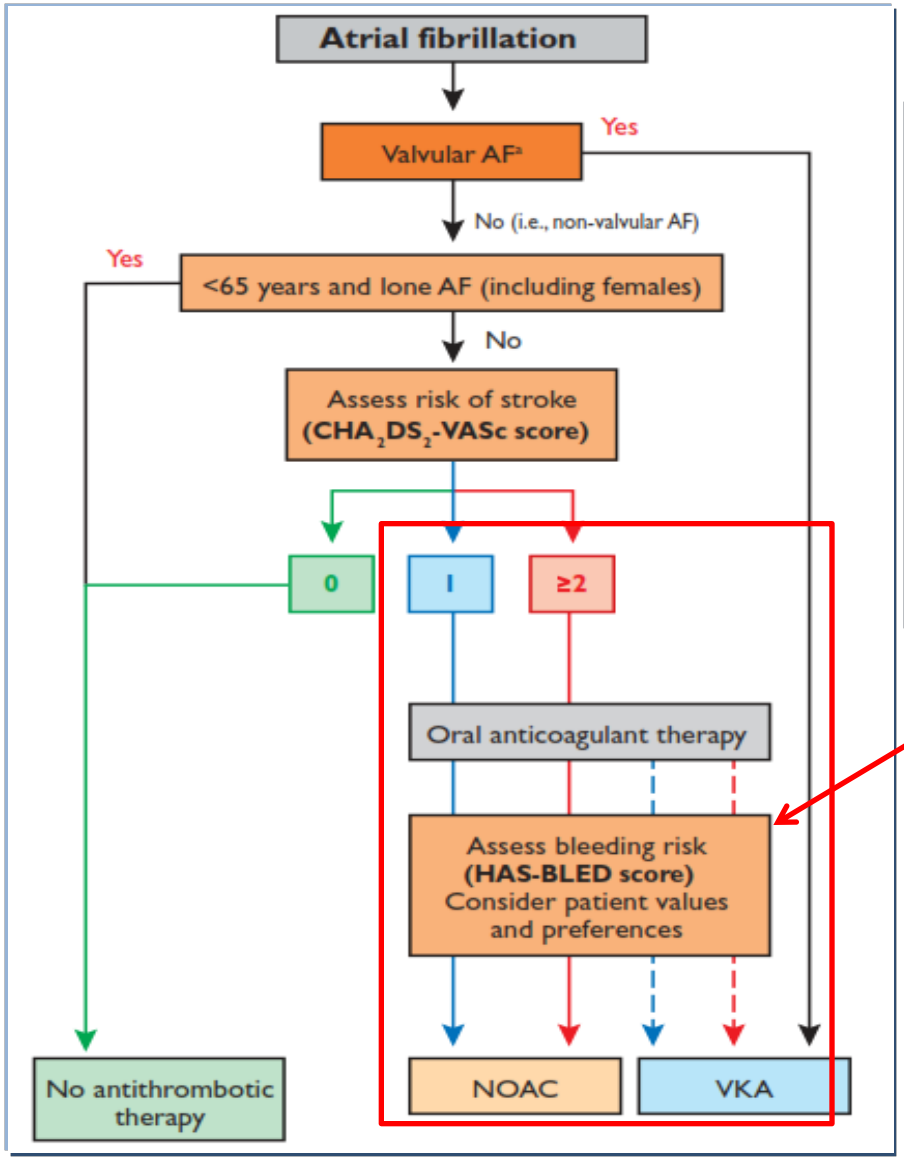
VIII CONGRESSO NAZIONALE ECOCARDIOCHIRURGIA 2016
21-23 Marzo 2016

I NAO nella pratica clinica: hanno mantenuto le promesse dei grandi trial?

Prof. Alberto Margonato
Università Vita-Salute San Raffaele
Unità di Cardiologia Clinica-UTIC

Linee Guida 2012 - European Society of Cardiology



Antiplatelet therapy with aspirin plus clopidogrel, or—less effectively—aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered.

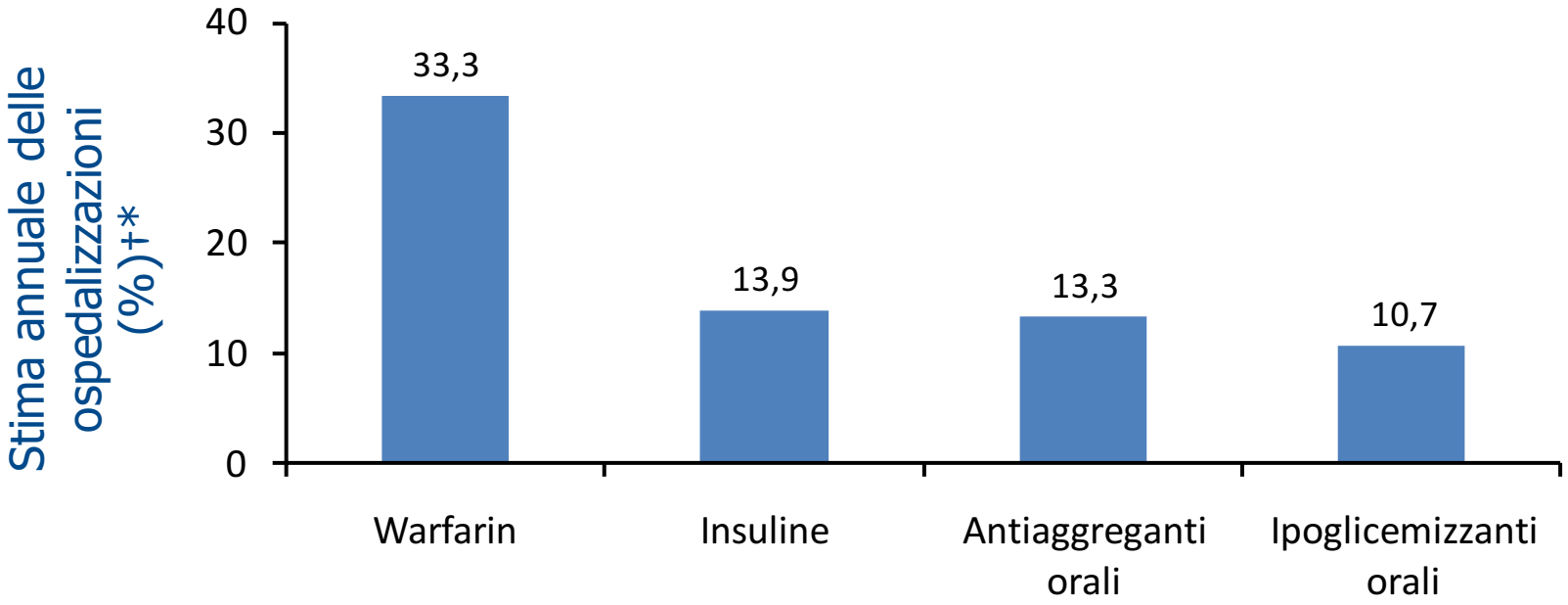
Colour: CHA_2DS_2-VASc; green = 0, blue = 1, red ≥2.

Line: solid = best option; dashed = alternative option.

AF = atrial fibrillation; CHA_2DS_2-VASc = see text; HAS-BLED = see text; NOAC = novel oral anticoagulant; OAC = oral anticoagulant; VKA = vitamin K antagonist.

Camm AJ *et al. European Heart Journal* (2012) 33, 2719–2747

AVK e ospedalizzazioni



- **Il 63.3% delle ospedalizzazioni correlate al warfarin sono dovute ad emorragie[1]**
- La stima dei costi per le emorragie correlate al warfarin ammonta a centinaia di milioni di dollari ogni anno

†Dati da US National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance project (2007–2009); n=99 628 ospedalizzazioni in emergenza

*Sono riportate le classi di farmaci associate ad un tasso di ospedalizzazione ≥10%

VKA = antagonisti della vitamina K

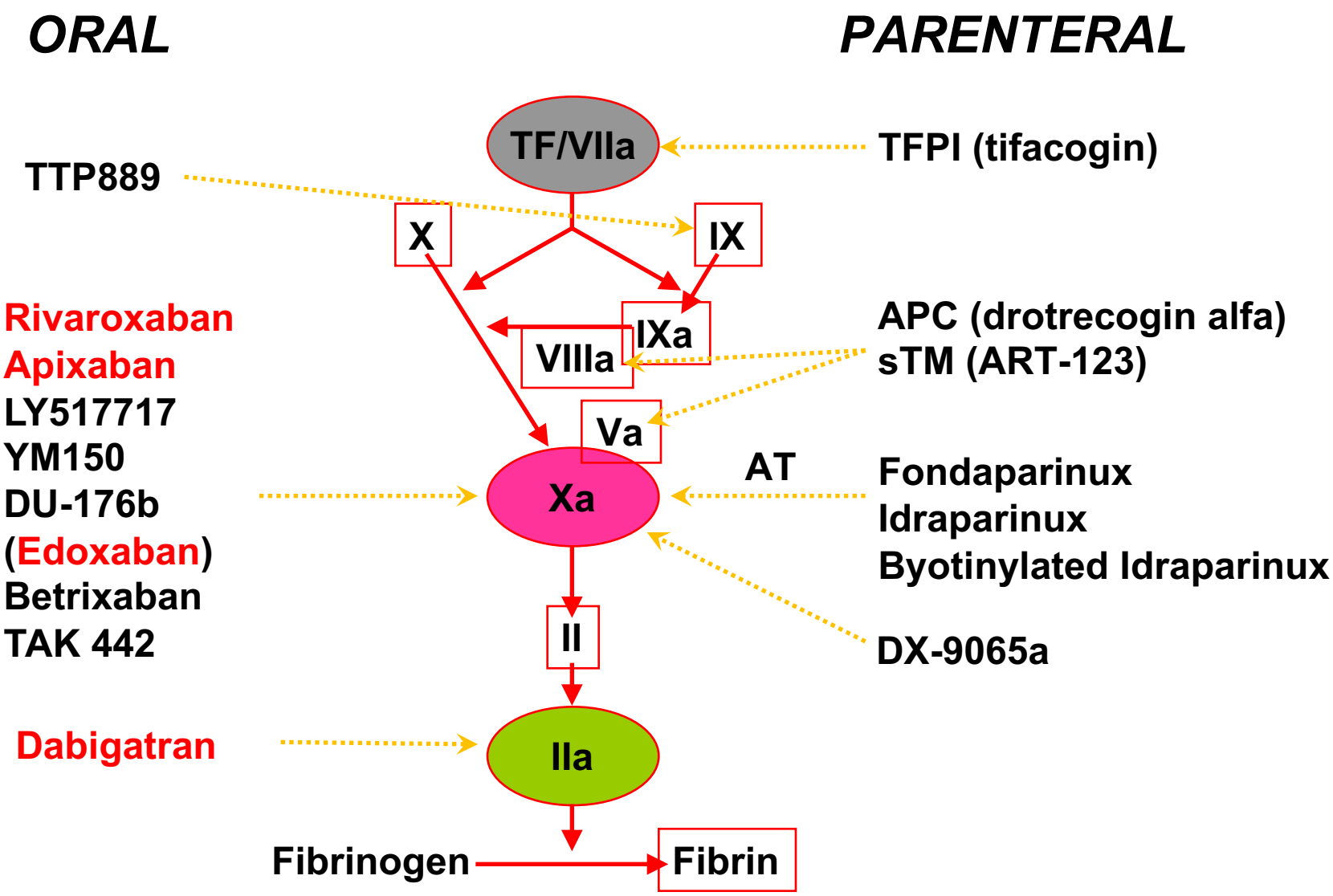
1. Budnitz DS et al. N Engl J Med 2011;365:2002–12

