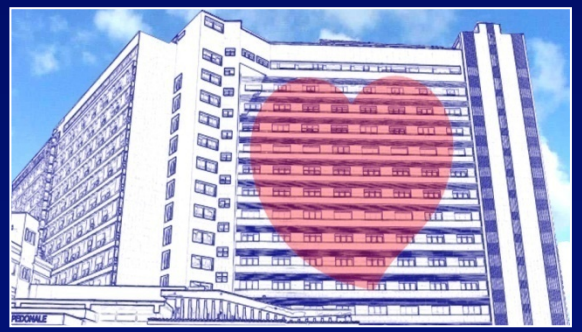
I NAO NELLA FIBRILLAZIONE ATRIALE: DALLA RICERCA CLINICA AL MONDO REALE

Emoclinic Symposium “Focus in cardioncologia e implicazioni medico-legali nell’emergenza-urgenza”

Baveno (VB), 6 Maggio 2016

Giuseppe Di Pasquale
Direttore Dipartimento Medico ASL Bologna
Direttore Unità Operativa Cardiologia
Ospedale Maggiore, Bologna



Giuseppe Di Pasquale Disclosures

- Member of the Steering Committee of the RELY, PALLAS, and GLORIA AF
- Member of Advisory Board of Dabigatran, Rivaroxaban, Apixaban, Dronedarone, Edoxaban
- Consulting fees / honoraria
  Boehringer Ingelheim, Bayer AG, Sanofi Aventis
  BMS / Pfizer, Daiichi Sankyo

Stroke Prevention in Atrial Fibrillation

Major Advantages of NOACs

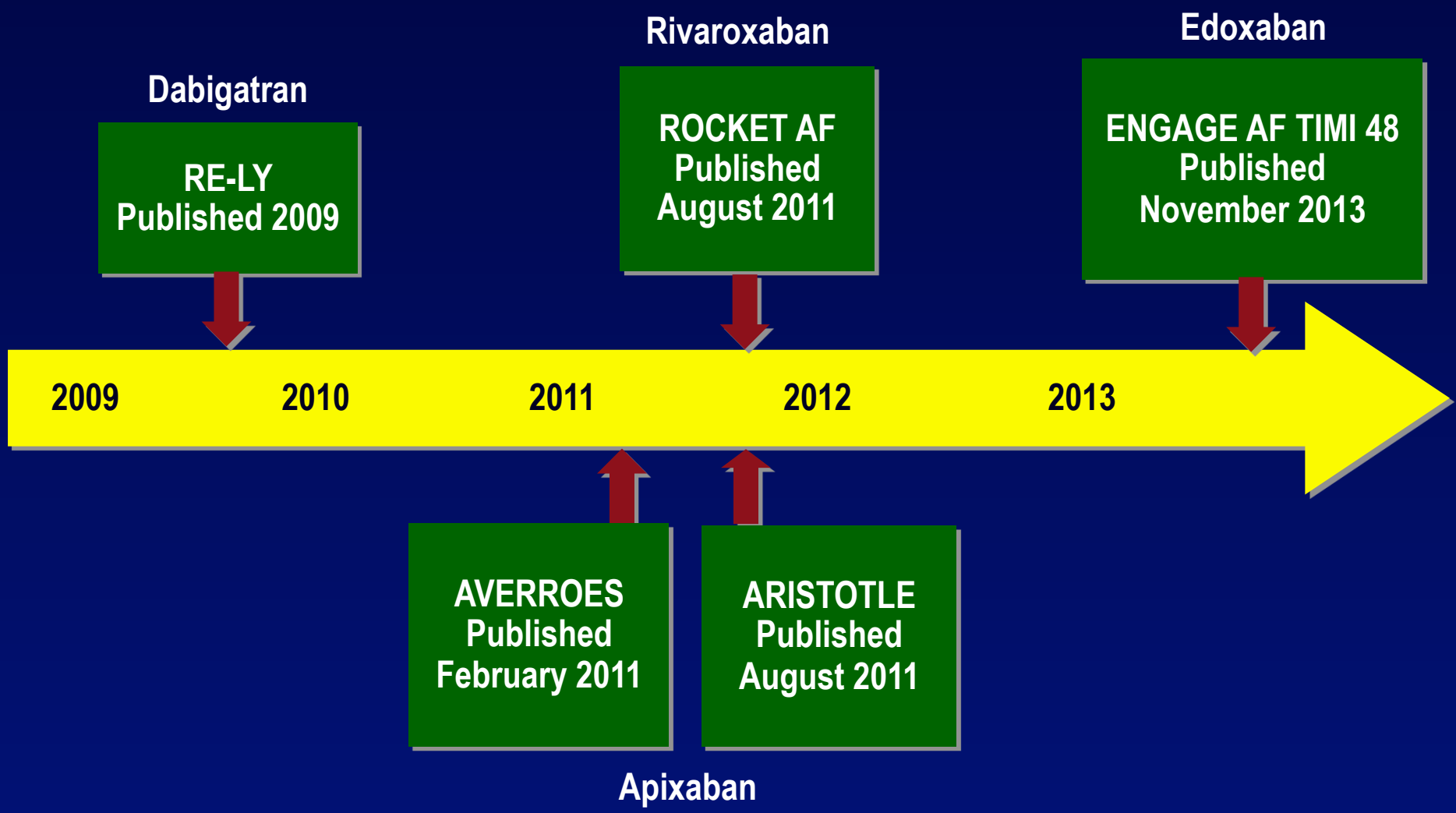
- Efficacy
- Safety
- Convenience

Advantages of NOACs vs. Warfarin

Feature	Warfarin	New agents
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Interactions	Many	Few
Monitoring	Yes	No
Offset	Long	Shorter

Weitz JI, Gross PL, Am Soc Hematol Educ Program 2012;2012:536-40

Atrial Fibrillation: NOACs Phase 3 Study Timelines



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

November 19, 2013

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

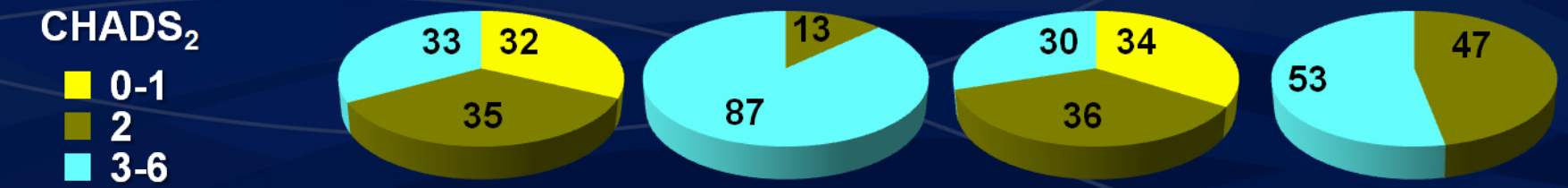
NOACs Trials Summary

	RE-LY[5]	ROCKET-AF[6]	ARISTOTLE[7]	ENGAGE-AF[8]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Drug target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Renal clearance	~80%	~35%	~25%	~50%
Drug dosing	150 mg twice a day; 110 mg twice a day	20 mg once a day (15 mg for creatinine clearance <50 mL/min)	5 mg twice a day (2·5 mg when two of three following criteria are met: age ≥80 years, weight ≤60 kg, creatinine ≥1·5 mg/dL [133 µmol/L])	60 mg once a day (30 mg for creatinine clearance 30–50 mL/min, weight ≤60 kg, or strong P-glycoprotein inhibitor
Drug metabolism	P-glycoprotein and CYP3A4	P-glycoprotein and CYP3A4	P-glycoprotein and CYP3A4	P-glycoprotein
Mean CHADS score	2·1	3·5	2·1	2·8
Design	Open label (dabigatran *vs* warfarin)	Blinded	Blinded	Blinded

Freek W A Verheugt, Christopher B Granger. The lancet Published online March 14, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60245-8 3

NOAC AF Studies: Baseline characteristics

	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF (Edoxaban)
Randomized, n	18,113	14,264	18,201	21,105
Age, years	72 ± 9	73 [65-78]	70 [63-76]	72 [64-78]
Female, %	37	40	36	39
Ø $CHADS_2$ score	2.1	3.5	2.1	2.8
Paroxysmal AF, %	32	18	15	25
Prior stroke/TIA, %	20	55	19	28
VKA naïve, %	50	38	43	41
Aspirin use, %	40	36	31	29
Median follow-up, years	2.0	1.9	1.8	2.8
Median TTR, %	66	58	66	68

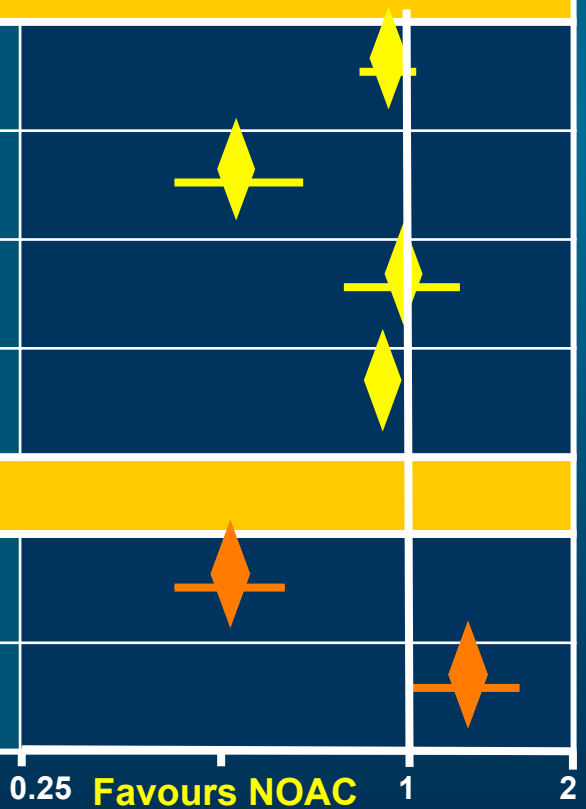


1. Connolly SJ et al. N Engl J Med 2009;361:1139-1151; 2. Patel MR et al. N Engl J Med 2011;365:883-891;
3. Granger CB et al. N Engl J Med 2011;365:981-992; 4. Giugliano RP et al. N Engl J Med 2013;369:2093-2104.

Efficacy and Safety of NOACs

4-trial Meta-analysis Full Dose

Measure	Pooled NOAC Events /Total	Pooled Warfarin Events /Total	Risk Ratio	95% CIs	p	Outcome
Efficacy						
Ischaemic Stroke	665 /29292	724 /29221	0.92	0.83-1.02	0.10	
Hemorrhagic stroke	130 /29292	263 /29221	0.49	0.38-0.64	<0.0001	
Myocardial Infarction	413 /29292	432 /29221	0.97	0.78-1.20	0.97	
All-cause mortality	2022 /29292	2245 /29221	0.90	0.851-0.95	0.0003	
Safety						
Intracranial hemorrhage	204 /29287	425 /29211	0.48	0.39-0.59	<0.0001	
Gastrointestinal bleeding	751 /29287	591 /29211	1.25	1.01-1.55	0.043	



