ADVANCES IN CARDIAC ARRHYTHMIAS and GREAT INNOVATIONS IN CARDIOLOGY
XXVII GIORNATE CARDIOLOGICHE TORINESI

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Dabigatran Evidence in Real Practice

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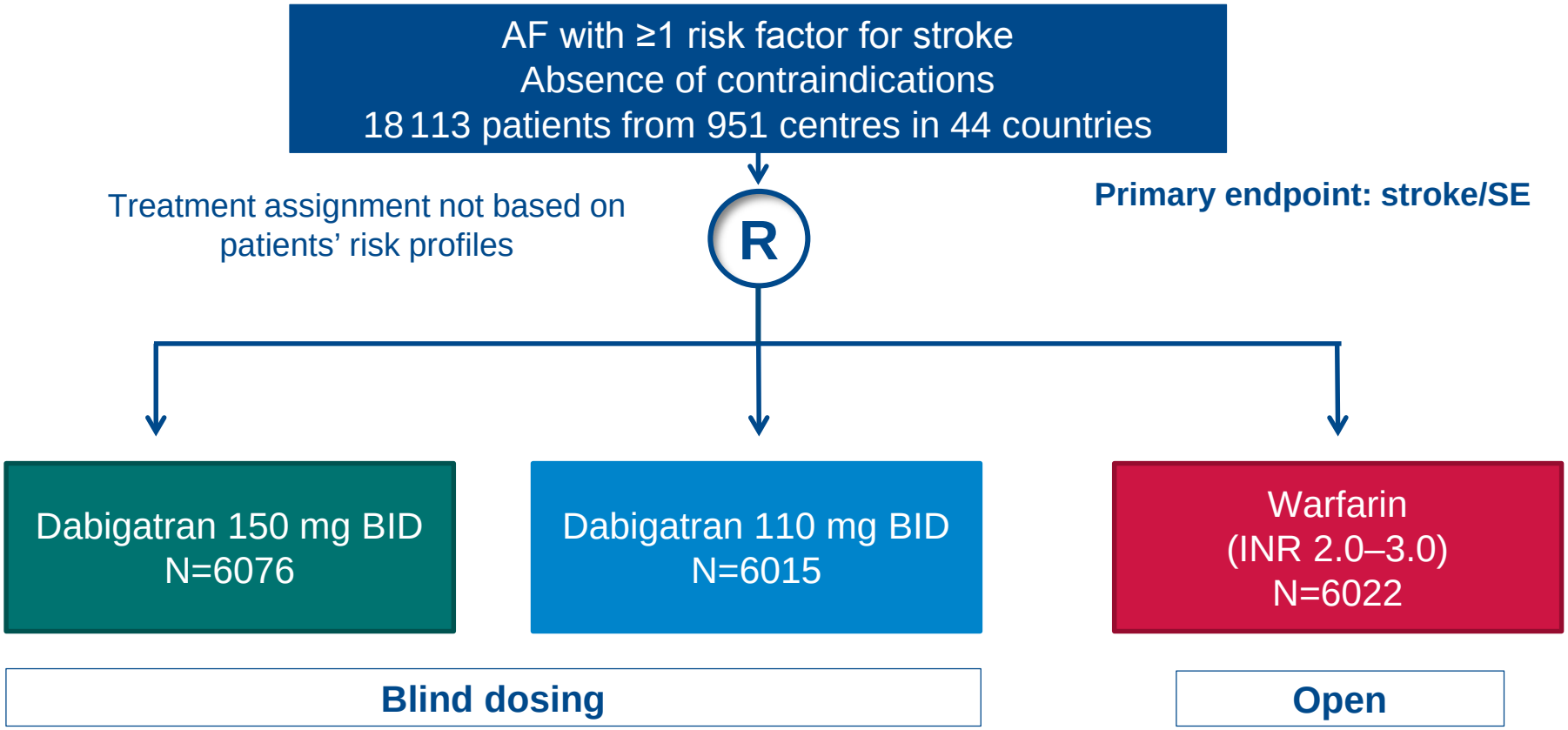
RE-LY: Pivotal RCT for SPAF and a Global Non-inferiority Trial of Exemplary Design

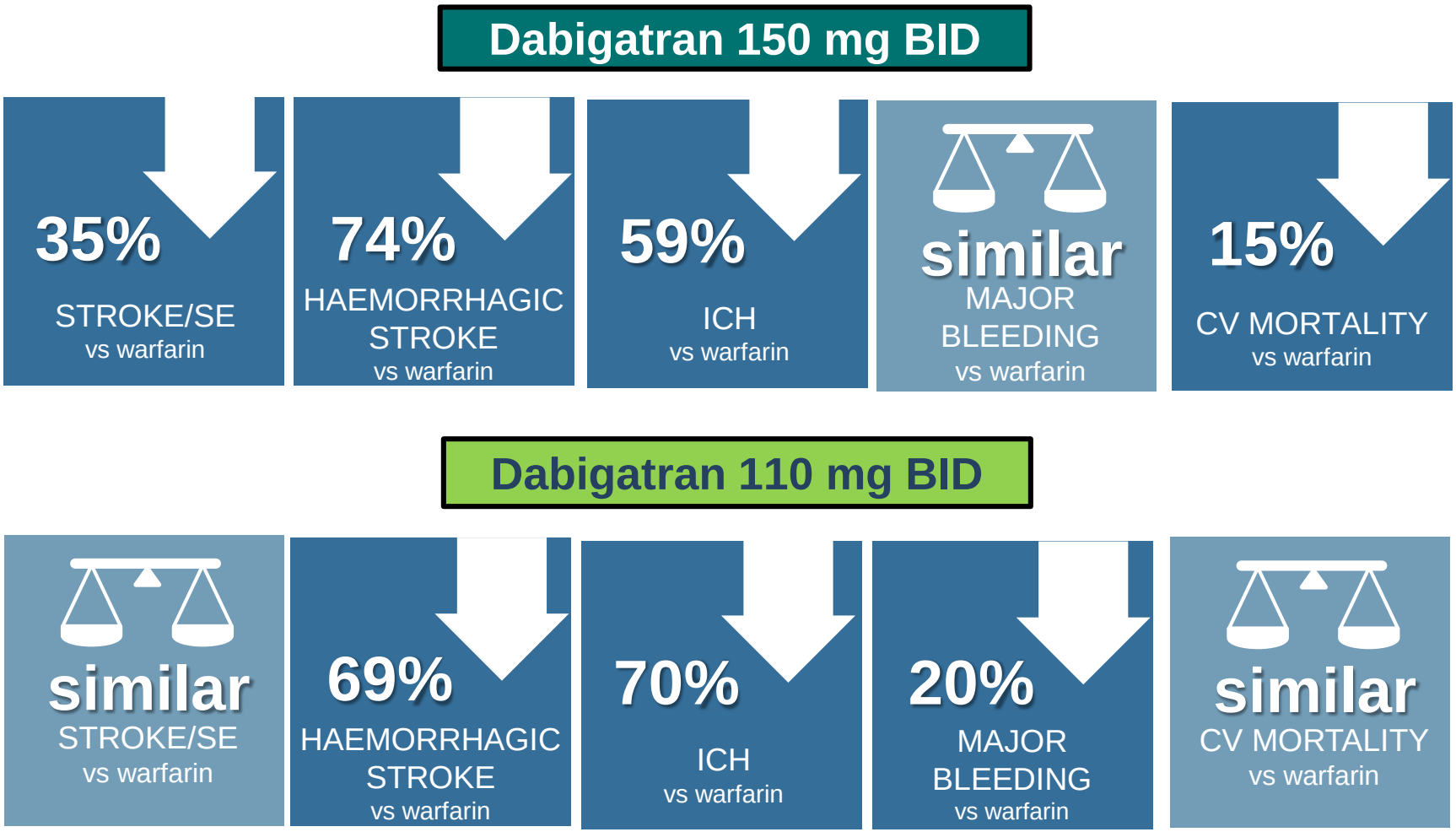


Only NOAC trial sufficiently powered to evaluate two independent doses (large, fully randomized patient populations)

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

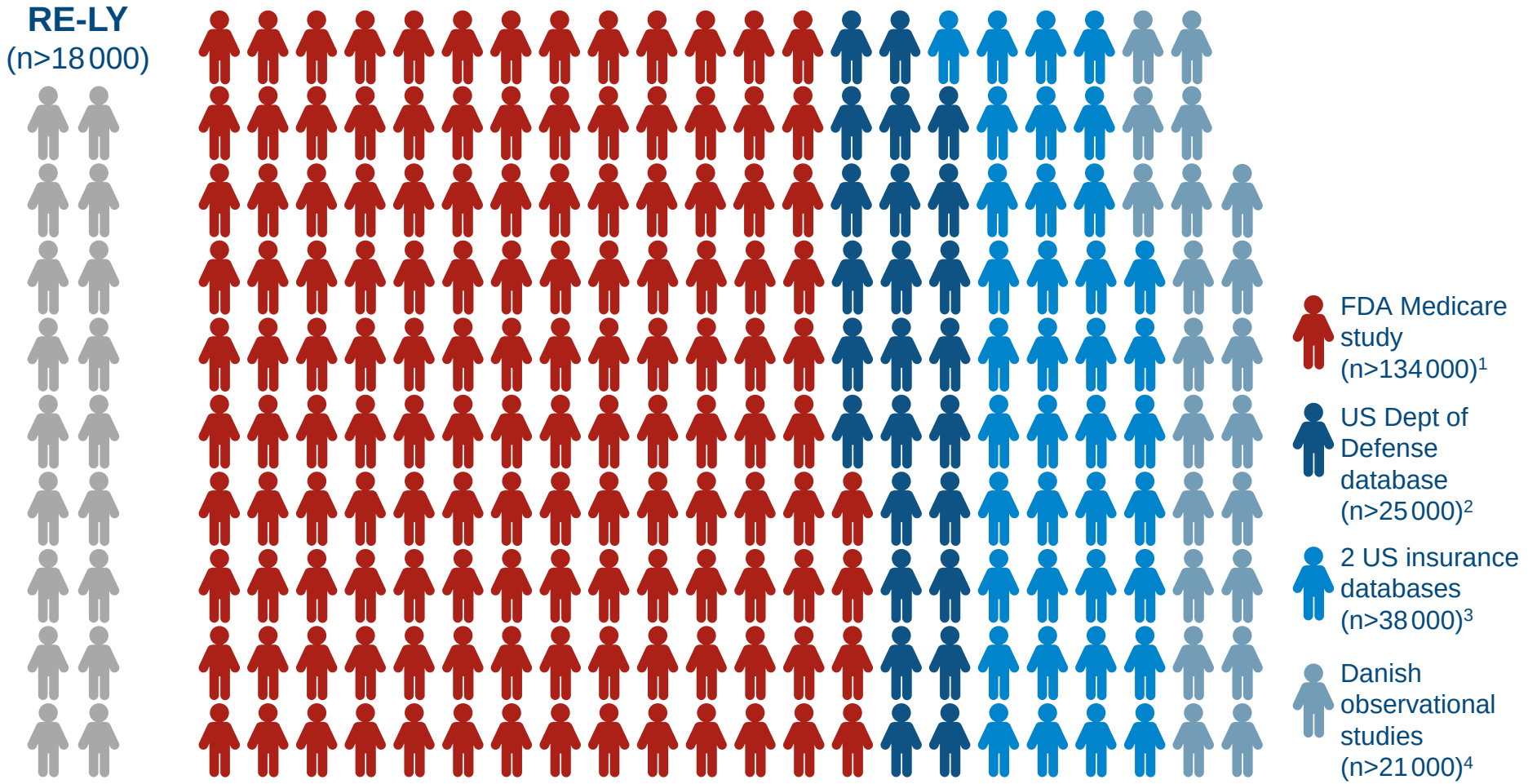
Ezekowitz MD et al. Am Heart J 2009;157:805
Connolly SJ et al. N Engl J Med 2009;361:1139