Assume that NOACs have been on the market for 5 years:

The new drug shows in RCT:

- 21 % increase of stroke and sytemic embolism
- 50 % increase of fatal bleeding
- 33 % increase of intracranial hemorrages
- Requirement for monthly monitoring to adjust dose
- Falls out of target anticoagulation one third of the time in RCT and one half in GP
- Many food and drug interactions

Novel Anticoagulants



Adapted from Weitz & Bates, *J Thromb Haemost* 2007

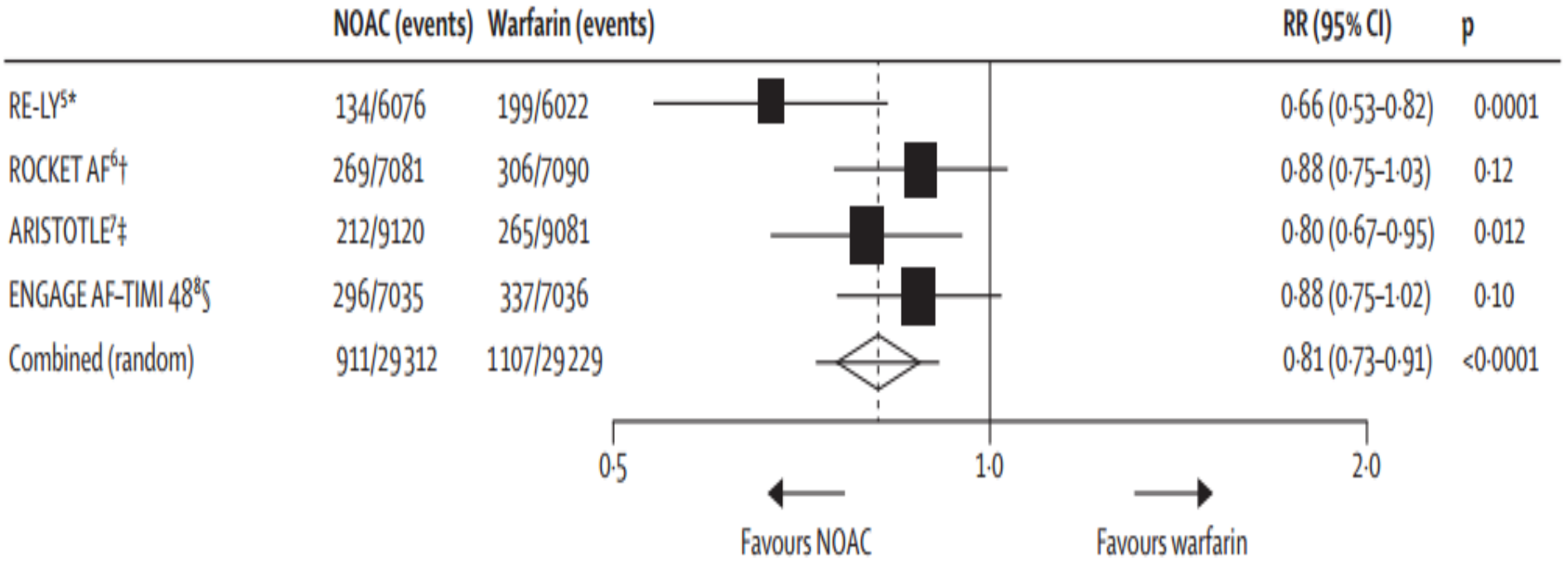
NOACs


INR
DARLING! YOU CAN GET DOWN OFF THAT CROSS!!!
THERE'S A NEW MEDICINE TO REPLACE COUMADIN!!
NIGRO STAINO

Stroke and SE in NOACs Phase III Trials

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



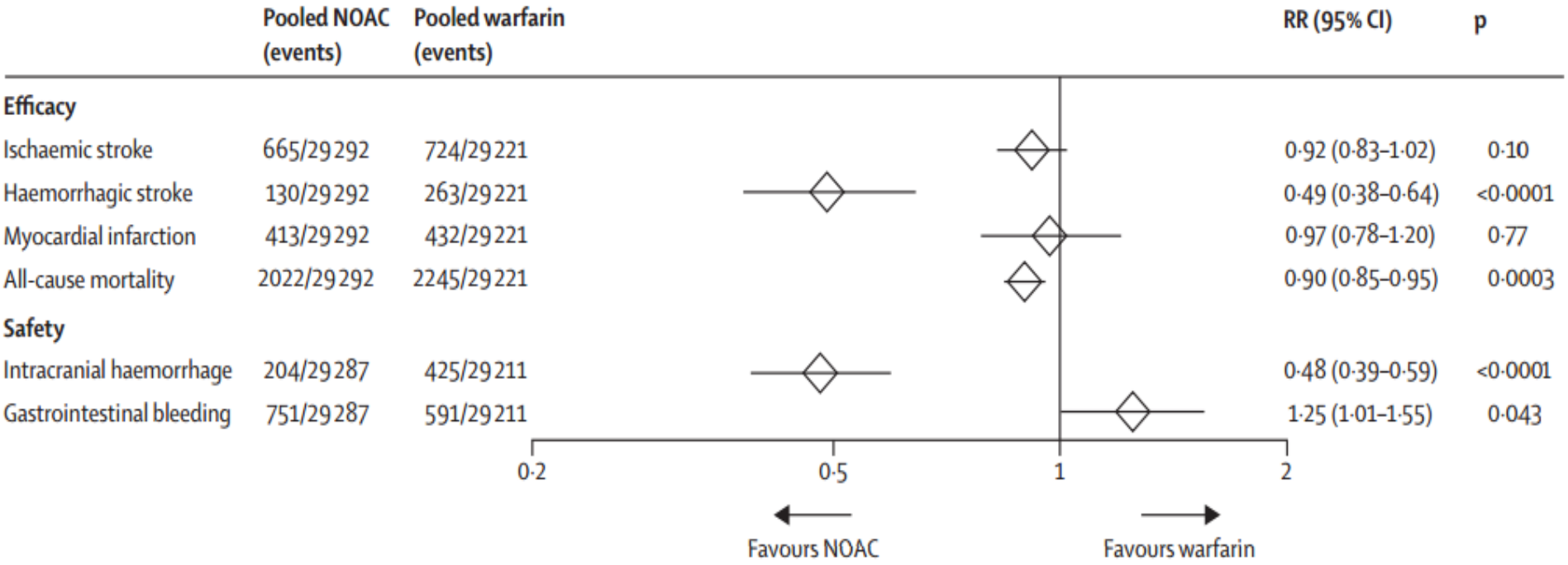
*Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily.
‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Ruff CT et al. Lancet 2014; 383:955-962