Ruff C, et al. Lancet 2014;383:955-62

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

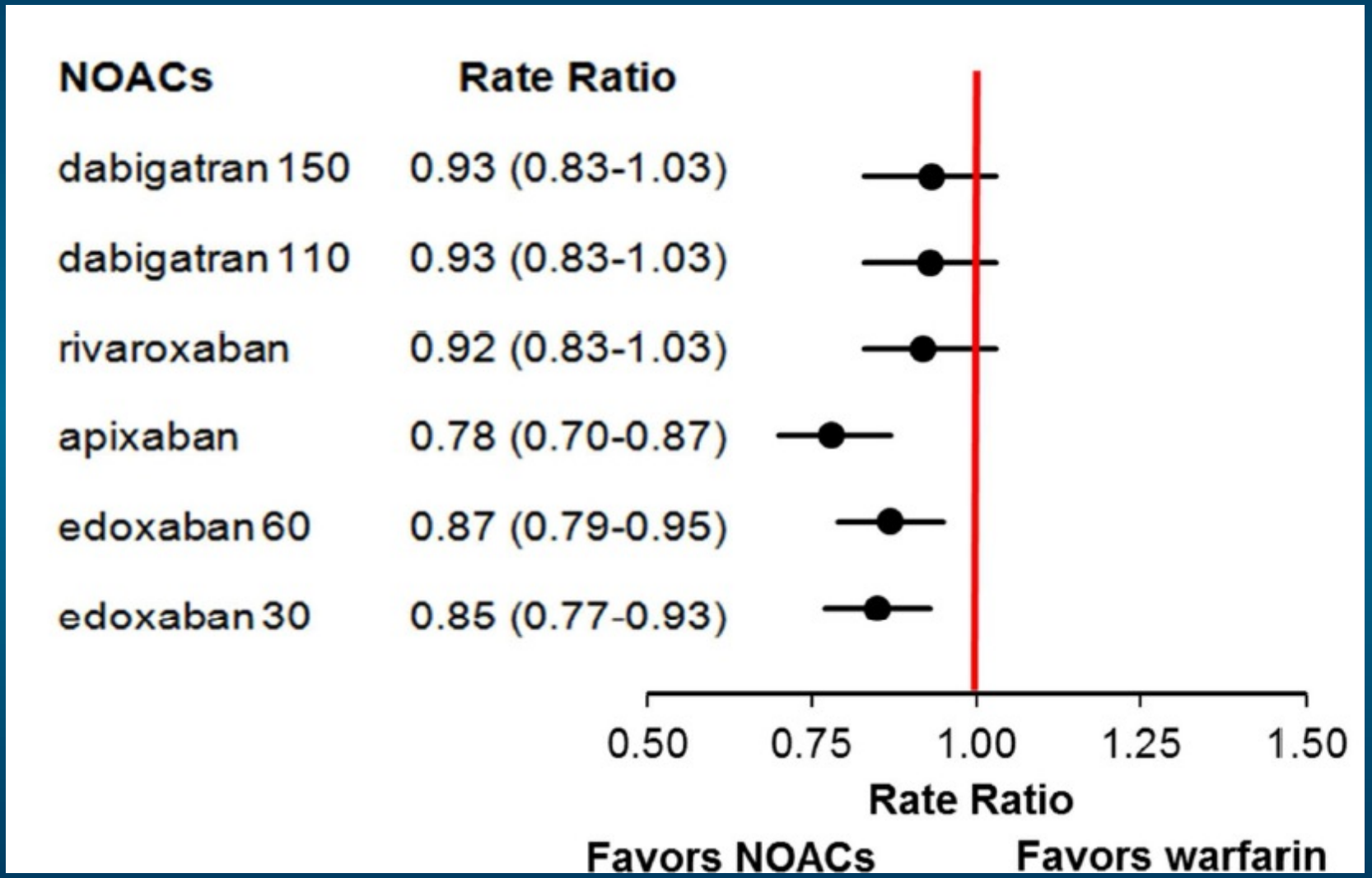
Net Clinical Benefit of Non-vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Phase III Atrial Fibrillation Trials

Giulia Renda, MD, PhD,[a] Marta di Nicola, PhD,[b] Raffaele De Caterina, MD, PhD[a,c]

[a]*Institute of Cardiology, Department of Neurosciences, Imaging and Clinical Sciences-Center of Excellence on Aging, "G. d'Annunzio" University, Chieti, Italy;* [b]*Laboratory of Biostatistics, Department of Experimental and Clinical Sciences, "G. d'Annunzio" University, Chieti, Italy;* [c]*"G. Monasterio" Foundation, Pisa, Italy.*

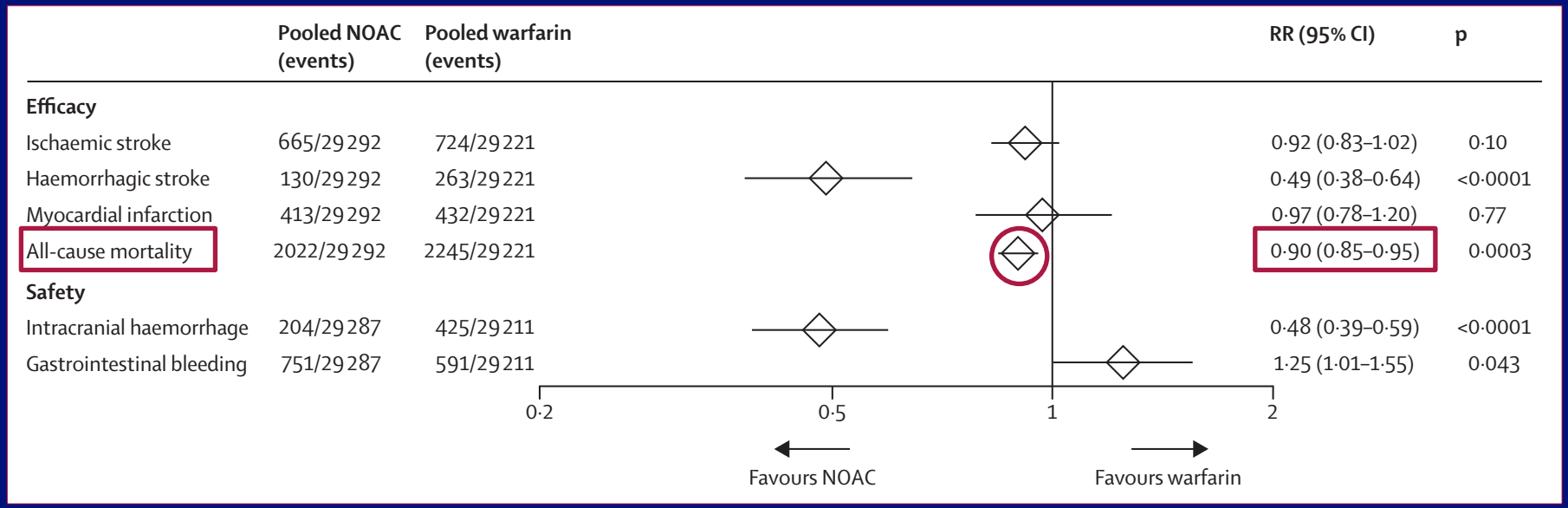
Am J Med. 2015; 128: 1007-1014

Unweighed composite of ischemic stroke + SE + MI + hemorrhagic stroke + adjusted major bleeding



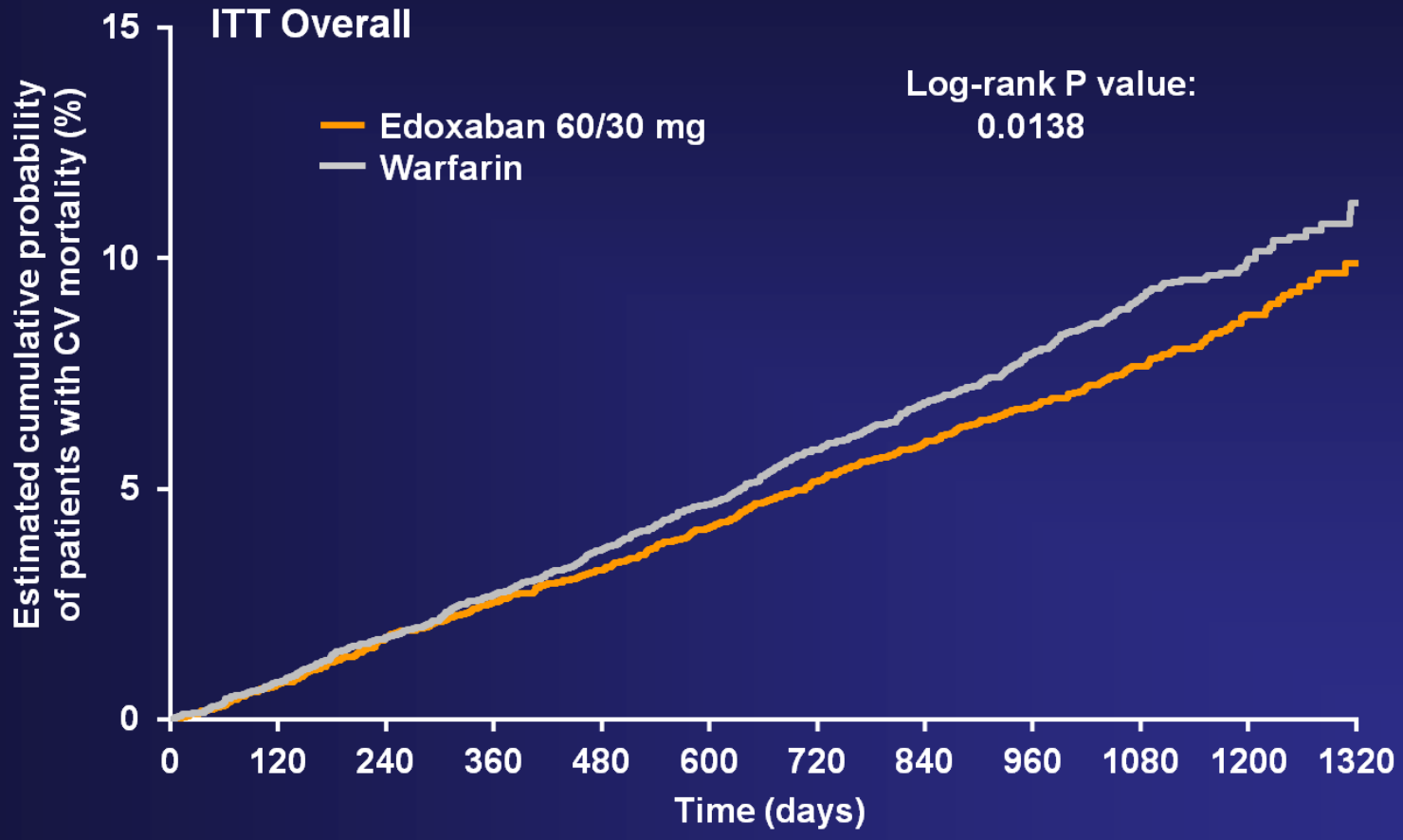
Renda G. et al. The American Journal of Medicine 2015

Secondary efficacy and safety outcomes



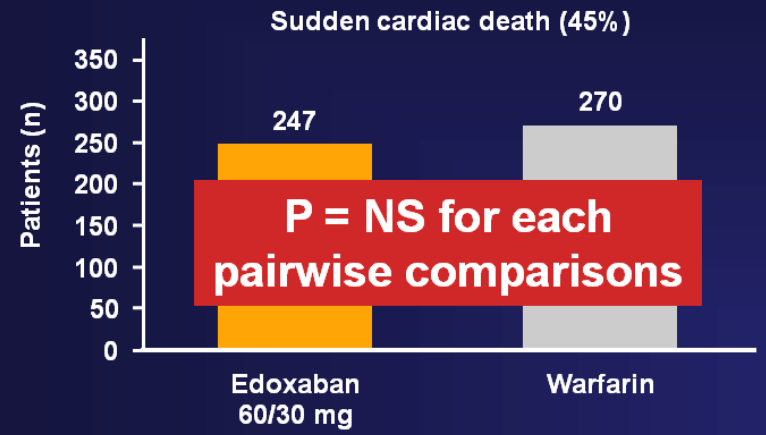
Ruff CT et al. Lancet, December 4 , 2013

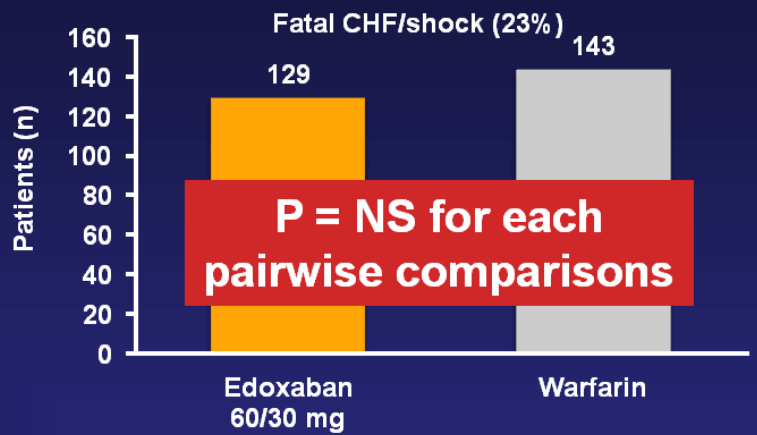
Cardiovascular Mortality
(KM Estimate)

