DABIGATRAN: EVIDENZE DI SICUREZZA NELLA VITA REALE

Niccolò Marchionni

Cardiologia e Medicina Geriatrica,
Università di Firenze e
Azienda Ospedaliero-Universitaria Careggi

Presidente Società Italiana di Cardiologia Geriatrica (SICGe)
Chaiperson, Geriatric Expert Group, European Medicines Agency, London

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

RE-LY®: a non-inferiority phase III trial of dabigatran vs. warfarin for SPAF

AF with ≥1 risk factor for stroke
in absence of contraindications #

18 113 patients
951 centres in 44 countries

R

Warfarin (INR 2.0–3.0) N = 6022	D150 B.I.D. N = 6076	D110 B.I.D. N = 6015

Open | **Doses blinded**

- Designed to reflect clinical practice
  - 50% patients VKA naïve
  - Included patients with a range of $CHADS_2$ scores
  - Allowed investigation of temporary discontinuation for interventional procedures

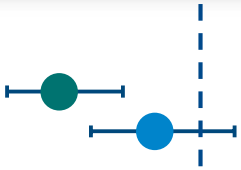
- Good INR control for warfarin
  - Median 64% TTR
- 99.9% patients completed follow-up

CrCl, creatinine clearance (Cockroft–Gault formula)<30 mL/min;
D, dabigartan etexilate; R, randomization; TTR, time in therapeutic range; VKA, Vitamin K antagonist

Ezekowitz MD et al. Am Heart J 2009;157:805–10; Connolly SJ et al. N Engl J Med 2009;361:1139–51

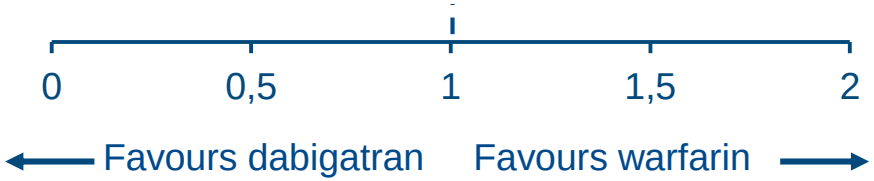
Efficacy of dabigatran for preventing stroke or SE vs. warfarin in the pivotal RE-LY® study, as demonstrated by two blinded doses

	Relative risk (95% CI)	P value
Stroke or SE (primary efficacy outcome)	0.65 (0.52–0.81)	<0.001
	0.89 (0.73–1.09)	0.27



150 mg BID

110 mg BID

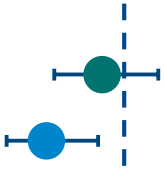


RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6; Connolly SJ et al. N Engl J Med 2014; 371:1464–5; Pradaxa®: EU SPC, updated Oct 2014

Safety of dabigatran vs. warfarin for both doses in the pivotal RE-LY® study

	Relative risk (95% CI)	P value
Major bleeding (primary safety outcome)	0.94 (0.82–1.08)	0.41
	0.80 (0.70–0.93)	0.003



150 mg BID

110 mg BID

RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study

ICH, intracranial haemorrhage

Connolly SJ et al. N Engl J Med 2010;363:1875–6; Connolly SJ et al. N Engl J Med 2014; 371:1464–5

Both doses of dabigatran provide significant **efficacy** and **safety** benefits vs. warfarin

Only NOAC to significantly reduce ischaemic stroke in a Phase III trial vs. warfarin

Greatest reduction in haemorrhagic stroke of any NOAC in a Phase III trial vs. warfarin

Non-inferior

Superior

Dabigatran 150 mg BID

24%

ISCHAEMIC STROKE vs. warfarin

35%

STROKE/SE

vs. warfarin

74%

HAEMORRHAGIC STROKE

vs. warfarin

Dabigatran 110 mg BID

similar

STROKE/SE

vs. warfarin

20%

MAJOR BLEEDING

vs. warfarin

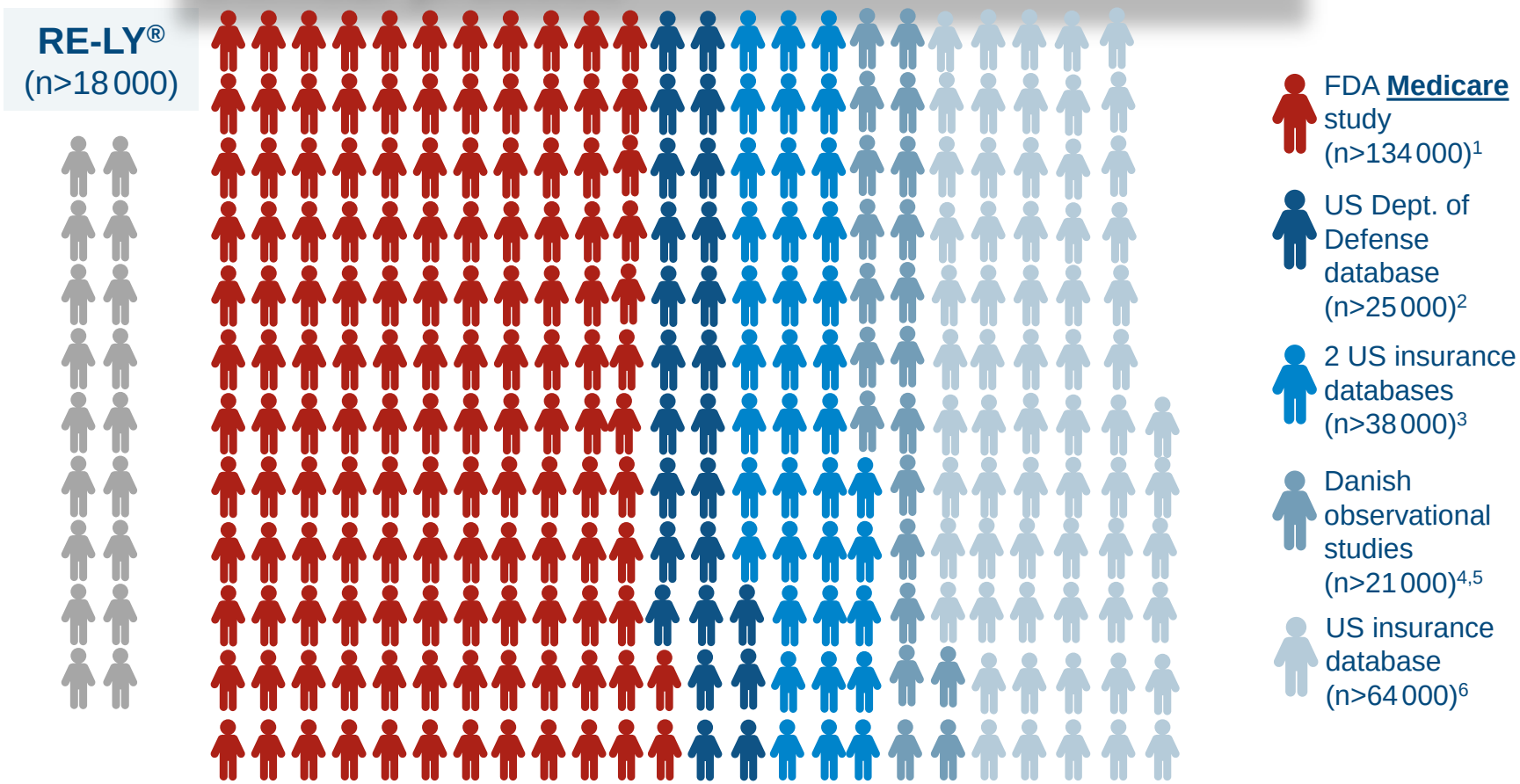
RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study

NOAC, non-Vitamin K antagonist oral anticoagulant

Connolly et al. N Engl J Med 2014;
Pradaxa®: EU SPC, 2015

Growing body of experience aimed at exploring **efficacy** & **safety** profile of dabigatran in **real-world**

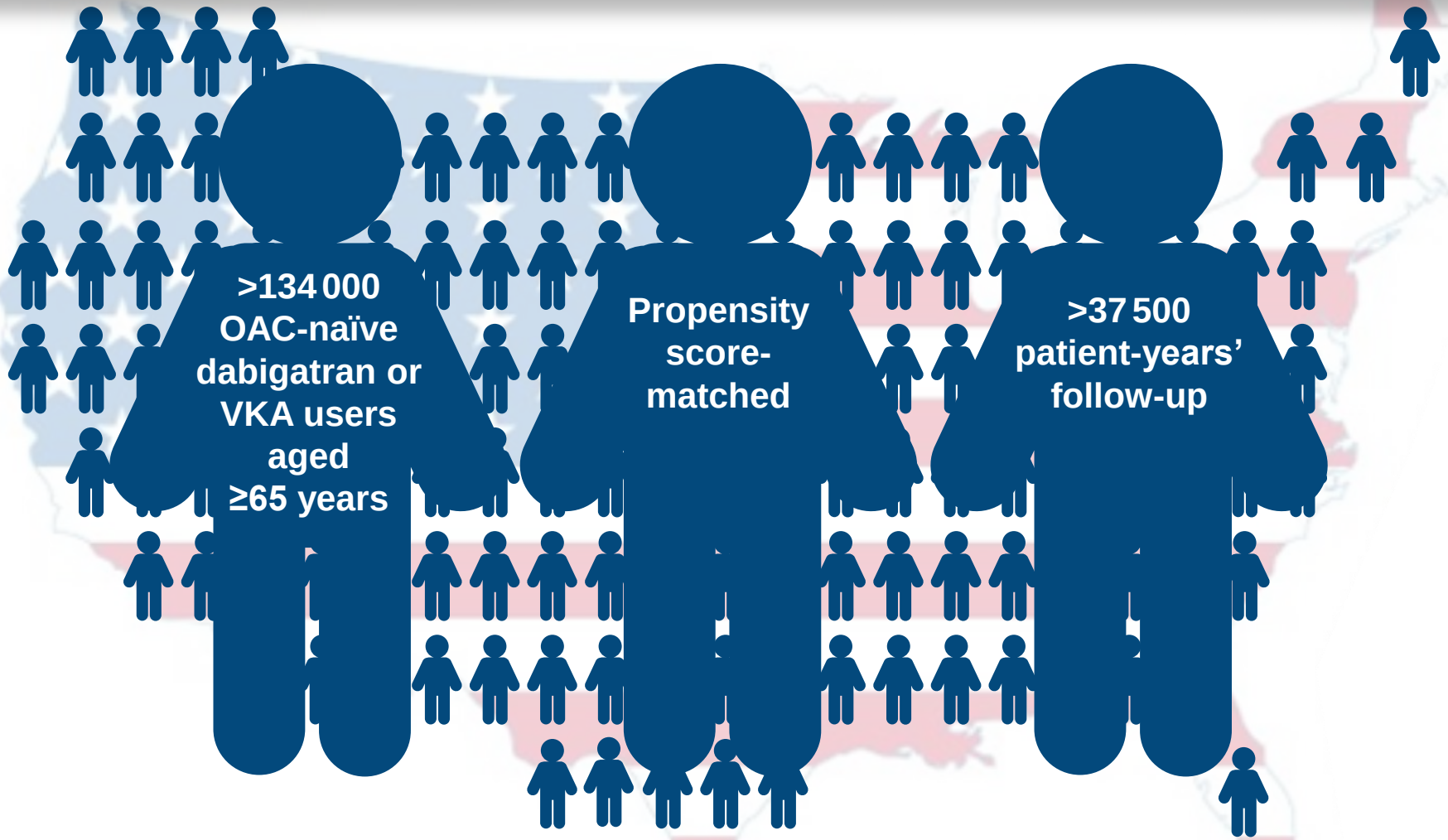
Clinical practice (n>250 000 patients)