Haemorrhagic Stroke and Mortality in NOACs Phase III Trials

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

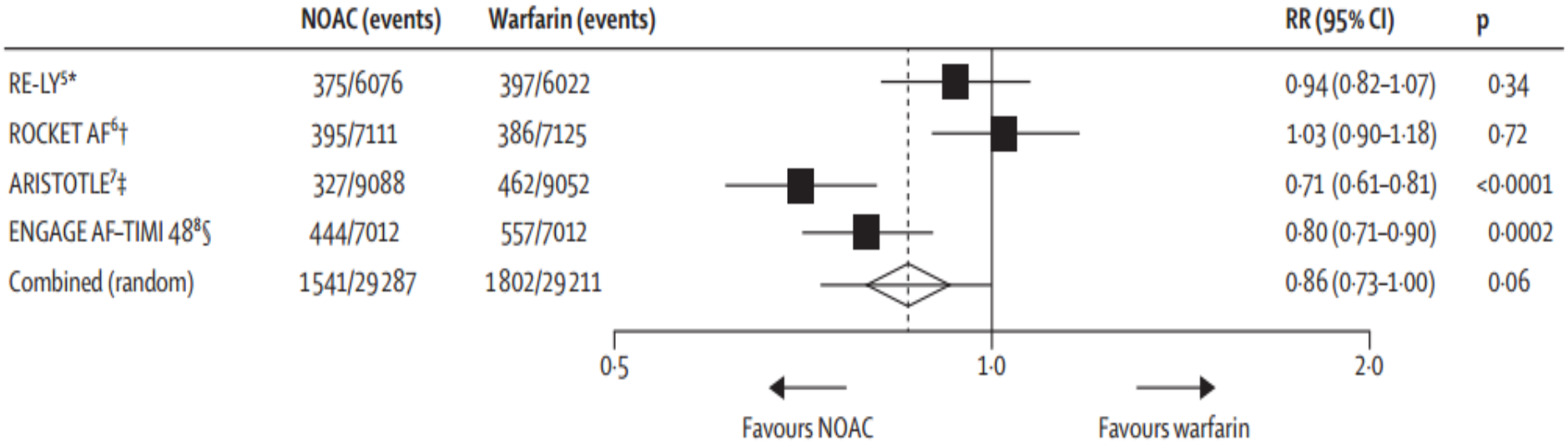


Ruff CT et al. Lancet 2014; 383:955-962

Major Bleeding in NOACs Phase III Trials

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

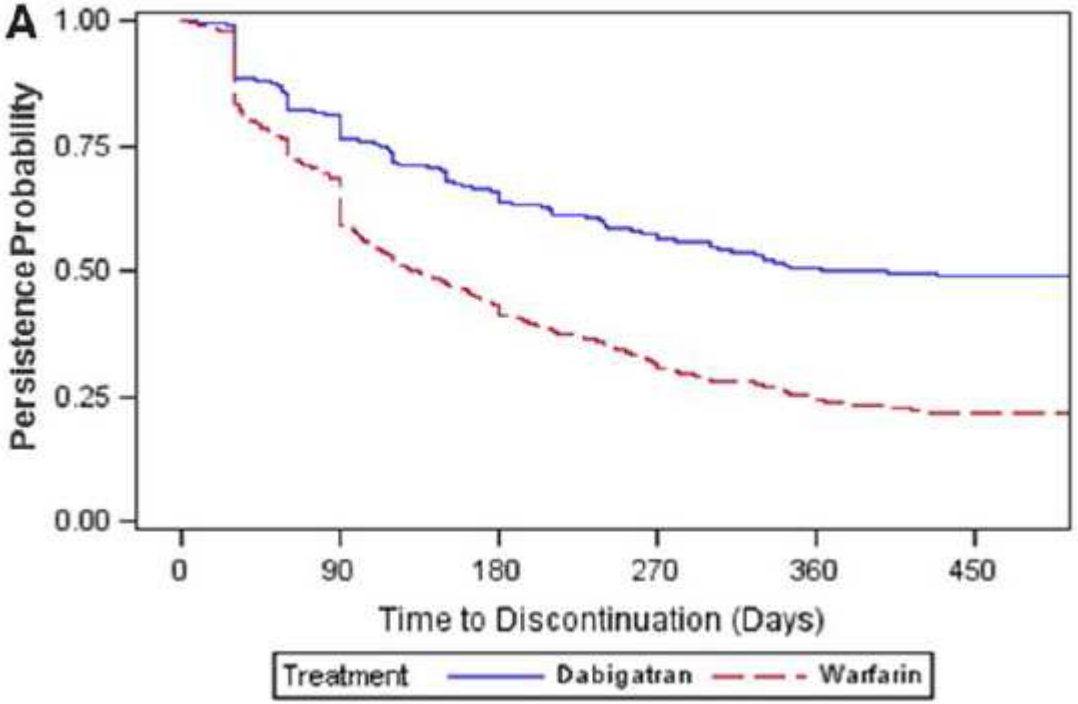


*Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily.
‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Ruff CT et al. Lancet 2014; 383:955-962

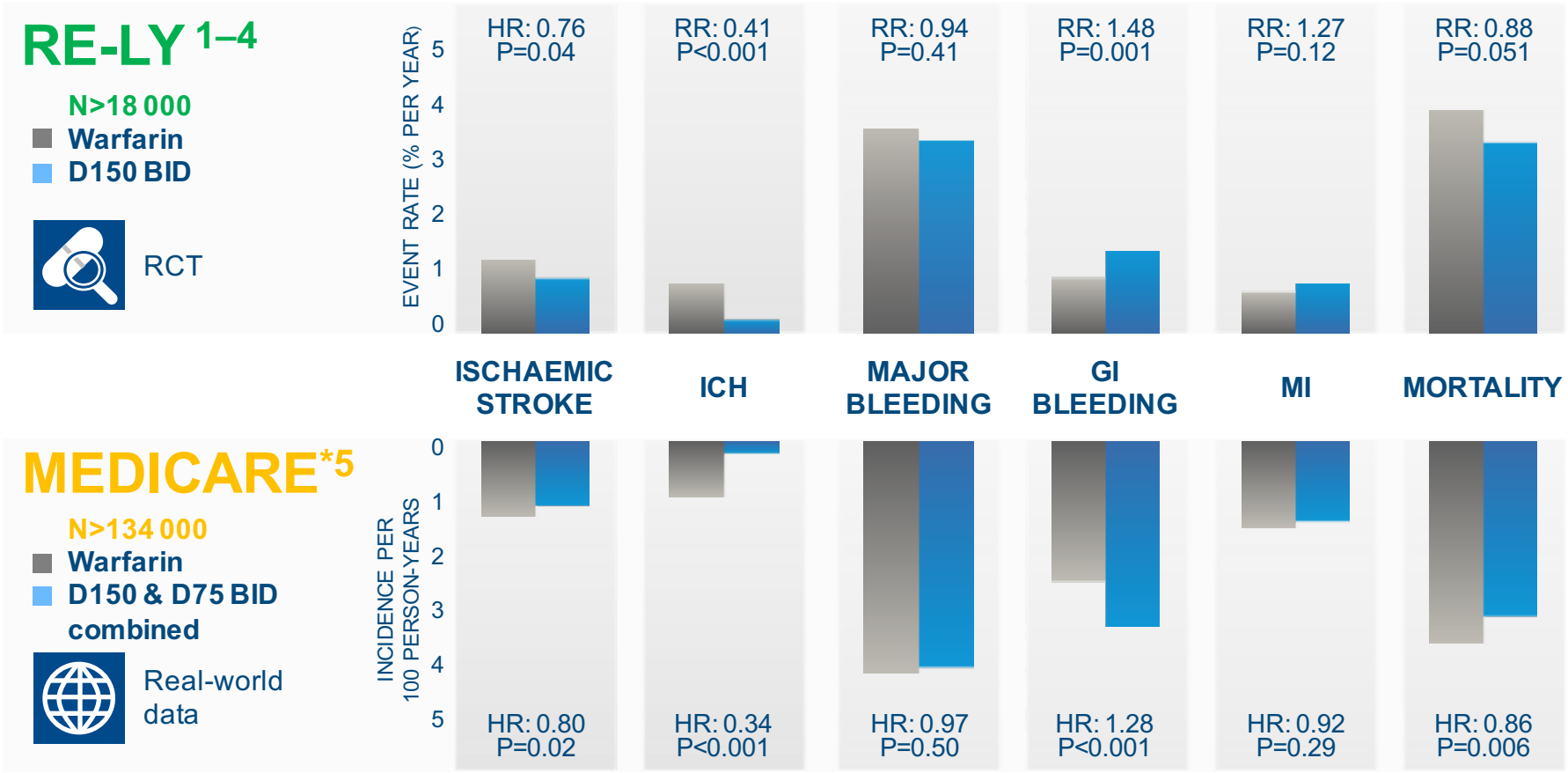
Higher Persistence in Newly Diagnosed Nonvalvular Atrial Fibrillation Patients Treated With Dabigatran Versus Warfarin

Martin Zalesak, MD, PhD; Kimberly Siu, MD, MPH; Kevin Francis, BS; Chen Yu, BA; Hasmik Alvrtsyan, MS; Yajing Rao, MS; David Walker, PhD; Stephen Sander, PharmD; Gavin Miyasato, MS; David Matchar, MD; Herman Sanchez, MBA



Zalesak M et al, Circ Cardiovasc Qual Outcomes, September 2013

Independent FDA study of Medicare confirmed the positive safety and efficacy of Dabigatran in clinical practice



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

*Primary findings for dabigatran are based on analysis of both 75 mg &150 mg together without stratification by dose

1. Connolly SJ et al. N Engl J Med 2009;361:1139–51
2. Connolly SJ et al. N Engl J Med 2010;363:1875–6
3. Pradaxa®: EU SPC, January 2015
4. Connolly SJ et al. N Engl J Med 2014;371:1464–5
5. Graham DJ et al. Circulation 2015;131:157–64

Intracranial Hemorrhage Mortality in Atrial Fibrillation Patients Treated With Dabigatran or Warfarin

Alvaro Alonso, MD, PhD; Lindsay G.S. Bengtson, PhD; Richard F. MacLehose, PhD; Pamela L. Lutsey, PhD; Lin Y. Chen, MD, MSc; Kamakshi Lakshminarayan, MBBS, PhD, MSc

Table 3. Risk Ratios (95% Confidence Intervals) of In-Hospital Death in Current Users of Dabigatran Compared With Current Users of Warfarin Admitted With Intracranial Bleeding by Bleeding Subtype, MarketScan Databases, 2009 to 2012

	Warfarin	Dabigatran
Intracerebral hemorrhage		
n	723	25
In-hospital deaths (% mortality)	244 (33.8)	11 (44.0)
Model 1	1 (Ref)	1.30 (0.83–2.04)
Model 2	1 (Ref)	1.28 (0.82–2.01)
Model 3	1 (Ref)	1.28 (0.82–1.99)
Model 4	1 (Ref)	1.00 (0.59–1.69)
Subdural		
n	1178	55
In-hospital deaths (% mortality)	179 (15.2)	4 (7.3)
Model 1	1 (Ref)	0.50 (0.19–1.30)
Model 2	1 (Ref)	0.50 (0.19–1.30)
Model 3	1 (Ref)	0.47 (0.18–1.23)
Model 4	1 (Ref)	0.49 (0.18–1.34)
Subarachnoid/intracranial bleeding not otherwise specified		
n	389	21
In-hospital deaths (% mortality)	88 (22.6)	5 (23.8)
Model 1	1 (Ref)	1.01 (0.46–2.23)
Model 2	1 (Ref)	0.95 (0.43–2.08)
Model 3	1 (Ref)	0.99 (0.44–2.20)
Model 4	1 (Ref)	1.13 (0.36–3.50)

Model 1: adjusted for age and sex. Model 2: model 1, additionally adjusted for CHA_2DS_2-VASc score and ATRIA bleeding score. Model 3: adjusted for age, sex, and propensity score deciles. Model 4: propensity score–matched analysis adjusting for age and sex. ATRIA indicates anticoagulation and risk factors in atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 65-74, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, sex; and Ref, reference.