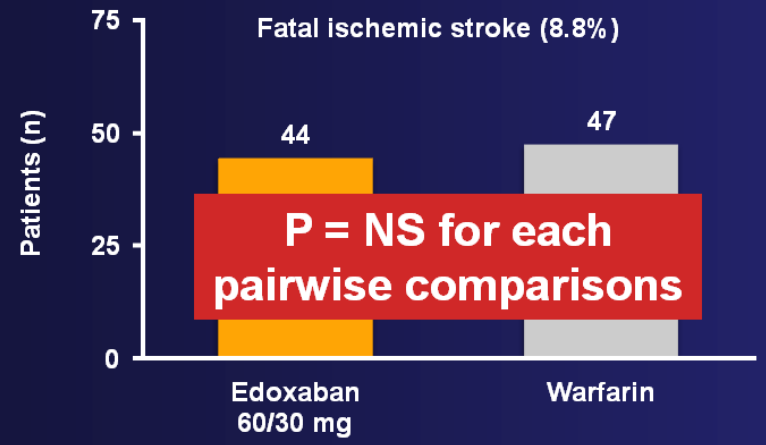


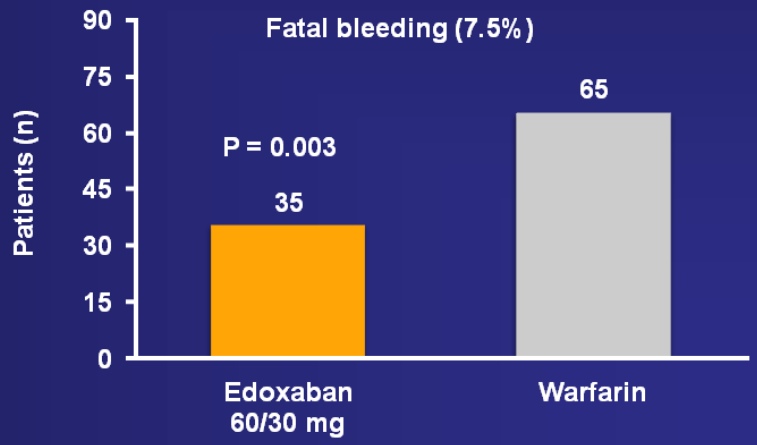
Giugliano et al. NEJM 2013;369:2093–104

Top Four Types of CV Death



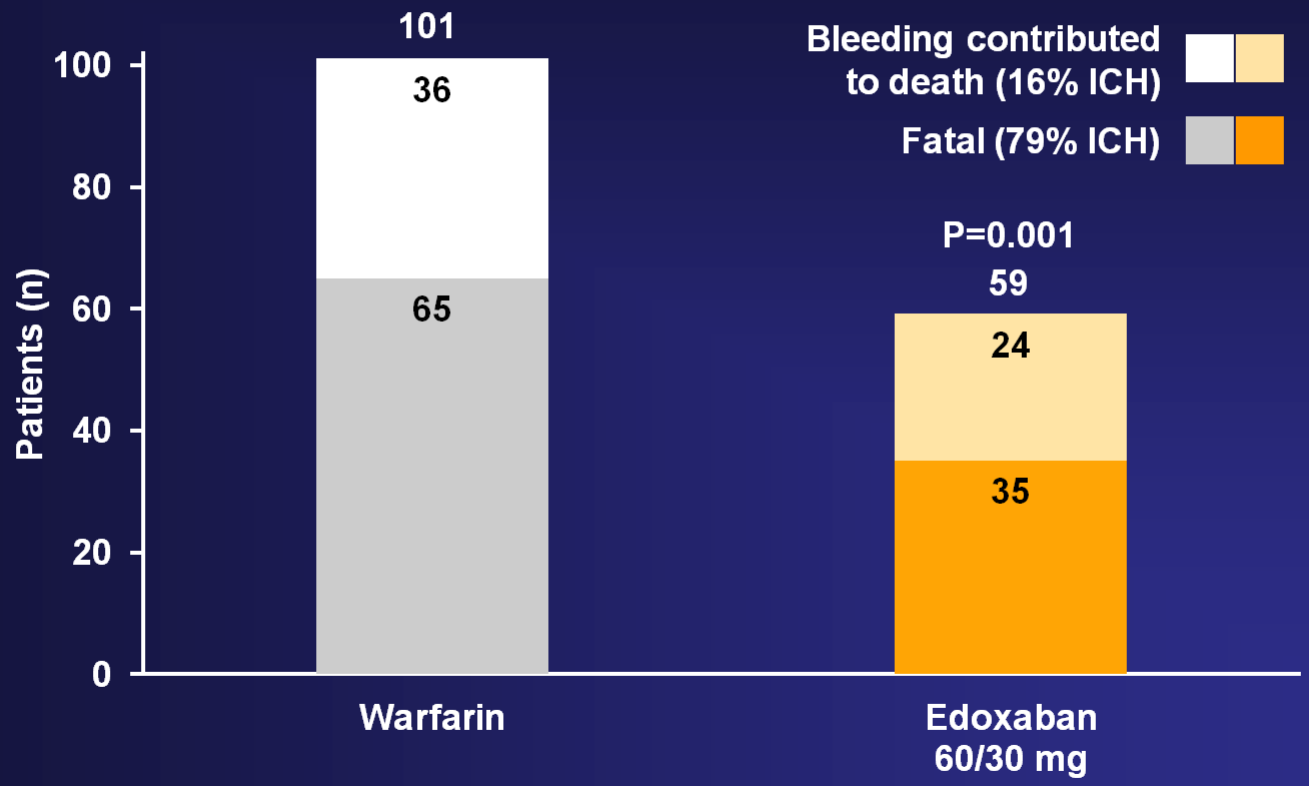






Giugliano et al. Eur Heart J. 2014;35(Suppl 1):867

Fatal Bleeds and Bleeds Contributing to Death

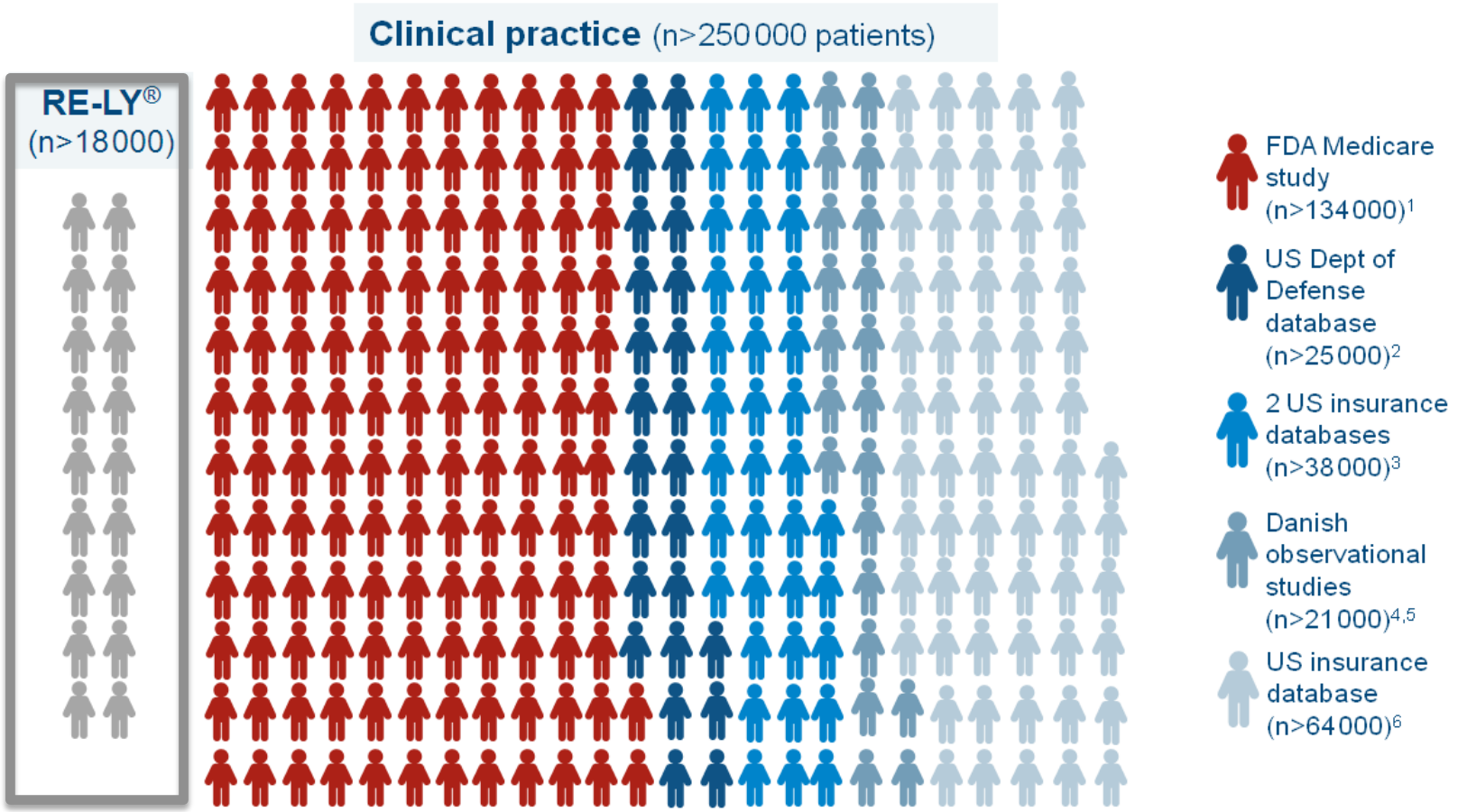


mITT Overall
ICH = Intracranial hemorrhage

Giugliano et al. Eur Heart J. 2014;35(Suppl 1):867

Dai trial al real world

Growing body of real-world experience from >250 000 patients confirms safety and efficacy profile of dabigatran



In the USA, the licensed doses for Pradaxa® are: Pradaxa® 150 mg BID and Pradaxa® 75 mg BID for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF

1. Graham DJ et al. Circulation 2015; **2.** Villines TC et al. Circulation 2014; **3.** Seeger J et al. Circulation 2014; **4.** Larsen TB et al. Am J Med 2014a; **5.** Larsen TB et al. Am J Med 2014b; **6.** Lauffenburger JC et al. J Am Heart Assoc 2015

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Rongmei Zhang, PhD; Mary Ross Southworth, PharmD; Mark Levenson, PhD; Ting-Chang Sheu, MPH; Katrina Mott, MHS; Margie R. Goulding, PhD; Monika Houstoun, PharmD, MPH; Thomas E. MaCurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMSc

Background—The comparative safety of dabigatran versus warfarin for treatment of nonvalvular atrial fibrillation in general practice settings has not been established.

Methods and Results—We formed new-user cohorts of propensity score–matched elderly patients enrolled in Medicare who initiated dabigatran or warfarin for treatment of nonvalvular atrial fibrillation between October 2010 and December 2012. Among 134 414 patients with 37 587 person-years of follow-up, there were 2715 primary outcome events. The hazard

Circulation 2015;131:157-64

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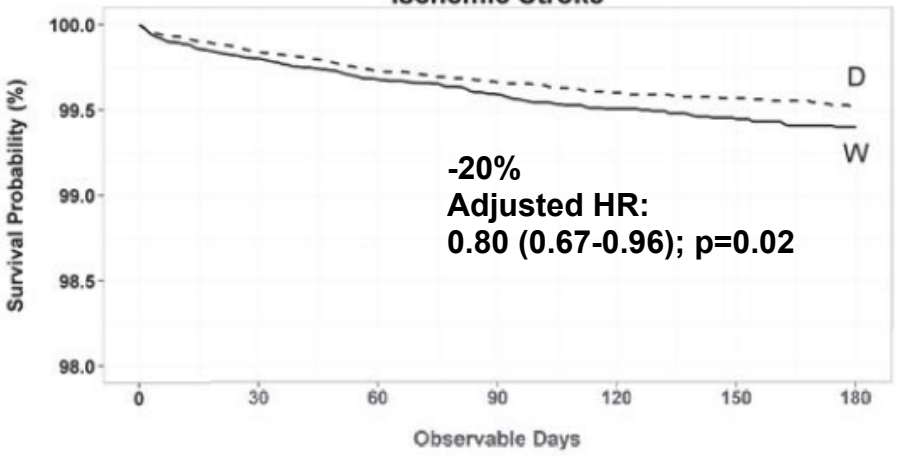
Conclusions—In general practice settings, dabigatran was associated with reduced risk of ischemic stroke, intracranial hemorrhage, and death and increased risk of major gastrointestinal hemorrhage compared with warfarin in elderly patients with nonvalvular atrial fibrillation. These associations were most pronounced in patients treated with dabigatran 150 mg twice daily, whereas the association of 75 mg twice daily with study outcomes was indistinguishable from warfarin except for a lower risk of intracranial hemorrhage with dabigatran. **(*Circulation*. 2015;131:157-164. DOI: 10.1161/CIRCULATIONAHA.114.012061.)**

Ischemic Stroke

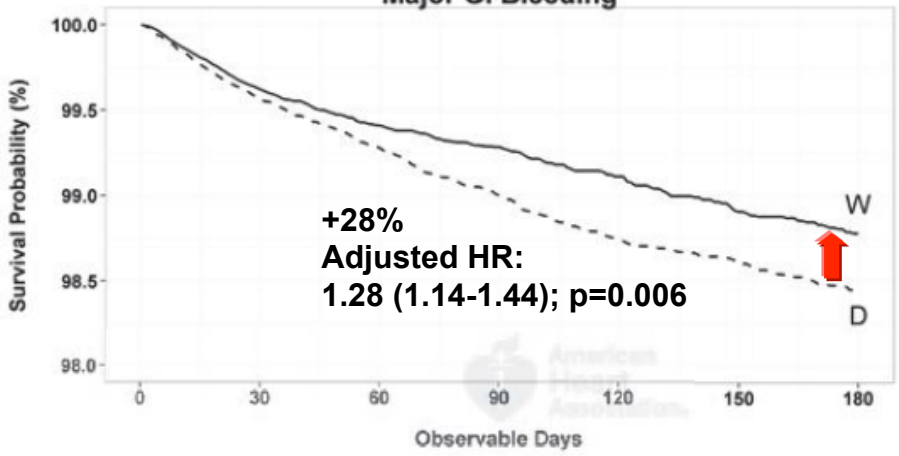


-20%
Adjusted HR:
0.80 (0.67-0.96); p=0.02

Number at Risk

Warfarin (W)	67,207	60,238	40,757	31,740	17,550	13,812	11,389
Dabigatran (D)	67,207	61,498	34,258	25,686	17,365	13,715	11,208

