

Practical patient protection with dabigatran: What have we learned?

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Bayer, Portola, sanofi-aventis, J and J, Boston Scientific, St.
Jude Medical**

RE-LY Design – Non-Inferiority Trial

Atrial fibrillation ≥ 1 risk factor with absence of contraindications
18113 patients (~50% VKA naïve)
951 centers in 44 countries

Randomization

Open

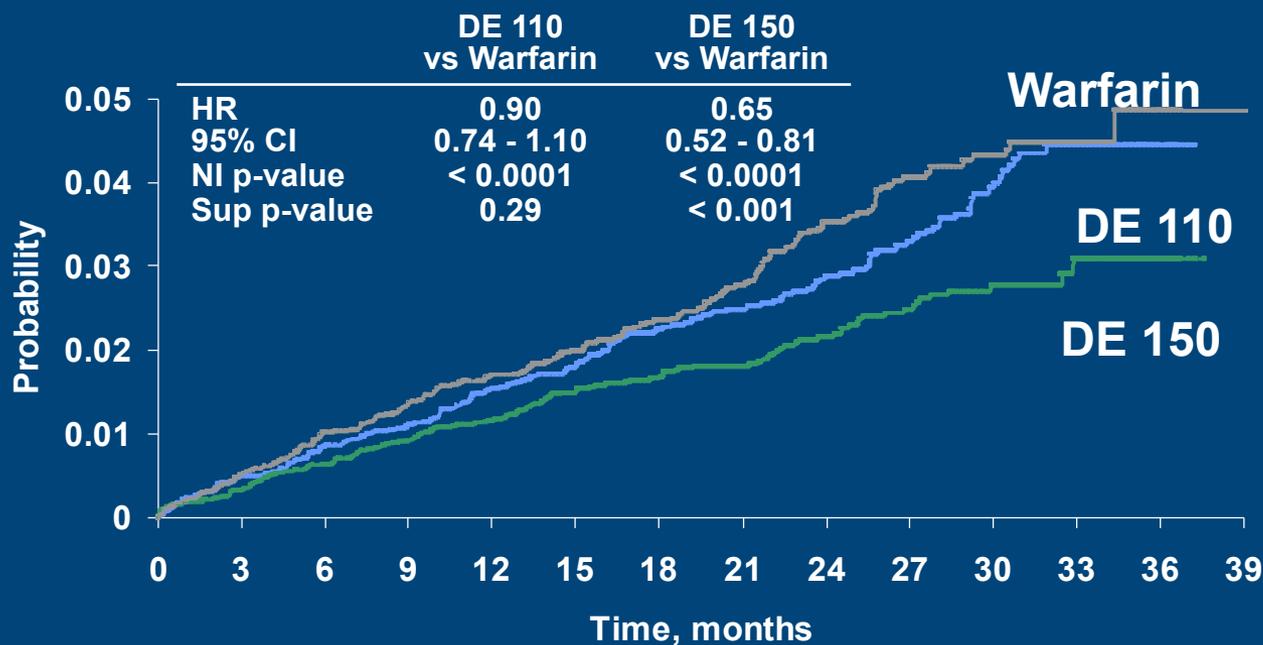
Blinded

Warfarin
(INR 2.0 - 3.0)
N = 6015

DE 110
N = 6076

DE 150
N = 6022

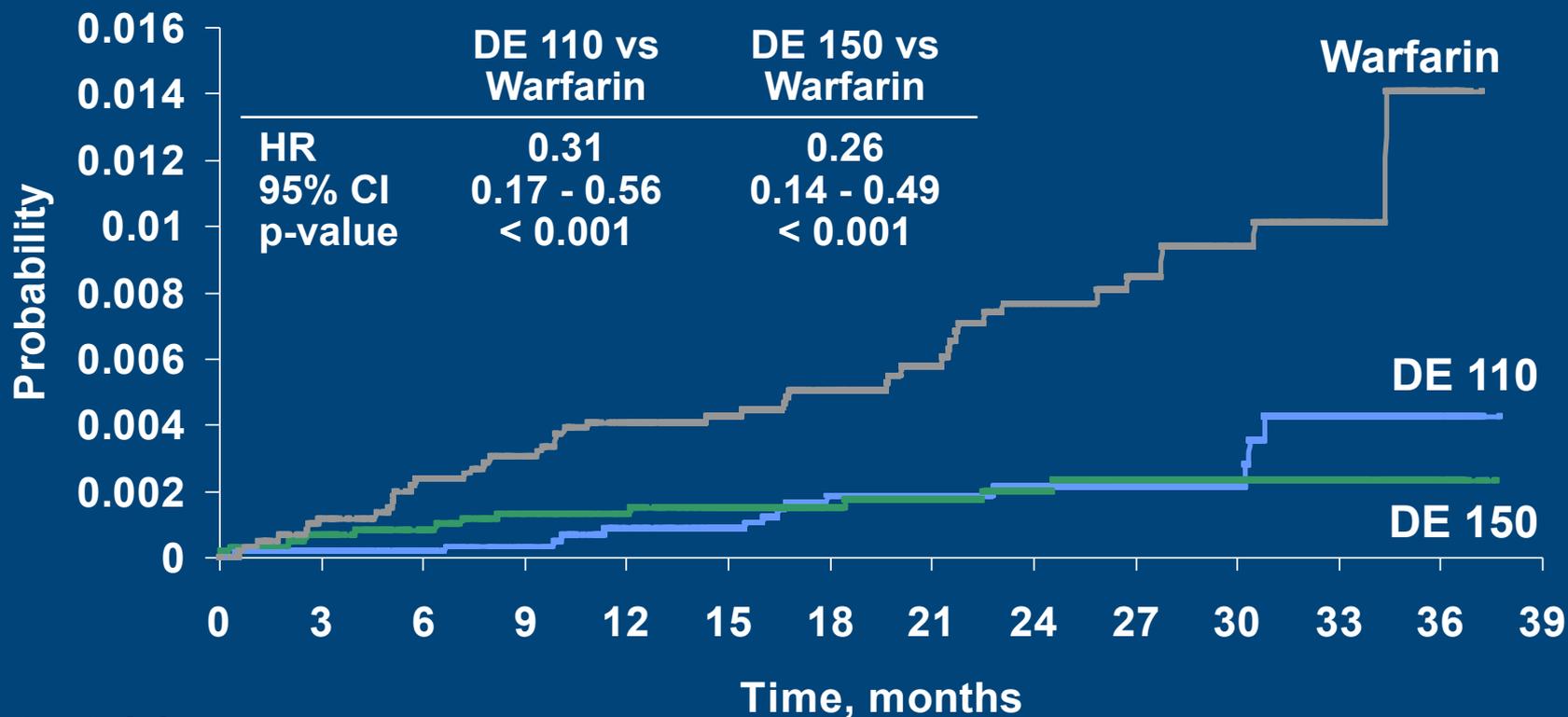
Stroke or systemic Embolism



Patients at risk

DE 110	6015	5862	5713	4615	3132	1446	87
DE 150	6076	5940	5782	4700	3238	1481	90
Warfarin	6022	5862	5719	4615	3092	1364	76

