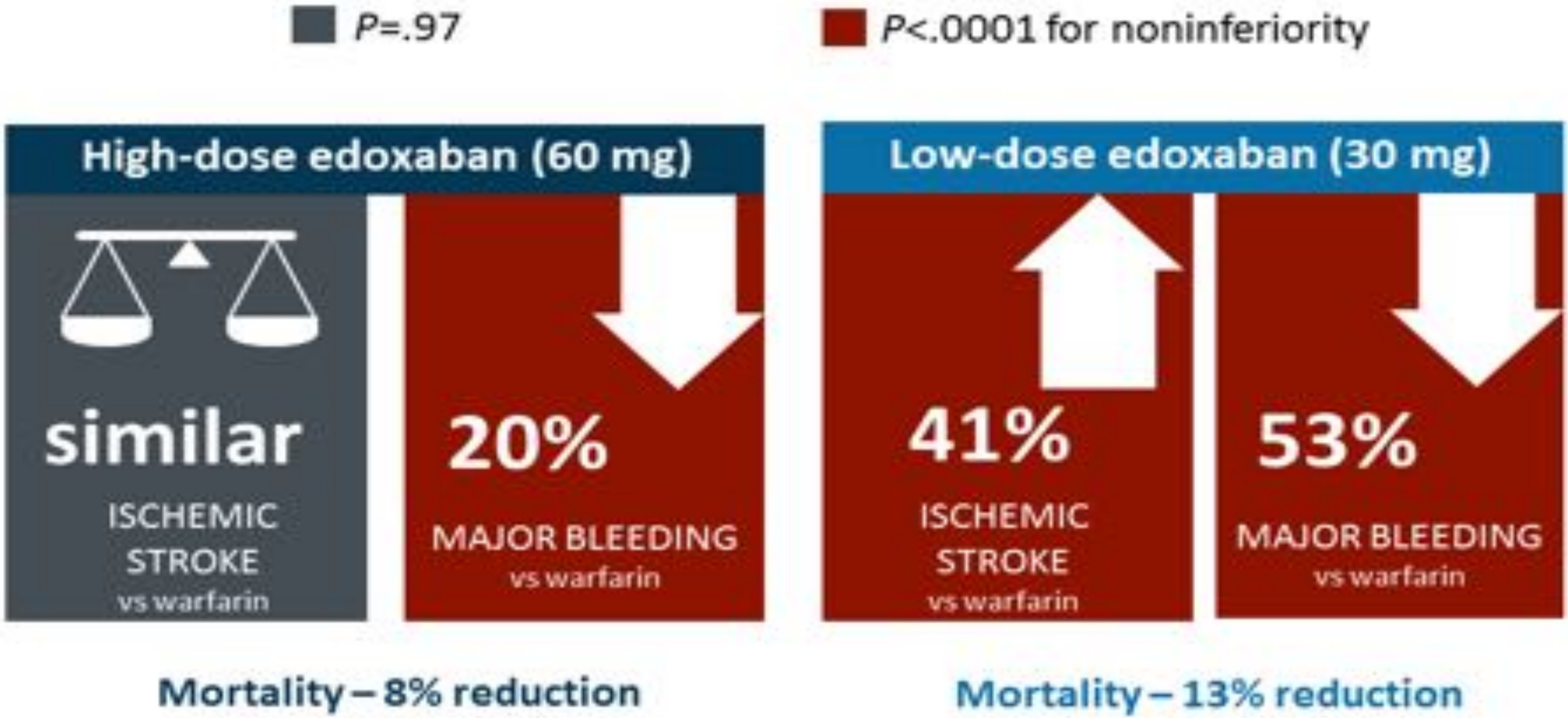
Net Benefit Analysis



MI = myocardial infarction

Eikelboom JW, et al. *J Am Coll Cardiol*. 2013;62:900-908.