Major GI Bleeding

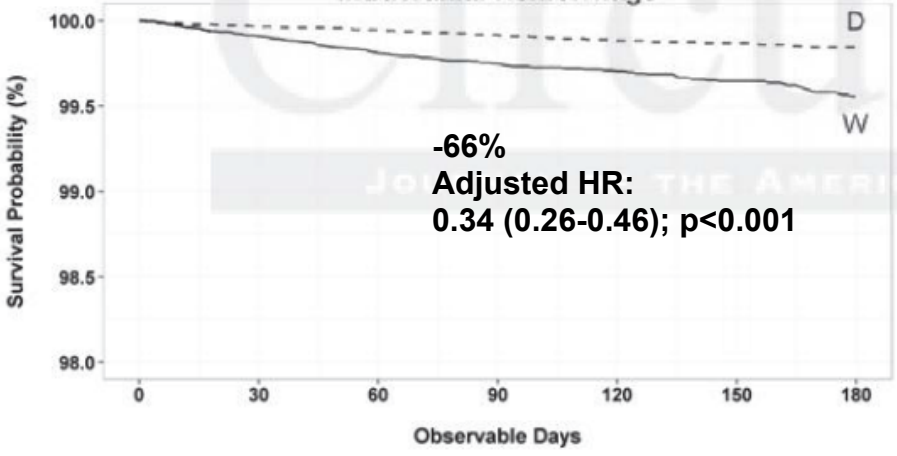


+28%
Adjusted HR:
1.28 (1.14-1.44); p=0.006

Number at Risk

Warfarin (W)	67,207	60,238	40,757	31,740	17,550	13,812	11,389
Dabigatran (D)	67,207	61,498	34,258	25,686	17,365	13,715	11,208

Intracranial Hemorrhage

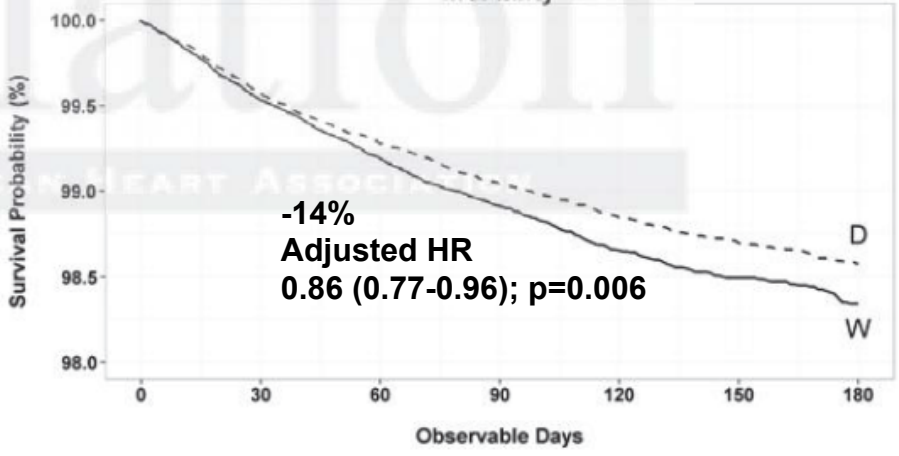


-66%
Adjusted HR:
0.34 (0.26-0.46); p<0.001

Number at Risk

Warfarin (W)	67,207	60,238	40,757	31,740	17,550	13,812	11,389
Dabigatran (D)	67,207	61,498	34,258	25,686	17,365	13,715	11,208

Mortality



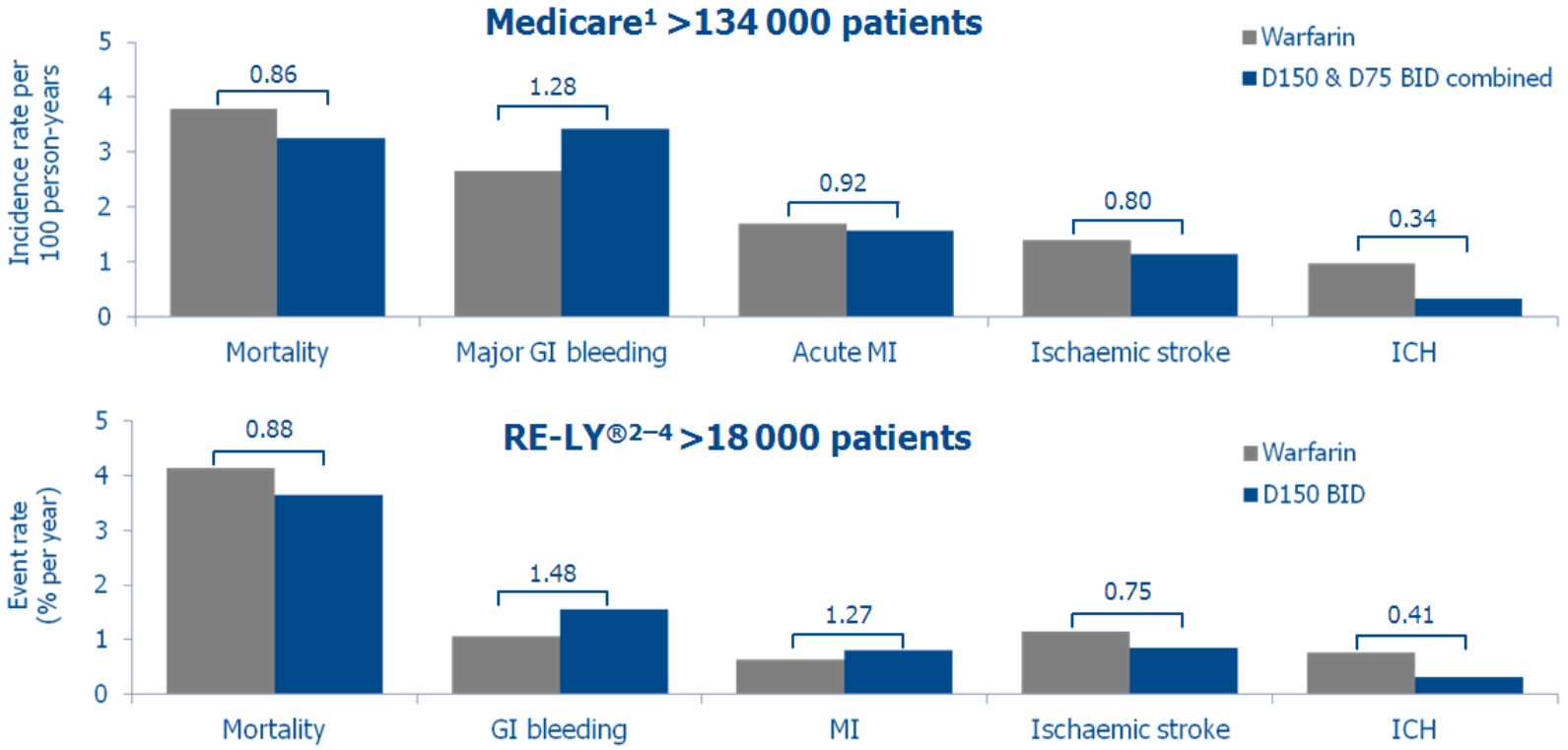
-14%
Adjusted HR
0.86 (0.77-0.96); p=0.006

Number at Risk

Warfarin (W)	67,207	60,921	41,062	31,907	17,659	13,875	11,440
Dabigatran (D)	67,207	62,145	34,537	25,852	17,468	13,765	11,255

Graham DJ et al. Circulation 2014; October 30

Independent FDA Medicare analysis findings are consistent with findings from RE-LY®



Independent FDA analysis confirmed the favourable benefit–risk profile of dabigatran in clinical practice

In the USA, the licensed doses for Pradaxa® are: Pradaxa® 150 mg BID and Pradaxa® 75 mg BID for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF

Numbers on bars denote HRs vs warfarin. D75 = dabigatran 75 mg; D150 = dabigatran 150 mg

1. Available at http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm; accessed September 2014; **2.** Connolly SJ et al. N Engl J Med 2009;361:1139–51; **3.** Connolly SJ et al. N Engl J Med 2010;363:1875–6; **4.** Pradaxa®: EU SPC, 2014

The increased risk of major gastrointestinal bleeding with dabigatran was restricted to women aged ≥75 years and to men aged ≥85 years

	Age-group (n)	Men Hazard ratio (95% CI)	Women Hazard ratio (95% CI)
Ischemic stroke			
	65-74 (55,761)	0.69 (0.42-1.14)	0.81 (0.51-1.31)
	75-84 (57,345)	0.98 (0.64-1.51)	0.89 (0.64-1.26)
	≥ 85 (21,308)	0.89 (0.41-1.90)	0.60 (0.40-0.91)
Intracranial hemorrhage			
	65-74 (55,761)	0.32 (0.15-0.68)	0.13 (0.04-0.44)
	75-84 (57,345)	0.27 (0.14-0.50)	0.59 (0.35-0.98)
	≥ 85 (21,308)	0.51 (0.18-1.48)	0.26 (0.12-0.56)
Major GI bleeding			
	65-74 (55,761)	0.83 (0.60-1.14)	0.99 (0.72-1.37)
	75-84 (57,345)	1.02 (0.79-1.31)	1.50 (1.20-1.88)
	≥ 85 (21,308)	1.55 (1.04-2.32)	2.18 (1.61-2.97)