RE-LY
At a Glance



Connolly et al. N Engl J Med 2010;
Connolly et al. N Engl J Med 2014

Real-World Experience from >200 000 Patients Confirms Positive Safety and Efficacy Profile of Dabigatran



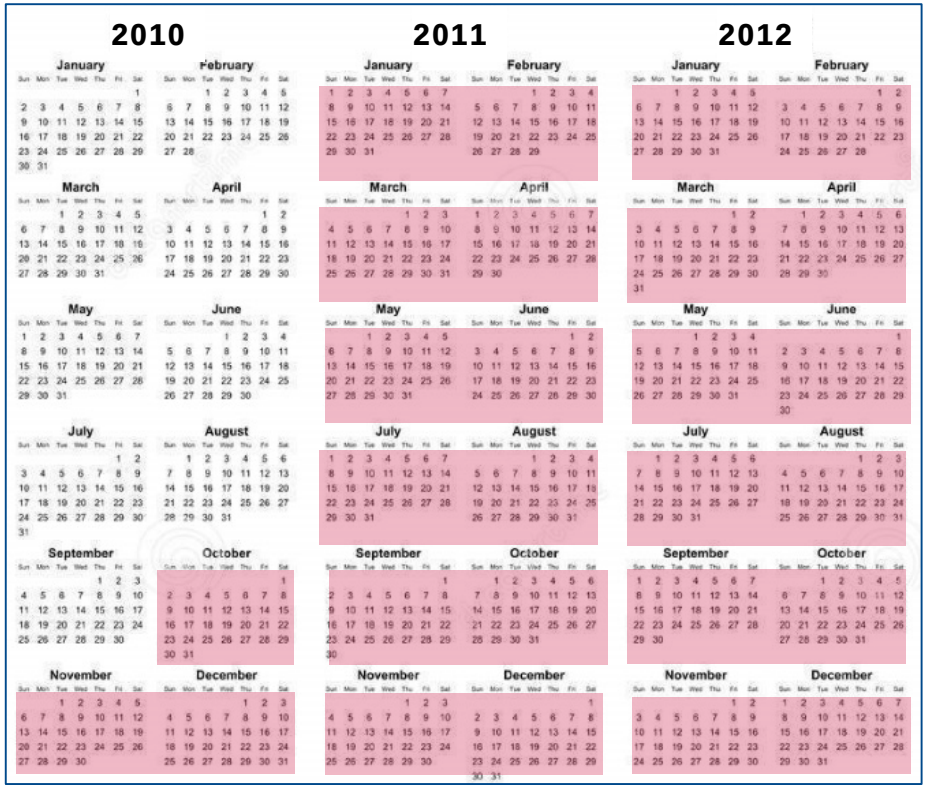
1. Graham et al. Circulation 2015; 2. Vilines et al. AHA 2014;
3. Seeger et al. AHA 2014; 4. Larsen et al. Am J Med 2014

Independent FDA Study of Medicare Patients in >134 000 New Users of Dabigatran or Warfarin

- Independent FDA study
- Observational cohort study
- US Medicare database
- Comparison of ischaemic stroke, ICH, major GI bleeding, acute MI, and mortality rates using insurance-claim and administrative data

- >134 000 new users (OAC treatment-naïve) of dabigatran or warfarin
- All recently diagnosed with AF
- All aged ≥65 years
- 37 500 person-years of follow-up
- Adjustments were made for confounding variables

Study period



Graham DJ et al. Circulation 2015;131:157

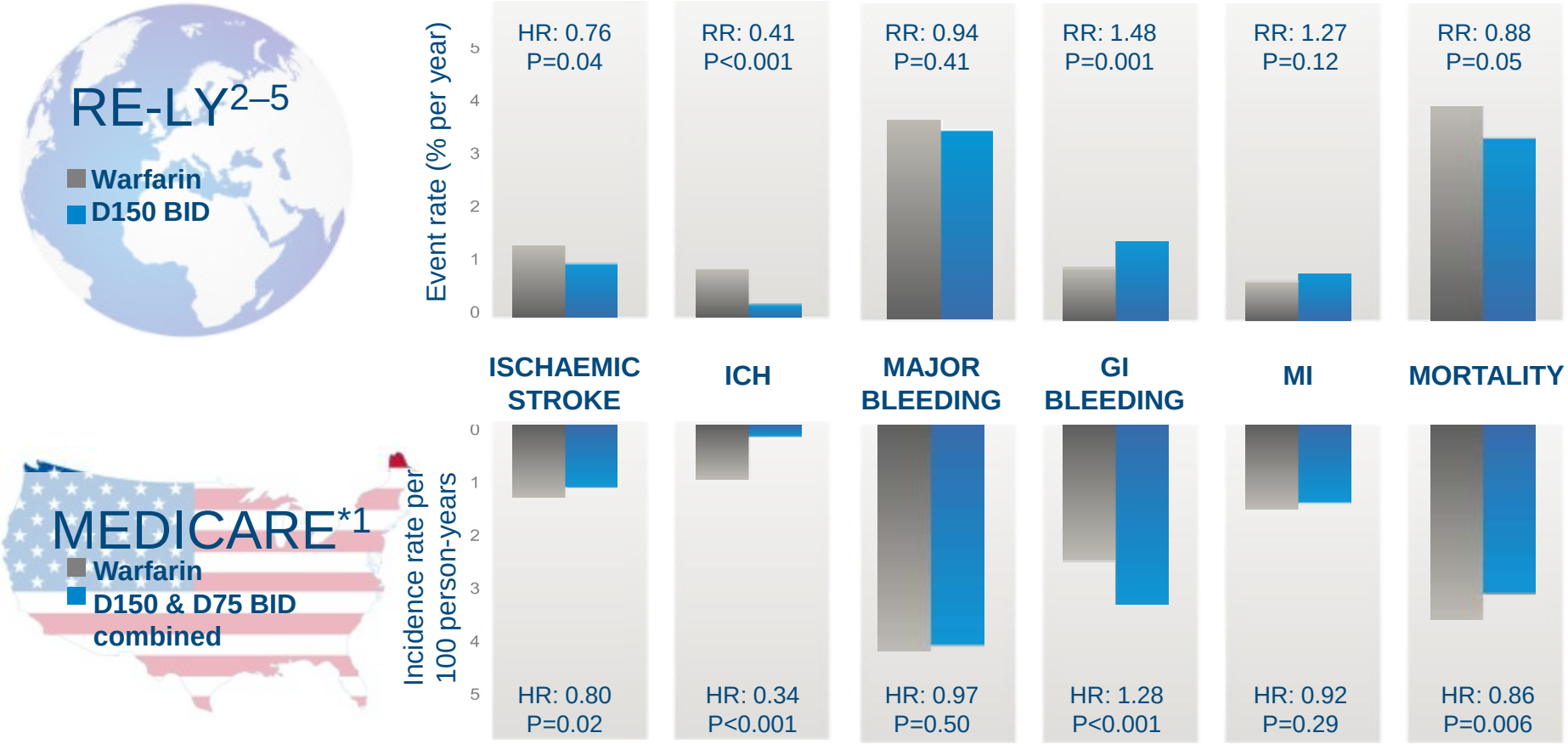
FDA Medicare Analysis Included > Patients with Certain Comorbidities vs RE-LY

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
Prior MI	2	2	17	16
Diabetes	33	34	23	23
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;131:157–64; **2.** Connolly SJ et al. N Engl J Med 2009;361:1139–51; **3.** Coppens M et al. Circulation 2012;126:abstract 15537; **4.** Eikelboom JW et al. Circulation 2011;123:2362–72

Independent FDA Study Mirrors the Favourable Benefit–Risk Profile of Dabigatran from RE-LY



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

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

Dabigatran 150 mg BID is the ONLY NOAC to Significantly Reduce Ischaemic Stroke vs Warfarin

92% of strokes associated with AF are ischaemic*[1]; consequences can be devastating for patients

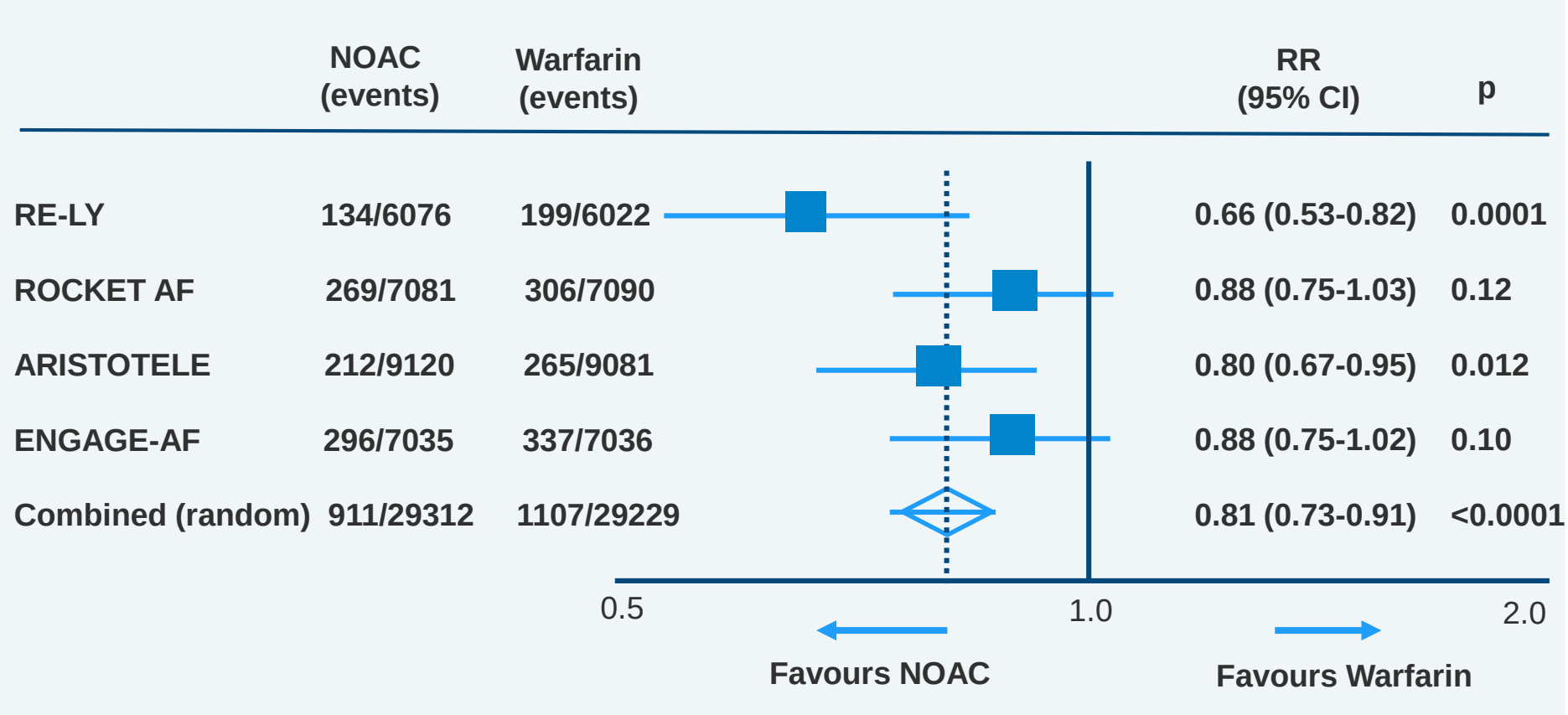
Dabigatran 150 mg BID:
24% reduction in risk of ischaemic stroke vs warfarin[2]