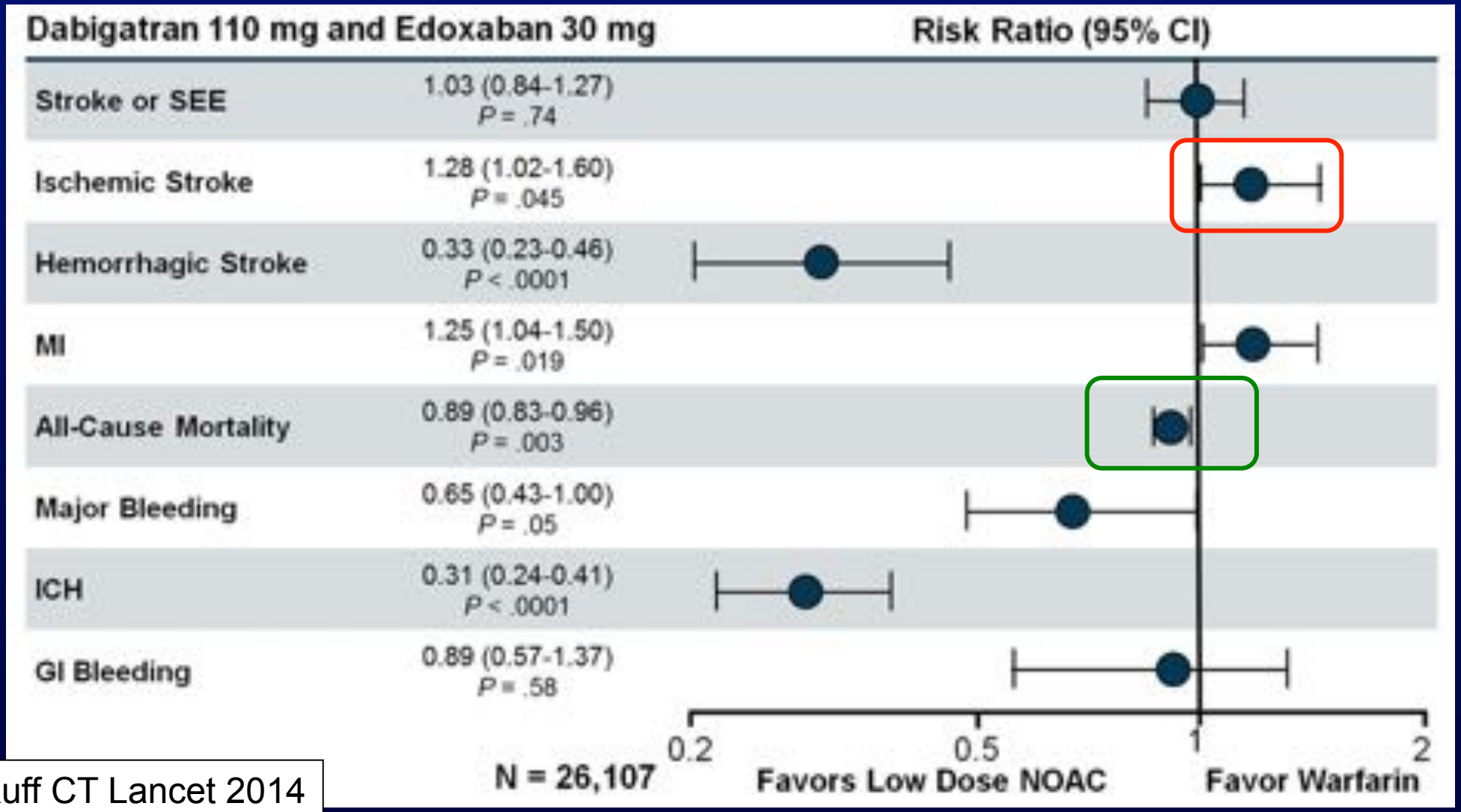
ENGAGE-AF: Does NOAC "Underdosing" Result in a Higher Ischemic Stroke Rate (vs Warfarin)?



Giugliano RP et al. *N Engl J Med*. 2013;369:2093-2104.

Low-Dose NOACs Regimens

The «Paradox» of Efficacy and Safety Outcome



Ruff CT Lancet 2014

NOAC Dosing and Dose Adjustments

	Dabigatran[a]	Rivaroxaban[a]	Apixaban[a]	Edoxaban[b] *
Doses (approved or studied)	150 mg/110 mg twice daily	20 mg/15 mg once daily	5 mg/2.5 mg twice daily	60 mg/30 mg/15 mg once daily
Dose adjustment (EU label or per study protocol)	• Patient age ≥80 years • Concomitant verapamil	CrCL 15-50 mL/min	At least 2 of the following characteristics: – Age ≥80 years – Body weight ≤60 kg – Serum Cr ≥1.5 mg/dL (133 µmol/L)	• CrCl 30-50 mL/min • Body weight ≤60 kg • Concomitant verapamil, quinidine, or dronedarone