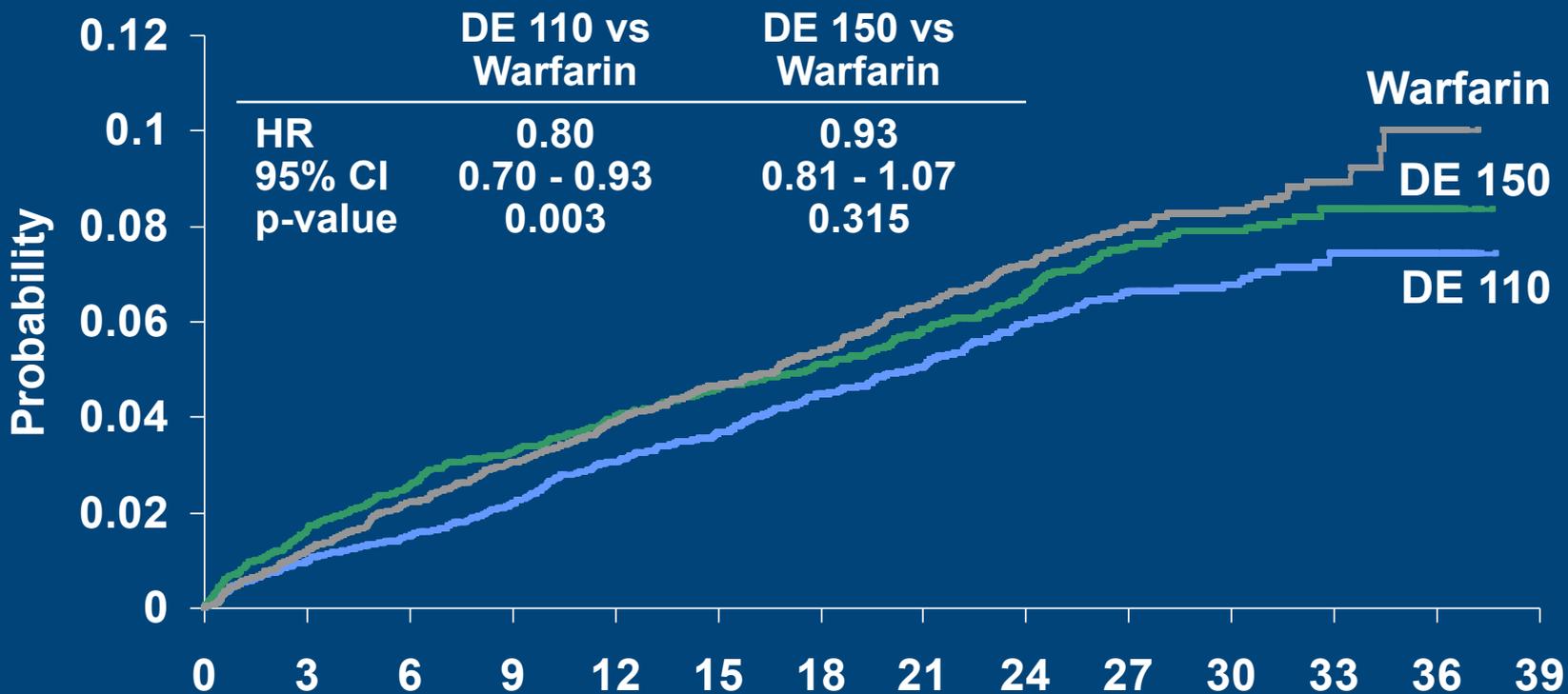
Hemorrhagic Stroke



Patients at risk

DE 110	6015	5865	5720	4626	3138	1450	87
DE 150	6076	5948	5794	4712	3245	1485	92
Warfarin	6022	5875	5734	4628	3105	1372	77