Graham DJ et al. Circulation 2014; 131: 157-164

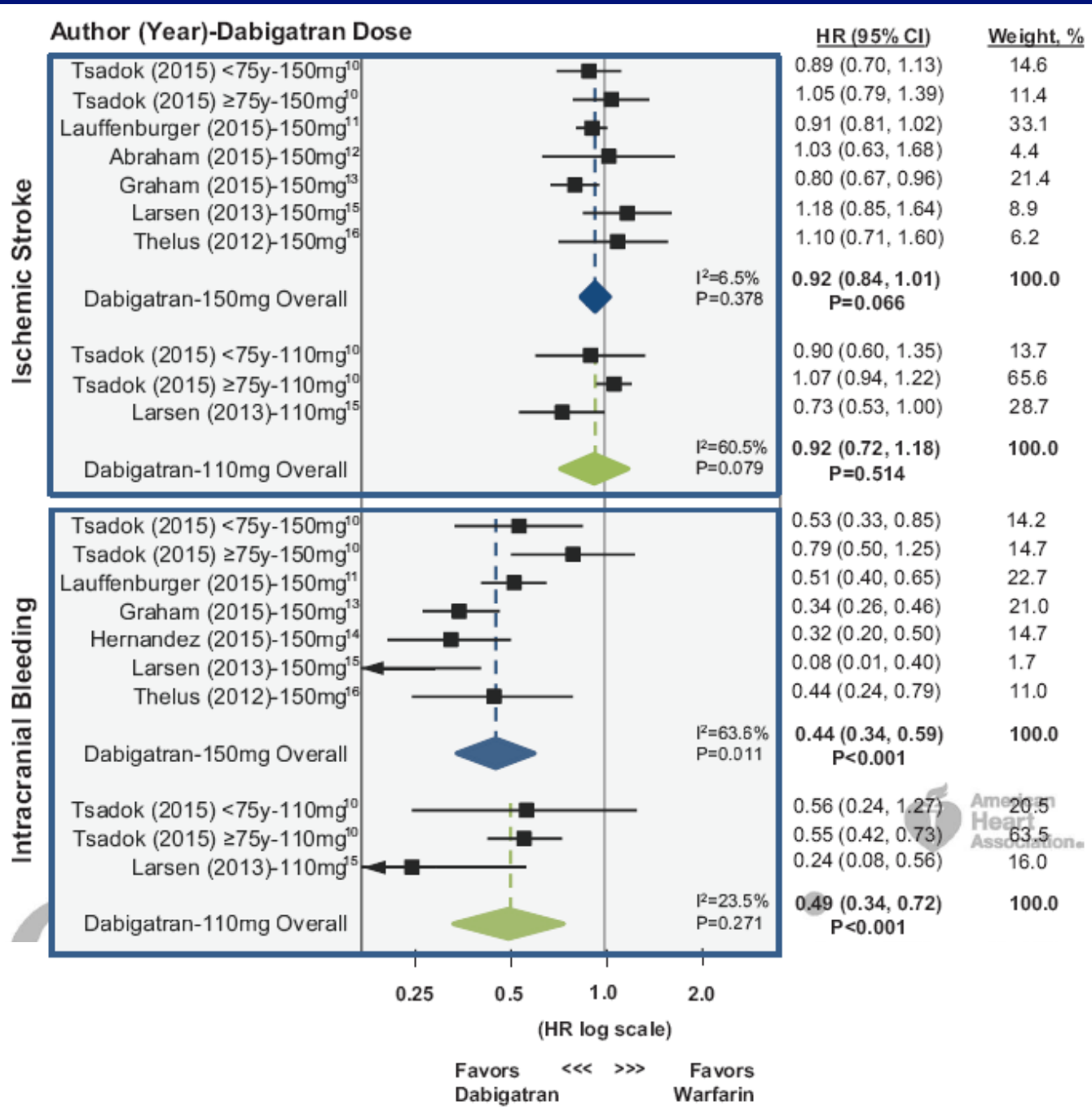
Original Article

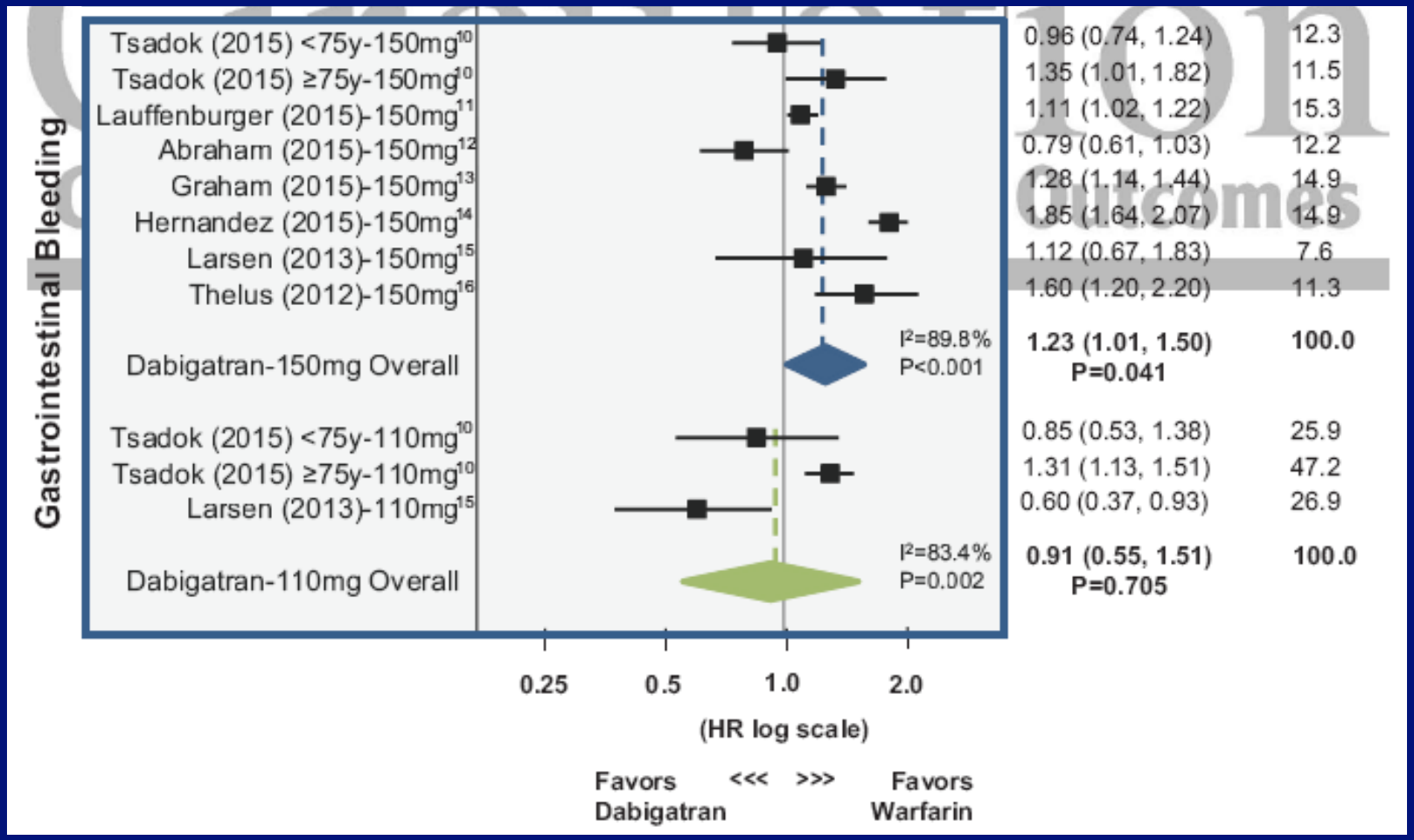
Dabigatran Versus Warfarin for Atrial Fibrillation in Real-World Clinical Practice

A Systematic Review and Meta-Analysis

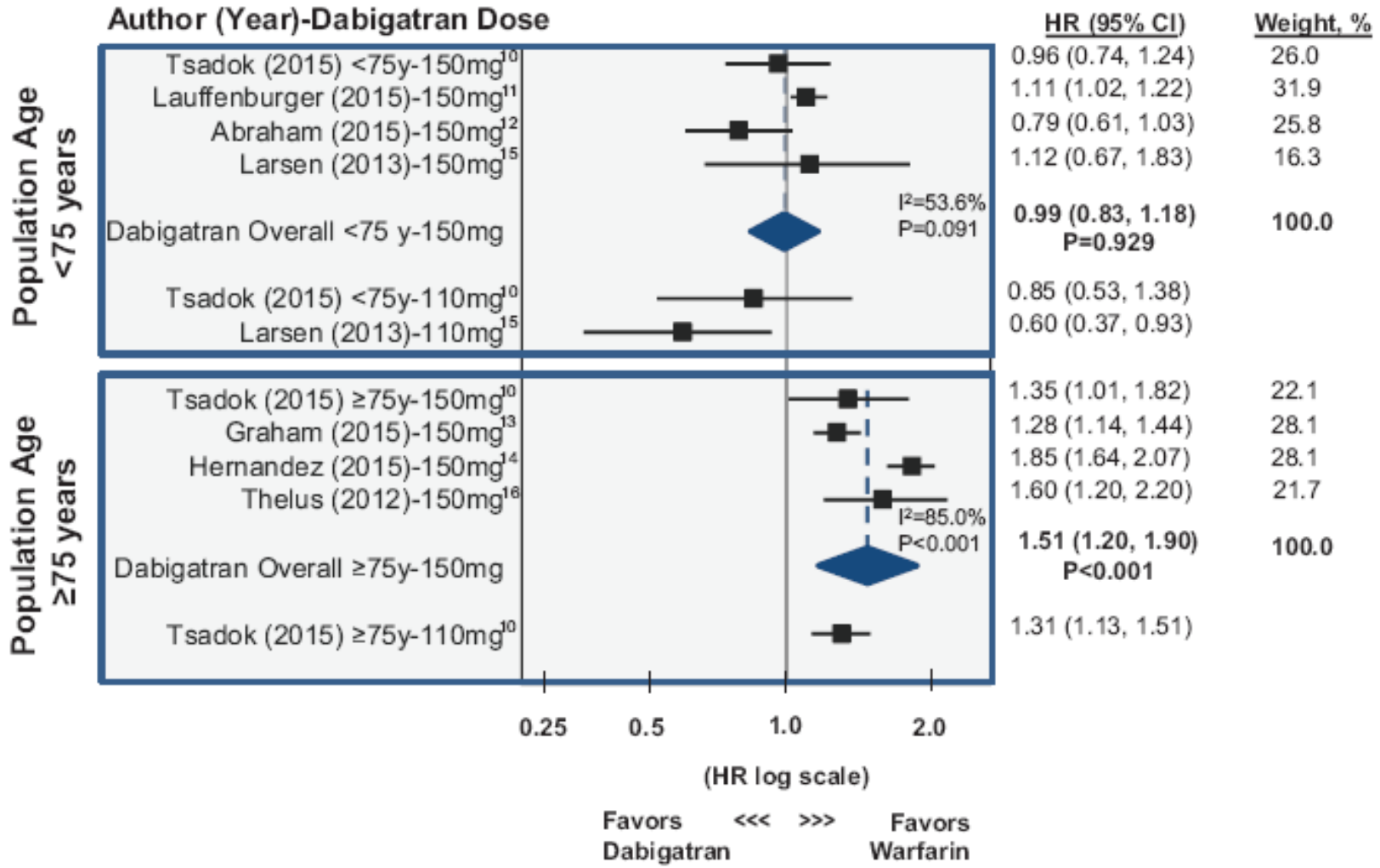
Robert J. Romanelli, PhD, MPH; Laura Nolting, BS; Marina Dolginsky, BS;
Eunice Kym, PharmD; Kathleen B. Orrico, PharmD

Circ Cardiovasc Qual Outcomes, March 2016


Author (Year)-Dabigatran Dose
HR (95% CI)
Weight, %
Ischemic Stroke
Tsadok (2015) <75y-150mg[10] 0.89 (0.70, 1.13) 14.6
Tsadok (2015) ≥75y-150mg[10] 1.05 (0.79, 1.39) 11.4
Lauffenburger (2015)-150mg[11] 0.91 (0.81, 1.02) 33.1
Abraham (2015)-150mg[12] 1.03 (0.63, 1.68) 4.4
Graham (2015)-150mg[13] 0.80 (0.67, 0.96) 21.4
Larsen (2013)-150mg[15] 1.18 (0.85, 1.64) 8.9
Thelus (2012)-150mg[16] 1.10 (0.71, 1.60) 6.2
Dabigatran-150mg Overall I²=6.5% P=0.378 0.92 (0.84, 1.01) P=0.066 100.0
Tsadok (2015) <75y-110mg[10] 0.90 (0.60, 1.35) 13.7
Tsadok (2015) ≥75y-110mg[10] 1.07 (0.94, 1.22) 65.6
Larsen (2013)-110mg[15] 0.73 (0.53, 1.00) 28.7
Dabigatran-110mg Overall I²=60.5% P=0.079 0.92 (0.72, 1.18) P=0.514 100.0
Intracranial Bleeding
Tsadok (2015) <75y-150mg[10] 0.53 (0.33, 0.85) 14.2
Tsadok (2015) ≥75y-150mg[10] 0.79 (0.50, 1.25) 14.7
Lauffenburger (2015)-150mg[11] 0.51 (0.40, 0.65) 22.7
Graham (2015)-150mg[13] 0.34 (0.26, 0.46) 21.0
Hernandez (2015)-150mg[14] 0.32 (0.20, 0.50) 14.7
Larsen (2013)-150mg[15] 0.08 (0.01, 0.40) 1.7
Thelus (2012)-150mg[16] 0.44 (0.24, 0.79) 11.0
Dabigatran-150mg Overall I²=63.6% P=0.011 0.44 (0.34, 0.59) P<0.001 100.0
Tsadok (2015) <75y-110mg[10] 0.56 (0.24, 1.27) 20.5
Tsadok (2015) ≥75y-110mg[10] 0.55 (0.42, 0.73) 63.5
Larsen (2013)-110mg[15] 0.24 (0.08, 0.56) 16.0
Dabigatran-110mg Overall I²=23.5% P=0.271 0.49 (0.34, 0.72) P<0.001 100.0
0.25
0.5
1.0
2.0
(HR log scale)
Favors Dabigatran
<<< >>>
Favors Warfarin



Circ Cardiovasc Qual Outcomes, March 2016



Circ Cardiovasc Qual Outcomes, March 2016

Rivaroxaban and real world

Quality and Outcomes

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

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 ≅ 0.22%/year	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.

US Department of Defense (DoD) EMRs served as the sole data source for this study

Tamayo et al., *Clin Cardiol* 2015

European Heart Journal Advance Access published September 1, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv466