EU = European Union

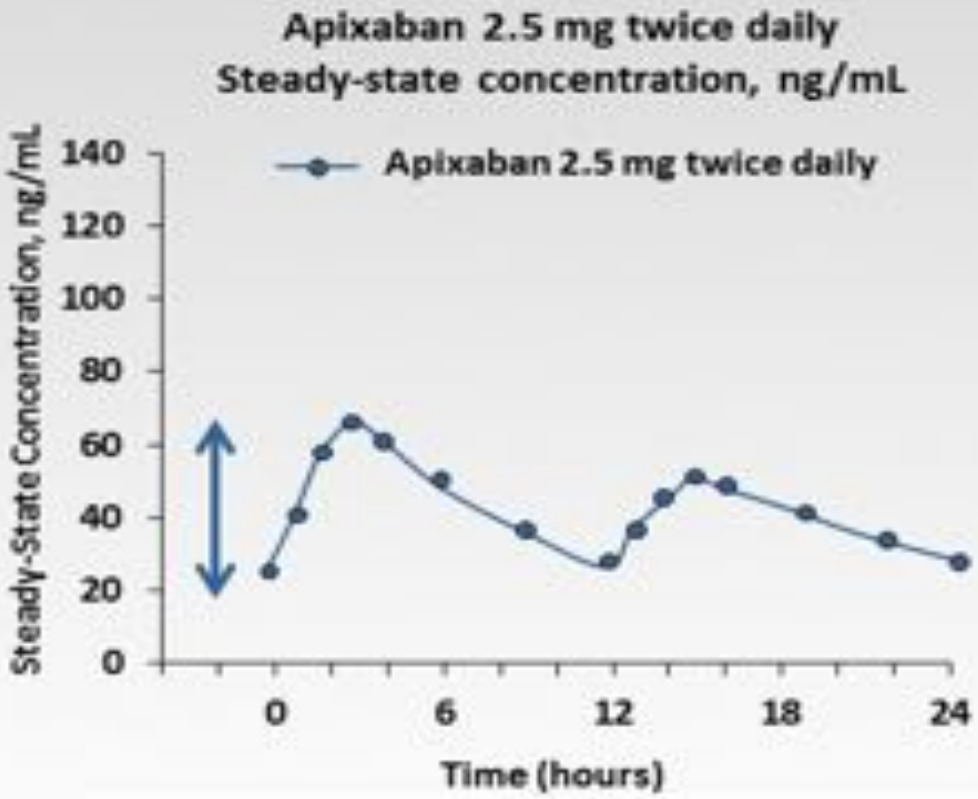
*Edoxaban is not approved for clinical use.

a. European Medicines Agency. http://www.ema.europa.eu/ema/
b. Giugliano RP, et al. *N Engl J Med*. 2013;369(22):2093-2104.

NOAC Dosing Frequency and Plasma Concentrations

Apixaban[a]

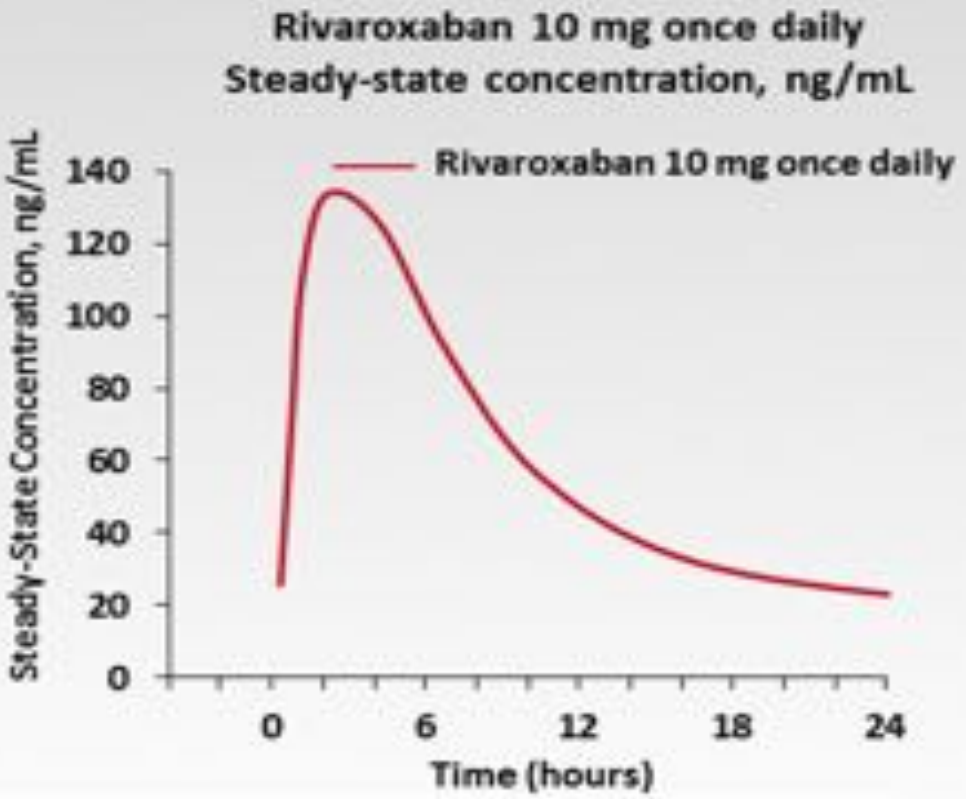
Peak-to-trough ratio: ~3 hours



Frost C, et al. *Br J Clin Pharmacol*. 2013;75(2):476-487.

Rivaroxaban[b]

Peak-to-trough ratio: ~18 hours



Mueck W, et al. *Thromb J*. 2013;11(1):10.