Unique in the NOAC class, emphasizing best patient protection

*Based on data collected in the Danish National Indicator Project for 39 484 patients hospitalized for stroke (including 6294 AF)

1. Andersen et al. Stroke 2009; 2. Pradaxa® SPC, 2015

Clear Benefit of Dabigatran on Stroke or Systemic Embolic Events

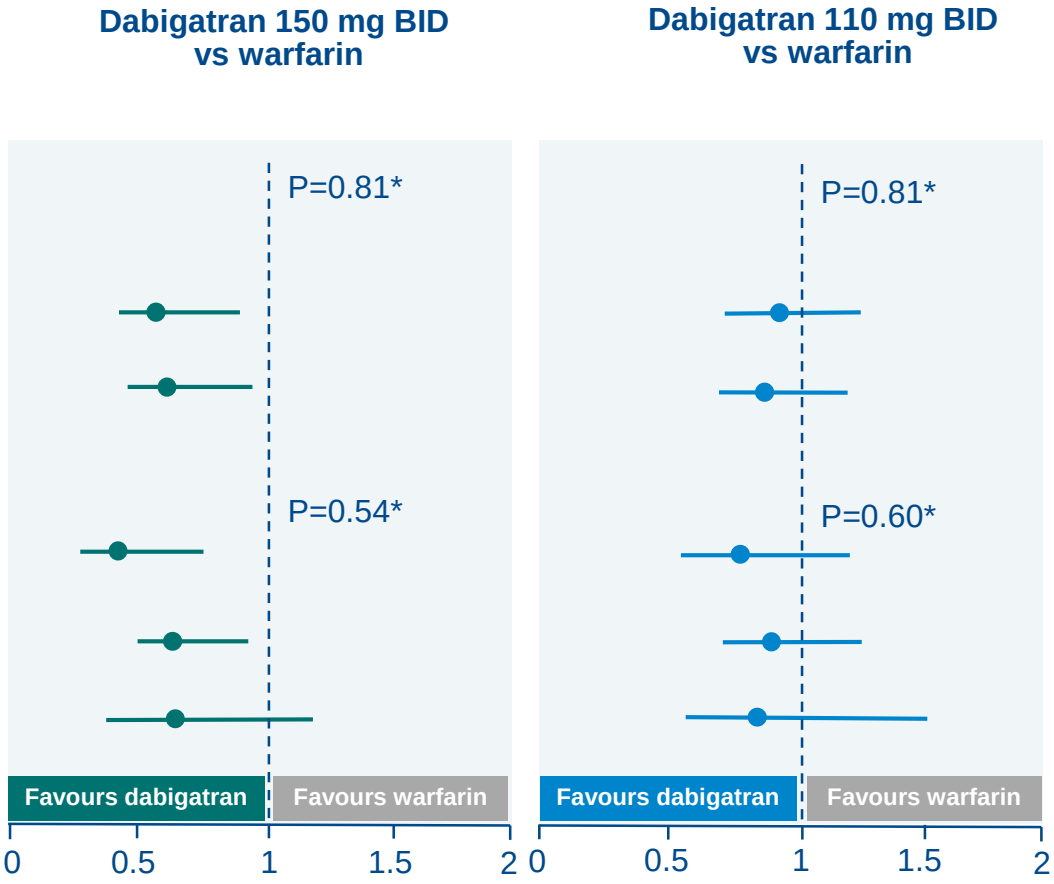


Ruff CT, et al. Lancet 2014; 383: 955

Efficacy Benefits vs Warfarin are Maintained Irrespective of Age or Renal Function

Stroke/SE

	Annual rate (%)		
	D 110 mg BID	D 150 mg BID	Warfarin
Age (yrs)			
<75	1.32	0.90	1.43
≥75	1.89	1.43	2.14
CrCl (mL/min)			
<50	2.15	1.52	2.78
50–79	1.70	1.20	1.76
≥80	0.94	0.75	0.98



*P values for interaction

Connolly et al. New Engl J Med 2009;
Eikelboom et al. Circulation 2011

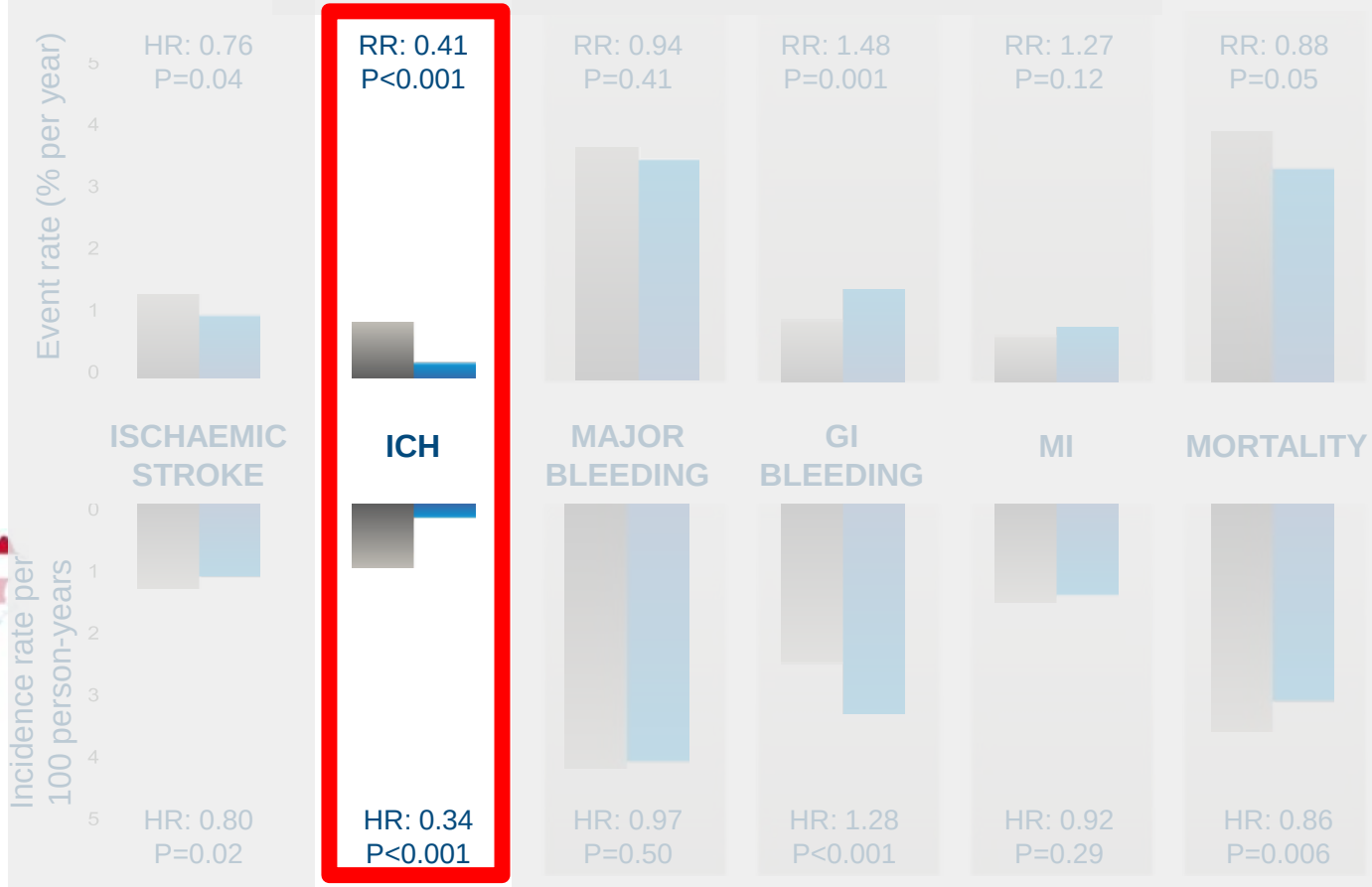
Independent FDA Study Mirrors the Favourable Benefit–Risk Profile of Dabigatran from RE-LY

RE-LY[2–5]

- Warfarin
- D150 BID

MEDICARE*[1]

- Warfarin
- D150 & D75 BID combined



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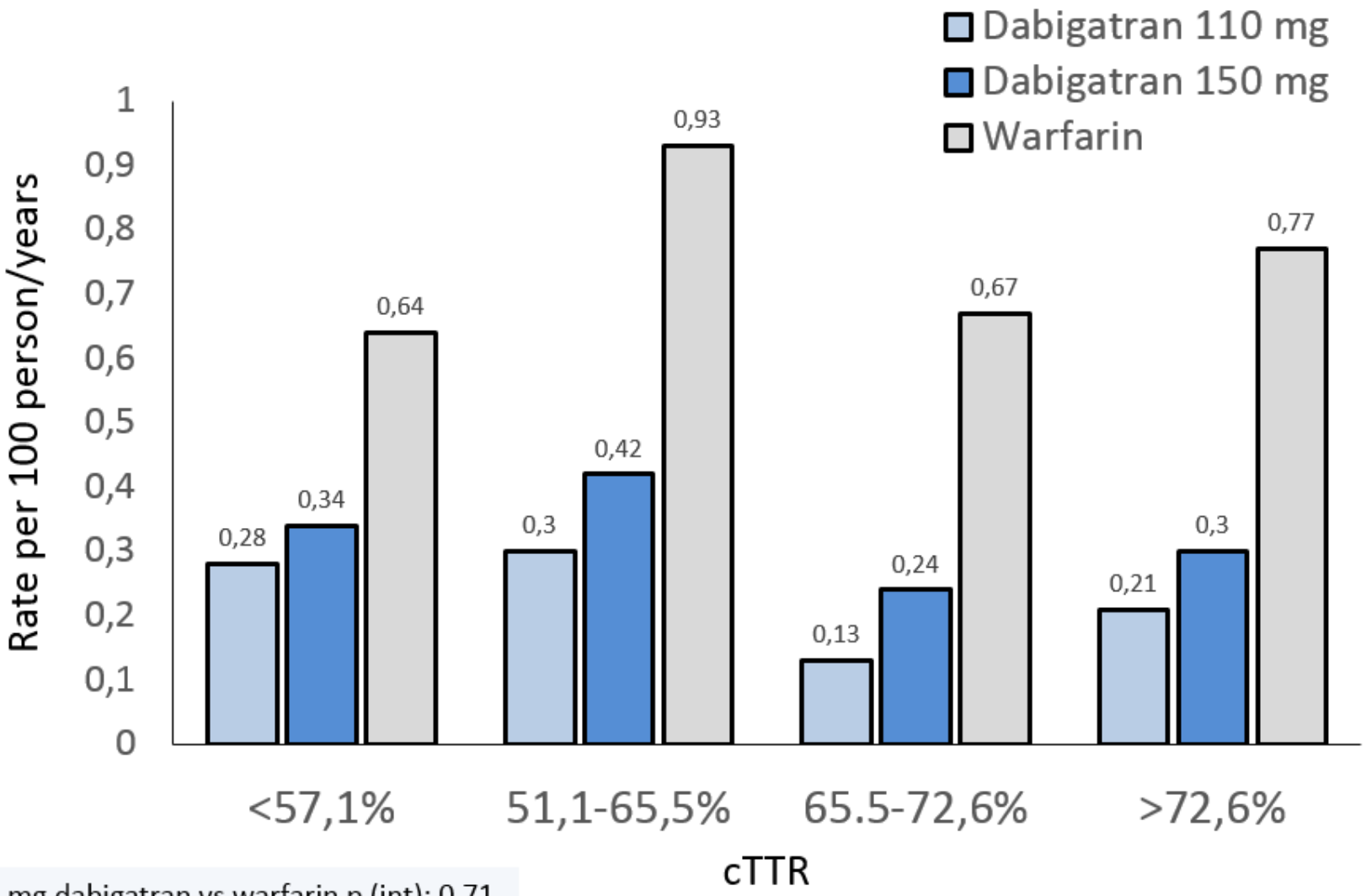
Drastic Reduction in ICH with Dabigatran Compared to Warfarin at any Level of TTR