Table 4. Risk Ratios (95% Confidence Intervals) of In-Hospital Mortality in Dabigatran Users Versus Warfarin Users Across Selected Subgroups, MarketScan Databases, 2009 to 2012

	Warfarin		Dabigatran		
	n	In-Hospital Deaths, n (%)	n	In-Hospital Deaths, n (%)	RR (95% CI)
Men	1272	305 (24.0)	54	6 (11.1)	0.53 (0.25–1.14)
Women	1018	206 (20.2)	47	14 (29.8)	1.49 (0.96–2.29)
Interaction *P* value					0.03
Age ≤77 y	1071	224 (20.9)	60	10 (16.7)	0.92 (0.51–1.64)
Age >77 y	1219	287 (23.5)	41	10 (24.4)	1.05 (0.61–1.81)
Interaction *P* value					0.74
Previous kidney disease	439	120 (27.3)	21	6 (28.6)	1.14 (0.56–2.29)
No kidney disease	1851	391 (21.1)	80	14 (17.5)	0.93 (0.57–1.50)
Interaction *P* value					0.95
ATRIA bleeding score ≤4	1498	320 (21.4)	63	12 (19.1)	0.96 (0.57–1.59)
ATRIA bleeding score >4	792	191 (24.1)	38	8 (21.1)	1.06 (0.57–1.97)
Interaction *P* value					0.83

Models adjusted for age, sex (where appropriate), hemorrhage subtype, and propensity score deciles. ATRIA indicates anticoagulation and risk factors in atrial fibrillation; CI, confidence interval; and RR, risk ratio.

Conclusions—In this sample of AF patients with ICB on oral anticoagulants, dabigatran was not associated with higher in-hospital mortality compared with warfarin. Hence, reluctance to use dabigatran because of a lack of approved reversal agents is not supported by our results. (*Stroke*. 2014;45:2286-2291.)

Stroke. 2014;45:2286-2291

Idracizumab

ALLEGATO

Inserimento, in accordo all'articolo 12, comma 5 della Legge 189/2012, in apposita sezione (denominata Classe C (nn)) dedicata ai farmaci non ancora valutati ai fini della rimborsabilità nelle more della presentazione da parte dell'azienda interessata di un'eventuale domanda di diversa classificazione. Le informazioni riportate costituiscono un estratto degli Allegati alle Decisioni della Commissione Europea relative all'autorizzazione all'immissione in commercio dei farmaci. Si rimanda quindi alla versione integrale di tali documenti.

Farmaco di nuova registrazione

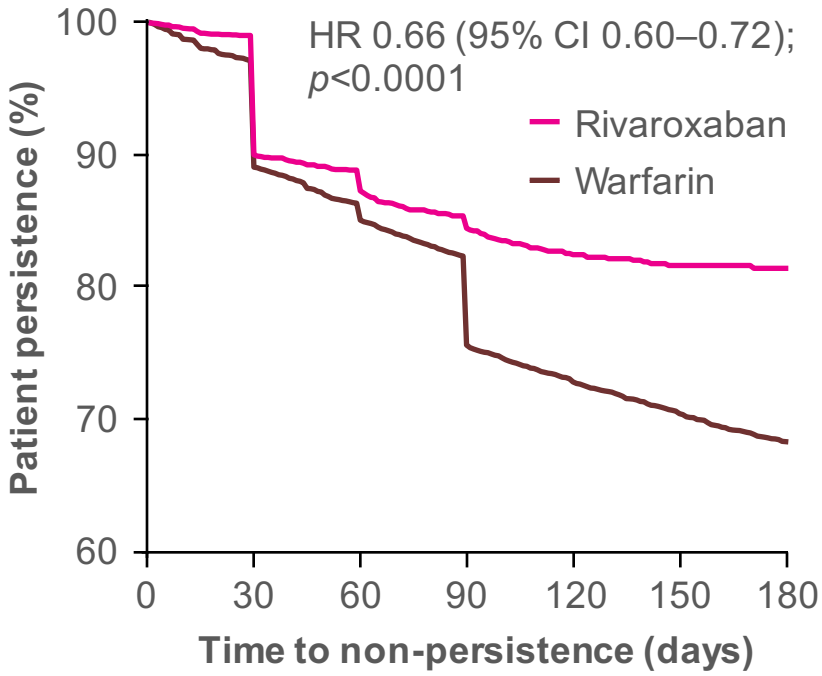
PRAXBIND

Codice ATC - Principio Attivo: V03AB - idarucizumab
Titolare: BOEHRINGER INGELHEIM INTERNATIONAL GMBH
GUUE 30/12/2015

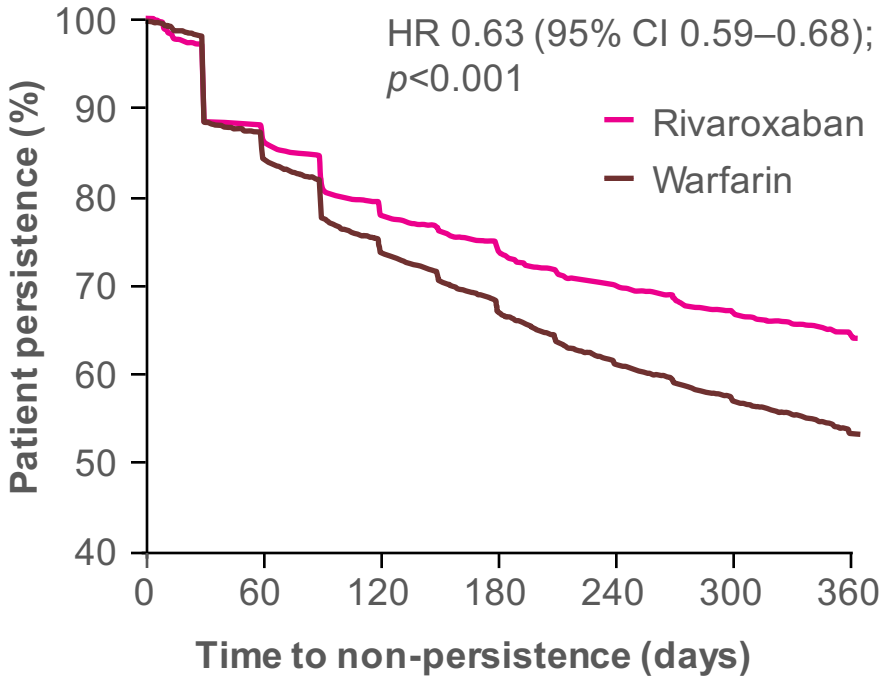
In Real World AF Patients Stayed Longer on Rivaroxaban Than on Warfarin

Two retrospective U.S. database analyses

- Matched sample included 3,654 Rivaroxaban and 14,616 Warfarin patients[1]



- 7,259 Rivaroxaban patients were matched 1:1 with Warfarin patients[2]



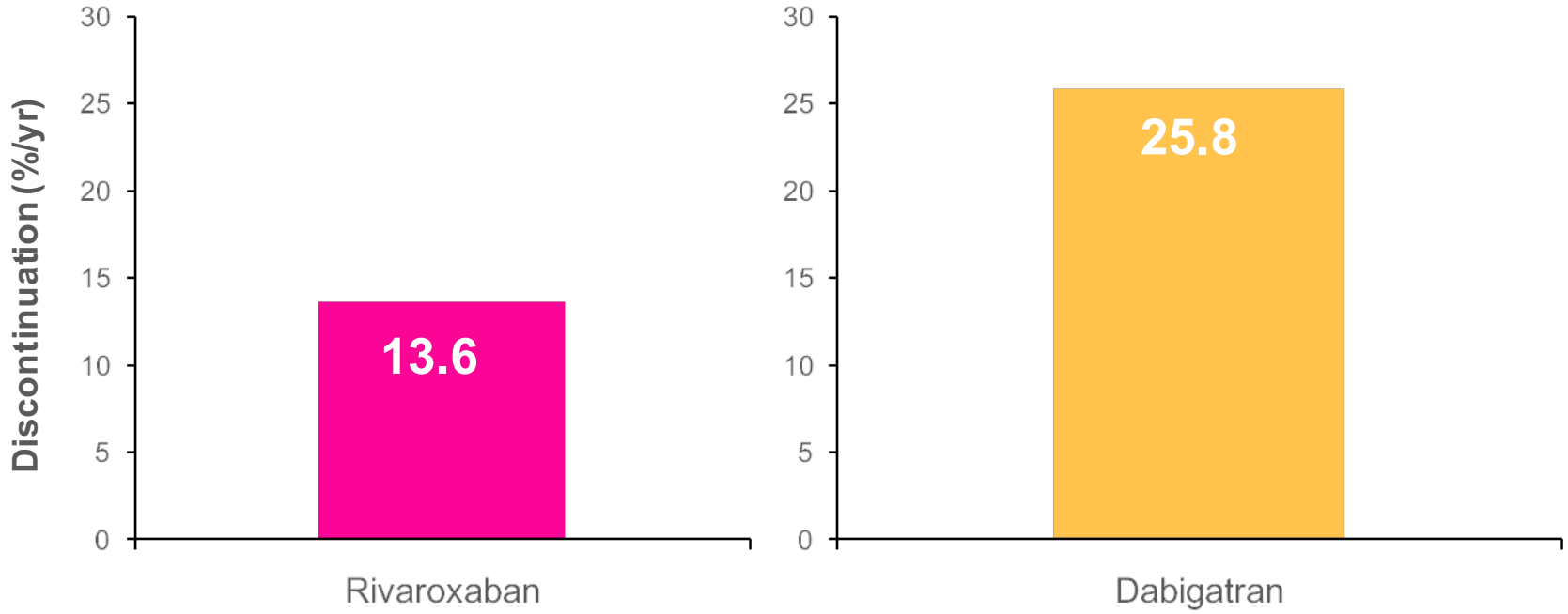
Patients were significantly more persistent with Rivaroxaban than with Warfarin

1. Laliberté F et al. Curr Med Res Opin. 2014;30(7):1317-1325; 2. Nelson WW et al. Curr Med Res Opin. 2014;30(12):2461-2469