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. Thromb Haemost 2015; **3.** Seeger J et al. Thromb Haemost 2015; **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 non-valvular atrial fibrillation



16% of patients were aged ≥85 years;
16% of patients were taking dabigatran 75 mg BID

1. Graham DJ et al. Circulation 2015

Graham DJ et al. Circulation 2015;131:157–64

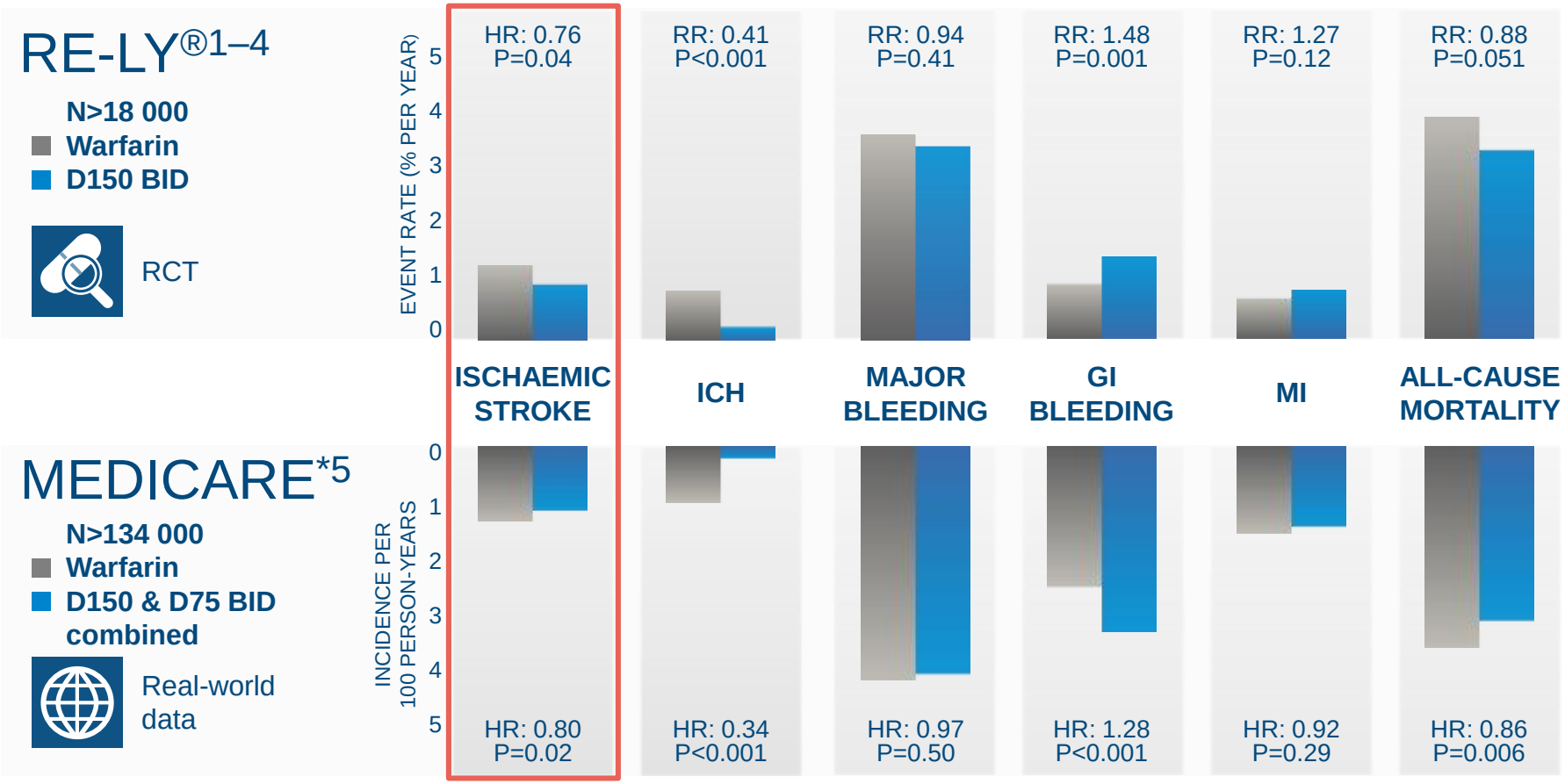
FDA Medicare analysis included more elderly and female patients and hypertensive or diabetic patients vs. RE-LY®

Characteristics, %	Medicare[1]		RE-LY® [2–4]	
	Dabigatran (n=67 207)	Warfarin (n=67 207)	Dabigatran 150 mg (n=6076)	Warfarin (n=6022)
Age 65–74 years	42	41	44	
Age 75–84 years	43	43	36	
Age ≥85 years	16	16	4	
Male sex	49	48	63	63
$CHADS_2$ score ≥3	31	32	33	32
Hypertension	87	87	79	79
Diabetes	33	34	23	23
Prior MI	2	2	17	16
Heart failure	18	18	32	32
Prior stroke	3	4	20†	20†
Prior TIA	7	7		

†Prior stroke or TIA combined

1. Graham DJ et al. Circulation 2015; **2.** Connolly SJ et al. N Engl J Med 2009; **3.** Coppens M et al. Circulation 2012;126:abstract 15537; **4.** Eikelboom JW et al. Circulation 2011

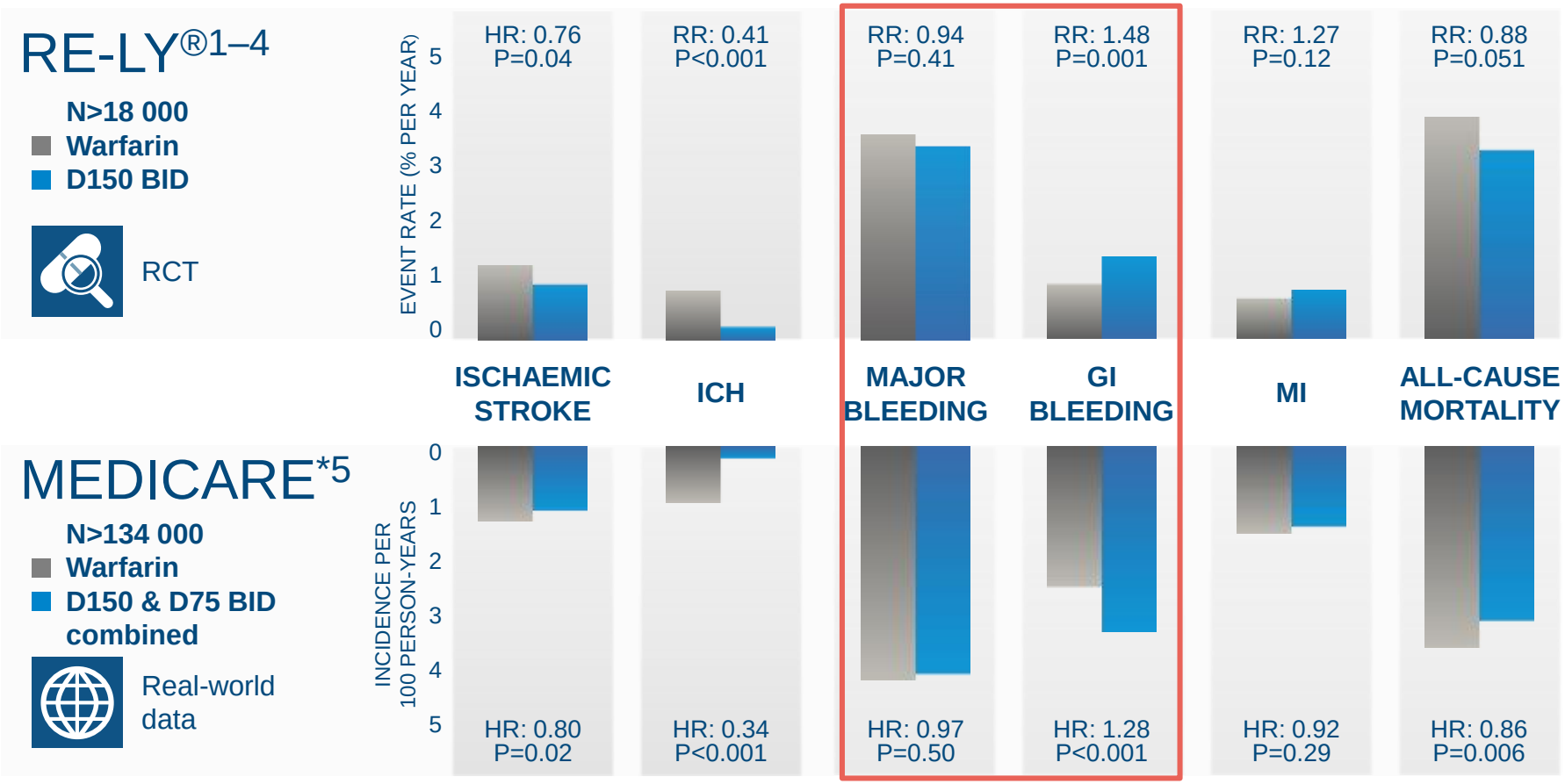
Independent FDA study of Medicare patients **mirrors** the favourable benefit–risk profile of dabigatran established in RE-LY®