110 mg dabigatran vs warfarin p (int): 0.71
150 mg dabigatran vs warfarin p (int): 0.89

Walentin L, et al. Lancet 2010; 376: 975

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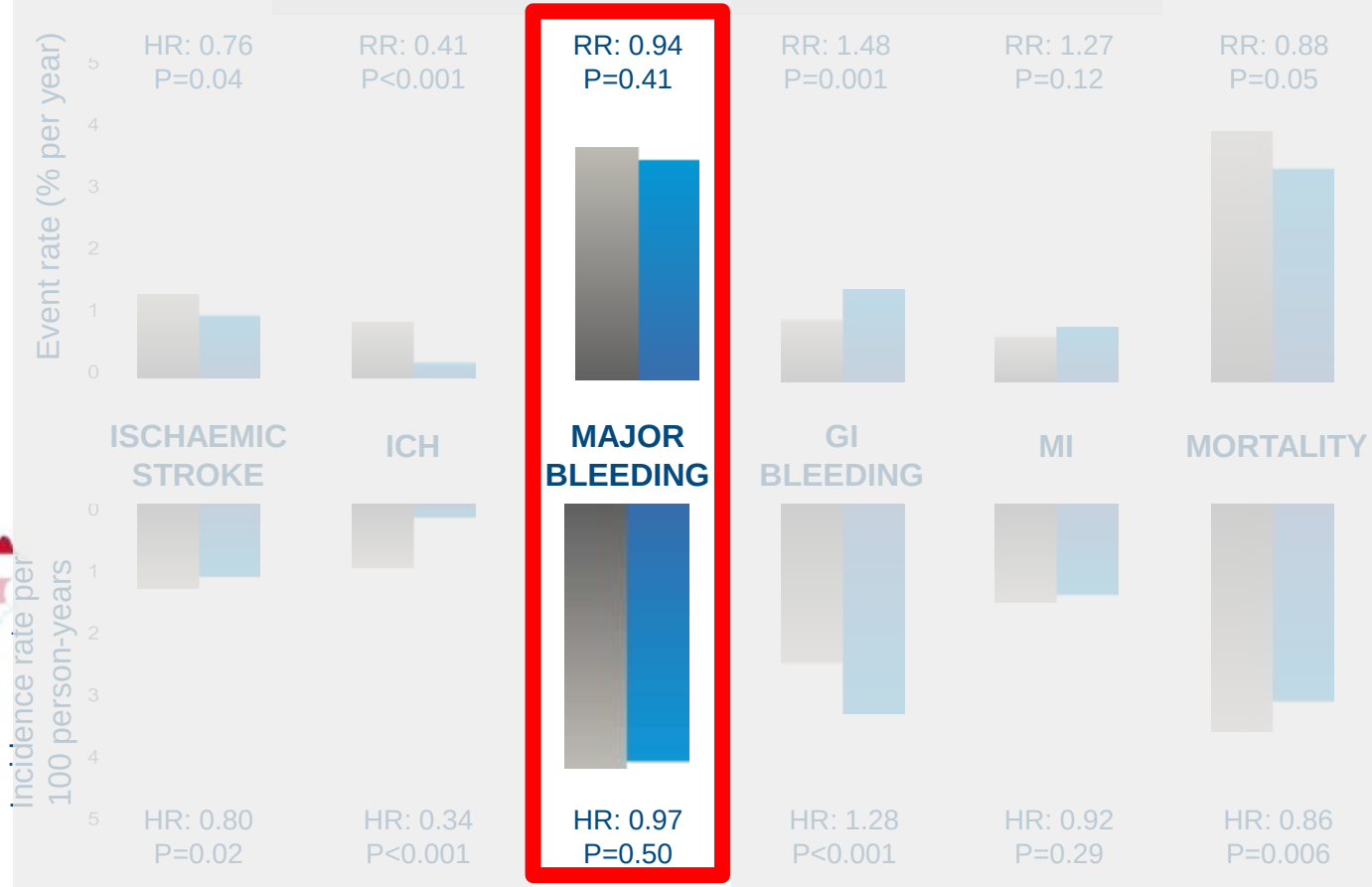

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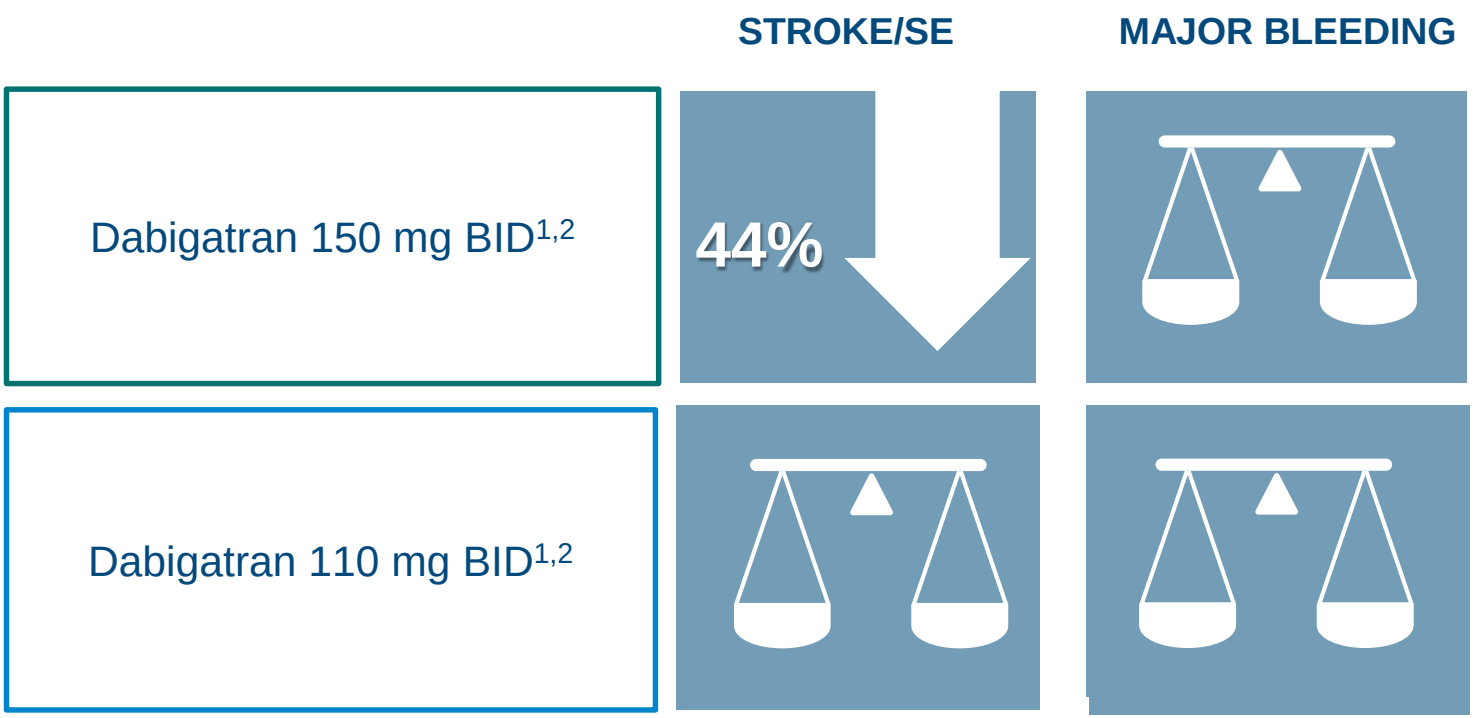
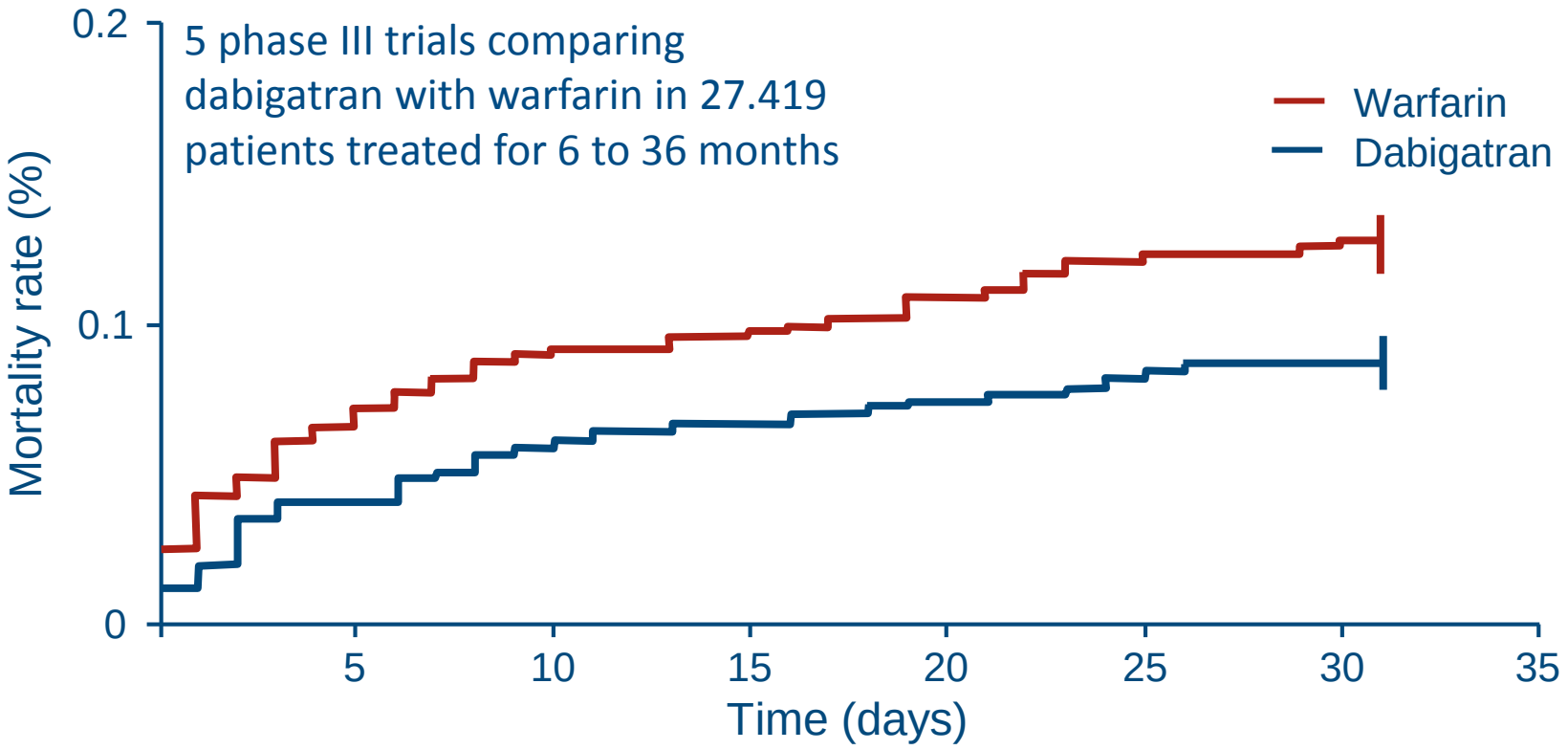
Benefit-Risk Profile of NOACs in Patients with Moderate Renal Impairment (CrCl 30-49 mL/min)