Dresden NOAC Registry: In Real World AF Patients Stayed Longer on Rivaroxaban than on Dabigatran

Two analyses of the prospective Dresden NOAC registry

Treatment Discontinuation with Rivaroxaban and Dabigatran



Median follow-up: 544 days

1204 AF patients treated with rivaroxaban[1]

Median follow-up: 671 days

341 AF patients treated with dabigatran[2]

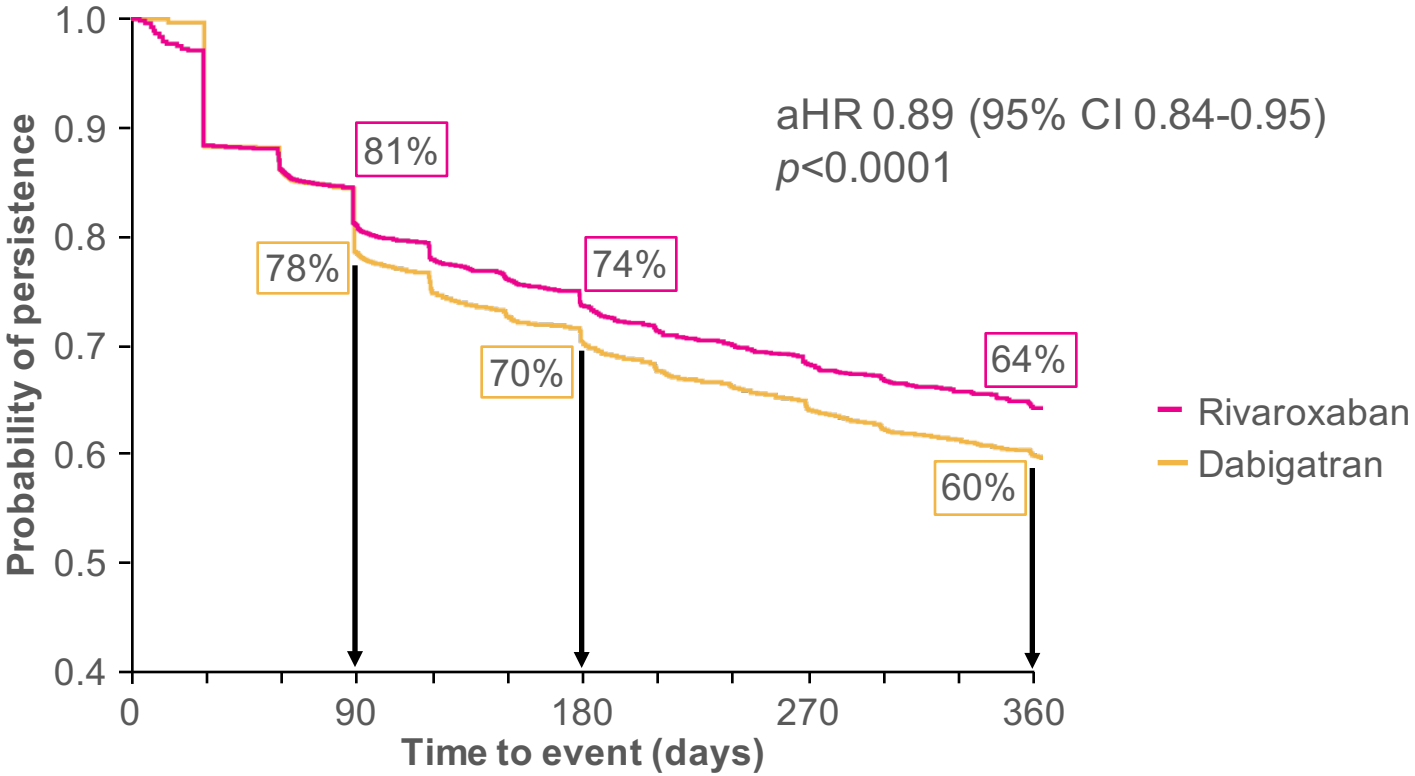
Treatment discontinuation with Rivaroxaban was lower than discontinuation with Dabigatran (two different analyses from the same registry)

1. Beyer-Westendorf J et al. Europace 2015;17(4):530-538; 2. Beyer-Westendorf J et al. Thromb Haemost. 2015;113(6):1247-1257

Higher Persistence with Rivaroxaban vs. Dabigatran in Patients with NVAF

Retrospective U.S. database analysis

- 7,259 Rivaroxaban patients were matched 1:1 with Dabigatran patients



Use of Rivaroxaban led to higher rates of persistence compared to Dabigatran among patients with AF

Nelson WW *et al. Curr Med Res Opin* 2015;doi: 10.1185/03007995.2015.1074064

Quality and Outcomes

Characterizing Major Bleeding in Patients With Nonvalvular Atrial Fibrillation: A Pharmacovigilance Study of 27 467 Patients Taking Rivaroxaban

- Observational cohort study
- US Department of Defense electronic health care records
- Rates of major bleeding, any bleeding, ICH, fatal bleeding, GI bleeding
- Endpoint definition approved by **FDA**

- 27.467 rivaroxaban users
- Diagnosed with NVAF
- 455 days of follow-up

Study period

Tamayo et al., *Clin Cardiol* 2015

Low rate of MB with rivaroxaban in a pharmacovigilance study of 27.467 patients with NVAF

Quality and Outcomes

Characterizing Major Bleeding in Patients With Nonvalvular Atrial Fibrillation: A Pharmacovigilance Study of 27 467 Patients Taking Rivaroxaban

Patient Characteristics

Characteristic	MB, n = 478	No MB, n = 26 989
Age, y, mean (SD)[a]	78.4 (7.7)	75.7 (9.7)
Comorbid condition, %[b]	100.0	87.0
HF	48.5	23.7
Hypertension	95.6	75.8
CHD	64.2	36.7
Renal disease	38.7	16.7
$CHADS_2$ score, mean (SD)	3.0 (1.2)	2.2 (1.3)
CHA_2DS_2-VASc score, mean (SD)	4.8 (1.5)	3.7 (1.7)

Major Bleed Characteristics*

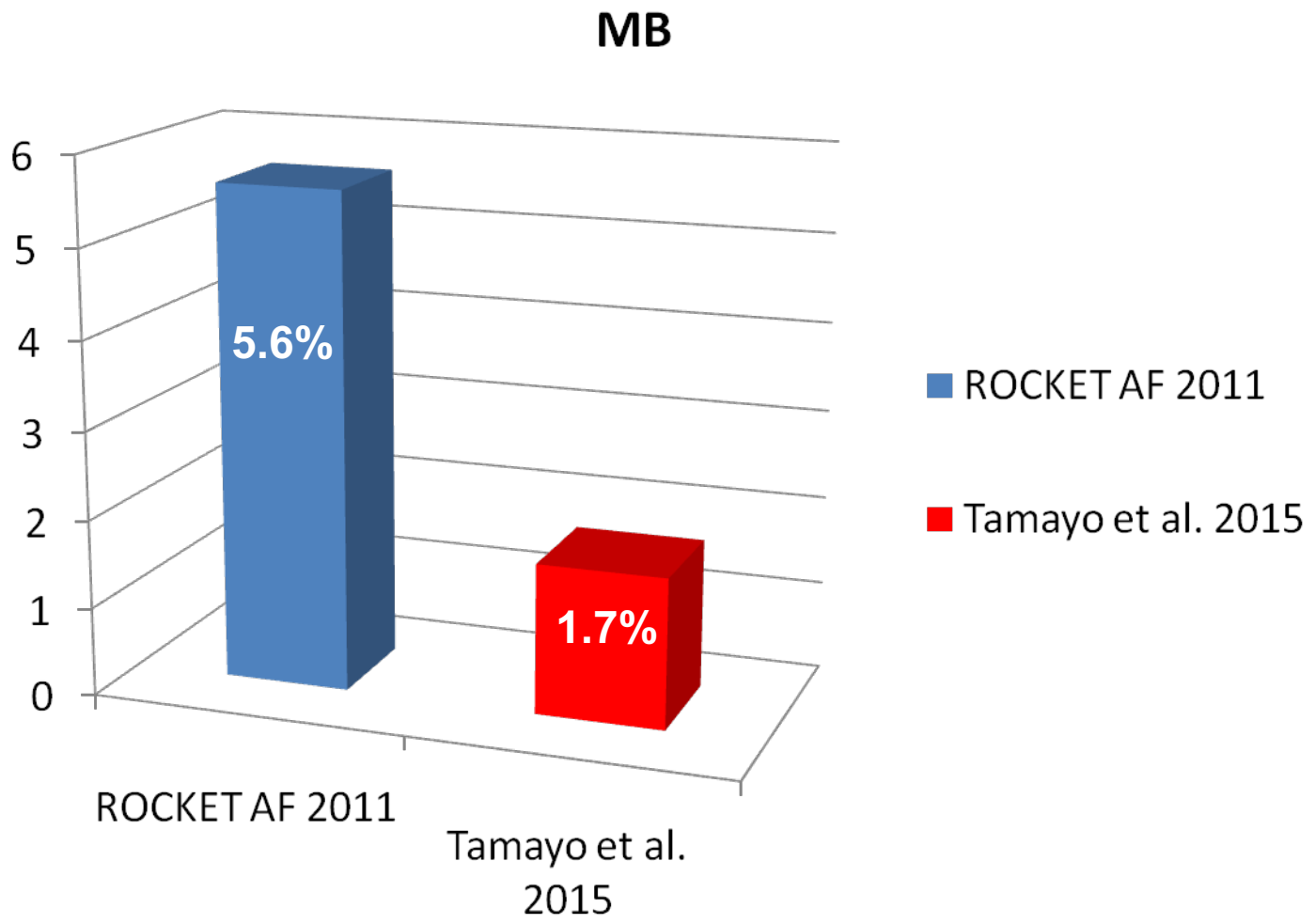
	MB Cases (N = 478)
MB cases with fatal outcome	14
Patients with multiple MB events	16
MB incidence rate per 100 person-years (95% CI)[b]	2.86 (2.61-3.13)
Bleeding cases with fatal outcome (95% CI)	0.08 (0.05-0.14)
MB location, n	
GI hemorrhage	423
ICH	36
Genitourinary hemorrhage	2
Other	12
Length of hospitalization, d, mean (SD)[c]	3.8 (3.0)
Blood transfusion received, %	46.7
Transferred to ICU, %	43.3
Surgical intervention needed, %	25.1

Endpoint definition approved by **FDA**

*MB classified using the Cunningham et al. defintion including: GI bleeding, hemorragic Strokes and other intracranial bleeds, genitourinarybleeding and bleeding at other sites.