*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; **2**. Connolly SJ et al. N Engl J Med 2010; **3**. Pradaxa®: EU SPC, January 2015 **4.** Connolly SJ et al. N Engl J Med 2014; **5.** Graham DJ et al. Circulation 2015

Independent FDA study of Medicare patients **mirrors** the favourable benefit–risk profile of dabigatran established in RE-LY®



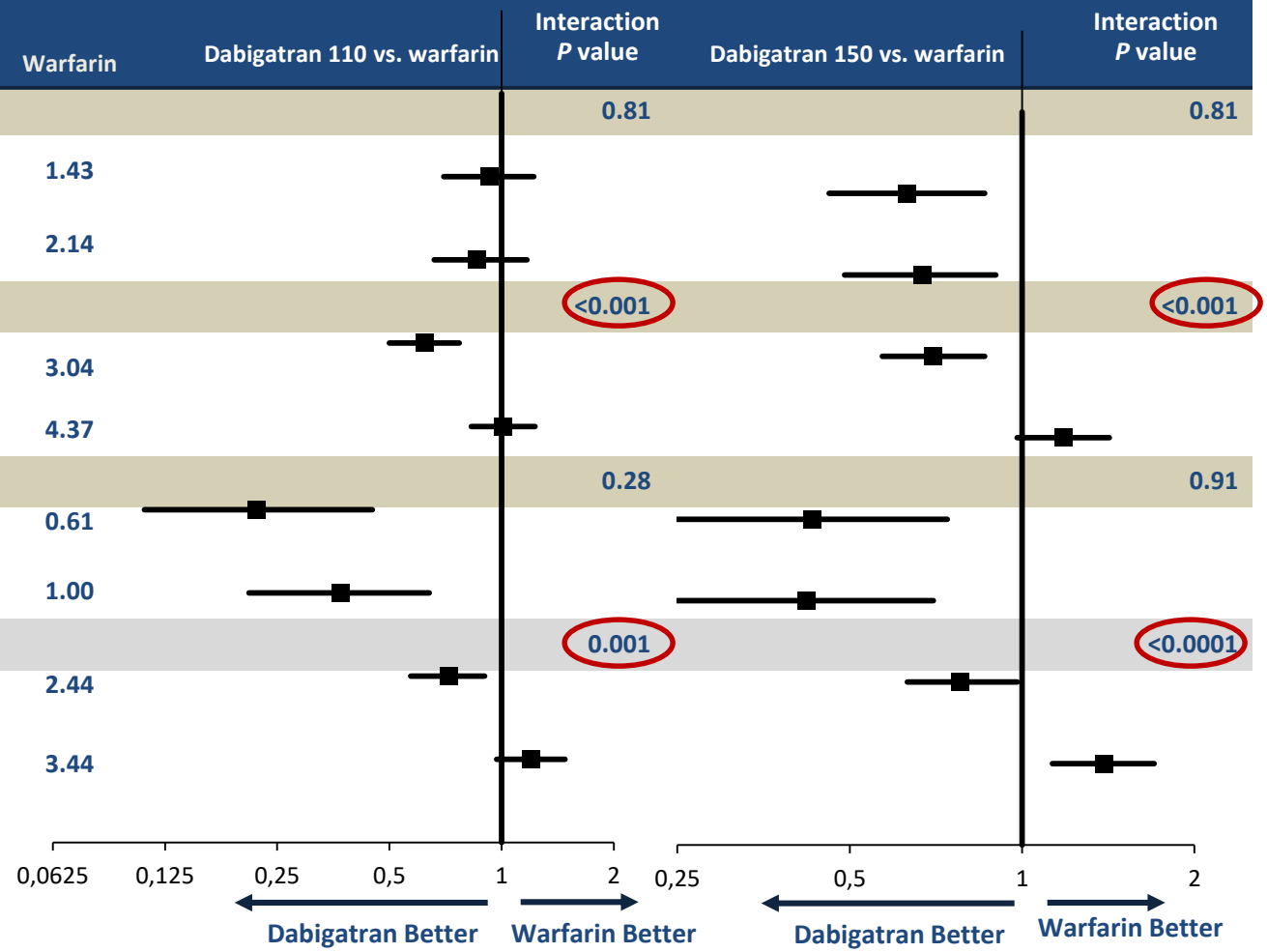
*Primary findings for dabigatran are based on analysis of both **75 mg &150 mg together** without stratification by dose

1. Connolly SJ et al. N Engl J Med 2009; **2**. Connolly SJ et al. N Engl J Med 2010; **3**. Pradaxa®: EU SPC, January 2015 **4.** Connolly SJ et al. N Engl J Med 2014; **5.** Graham DJ et al. Circulation 2015

RE-LY: With comparable efficacy for Stroke/SE and safety for ICH, rates of major bleeding and extracranial bleeding were higher in subjects ≥ 75 years compared to younger subjects

Rates of stroke, major bleeding, ICH and extracranial bleeding with Dabigatran 110 and 150 mg BD vs. warfarin in patients aged < 75 (n=10,865) and ≥ 75 (n=7258) years

	Dabigatran 110 BD	Dabigatran 150 BD	Warfarin	Interaction *P* value	Interaction *P* value
Stroke/SE				0.81	0.81
Age < 75	1.32	0.90	1.43		
Age ≥ 75	1.89	1.43	2.14		
Major Bleeding				<0.001	<0.001
Age < 75	1.89	2.12	3.04		
Age ≥ 75	4.43	5.10	4.37		
ICH				0.28	0.91
Age <75	0.14	0.26	0.61		
Age ≥75	0.37	0.41	1.00		
Extracranial Bleeding				0.001	<0.0001
Age <75	1.76	1.91	2.44		
Age ≥75	4.10	4.68	3.44		



1. Adapted from Eikelboom JW et al. *Circulation* 2011;123:2363-2372.

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

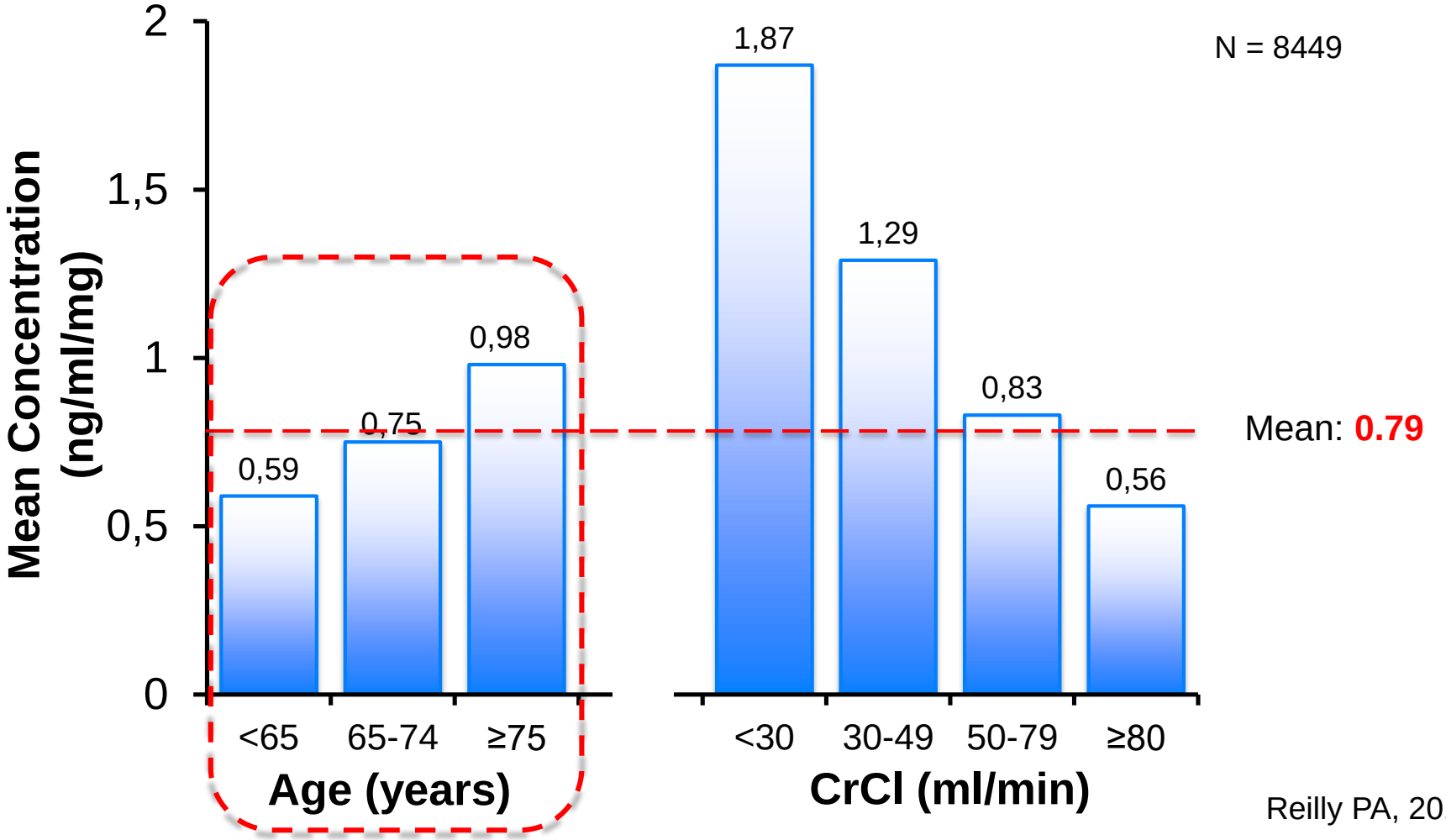
Heidbuchel H, 2013

Assorbimento e metabolismo dei NAO

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Biodisponibilità	3-7%	50%	62%	66% 100% pasti
Profarmaco	Si	No	No	No
Eliminazione renale	80%	27%	50%	35%
CYP3A4	No	Minore	Minima	Si
Interazione con cibo	No	No	+ 6-22%	+ 39%
Raccomandato ai pasti	No	No	/	Si
Anti-H2/PPI	- 12-30%	No	No	No
Emivita	12-17	12	9-11	5-9 Y 11-13 E