1. Liesenfeld KH J Thromb Hemost 2011;
2. 2. Hijazi et al Circulation 2014;

In Patients who Experience a Major Bleed, Dabigatran is Associated with Improved Outcome

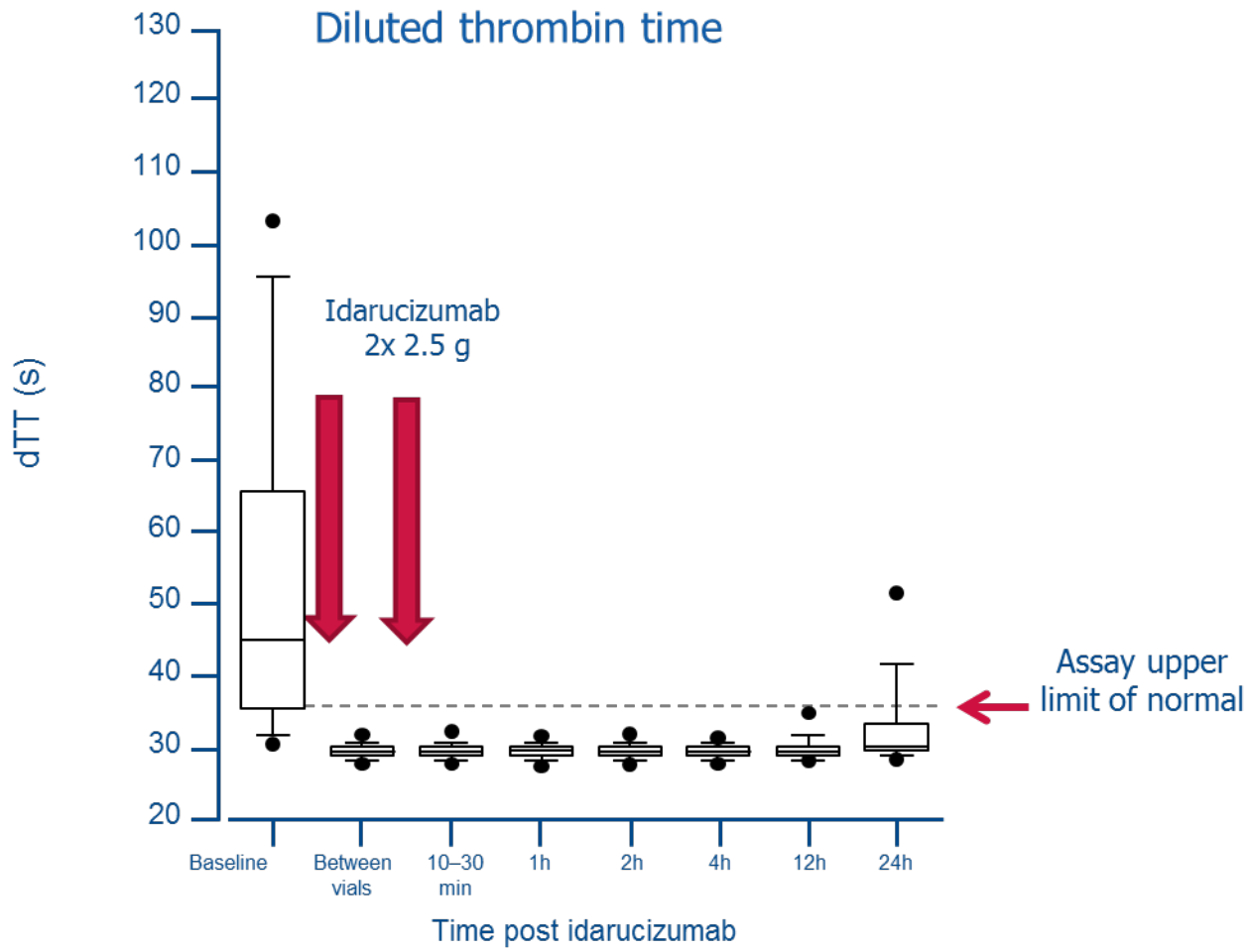


Reduced risk for death with dabigatran vs warfarin during 30 days after the bleeding (P=0.052) in the absence of a specific reversal agent*

*Combined data from dabigatran 150 mg and 110 mg BID treatment groups. Only first major bleed included. Analysis not adjusted for covariates

Majeed et al. Circulation 2013;128:2325

Reversal of Dabigatran Anticoagulation with Idarucizumab Based on dTT



Pollack CV, et al. N Engl J Med 2015;373:511

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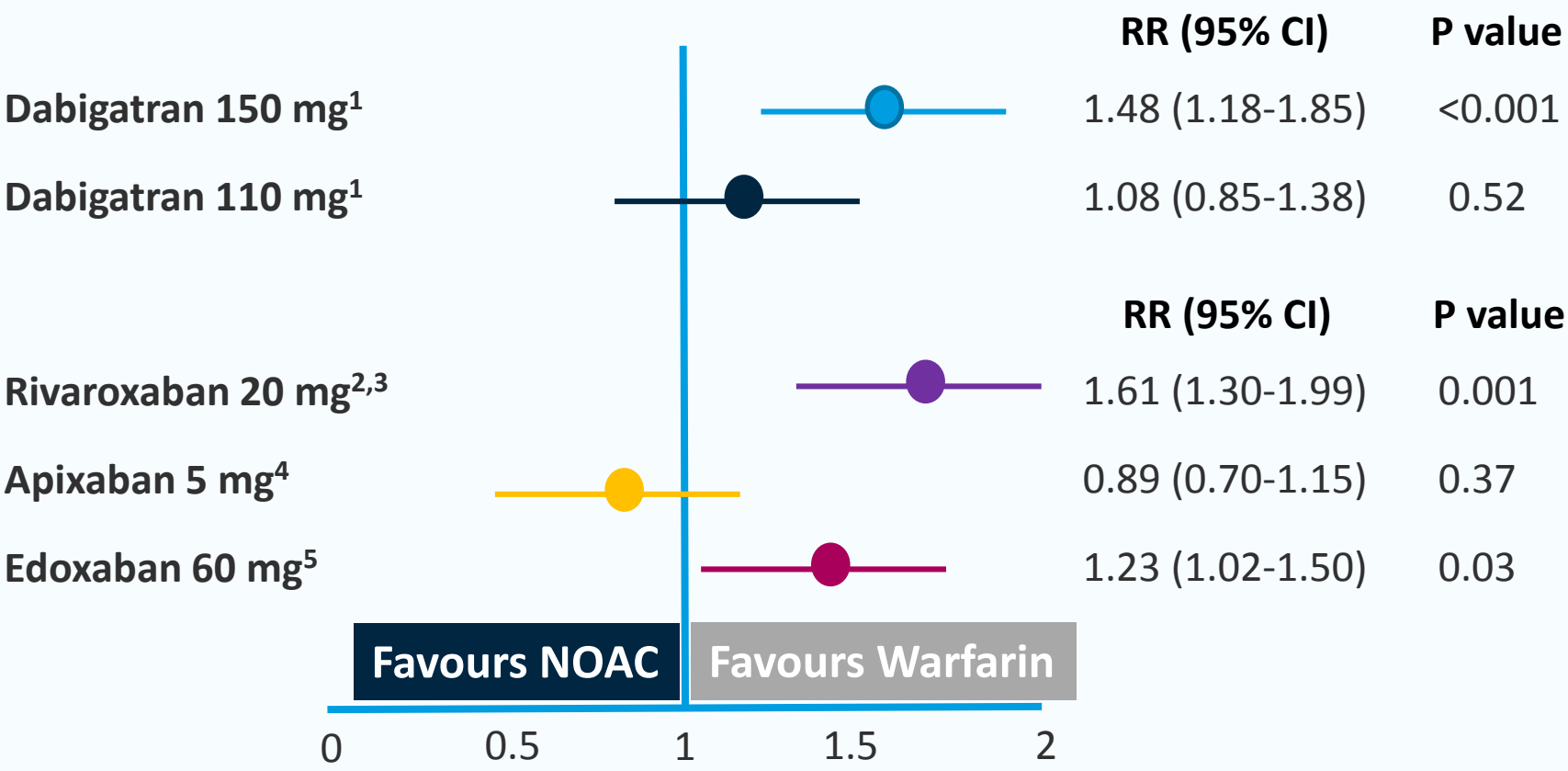
Risk of Major GI Bleeding in Phase III Trials on NOACs



Meta-analysis showed increased risk of GI bleeding for NOACs as a group[6]

1. Connlly et al. N Engl J Med 2010; 2. Patel et al. N Engl J Med 2011;
2. 3. Nessel et al Chest 2012; 4. Granger et al. N Engl J Med 2011;
3. 5. Giugliano et al. N Engl J Med 2013; 6. Ruff et al. Lancet 2014