Tamayo et al., *Clin Cardiol* 2015

Rivaroxaban: Any Major Bleeding



Modificato da Tamayo et al (Clin. Cardiol. 38, 2, 63–68 2015) e Aristotle Trial

European Heart Journal
doi:10.1093/eurheartj/ehv466

FASTTRACK
ESC Clinical Registry

XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation

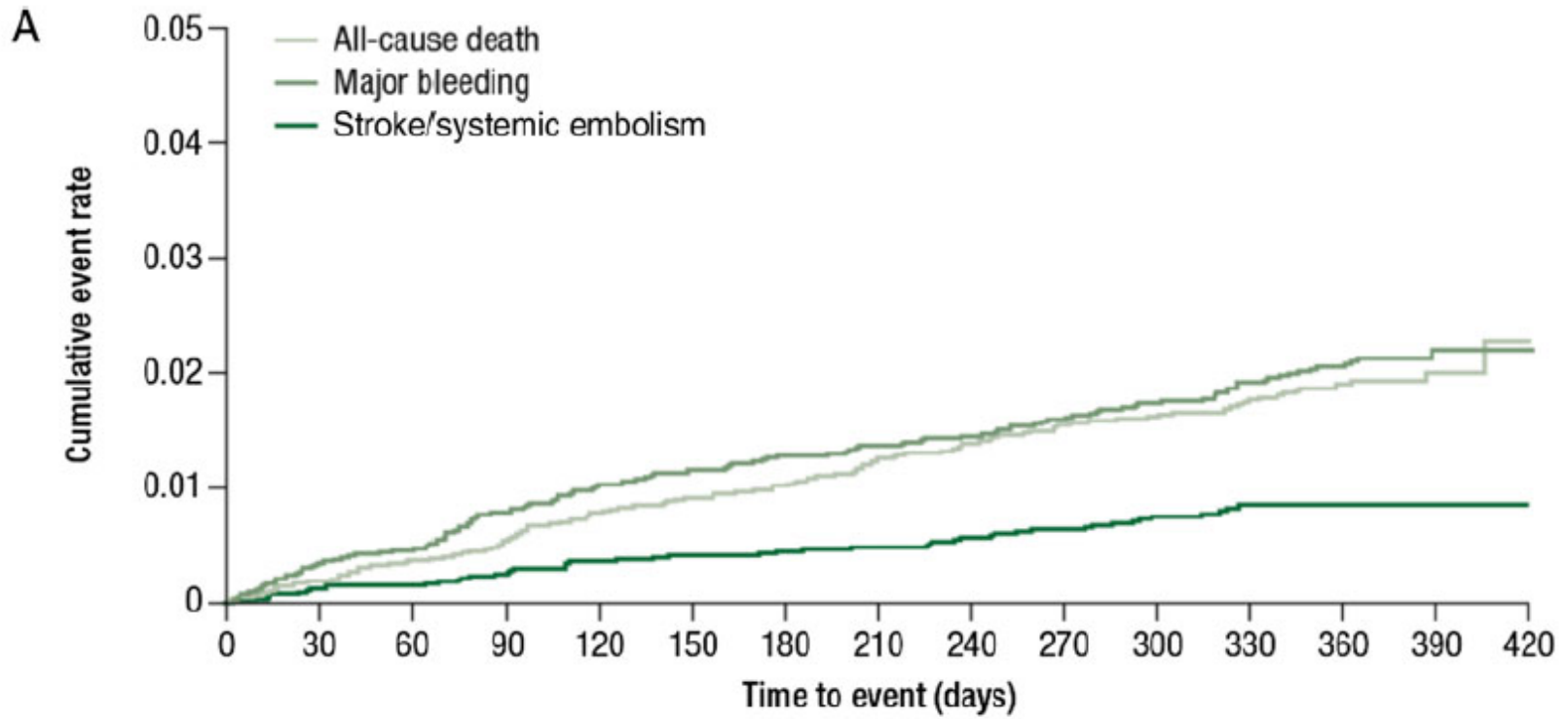
A. John Camm[1*], Pierre Amarenco[2], Sylvia Haas[3], Susanne Hess[4], Paulus Kirchhof[5,6], Silvia Kuhls[7], Martin van Eickels[4], and Alexander G.G. Turpie[8], on behalf of the XANTUS Investigators

- 6784 patients with NVAF newly started on rivaroxaban at 311 centres in Europe, Israel, and Canada
- Follow-up: 3-month intervals for 1 year, or for at least 30 days after permanent discontinuation
- Major outcomes: major bleeding, symptomatic thromboembolic events (stroke, systemic embolism, transient ischaemic attack, and myocardial infarction), and all-cause death
- Mean treatment duration: 329 days

Xantus Investigators, Eur Heart J. 2015 Sep 1

XANTUS Study: Major Outcomes

Major outcomes: all-cause death, major bleedings, and stroke/systemic embolism



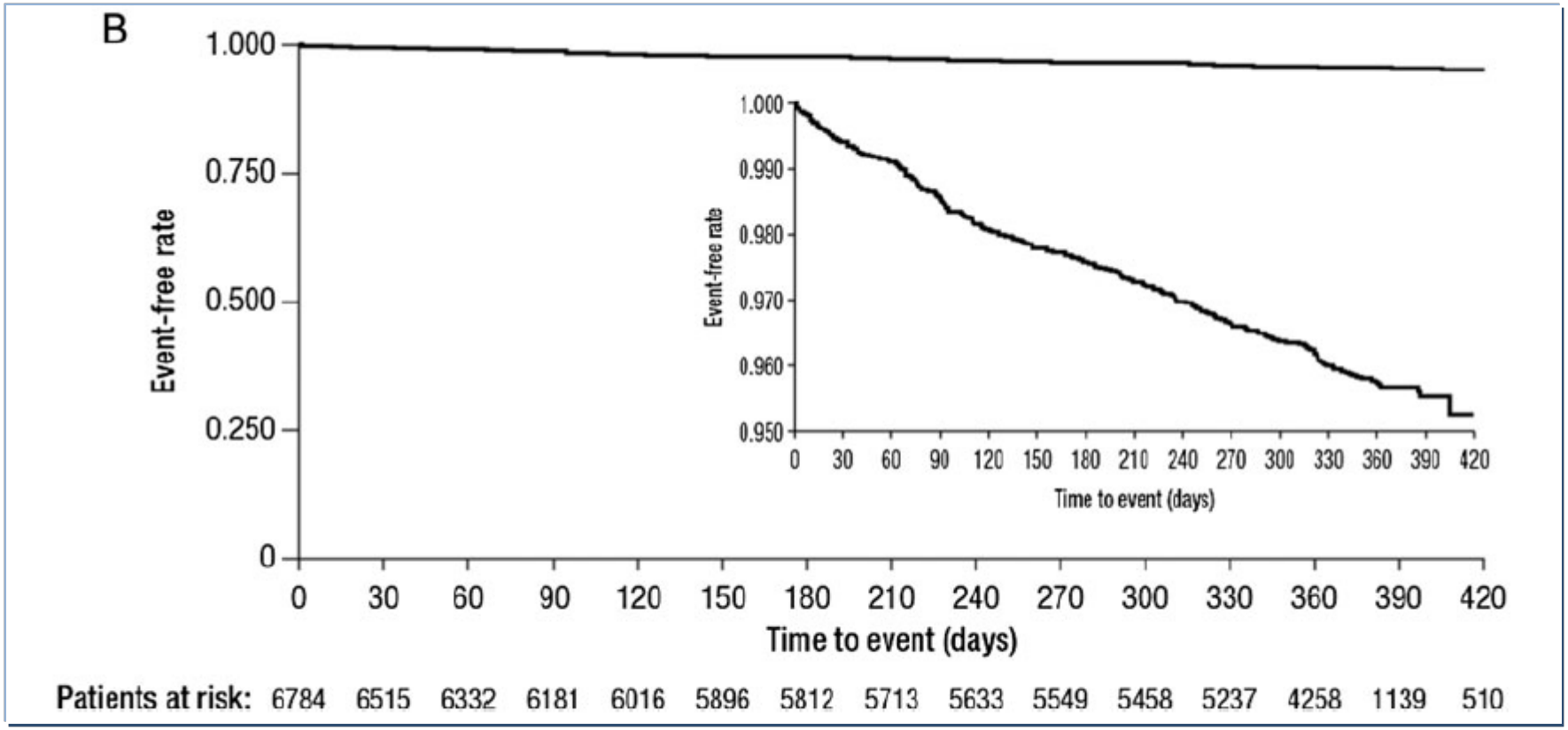
Patients at risk:

All-cause death	6784	6530	6349	6211	6054	5938	5853	5754	5679	5597	5512	5295	4307	1153	514
Major bleeding	6784	6522	6340	6197	6033	5909	5824	5726	5649	5559	5471	5256	4273	1144	513
Stroke/systemic embolism	6784	6532	6353	6216	6053	5933	5848	5752	5674	5587	5499	5282	4296	1149	513