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

Dose-Normalized Plasma Through Concentrations of Dabigatran by Demographic Characteristics in RE-LY® Trial



Reilly PA, 2014

Post hoc analysis of dabigatran used according to **EU label** recommendations

- D110 recommended for ≥80 years **or** HAS-BLED ≥3 **or** verapamil
- D150 recommended for <80 years **and** HAS-BLED <3

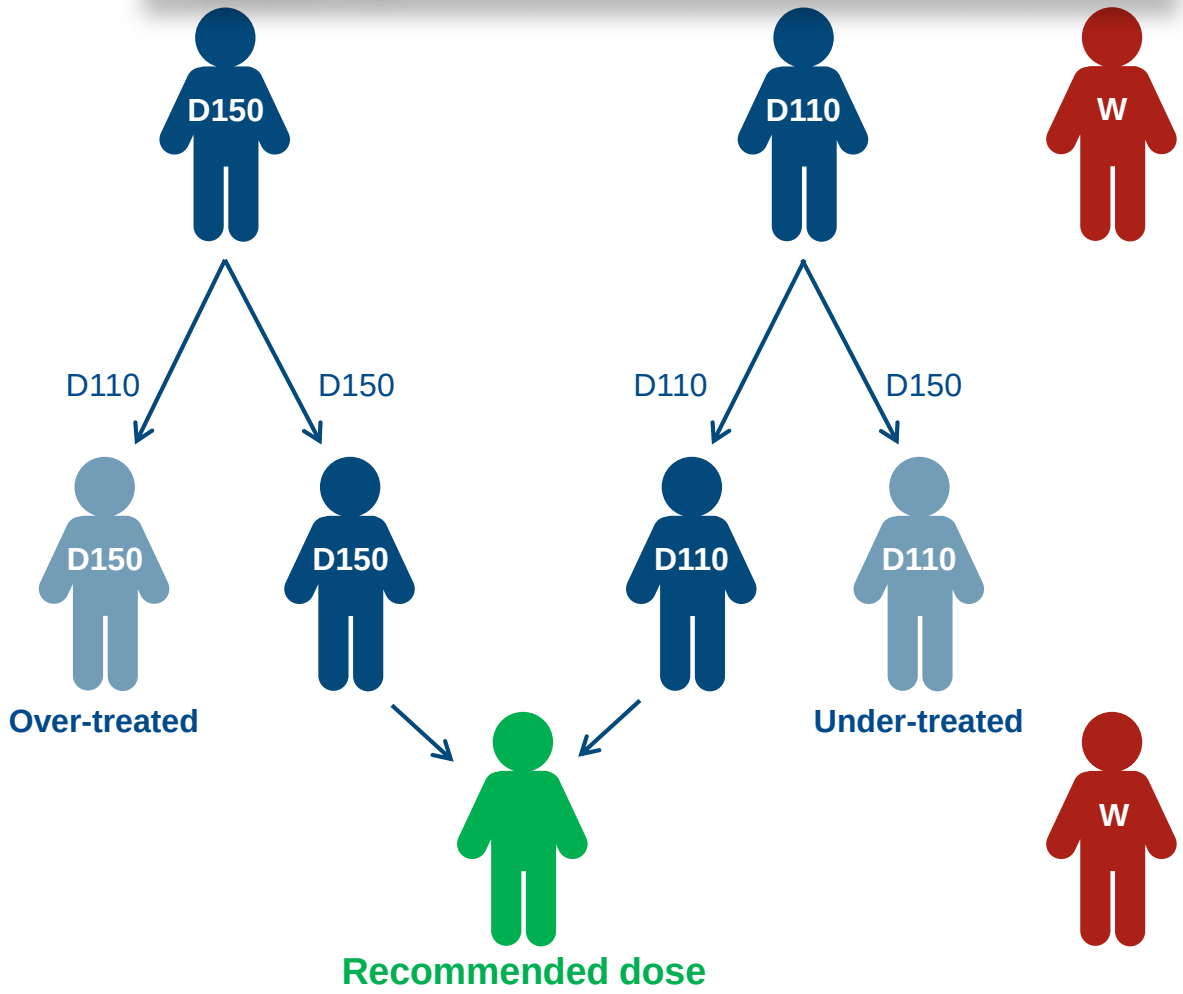
Full RE-LY® population

Post hoc analysis of patients' baseline characteristics

Recommended dose*

Dose received

Post hoc pooled analysis
'EU label-simulated dabigatran' vs warfarin



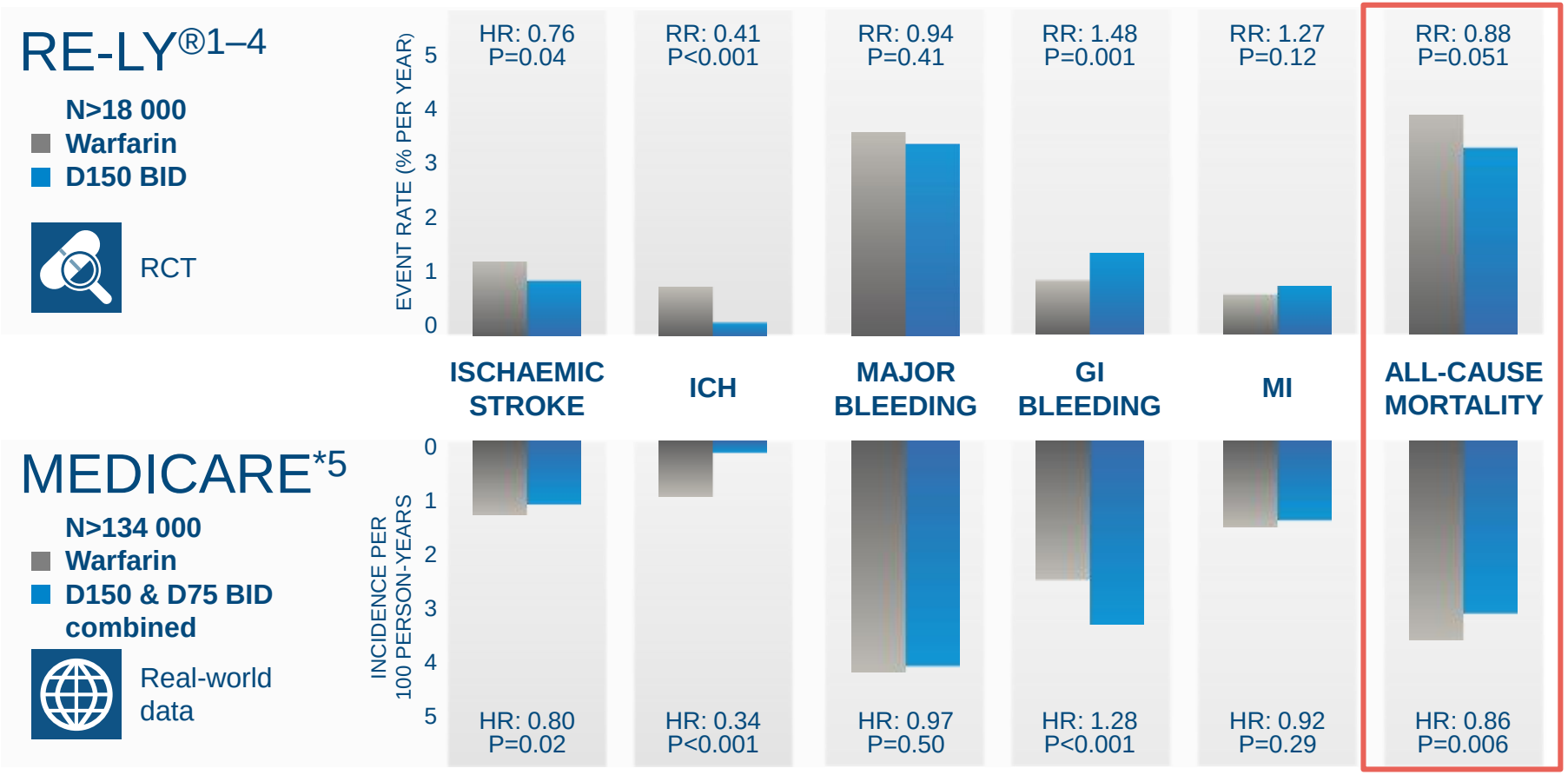
Lip et al. Thromb Haemost 2014

‘EU label-compliant’ dabigatran treatment provides a meaningful and clinically relevant benefit over warfarin

Stroke/SE	Major bleed	Mortality
HR (95% CI)	HR (95% CI)	HR (95% CI)
0.74	**0.85**	**0.86**
(0.60–0.91)	(0.73–0.98)	(0.75–0.98)