‘EU label’ Analysis: Outcomes when Dabigatran was Used According to EU Label

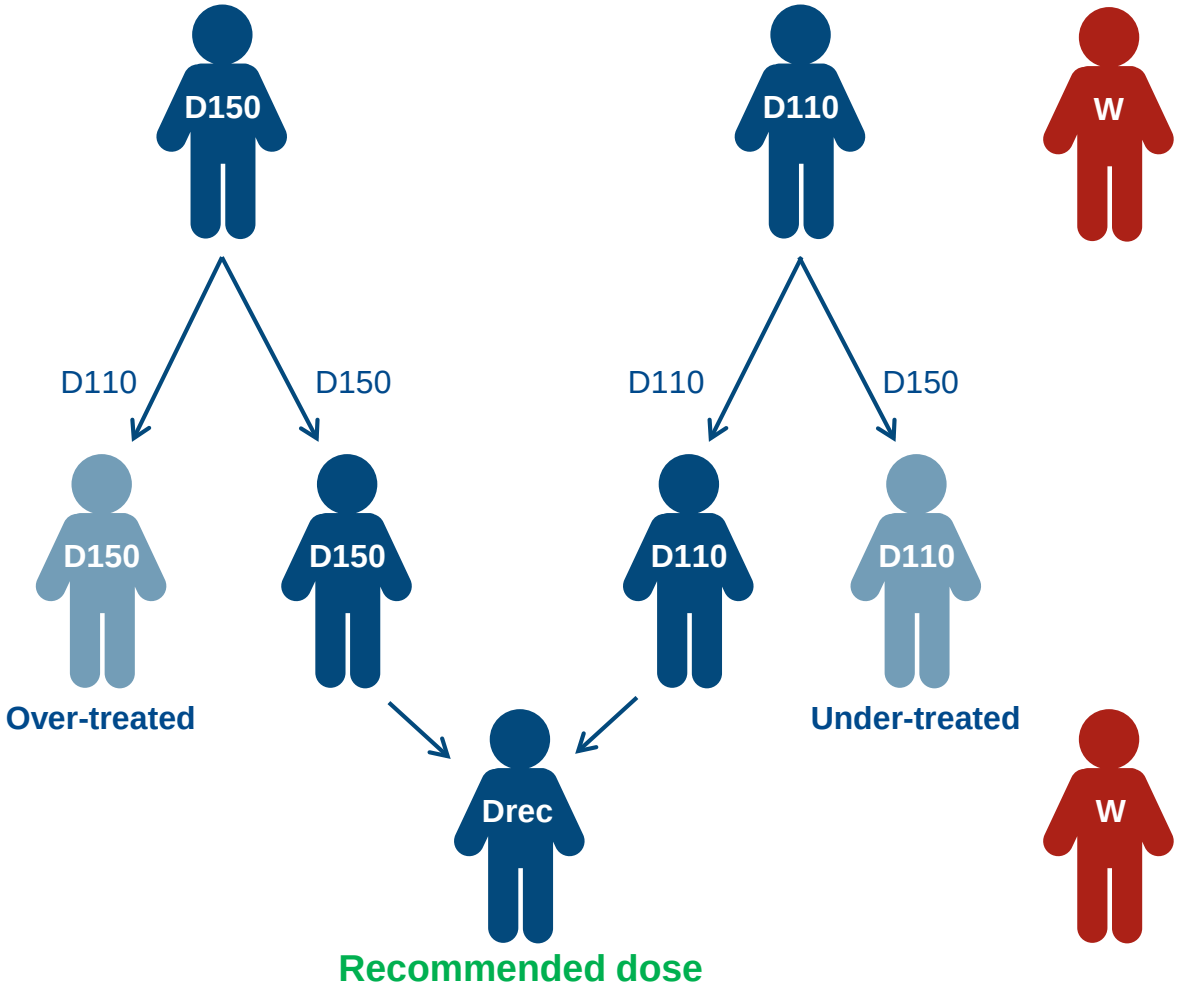
Full RE-LY population

Post hoc analysis of patients’ baseline characteristics

Recommended dose*

Dose received

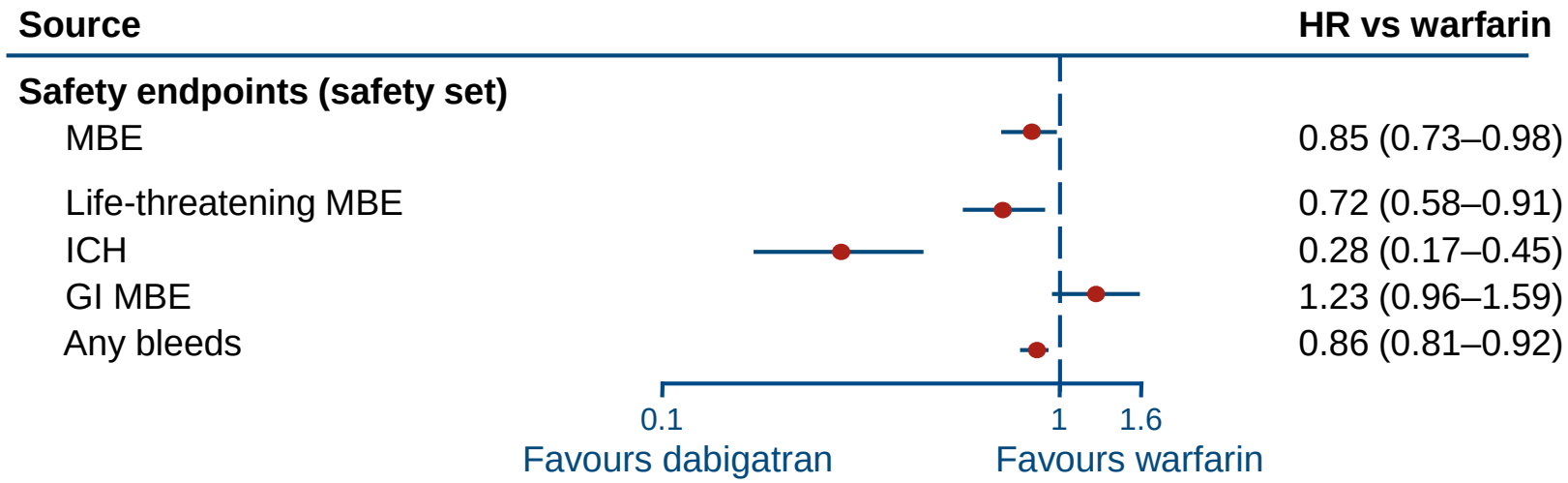
Post hoc pooled analysis
‘EU label-simulated dabigatran’ vs warfarin



*D110 recommended for ≥80 years *OR* HAS-BLED ≥3 *OR* verapamil; D150 recommended for <80 years *AND* HAS-BLED <3

Lip GY et al. Thromb Haemost 2014;111:933–42

‘EU Label-Compliant’ Dabigatran Rx Provides a Meaningful and Clinically Relevant Benefit



ICH RR (95% CI)	Major bleed RR (95% CI)	GI MBE RR (95% CI)
0.28 (0.17–0.45)	**0.85** (0.73–0.98)	**1.23** (0.96–1.59)

Lip GY et al. Thromb Haemost 2014;111:933

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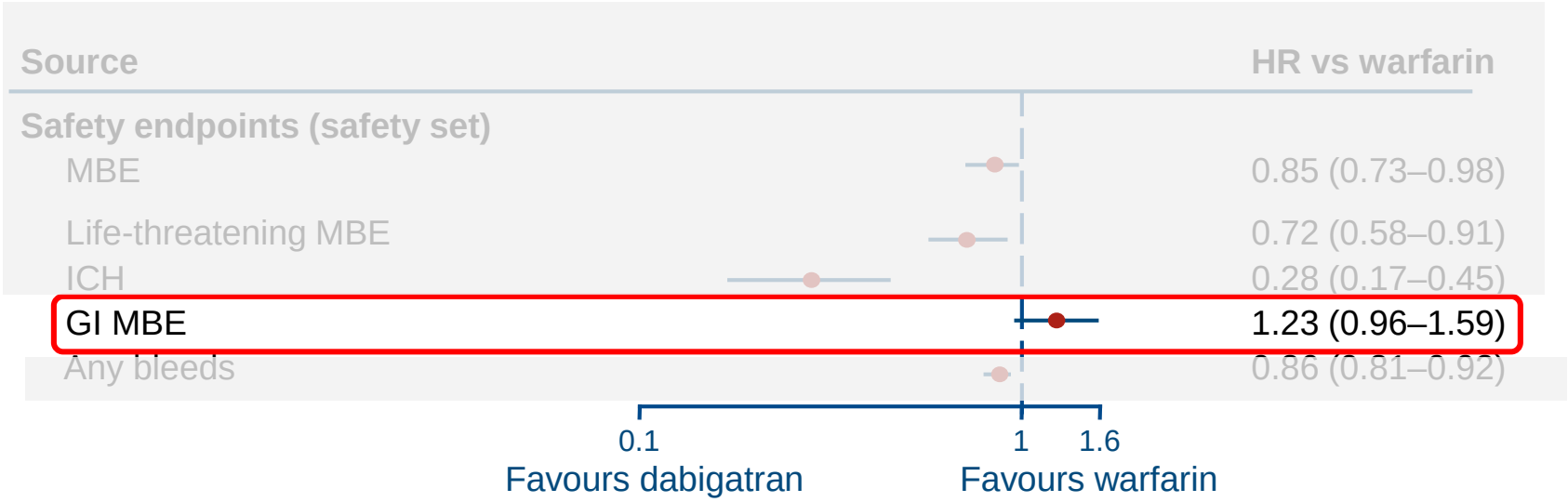

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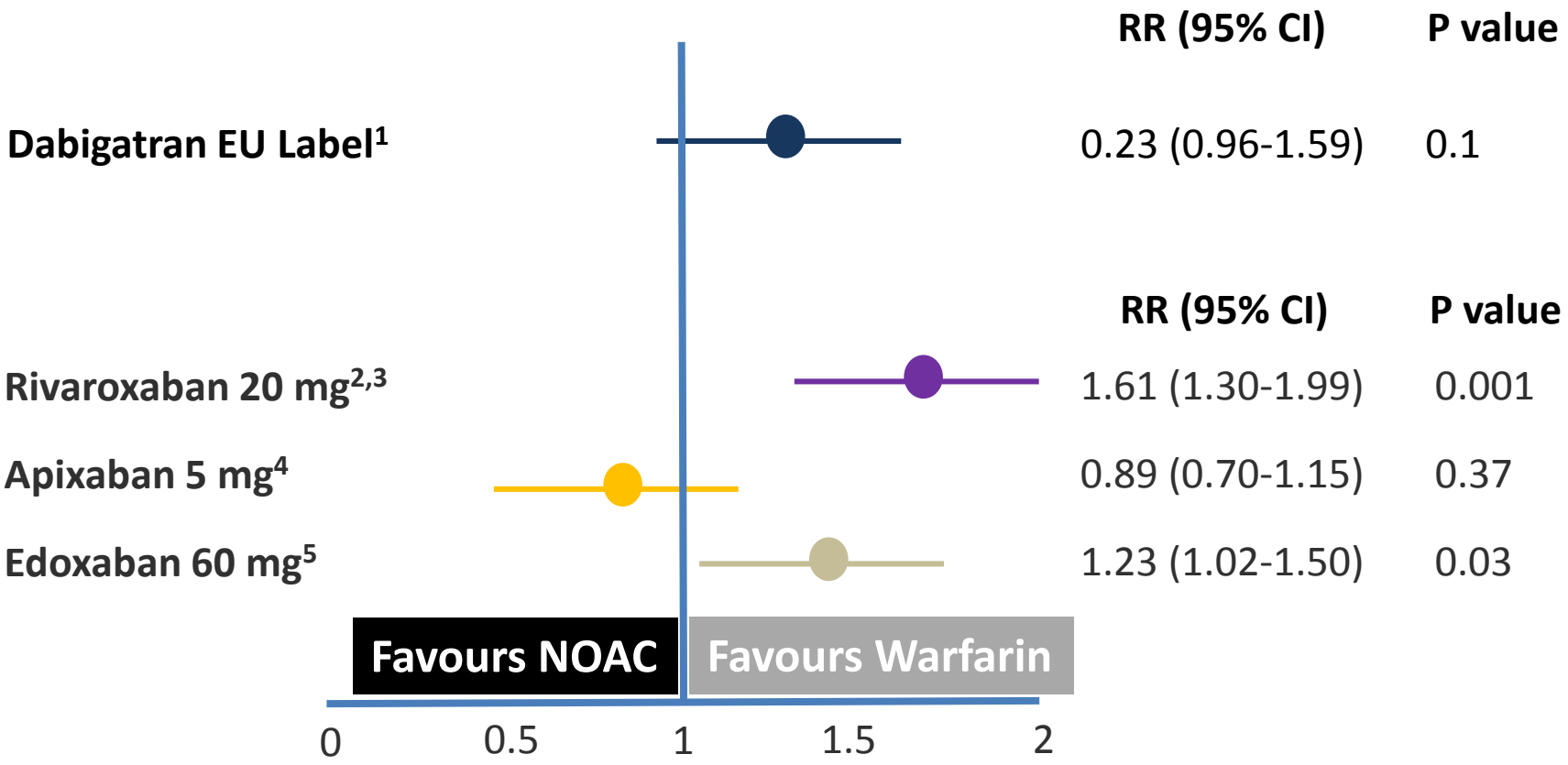