Xantus Investigators, Eur Heart J. 2015 Sep 1

XANTUS Study: Event-free rate

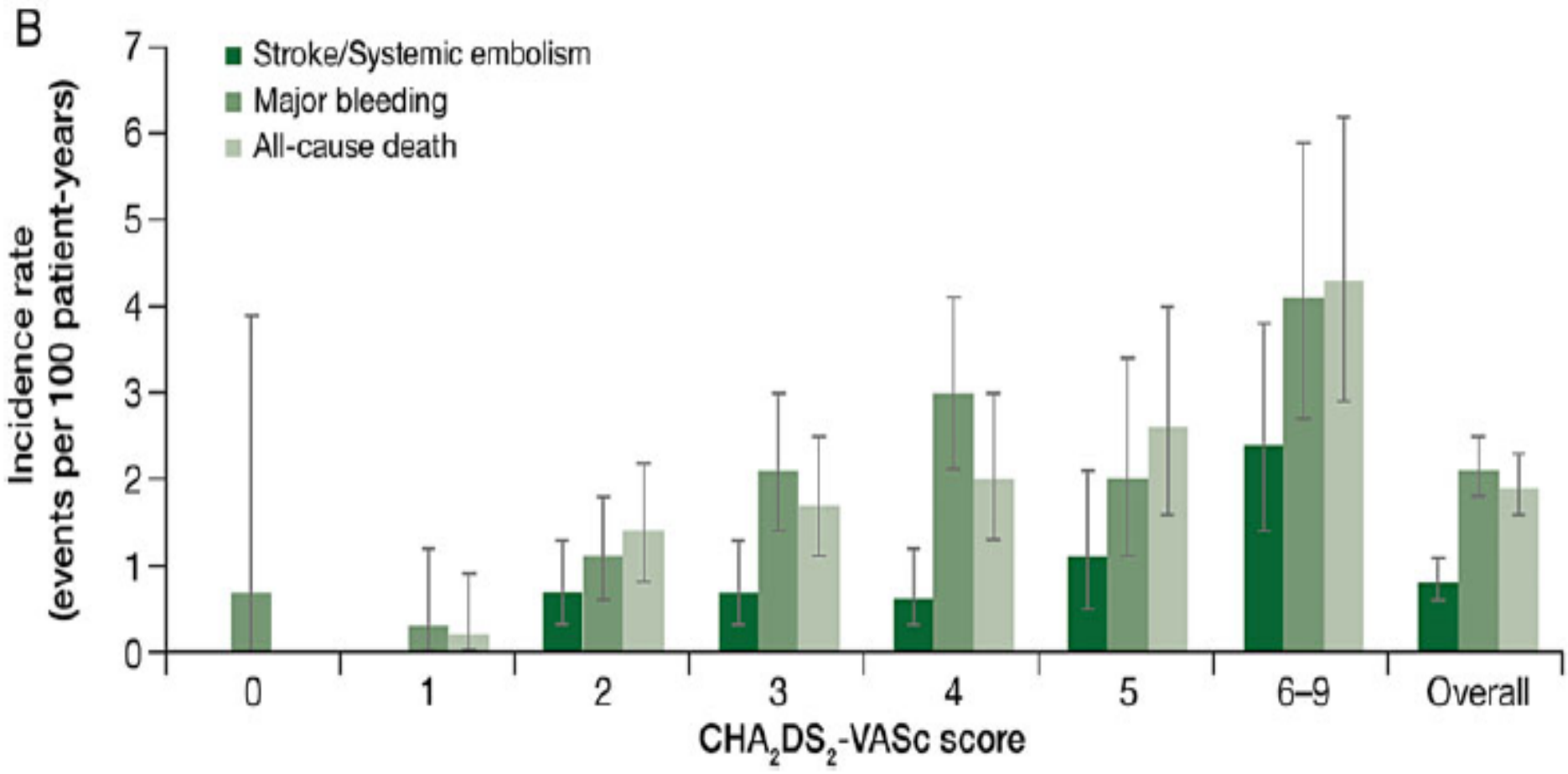
Event-free rate for treatment-emergent all-cause death, major bleeding events, and stroke/systemic embolism



In total, 6522 (96.1%) patients did not experience any of the outcomes of treatment-emergent all-cause death, major bleeding, or stroke/systemic embolism. Safety analysis set.

Xantus Investigators, Eur Heart J. 2015 Sep 1

XANTUS Study: Outcomes as a function of CHA2DS2-VASc score



Xantus Investigators, Eur Heart J. 2015 Sep 1

XANTUS Study: Crea Clearance

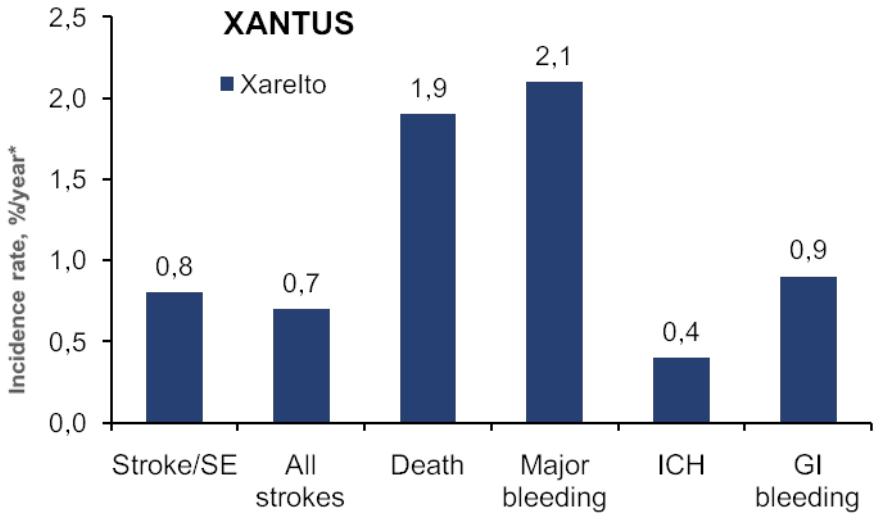
9.4% had documented severe or moderate renal impairment (creatinine clearance < 50 mL/min)

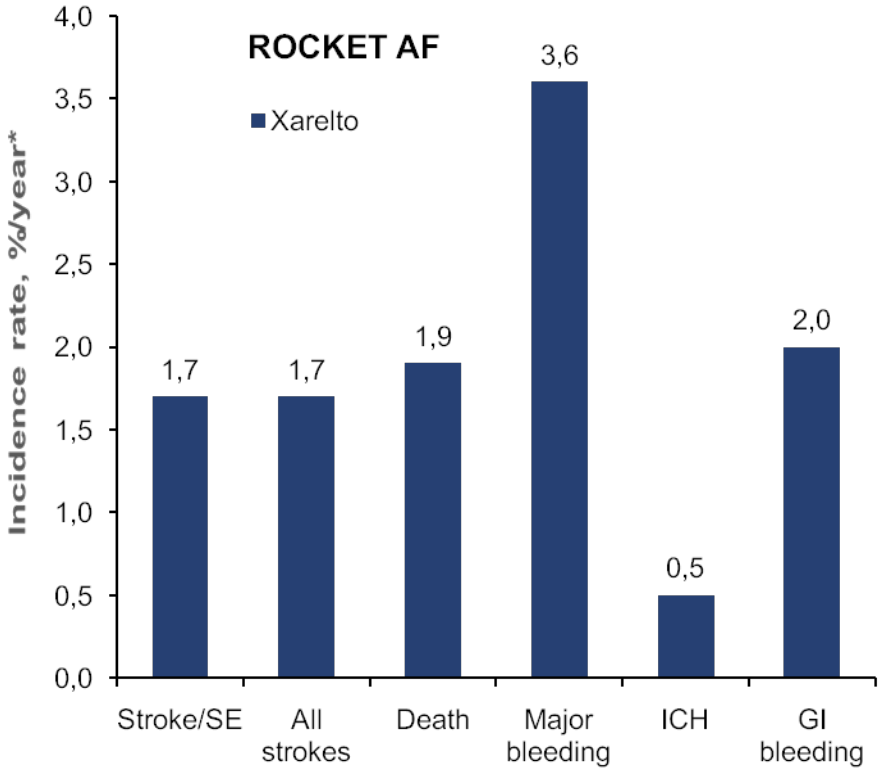
Creatinine clearance (mL/min), *n* (%)	
<15	20 (0.3)
≥15 to <30	75 (1.1)
≥30 to <50	545 (8.0)
≥50 to ≤80	2354 (34.7)
>80	1458 (21.5)
Missing	2332 (34.4)

Xantus Investigators, Eur Heart J. 2015 Sep 1

Comparison of Main Outcomes: XANTUS versus ROCKET AF

	$CHADS_2$	Prior stroke#
ROCKET AF[1]	3.5	55%
XANTUS[2]	2.0	19%





#Includes prior stroke, SE or TIA; *Events per 100 patient-years

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

International Journal of Cardiology 203 (2016) 882–884

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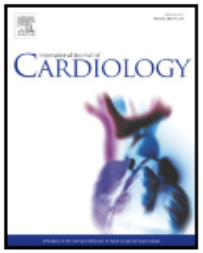


Correspondence

REal-LIfe Evidence of stroke prevention in patients with atrial Fibrillation — The RELIEF study

Craig I. Coleman [a,*], Matthias Antz [b], Birgit Ehlken [c], Thomas Evers [d]