Lip et al. Thromb Haemost 2014

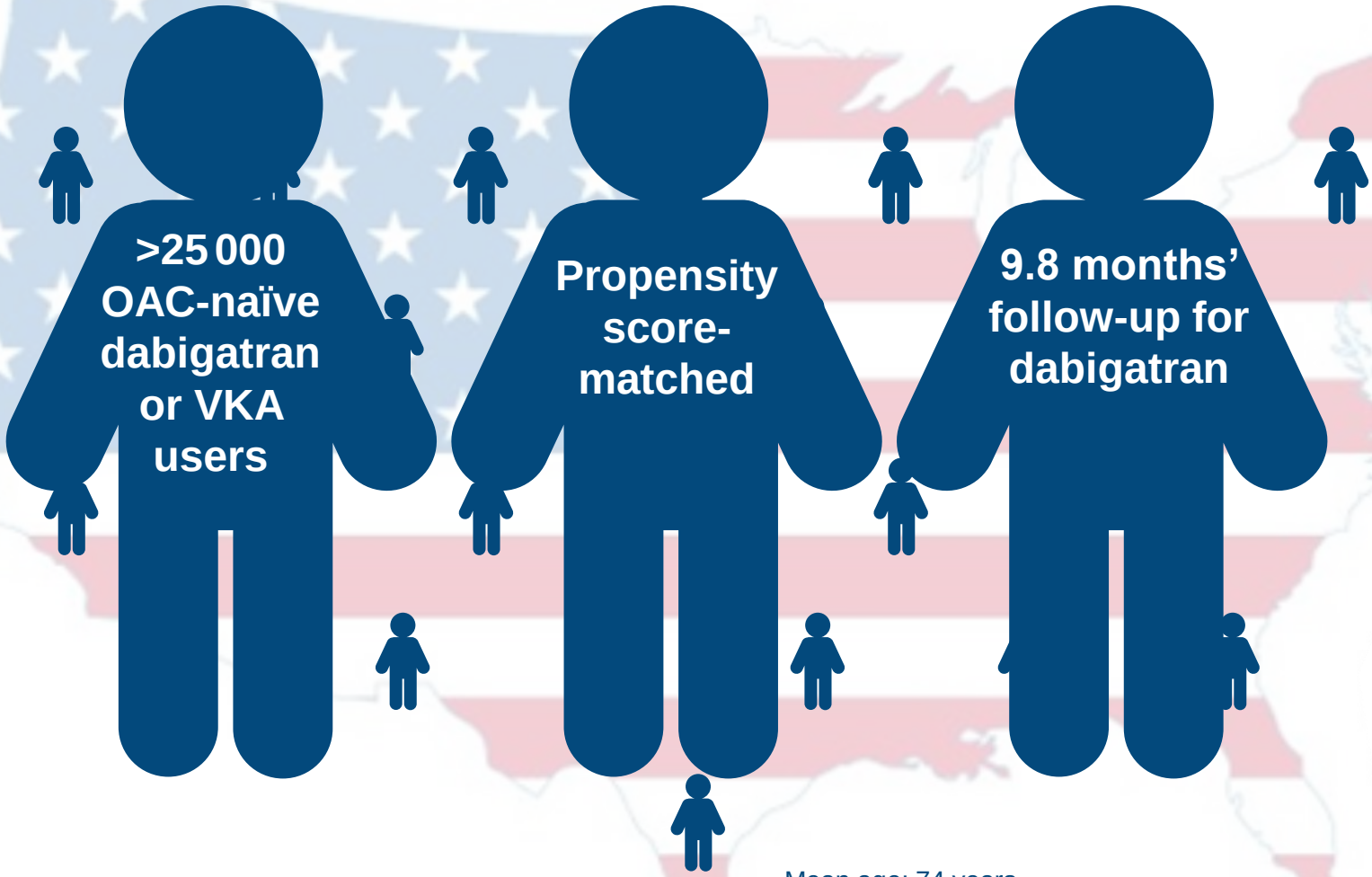
Independent FDA study of Medicare patients **mirrors** the favourable benefit–risk profile of dabigatran established in RE-LY®



*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; **2**. Connolly SJ et al. N Engl J Med 2010; **3**. Pradaxa®: EU SPC, January 2015 **4.** Connolly SJ et al. N Engl J Med 2014; **5.** Graham DJ et al. Circulation 2015

A comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrillation patients in a large healthcare system [US Dpt. of Defense]



Villines TC et al. Thromb Haemost 2015;115

Mean age: 74 years
OAC, oral anticoagulant; VKA, Vitamin K antagonist
1. Villines TC et al. Thromb Haemost 2015

US Dpt. of Defense analysis included older patients and **fewer** patients with **certain comorbidities** than RE-LY®

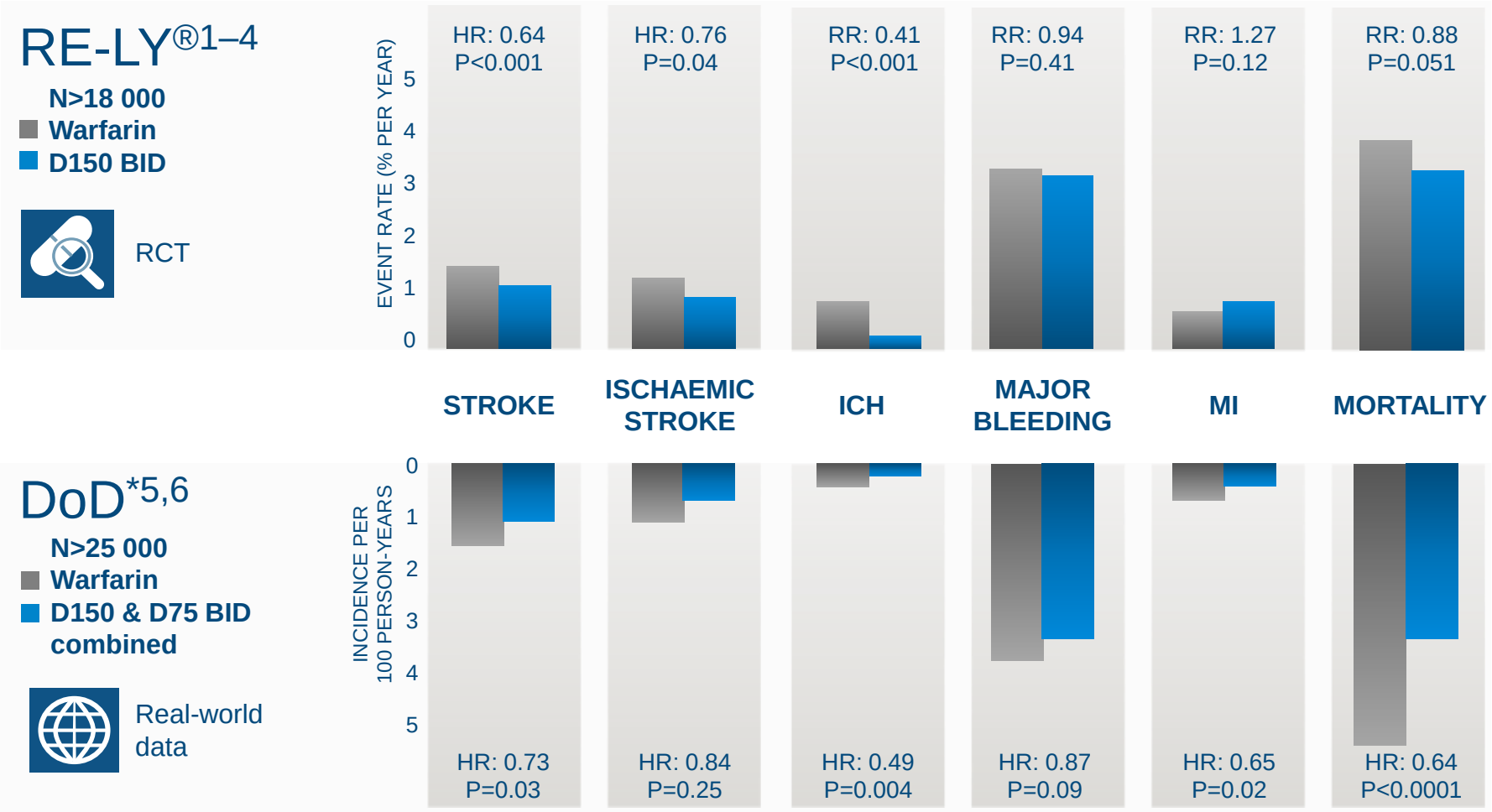
Characteristics, %	Dpt. of Defense database[1]		RE-LY® [2]	
	Dabigatran (n=12 793)	Warfarin (n=12 793)	Dabigatran 150 mg (n=6076)	Warfarin (n=6022)
Mean age, years	73.8	74.0	71.5	71.6
Male sex	59	59	63	63
CHA_2DS_2-VASc score ≥2	92	92	–	–
Hypertension	38	37	79	79
Prior MI	–	–	17	16
Coronary artery disease	20	19	–	–
Heart failure	13	12	32	32
Prior stroke	4	3	20†	20†
Prior TIA	2	2		
Mean follow-up, years	0.8	0.6	2 (median)	