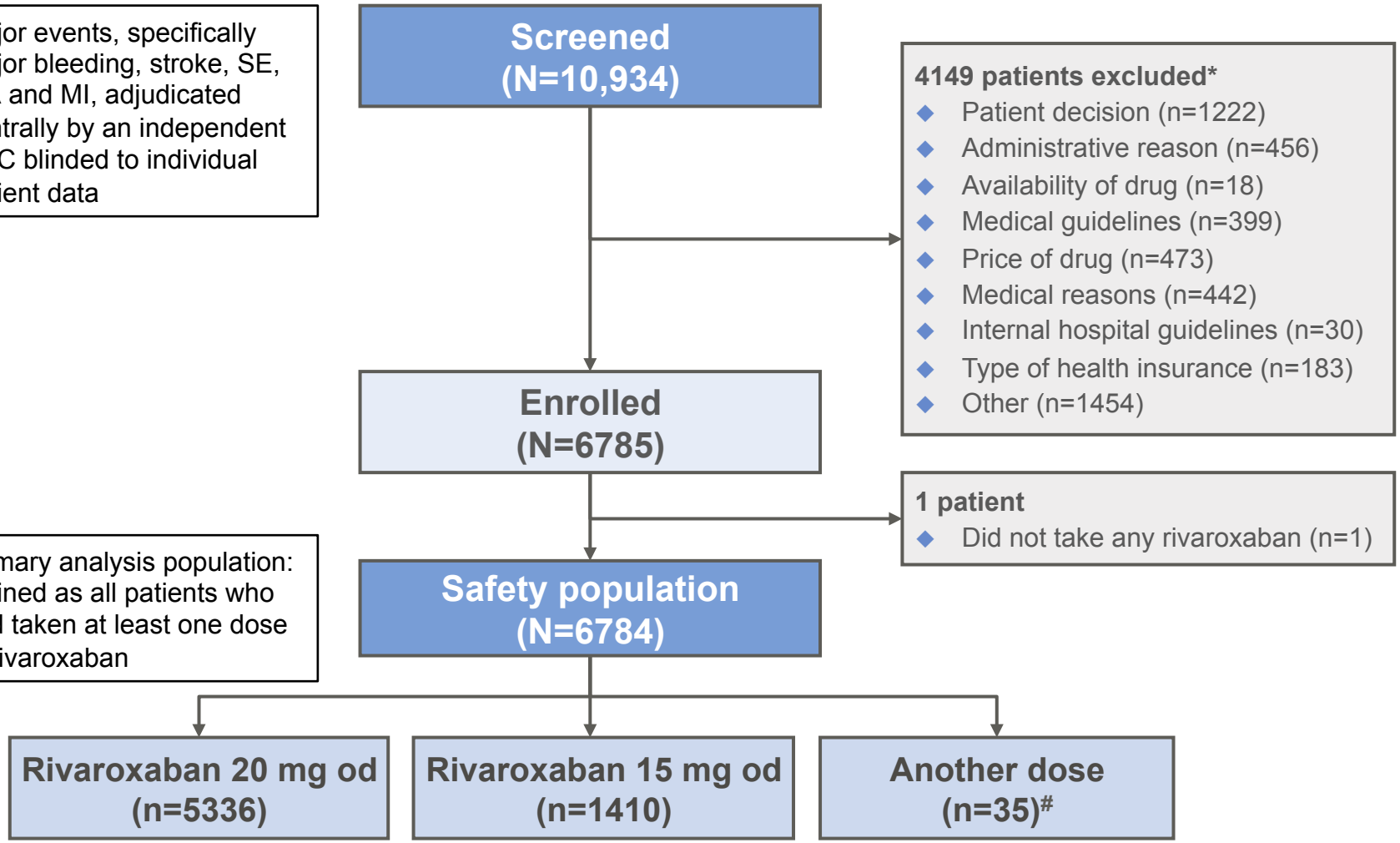
FASTTRACK
ESC Clinical Registry

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

XANTUS: Patient Flow

Major events, specifically major bleeding, stroke, SE, TIA and MI, adjudicated centrally by an independent CAC blinded to individual patient data



Primary analysis population: defined as all patients who had taken at least one dose of rivaroxaban

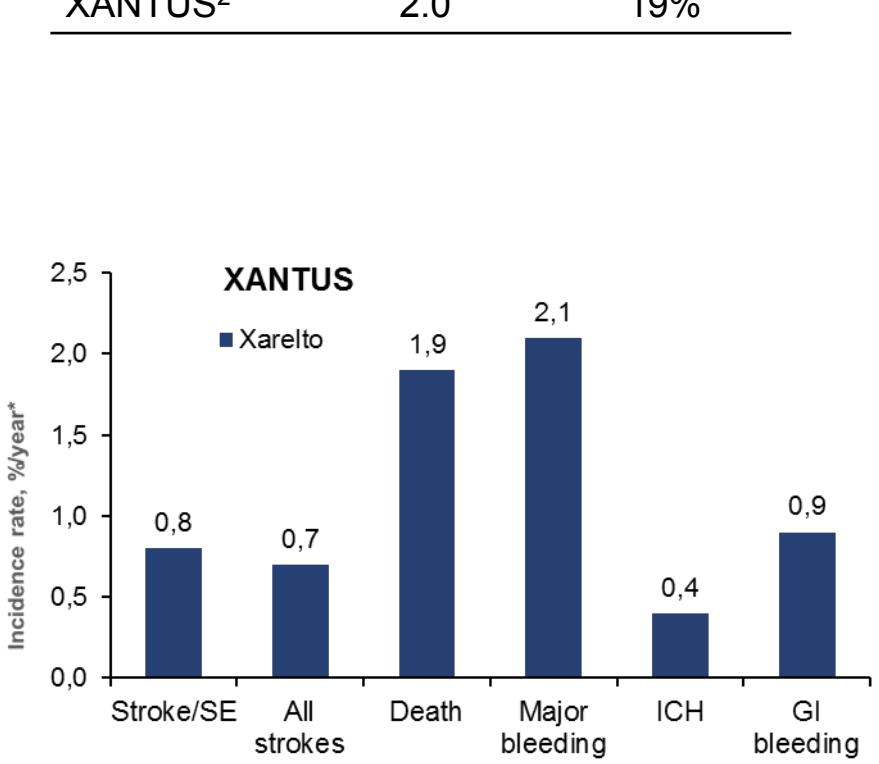
*Reasons for not continuing in the study included, but were not limited to, patient decision, administrative or medical reasons. Some patients could have more than one reason for exclusion; #other dose includes any initial daily rivaroxaban dose besides 15/20 mg od (excluding missing information, n=3)

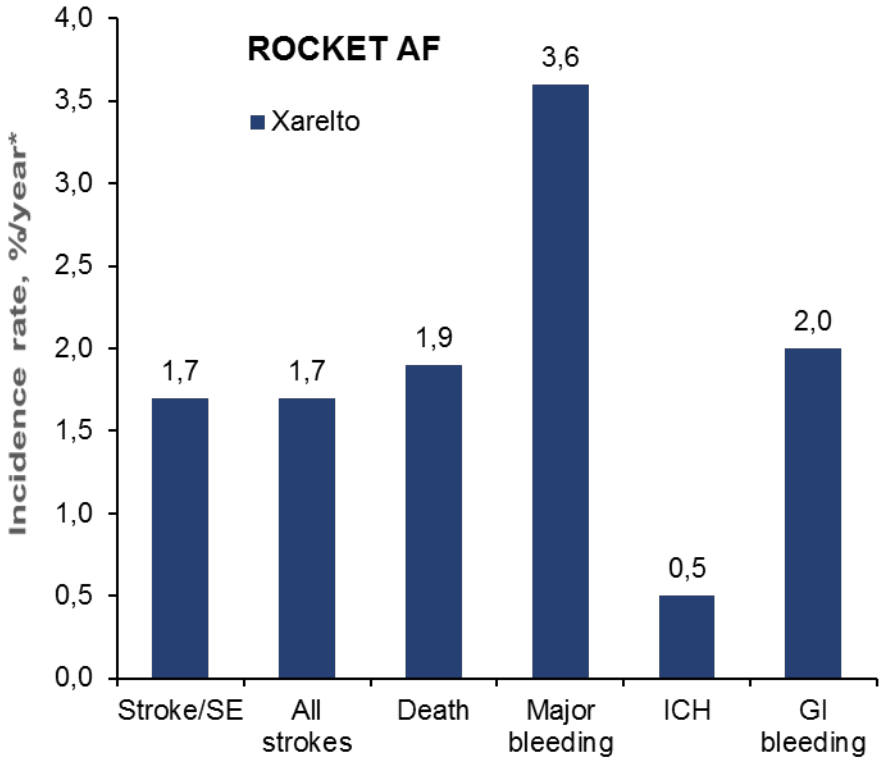
1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS

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

XANTUS

Apixaban and real world

Real World Comparison Of Major Bleeding Risk Among Non-valvular Atrial Fibrillation Patients Newly Initiated On Apixaban, Dabigatran, Rivaroxaban Or Warfarin

Lip GYH[1], Pan X[2], Kamble S[2], Kawabata H[2], Mardekian J[3], Masseria C[3], Bruno A[2], Phatak H[2]*

[1]University of Birmingham, Birmingham, UK; [2]Bristol-Myers Squibb, Princeton, NJ; [3]Pfizer, Inc, New York, NY

*At the time of research, Hemant Phatak was an employee of BMS

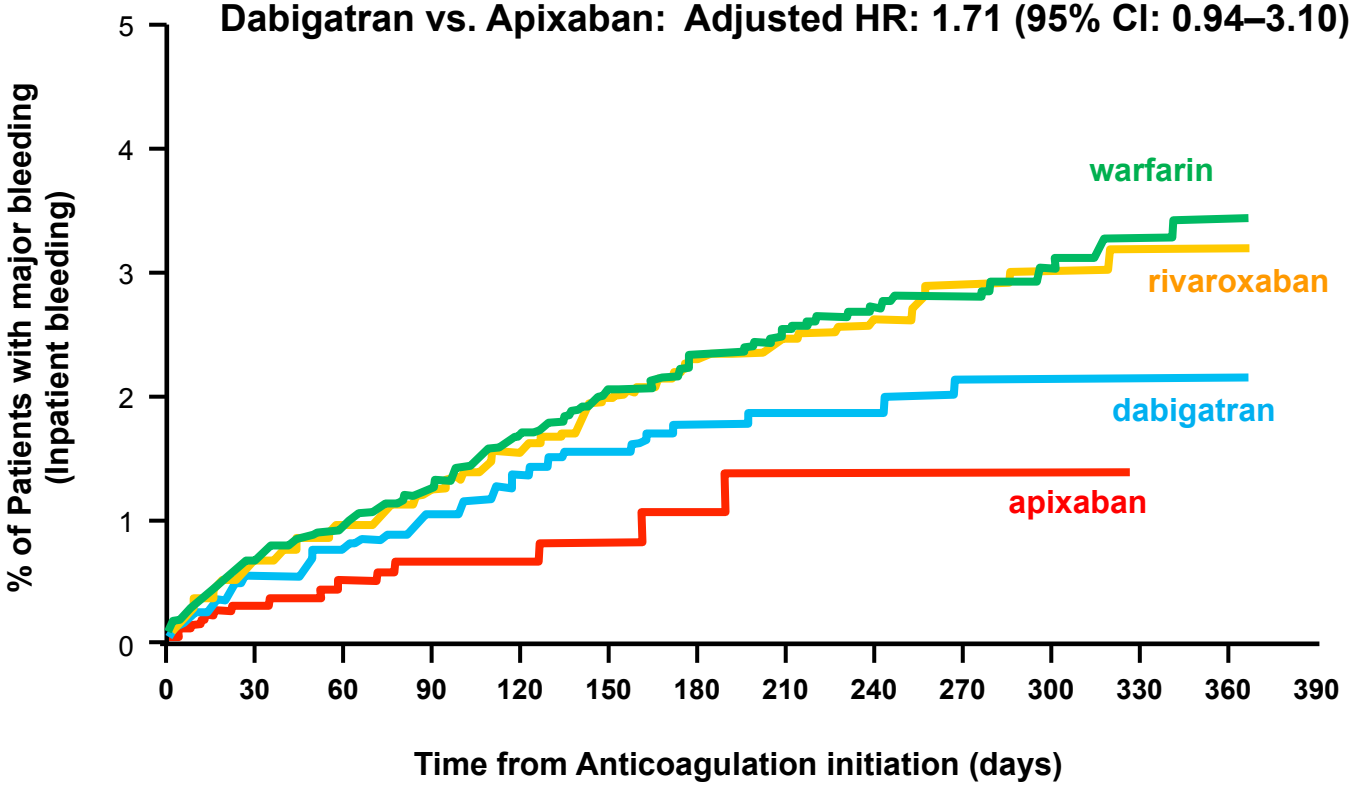
Sponsored by Bristol-Myers Squibb Company and Pfizer Inc

Lip et al. Poster presentation at ESC Aug/Sept 2015; London, UK Poster/oral poster no.P6217

Real-world bleeding risk among non-valvular AF patients newly-prescribed Apixaban, Dabigatran, Rivaroxaban, and Warfarin: Analysis of Electronic Health Records

Cumulative incidence of major bleeding

Warfarin vs. Apixaban: Adjusted HR: 1.93 (95% CI: 1.12–3.33) *P*=0.018
Rivaroxaban vs. Apixaban: Adjusted HR: 2.19 (95%CI: 1.26 –3.79) *P*=0.0052
Dabigatran vs. Apixaban: Adjusted HR: 1.71 (95% CI: 0.94–3.10) *P*= 0.079



Apixaban (N=2,402)	
5 mg	NR
N=2,057	N=345

Dabigatran (N=4,173)	
150 mg	NR
N=3,768	N=405

Rivaroxaban (N=10,050)	
20 mg	NR
N=8,066	N=1,984

Warfarin (N=12,713)

Truven MarketScan® Commercial and Medicare supplemental data

Lip et al. Poster presentation at ESC Aug/Sept 2015; Poster/oral poster no.P6217

432IT15NP05935

Real-world Bleeding Risk among Non-valvular Atrial Fibrillation Patients Prescribed Apixaban, Dabigatran, Rivaroxaban, and Warfarin: Analysis of Electronic Health Records

Lin I[1], Masseria C[2], Mardekian J[2], Frean M[1], Phatak H[3], Kamble S[3], Abdulsattar Y[2], Petkun W[2], Menzin J[1], Lip GYH[4]