Major Bleed



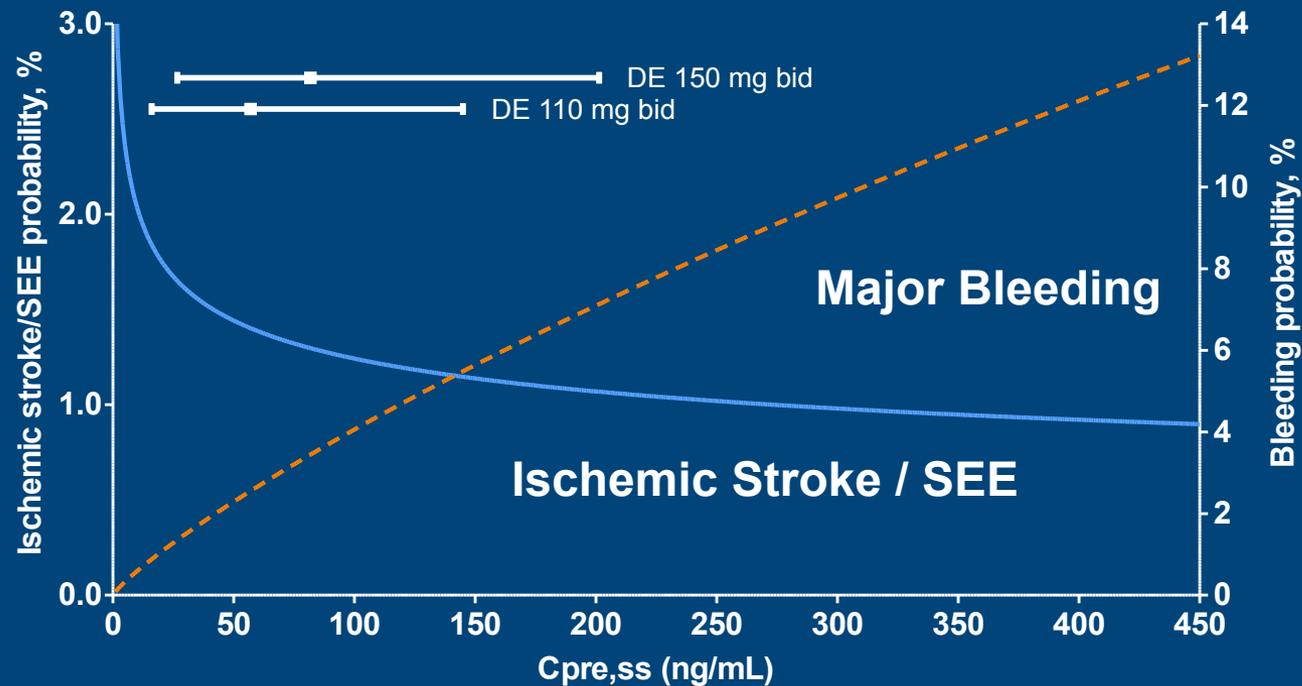
Patients at risk

Time, months

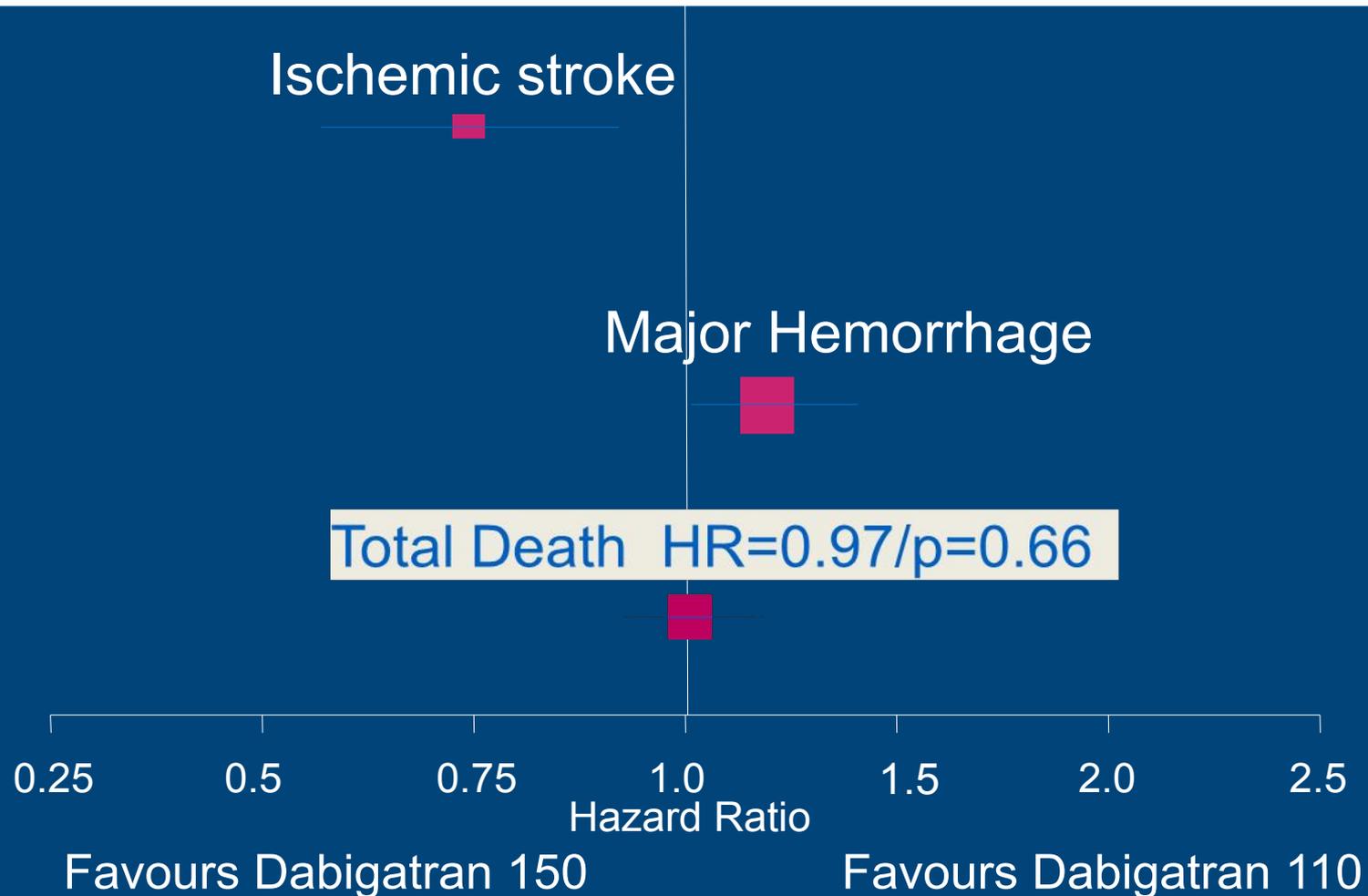
DE 110	6015	5826	5626	4515	3043	1405	83
DE 150	6076	5834	5635	4561	3109	1412	86
Warfarin	6022	5794	5596	4489	2985	1308	73

Dabigatran: Which dose?