†Prior stroke or TIA combined

1. Villines TC et al. Thromb Haemost 2015

2. Connolly SJ et al. N Engl J Med 2009

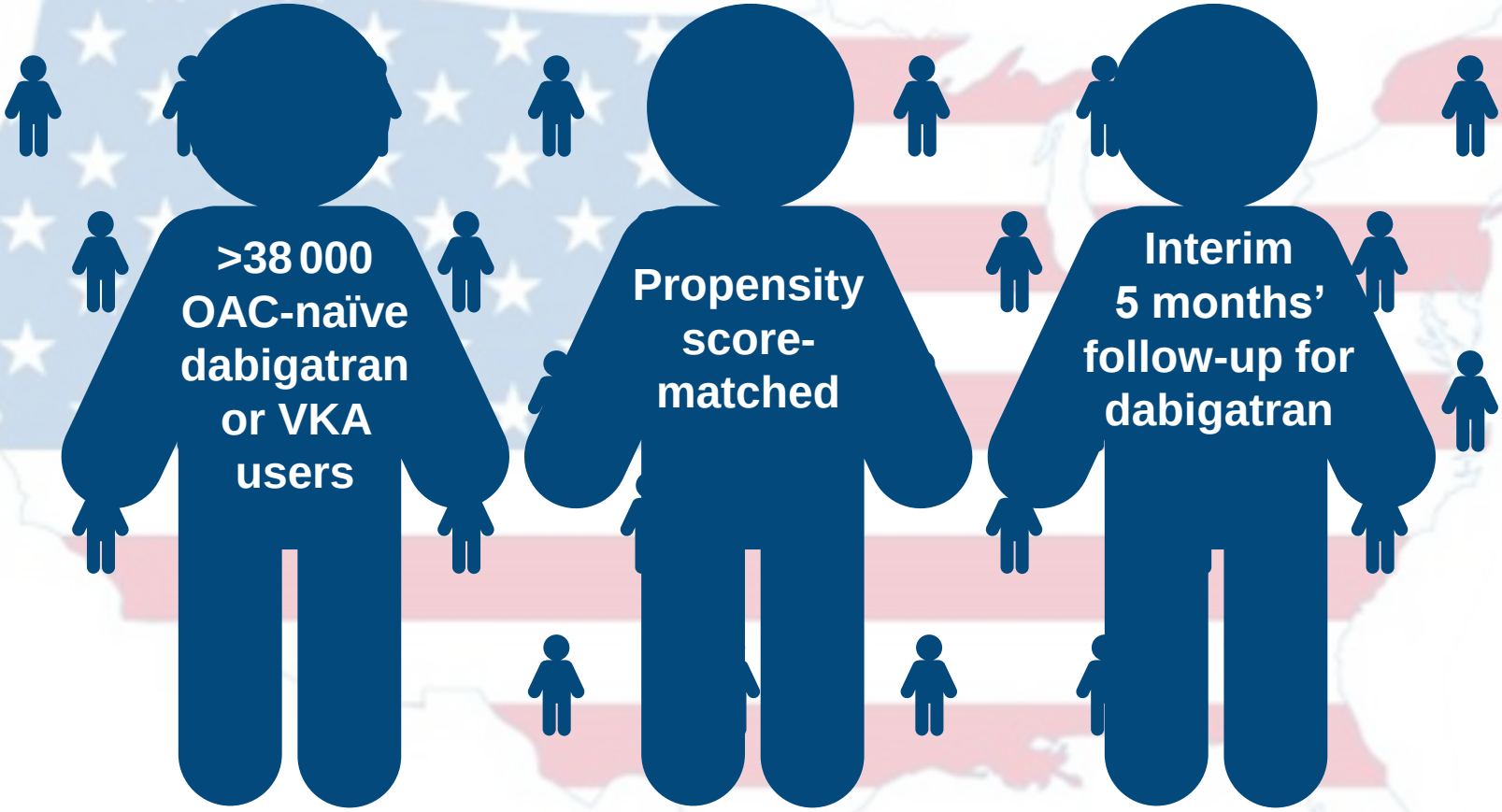
US Dpt. of Defense database showed clear consistency in outcomes with data from RE-LY®



*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;
2. Connolly SJ et al. N Engl J Med 2010; **3**. Pradaxa®: EU SPC, January 2015; **4.** Connolly SJ et al. N Engl J Med 2014;
5. Villines TC et al. Presented at AHA 2014;
6. Villines TC et al. Thromb Haemost 2015

Safety and effectiveness of dabigatran and warfarin in routine care of patients with atrial fibrillation



Seeger J et al. Thromb Haemost 2015;115

Mean age: 68 years. 36% of patients were female

1. Seeger J et al. Thromb Haemost 2015

Patients tended to be remarkably younger (and have fewer of certain comorbidities) compared with those in RE-LY®

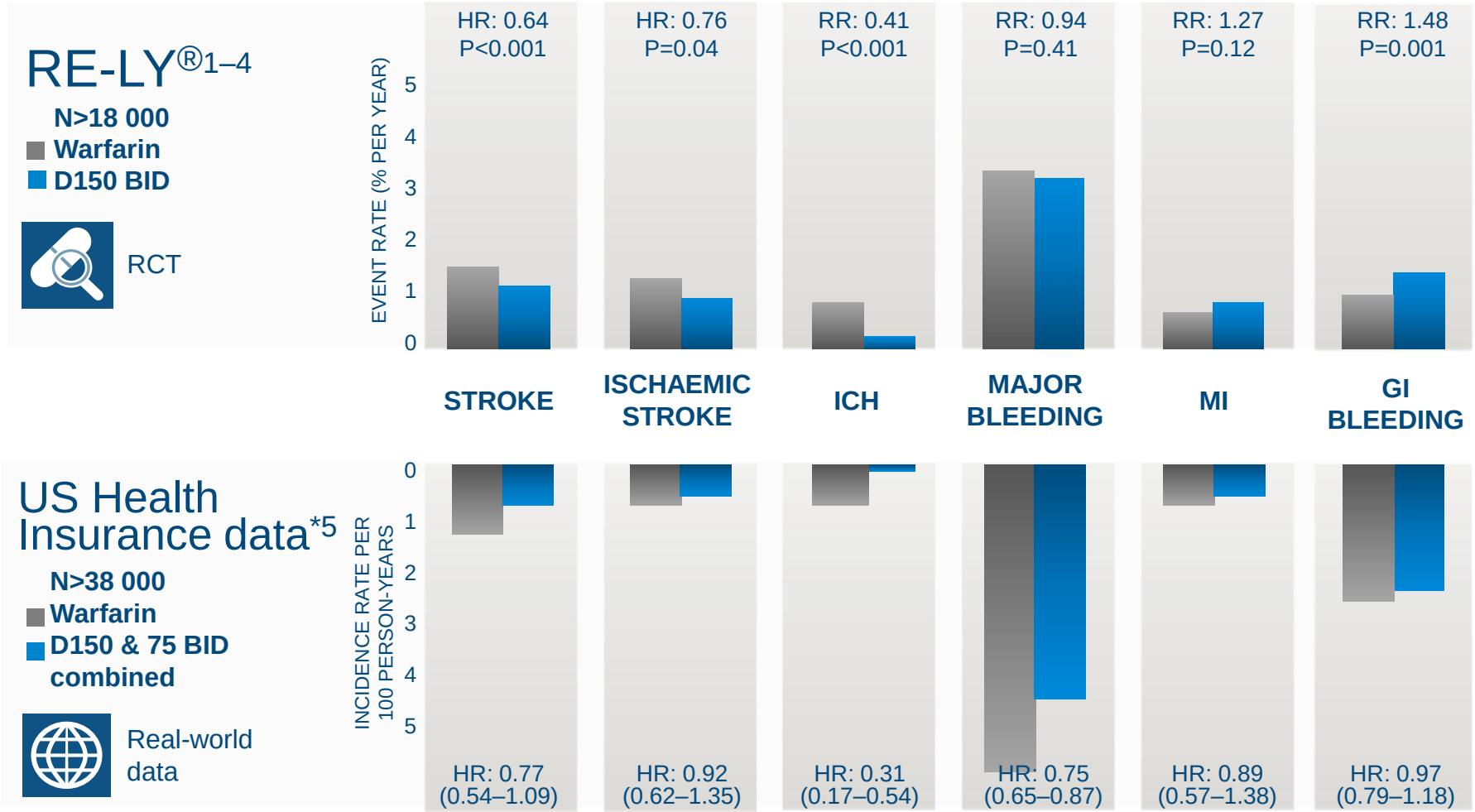
Characteristics, %	MarketScan database[1]		Clinformatics database[1]		RE-LY®[2]	
	Dabigatran (n=15 529)	Warfarin (n=15 529)	Dabigatran (n=3660)	Warfarin (n=3660)	Dabigatran (n=6076)	Warfarin (n=6022)
Mean age, years	68.7	68.3	63.4	63.1	71.5	71.6
Male sex	62	63	69	70	63	63
Hypertension	96	96	96	97	79	79
Prior MI*	4	4	5	5	17	16
Diabetes	21	20	28	29	23	23
Heart failure	18	18	18	18	32	32
Prior stroke	9	9	11	11	20†	20†

*'Recent' events only recorded in Seeger analysis

†Prior stroke or TIA combined

1. Seeger J et al. Thromb Haemost 2015;
2. Connolly SJ et al. N Engl J Med 2009

US Health Insurance data are consistent with RE-LY® and additional real-world data



*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; **2**. Connolly SJ et al. N Engl J Med 2010; **3**. Pradaxa®: EU SPC, January 2015 **4.** Connolly SJ et al. N Engl J Med 2014; **5.** Seeger DJ et al. Thromb Haemost 2015

Bleeding events among new starters and switchers to dabigatran compared with warfarin in atrial fibrillation

Bleeding events analysis[1]

Registry 1: median age 82 years (dabigatran 110 mg BID), 67 years (dabigatran 150 mg BID), 73 years (warfarin);