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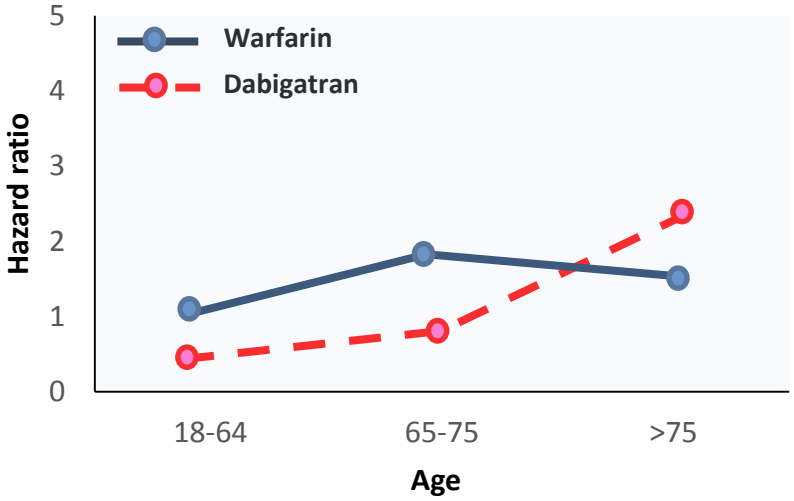
3. 5. Giugliano et al. N Engl J Med 2013; 6. Ruff et al. Lancet 2014

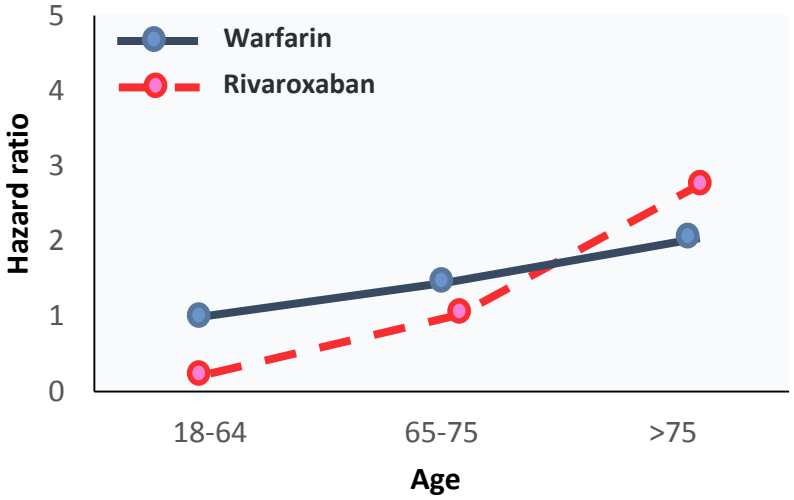
Comparative Risk of GI Bleeding with Dabigatran, Rivaroxaban, and Warfarin

- Optum Labs Data Warehouse
- Administrative claims data on privately insured and Medicare Advantage enrollees
- Propensity matched cohort study
- 7749 matched AF pts

Dabigatran vs Warfarin



Rivaroxaban vs Warfarin



Abraham NS, et al. BMJ 2015;350:h1857

GI Bleeding in the FDA Study of Medicare Patients

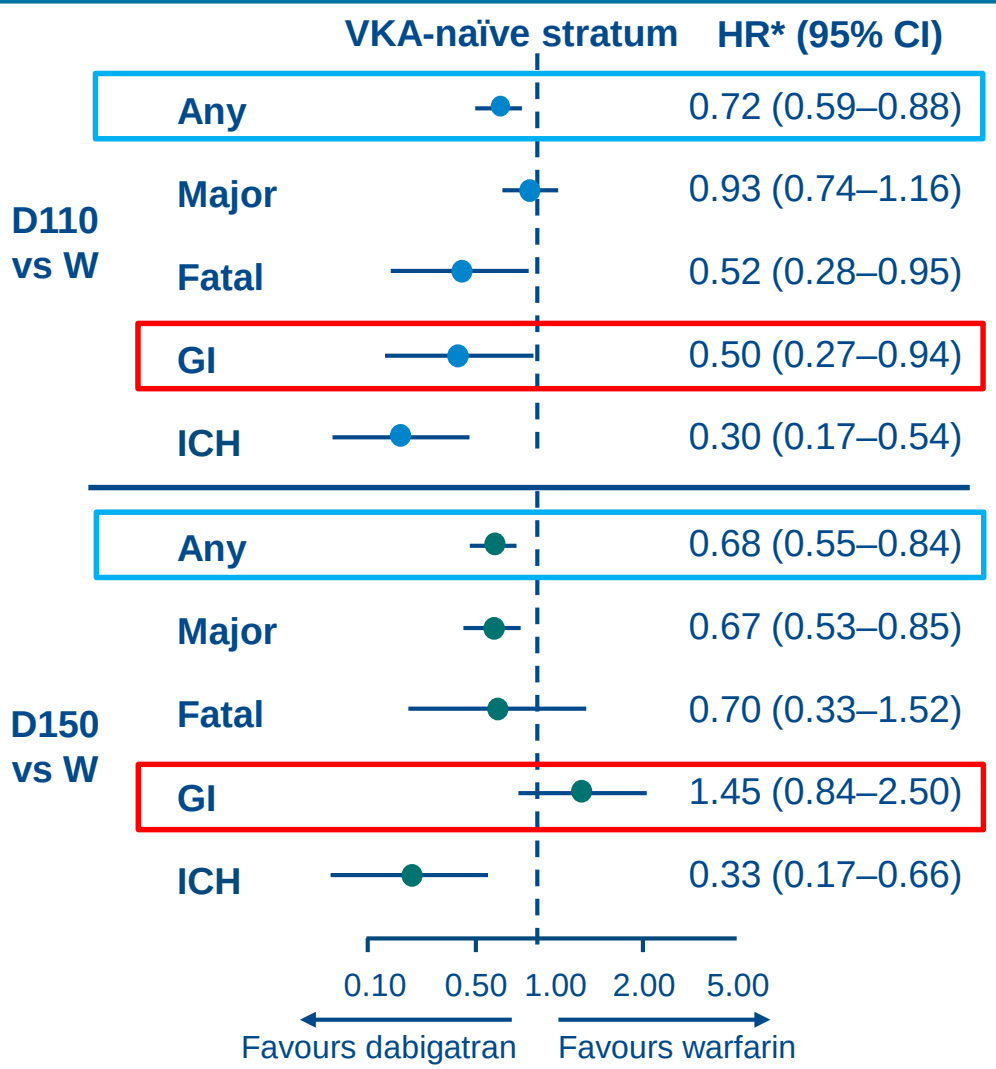
Age group (n)	Men HR (95% CI)	Women HR (95% CI)
65-74 (55.761)	0.83 (0.60-1.14)	0.99 (0.72-1.37)
75-84 (57.345)	1.02 (0.79-1.31)	1.50 (1.20-1.88)
≥85 (21.308)	1.55 (1.04-2.32)	2.18 (1.61-2.97)

The vast majority of Medicare patients (≈ 84%) received the 150 mg BID dose of Dabigatran

Graham DJ et al. Circulation 2015;131:157

Favourable Benefit–Risk Profile of Dabigatran in Real-World: Independent Danish Registry

11 315 first-time dabigatran users (7063 VKA-naïve) vs **22 630** matched warfarin users



*Adjusted HR: age, components of CHA_2DS_2-VASc, HAS-BLED, months since August 2011, time since initiation of VKA therapy

Larsen TB et al. Am J Med 2014;127:650

Independent FDA Study Mirrors the Favourable Benefit–Risk Profile of Dabigatran from RE-LY

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- D150 BID

MEDICARE*[1]

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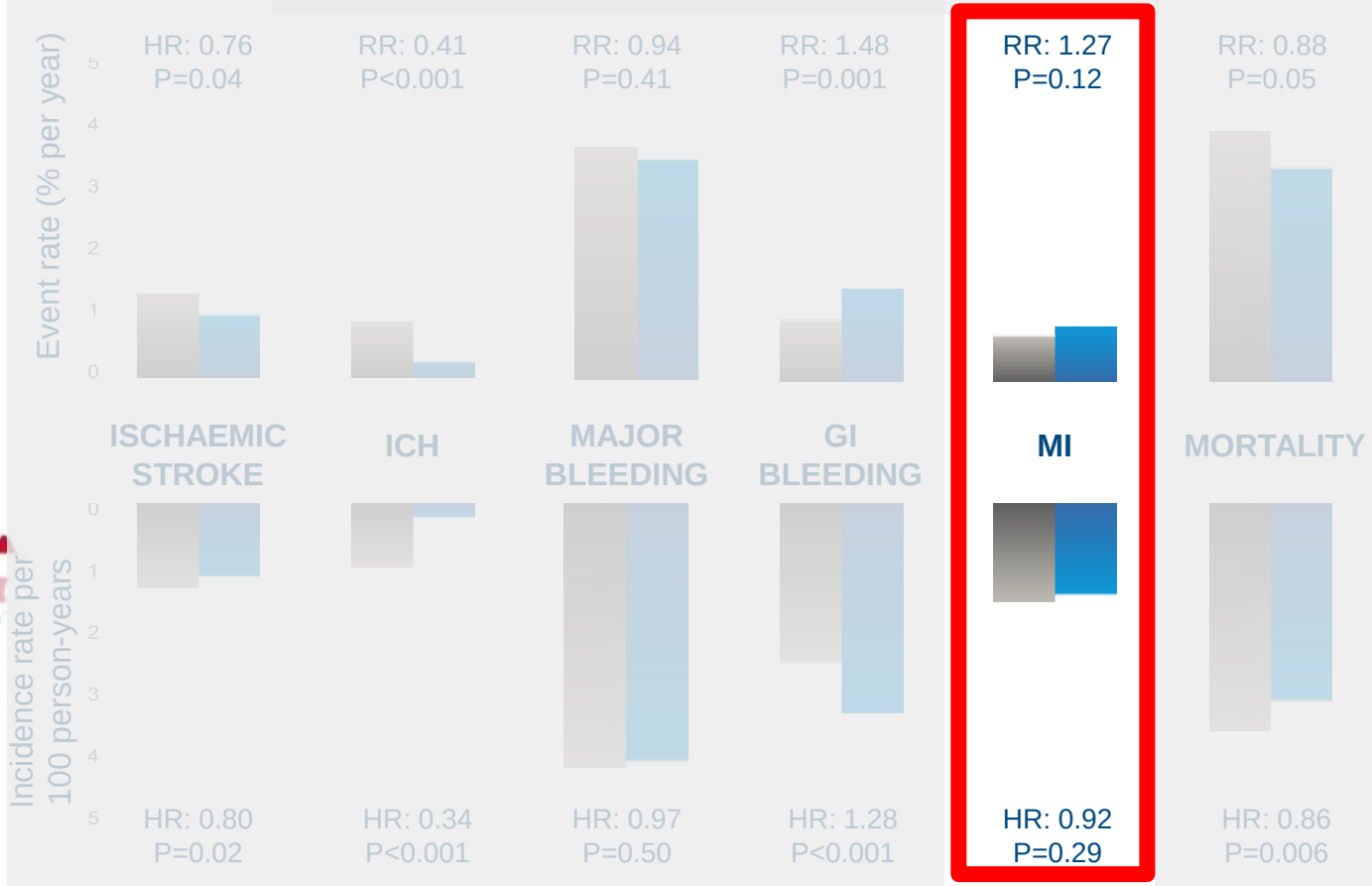
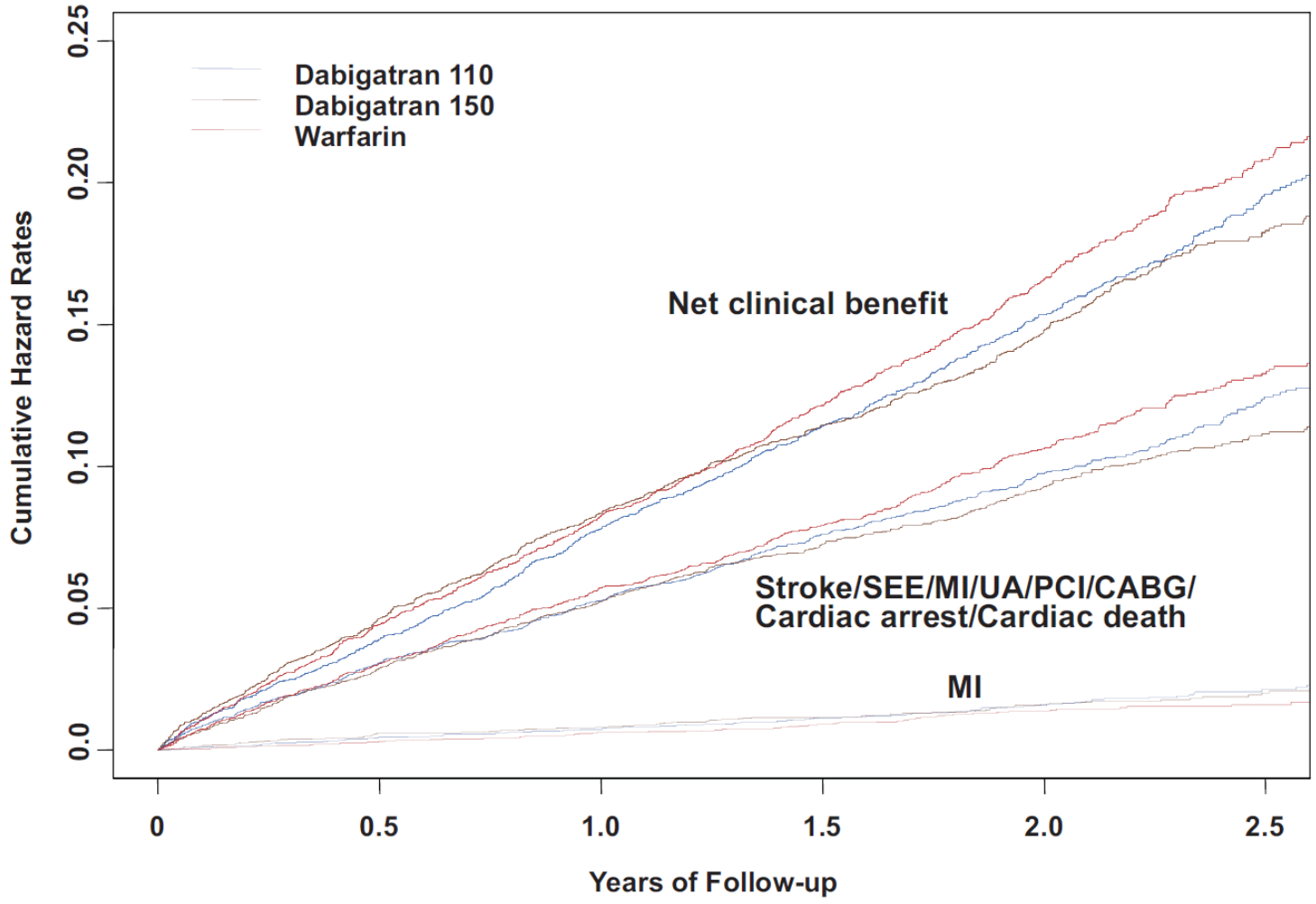
- D150 & D75 BID combined