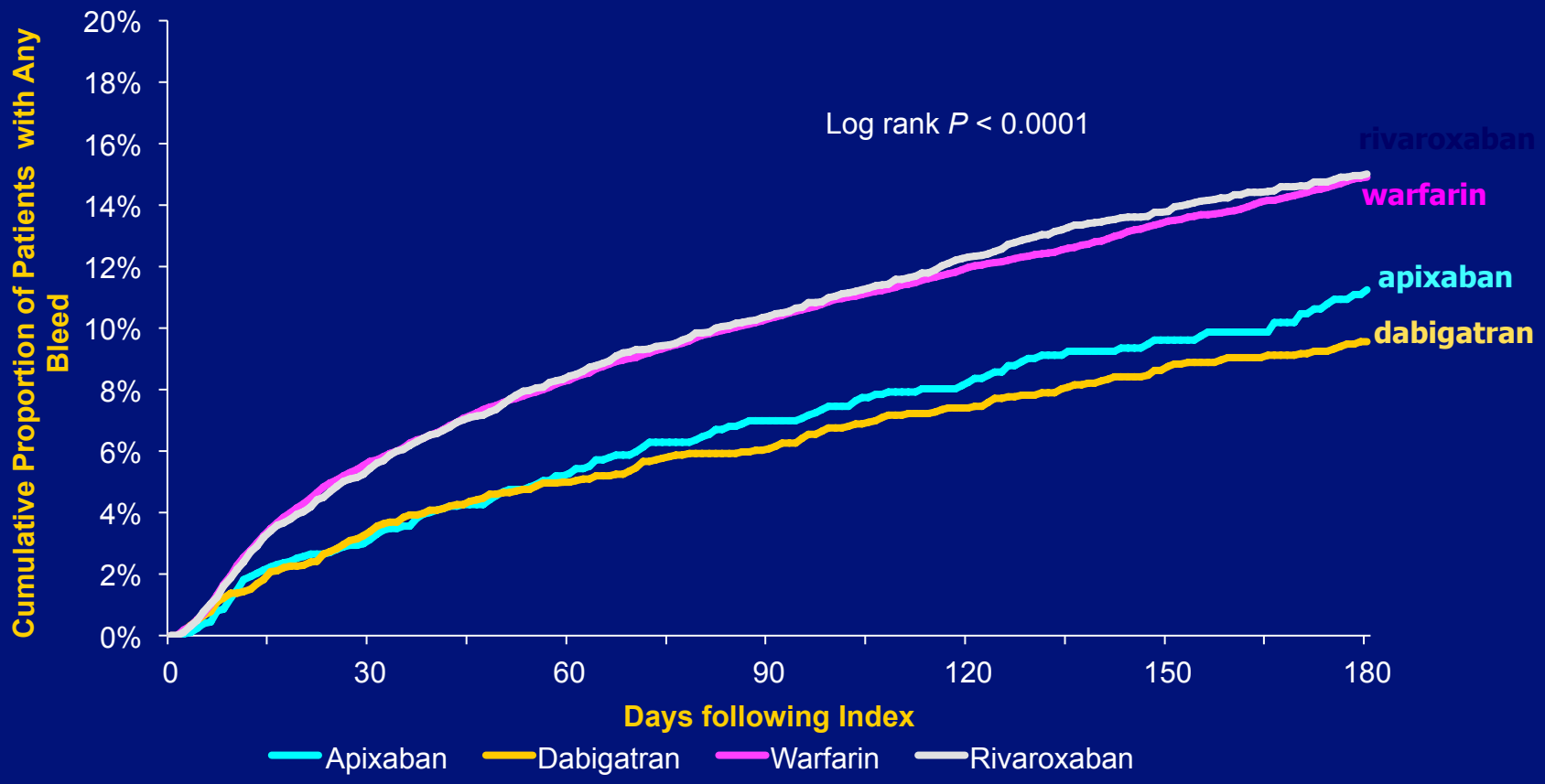
[1]Boston Health Economics - Waltham - United States of America, [2]Pfizer, Inc. - New York - United States of America, [3]Bristol-Myers Squibb - Princeton - United States of America, [4]University of Birmingham - Birmingham - United Kingdom.

Sponsored by Bristol-Myers Squibb Company and Pfizer Inc

Lin I et al. Poster presentation at ESC Aug/Sept 2015; London, UK Poster/oral poster no. P6215

Kaplan Meier Analysis of Any Bleed During Follow Up

- **Bleeding within 180 days**: 15% of patients in the warfarin and rivaroxaban cohorts, vs 9-11% of patients in the apixaban and dabigatran cohorts



Lin I et al. Poster presentation at ESC Aug/Sept 2015; London, UK Poster/oral poster no. P6215

Major Ongoing 'Real Life' Studies

Registry	Population Size	Patient Enrolment – Key Design Features	Follow-up Duration
GARFIELD-AF[a]	Target: 55,000 To date: 45,000	• Prospective patients (n = 50,000) **enrolled < 6 weeks after AF diagnosis** in 5 sequential cohorts • Retrospective patients (n = 5000) enrolled 6 to 24 months after diagnosis • ≥ 1 additional investigator-determined risk factor for stroke	≥ 2 years, up to 8 years
GLORIA-Af[b,c]	Target: 56,000 To date: 11,000	• Prospective patients **enrolled < 3 months after AF diagnosis** in 3 phases • CHA_2DS_2-VASc score ≥ 1	0 to 3 years Phase 1 (pre-NOAC): none Phase 2 (dabigatran): 2 years Phase 3 (VKA/NOAC): 3 years
ORBIT-AF I[d,e]	10,132	• **Incident or prevalent AF** • Patients excluded if anticipated life expectancy < 6 months	≥ 2 years
ORBIT-AF II[f]	Target: 15,000 To date: 1011	• Prospective patients **enrolled < 6 months after AF diagnosis**; or enrolled < 3 months after initiation or transition to a NOAC • Patients excluded if anticipated life expectancy < 6 months	≤ 2 years
PREFER-AF[g]	7243	• Prospective patients **enrolled < 12 months after AF diagnosis**	1 year

a. Thrombosis Research Institute website. http://www.tri-london.ac.uk/garfield/information; b. Huisman MV et al. *Am Heart J*. 2014;167:329-334; c. Boehringer Ingelheim Press Release Archive. http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2014/07_may_2014_gloria-af.html; d. Piccini JP et al. *Am Heart J*. 2011;162:606-612.e1; e. O'Brien EC, et al. *Am Heart J*. 2014;167:601-609.e1; f. Steinberg BA. *Am Heart J*. 2014;168:160-167; g. Kirchhof P, et al. *Europace*. 2014;16:6-14.

theheart.org | Medscape CARDIOLOGY

Adherence & persistence with NOACs

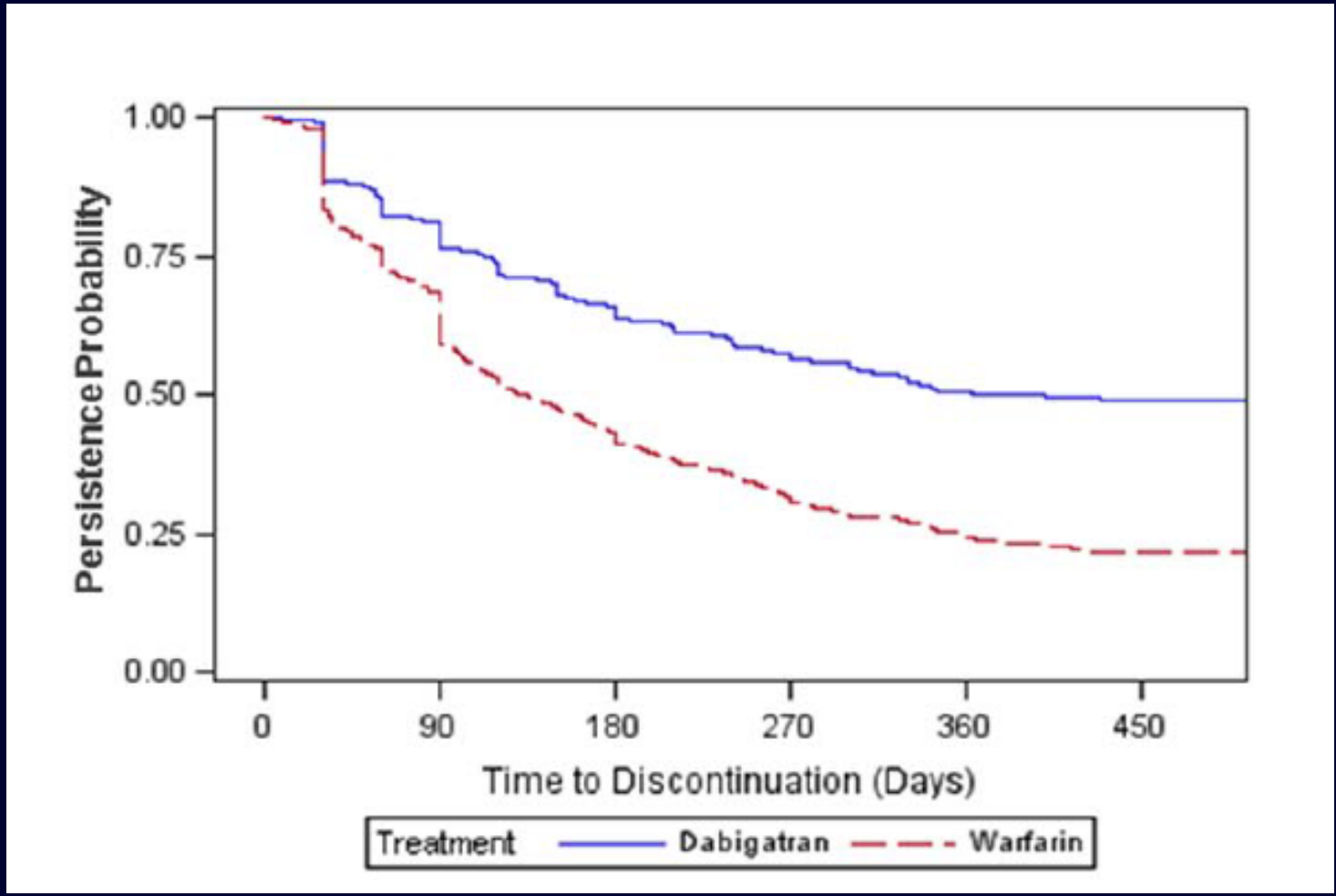
Original Article

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

Dabigatran vs Warfarin Persistence in AF



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

CMRO

Current Medical Research & Opinion 2014, 1–9

0300-7995
doi:10.1185/03007995.2014.933577

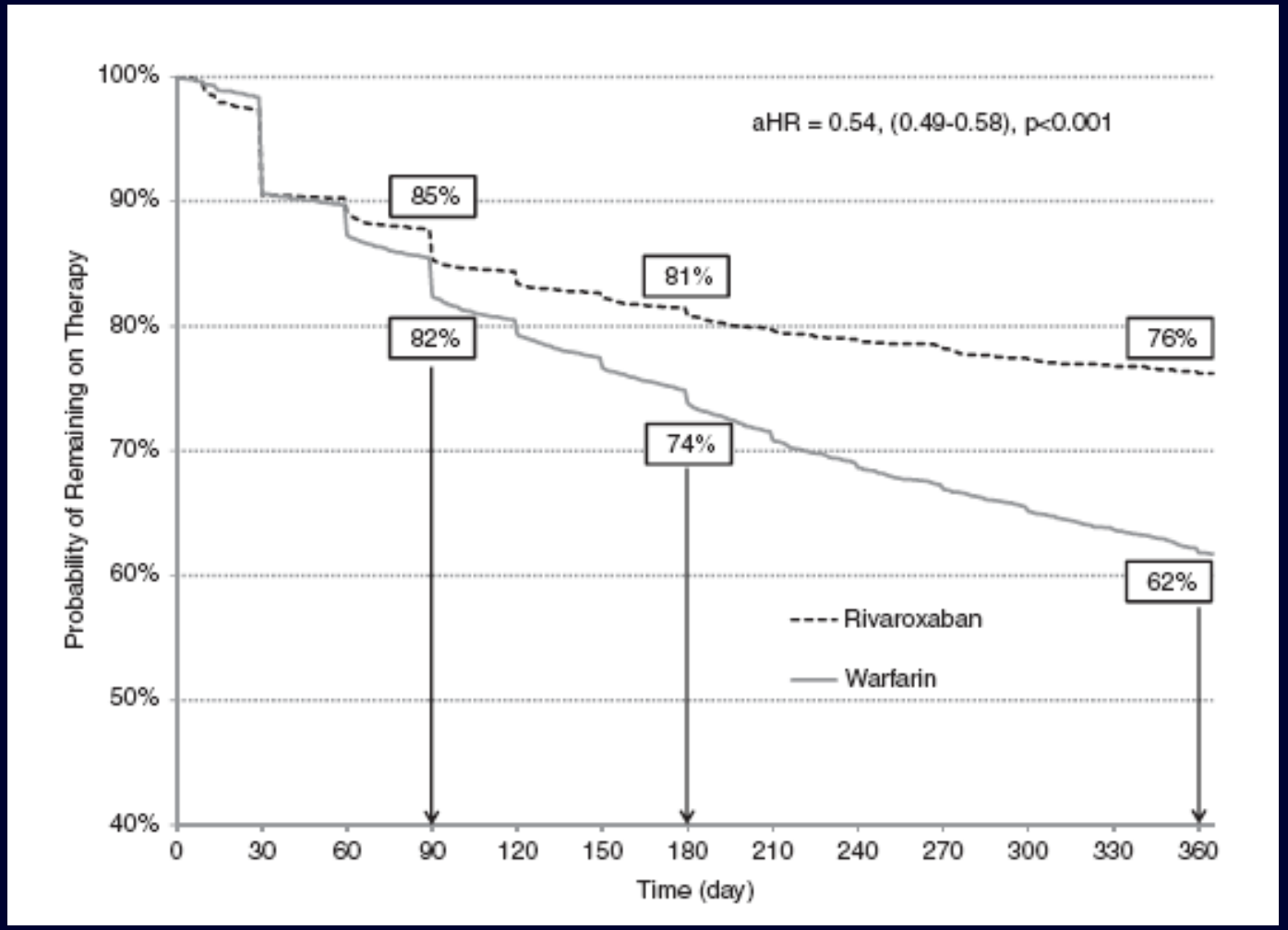
Article -/933577

Original article

Medication persistence and discontinuation of rivaroxaban versus warfarin among patients with non-valvular atrial fibrillation

Nelson WW et al. Curr Med Res Opin 2014; 1-9

Kaplan-Meier Curve for Therapy Continuation



Nelson WW et al. Curr Med Res Opin 2014; 1-9

Il problema dei dosaggi……..