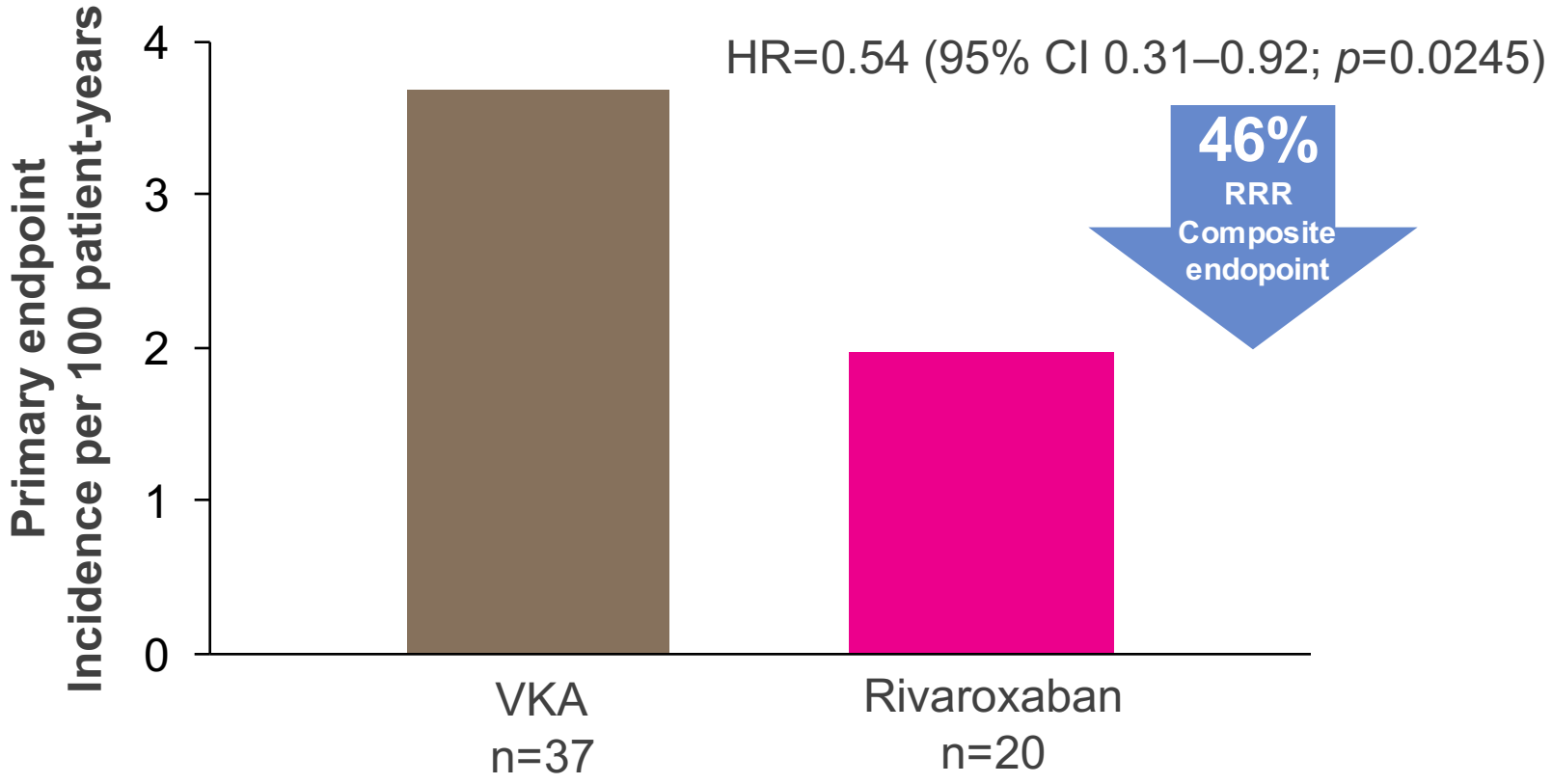
[a] University of Connecticut School of Pharmacy, Storrs, CT, USA
[b] Hospital Oldenburg, Department of Cardiology, Oldenburg, Germany
[c] IMS Health, Munich, Germany
[d] Bayer Pharma AG, Wuppertal, Germany

Primary objective: retrospective database analysis to compare the effectiveness of newly initiated Rivaroxaban or VKA in patients with NVAF in German primary care

Primary endpoint: Composite of ischaemic stroke, TIA , ICH, other non-traumatic ICH (including subdural haemorrhage), MI

Coleman CI et al., Int J Cardiol 203 (2016) 882-884

RELIEF Lower Rates of Clinically Relevant CV Events* Compared with VKA Treatment



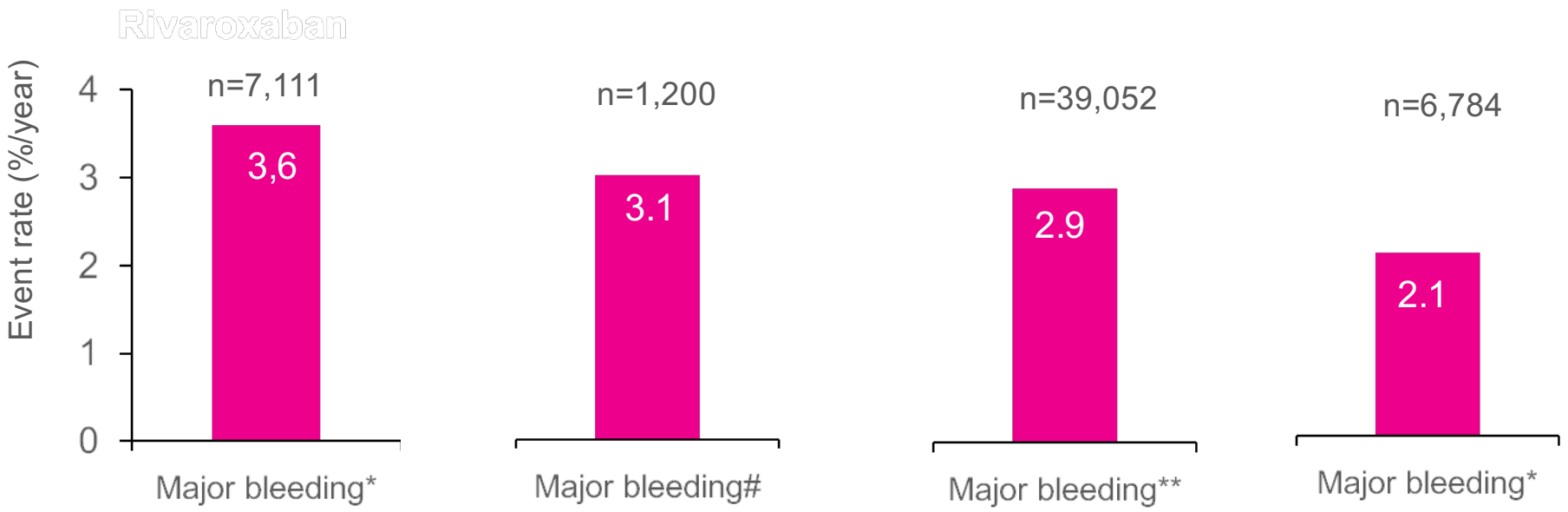
Rates of most individual endpoints of the composite were numerically less frequent with Rivaroxaban

* CV events include ischemic stroke, TIA, ICH, MI

Coleman CI et al., Int J Cardiol 2015

Major Bleeding Rates with Rivaroxaban: Low and consistent in clinical trial and real life setting

Data on more than **54.000** rivaroxaban treated patients

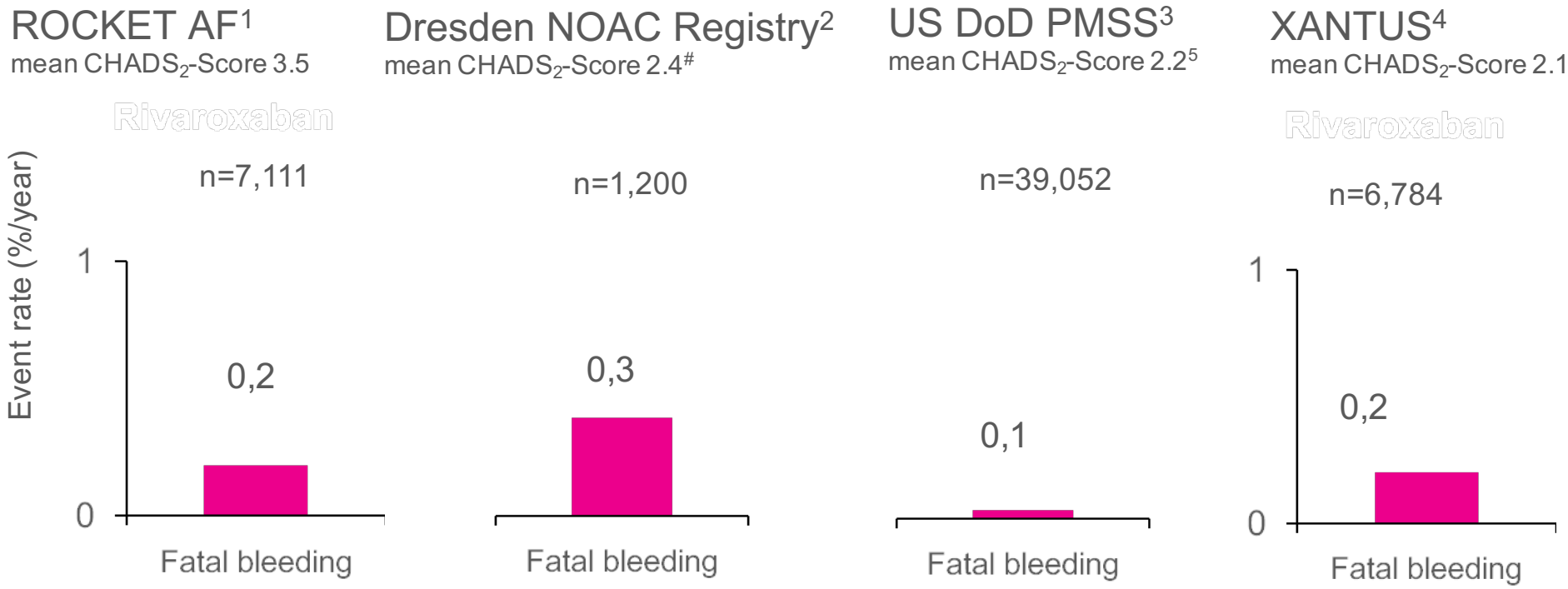


*Major bleeding definitions according to ISTH; # modified ISTH definition (additionally included surgical revision from bleeding)
**Major bleeding was defined by the Cunningham algorithm[3]
#55th ASH Meeting 2013, Oral presentation, Abstract 213, https://ash.confex.com/ash/2013/webprogram/Paper58333.html

1. Patel MR et al. *N Engl J Med* 2011; 365(10):883–891; 2. Beyer—Westendorf et al. Blood 2014;124(6); 955-962; 3. Peacok ESC 2015; 4. Camm et al Eur Heart J 2015; 5. Tamayo et al. *Clin Cardiol* 2015

Fatal Bleeding Rates with Rivaroxaban in Real Life Studies are Consistent with Findings from ROCKET AF

Data on more than **54.000** rivaroxaban treated patients



#55th ASH Meeting 2013, Oral presentation, Abstract 213, https://ash.confex.com/ash/2013/webprogram/Paper58333.html

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Indications for NOACs

Table 1 **Valvular indications and contraindications for NOAC therapy in AF patients**

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[8]

Grazie dell'attenzione