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

Time to Myocardial Ischemic Events in RE-LY



Hohnloser SH, et al. Circulation. 2012;125:669

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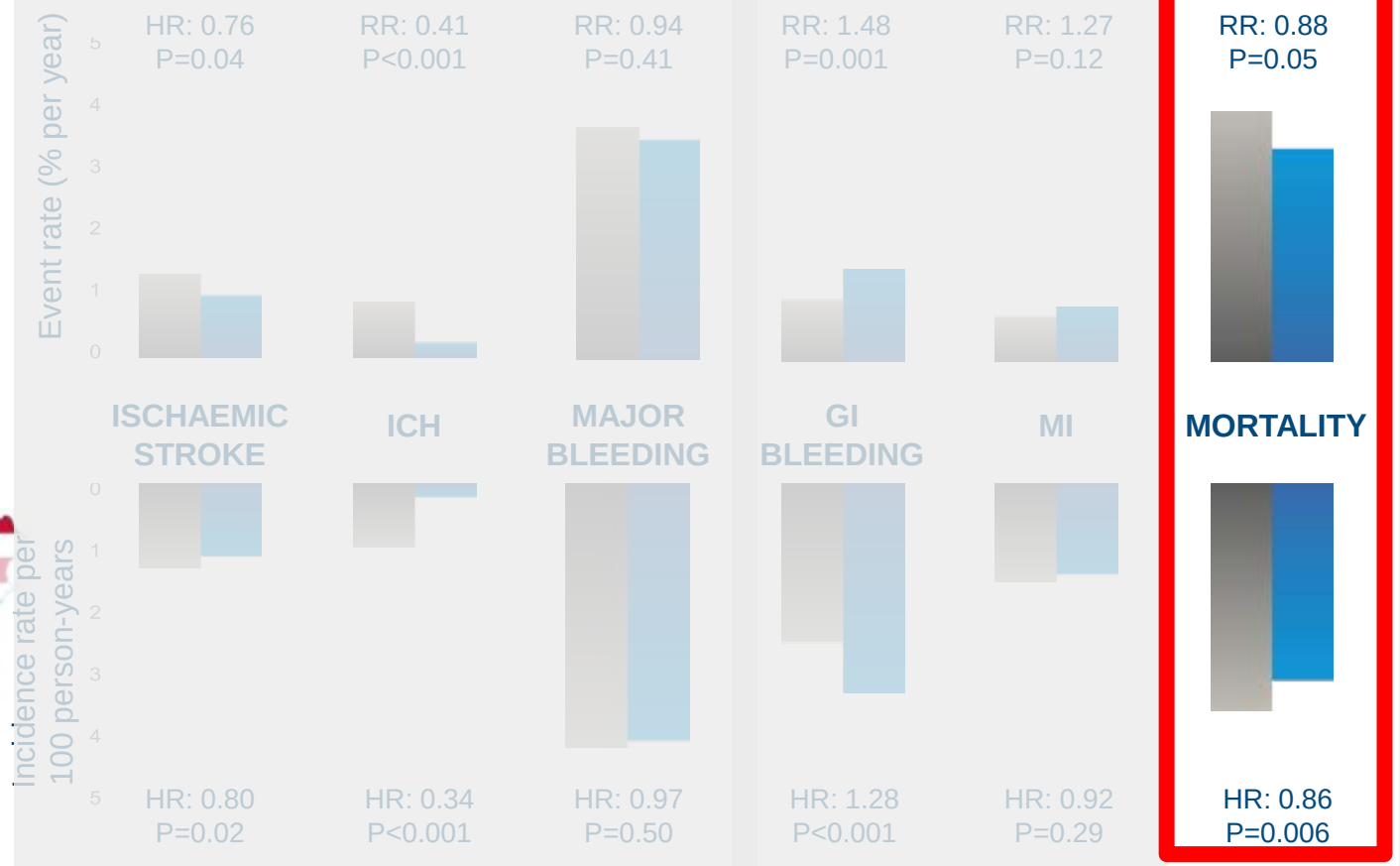

*1. Graham et al. Circulation 2015;
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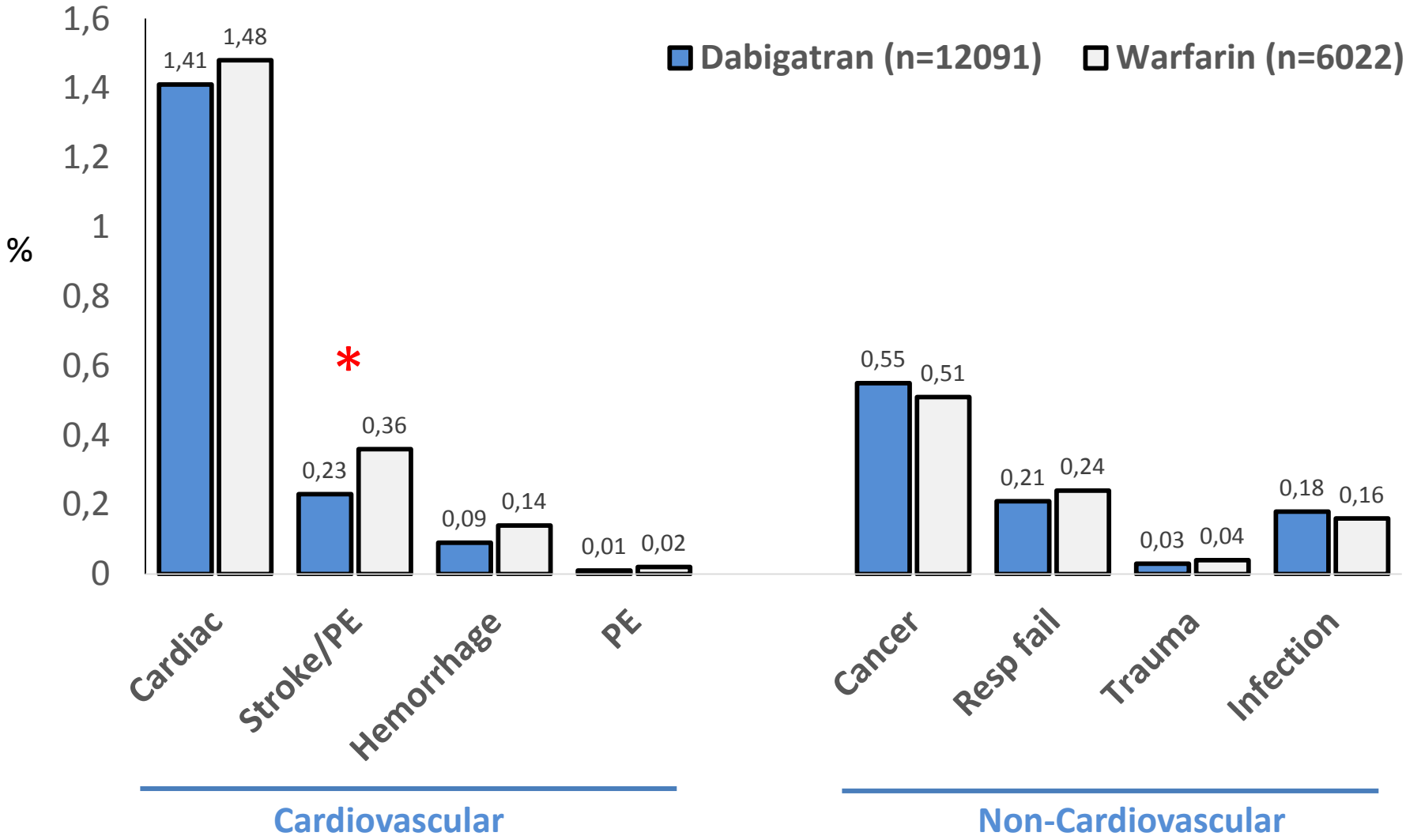
Causes of Death in RE-LY



* p<0,05

Marijon E, et al. Circulation. 2013;128:2192

Summary

1. **Dabigatran has been rigorously studied through well-designed and highly representative clinical trials**
2. **Dabigatran is the only NOAC with long-term follow-up data available confirming its safety profile**
3. **Dabigatran is supported by a wealth of robust real-world evidence, unparalleled among the NOACs**