Approved European labels for NOACs and their dosing in CKD-EHRA guideline

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%[52–55]	50%[36]	35%
Bioavailability	3–7%	50%	62%[51]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ …	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5] Note: 75 mg BID approved in US only[c]: if CrCl 15–30 mL/min if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID	30 mg OD when CrCl 15–49 mL/min	15 mg OD when CrCl 15–49 mL/min
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min

EHRA 2015 Europace doi:10.1093/europace/euv309

Stroke and Bleeding Outcomes with Apixaban vs. Warfarin in Patients with High Creatinine, Low Body Weight or High Age Receiving Standard Dose Apixaban for SPAF

Nella pratica clinica, si nota un'eccessiva proporzione delle prescrizione di Apixaban 2,5 mg BID, rispetto alla dose standard. Una simile situazione si riscontra anche con rivaroxaban e dabigatran.

	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%

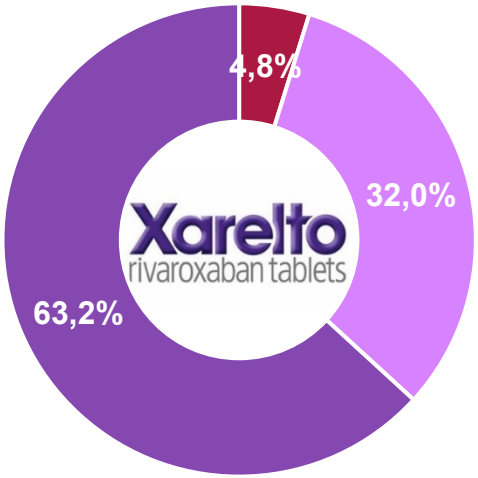
Alexander et al. Poster presentation at ESC Aug/Sept 2015; London, UK Poster/oral poster no.2032

Patient & Market Dynamics

Share by Strength (Values .000 – Aug 15)

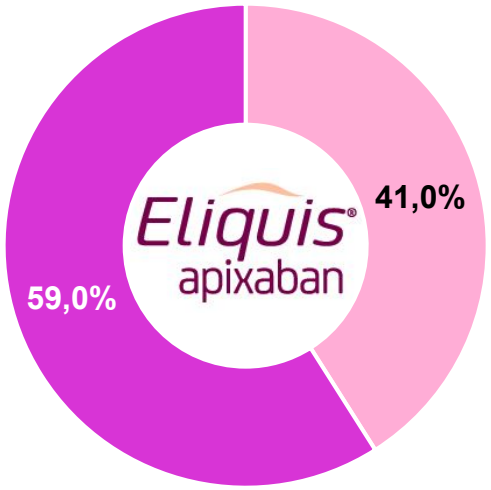
High use of Low dosages

Share by Strength
Qtr 07/15



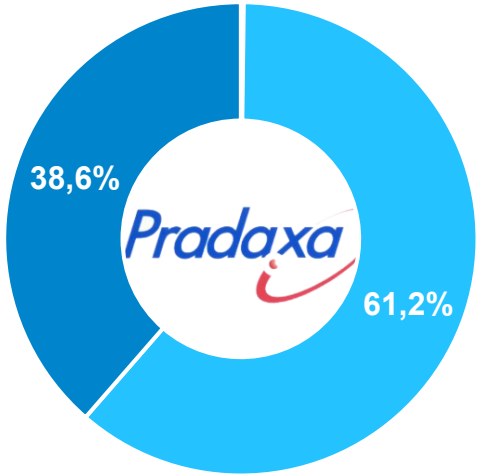
Xarelto 10 Xarelto 15
Xarelto 20

Share by Strength
Qtr 07/15



Eliquis 2,5 Eliquis 5

Share by Strength
Qtr 07/15



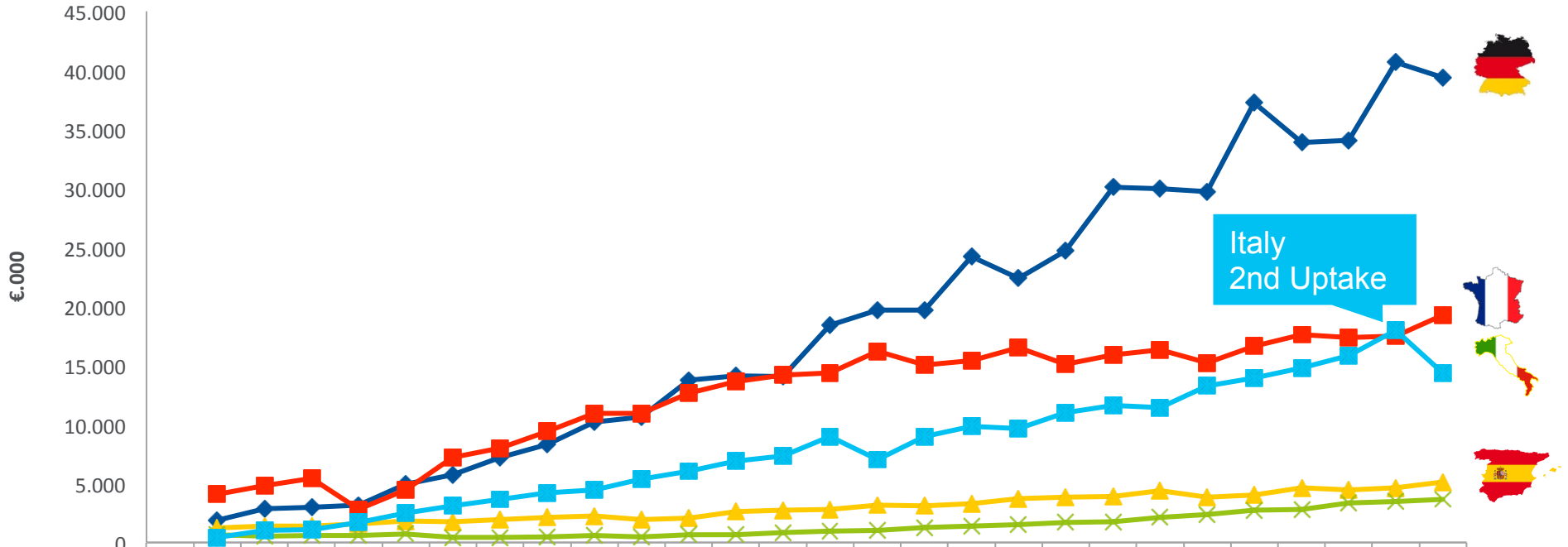
Pradaxa 75 Pradaxa 110
Pradaxa 150

L’uptake dei NAO in Italia

Patient & Market Dynamics

NOACs Sales Launch Uptake by Country Comparison (LEU .000 – Aug 15)

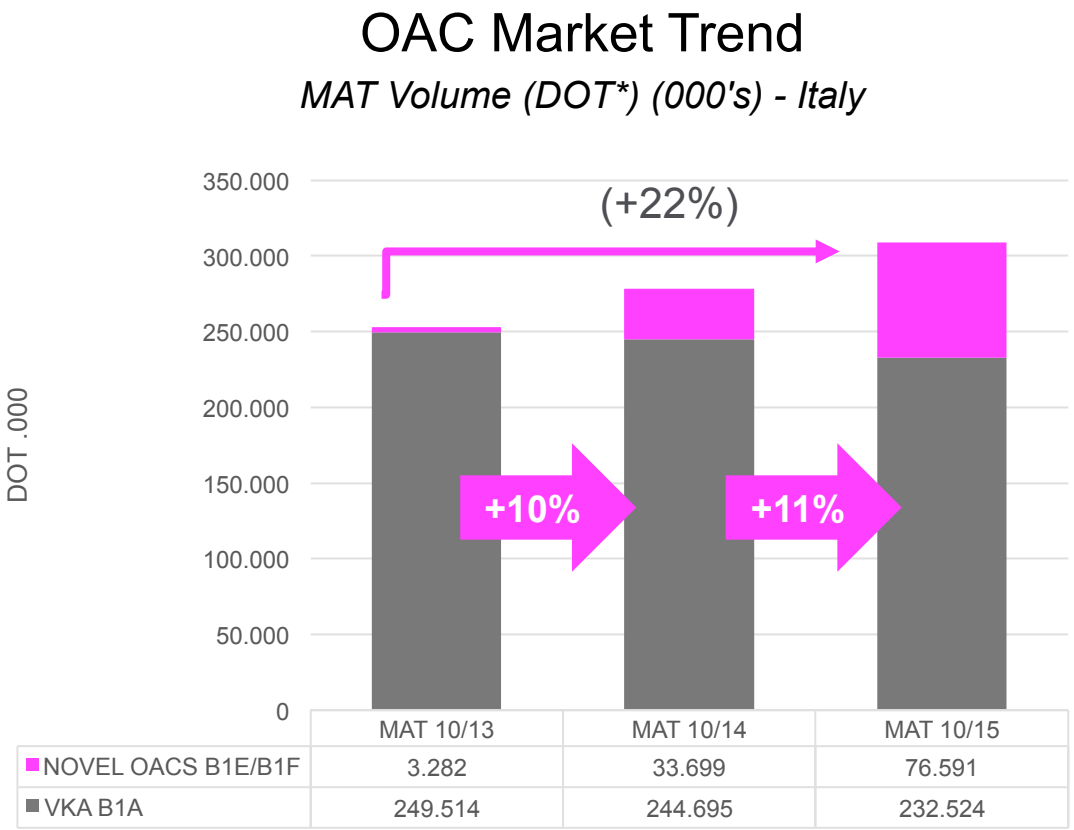
NOACs Launch Uptake by Country Comparison
Total NOAC - Cumulative Value (.000 LEU) - SPAF Launch - Total



	Mth 1	Mth 2	Mth 3	Mth 4	Mth 5	Mth 6	Mth 7	Mth 8	Mth 9	Mth 10	Mth 11	Mth 12	Mth 13	Mth 14	Mth 15	Mth 16	Mth 17	Mth 18	Mth 19	Mth 20	Mth 21	Mth 22	Mth 23	Mth 24	Mth 25	Mth 26	Mth 27
Germany	1.862	2.872	3.001	3.181	4.969	5.727	7.193	8.285	10.176	10.642	13.724	14.104	14.031	18.410	19.671	19.664	24.229	22.399	24.706	30.096	29.969	29.743	37.274	33.857	34.057	40.700	39.372
France	4.099	4.821	5.452	2.820	4.446	7.194	8.007	9.398	10.909	10.922	12.634	13.641	14.167	14.389	16.206	15.056	15.397	16.521	15.096	15.882	16.344	15.204	16.649	17.605	17.345	17.495	19.277
Spain	1.231	1.380	1.402	1.580	1.803	1.738	1.938	2.113	2.274	1.926	2.090	2.642	2.724	2.793	3.150	3.097	3.312	3.715	3.867	3.870	4.374	3.824	4.006	4.657	4.459	4.656	5.097
UK	638	560	591	616	704	433	436	479	575	491	682	683	853	961	1.028	1.255	1.396	1.485	1.700	1.753	2.095	2.342	2.746	2.784	3.367	3.486	3.676
Italy	426	1.055	1.102	1.708	2.499	3.084	3.655	4.180	4.449	5.371	6.022	6.911	7.332	8.956	6.998	8.956	9.824	9.655	10.974	11.635	11.411	13.276	13.909	14.769	15.857	17.956	14.384

Patient & Market Dynamics

OAC Market Sales Trend (DOT .000) MAT Oct 2015



I NAO STANNO ALLARGANDO IL MERCATO

10/2015

- VKA -5% (MAT)
- MS NOACs 24% (MAT)
- MS NOACs 33% (Mese)

*DOT: Giorni di trattamento