1 Larsen TB et al. Am J Med 2014

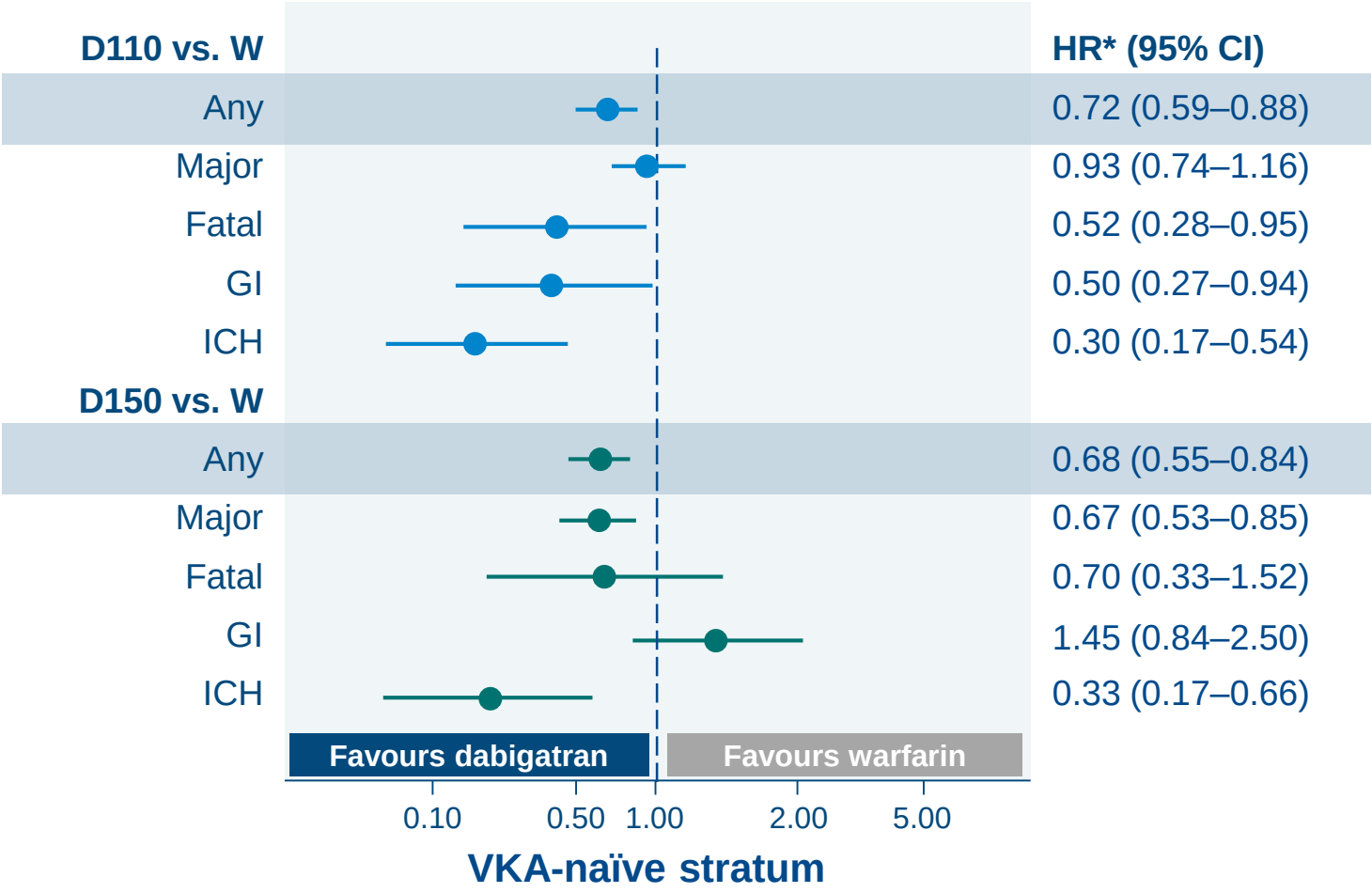
D110 users were older, more often female, and at higher bleeding and stroke risk vs. those on D150

Characteristic	VKA-naïve stratum		
	D110	D150	Warfarin
Patients, n	3045	4018	14 126
Median age (IQR), yrs	82 (77–86)	67 (62–72)	73 (66–80)
Age ≥65 yrs, %	95.3	63.6	76.8
Age ≥75 yrs, %	80.1	13.7	42.5
Female, %	55.1	36.6	41.3
HAS-BLED score, mean (SD)	2.32 (1.04)	1.70 (1.11)	1.97 (1.18)
$CHADS_2$ score, mean (SD)	1.91 (1.21)	0.94 (1.05)	1.33 (1.21)
CHA_2DS_2-VASc score, mean (SD)	3.70 (1.47)	2.12 (1.41)	2.80 (1.67)

IQR, interquartile range; SD, standard deviation

1. Larsen TB et al. Am J Med 2014

Reduced risk of any bleeding and ICH with both doses of dabigatran vs. warfarin



*HR adjusted for: age, components of CHA_2DS_2-VASc, HAS-BLED, months since August 2011

1. Larsen TB et al. Am J Med 2014

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

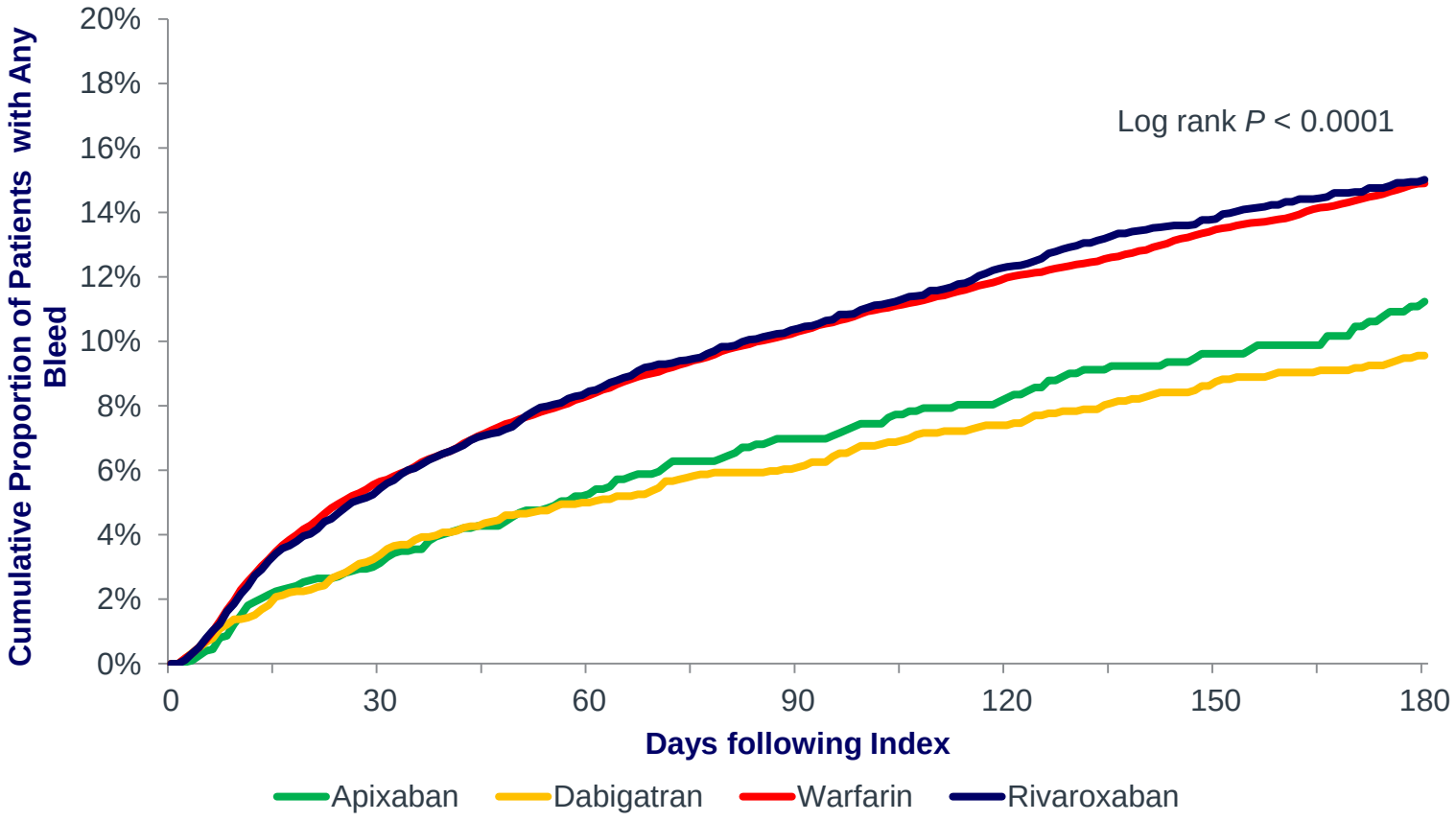
Characteristic	Apixaban	Rivaroxaban	Dabigatran	Warfarin	*P*-Value
N	2,038	6,407	2,440	24,872	
Age, mean (SD)	70.9 (10.6)	69.8 (11.0)	70.5 (10.3)	74.0 (9.6)	< 0.001
Female, N (%)	943 (46.3%)	2,869 (44.8%)	1,049 (43.0%)	11,042 (44.4%)	0.169
Chronic Kidney Disease*, N (%)	158 (7.8%)	501 (7.8%)	177 (7.3%)	3,039 (12.2%)	< 0.001
Baseline VTE, N (%)	13 (0.6%)	94 (1.5%)	25 (1.0%)	808 (3.2%)	< 0.001
Deyo-Charlson Comorbidity Index, mean (SD)	1.2 (1.6)	1.2 (1.7)	1.2 (1.6)	1.5 (1.9)	< 0.001
$CHADS_2$ Score (Stroke Risk), mean (SD)	1.5 (1.2)	1.4 (1.1)	1.5 (1.1)	1.8 (1.2)	< 0.001
HAS-BLED Score (Bleed Risk)¥, mean (SD)	1.7 (1.0)	1.7 (1.0)	1.6 (0.9)	1.8 (1.0)	< 0.001
ATRIA Score (Bleed Risk), mean (SD)	2.0 (1.8)	2.0 (1.8)	2.0 (1.8)	2.6 (2.0)	< 0.001
Baseline Resource Use, N (%)					
Stroke Event‡ (BENEFIT)	41 (2.0%)	126 (2.0%)	22 (0.9%)	346 (1.4%)	< 0.001
Bleeding Event† (RISK)	136 (6.7%)	572 (8.9%)	180 (7.4%)	2,531 (10.2%)	< 0.001
Myocardial Infarction Event‡	10 (0.5%)	38 (0.6%)	7 (0.3%)	131 (0.5%)	0.351

SD, standard deviation; VTE, venous thromboembolism; *Including stages I-IV, end stage renal disease, and unspecified; Stage V additionally includes end stage renal disease; ¥ Excluding labile INR component; ‡ Inpatient setting (any diagnosis); † Any setting/type; HAS-BLED, hypertension, abnormal renal or liver function, previous stroke/TIA, bleeding, labile INR, elderly, drugs or alcohol. ATRIA anaemia, severe renal disease, age ≥ 75, prior bleeding, hypertension; $CHADS_2$ - congestive heart failure, hypertension, age, diabetes, previous stroke/TIA; TIA, transient ischemic attack.

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

- Approximately 15% of patients in the warfarin and rivaroxaban cohorts had experienced a bleed by 180 days, compared to 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

Real-world Comparison of Bleeding Risks among Non-Valvular Atrial Fibrillation Patients on Apixaban, Dabigatran, Rivaroxaban:

Cohorts Comprising New Initiators and/or Switchers from Warfarin

P. Tepper, ESC 2015 FP Number: 1975

Sensitivity Analysis – Inpatient Bleeding Only
Unadjusted and adjusted Incidences of Bleeding Events

	Apixaban (N=8785)			Dabigatran (N=20963)			Rivaroxaban (N=30529)		
Inpatient bleeding	N	n/N (%)	Incidence %/year	N	n/N (%)	Incidence %/year	N	n/N (%)	Incidence %/year
Any	129	1.5	5.0	341	1.6	4.3	737	2.4	7.5
ICH	13	0.1	0.5	42	0.2	0.5	67	0.2	0.7
GI	80	0.9	3.1	225	1.1	2.9	482	1.6	4.9
Other	43	0.5	1.7	95	0.5	1.2	241	0.8	2.5

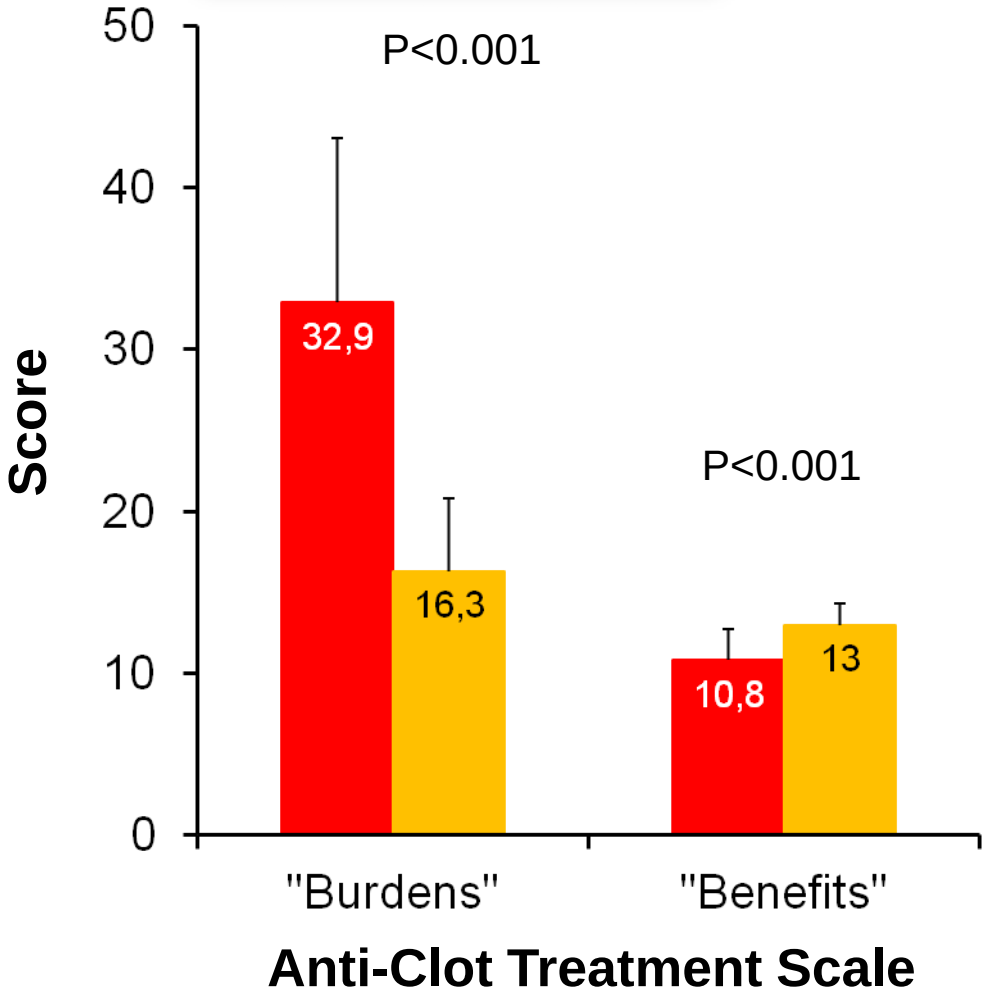
Adjusted HRs and 95% CI

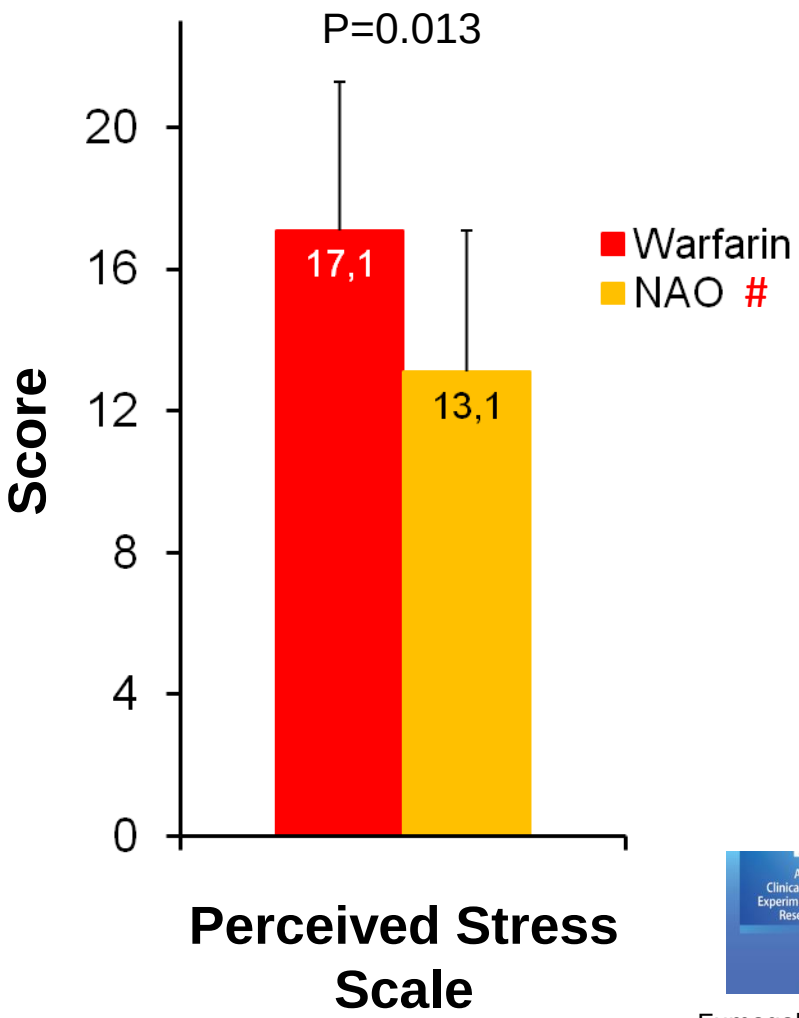
Inpatient bleeding	Adjusted HR (Dabigatran vs Apixaban)	Adjusted HR (Rivaroxaban vs Apixaban)
Any	0.95 (0.77,1.16)	**1.52 (1.26, 1.83)**
ICH	1.15 (0.61, 2.17)	1.39 (0.77, 2.53)
GI	1.00 (0.77, 1.29)	**1.60 (1.26, 2.03)**
Other	0.81 (0.56, 1.16)	**1.46 (1.05, 2.02)**

Psychological effects of treatment with new oral anticoagulants# in elderly patients with atrial fibrillation: a preliminary report

 # dabigatran in all cases

Warfarin – N=15; Age: **79** years; CHA_2DS_2-VASc: 4.2
NAO – N=15; Age: **84** years; CHA_2DS_2-VASc: 4.4





Fumagalli S, 2015

DABIGATRAN:
EVIDENZE DI SICUREZZA NELLA VITA REALE

Conclusioni (1/2)

- Dati da un enorme (>250 000) numero di pazienti con prolungato follow-up confermano che, rispetto a warfarin, dabigatran riduce il rischio di ictus ischemico (**superiore efficacia**) in corso di FANV
- Il lieve eccesso di sanguinamenti GI di alcuni degli studi di mondo reale è da attribuire al dosaggio troppo elevato (150 mg BID) utilizzato negli USA nella maggior parte dei casi
- A dosi secondo labeling europeo, dabigatran riduce il rischio di sanguinamenti rispetto a warfarin(**superiore sicurezza**)

DABIGATRAN:
EVIDENZE DI SICUREZZA NELLA VITA REALE

Conclusioni (2/2)

- La **mortalità per tutte le cause** è ridotta con dabigatran, rispetto a warfarin, in una popolazione di oltre 130,000 ultra65enni con FANV
- Il profilo di scurezza di dabigatran risulta simile a quello di apixaban e superiore a quello sia di warfarin sia di rivaroxaban
- La qualità della vita di anziani in trattamento con dabigatran per FANV sembra migliore rispetto al trattamento con warfarin