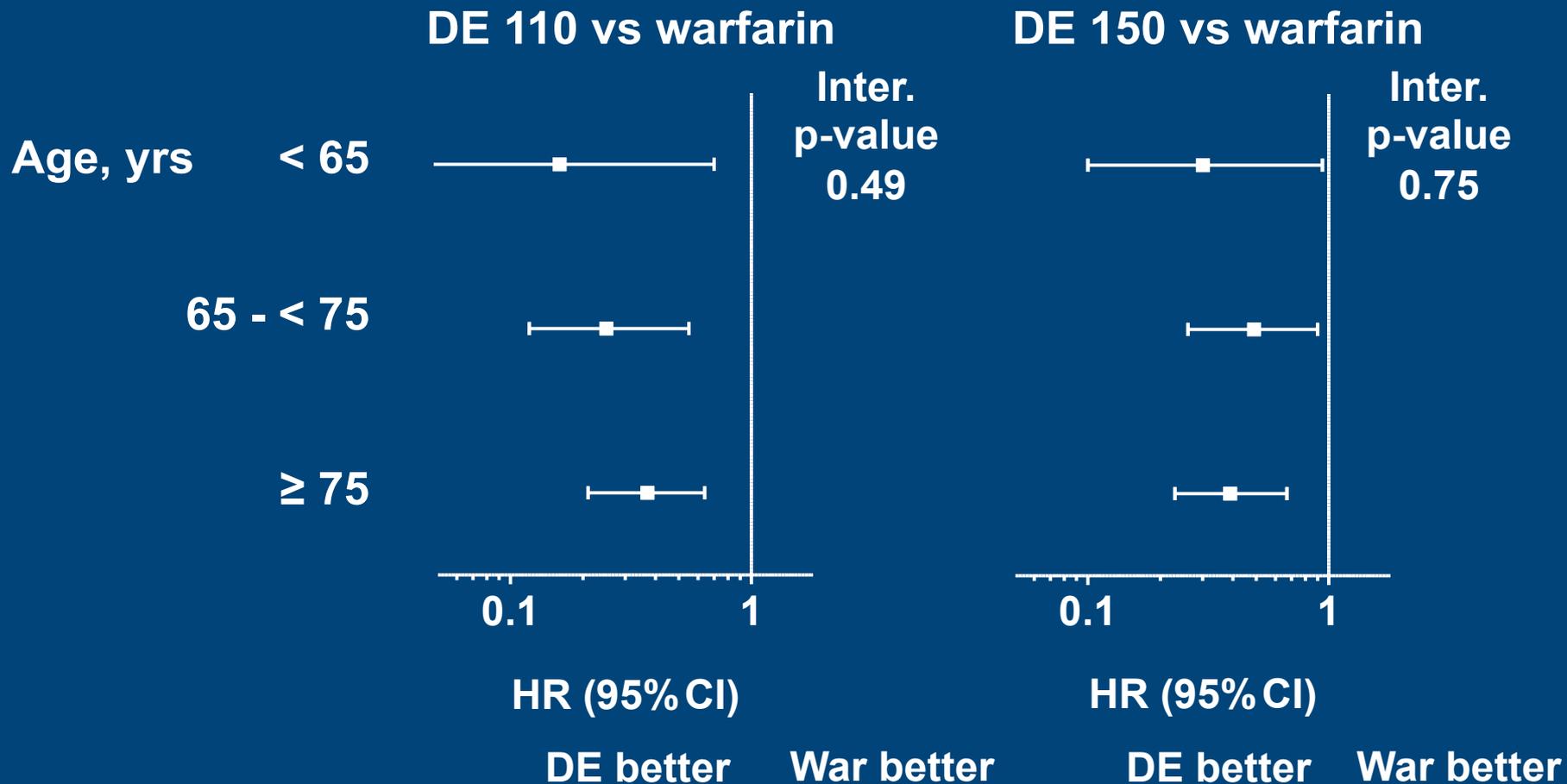
Predicted Effect of Various Dosages of DE bid on Ischemic Stroke/SEE and MBE



Dabigatran: 110 mg versus 150 mg

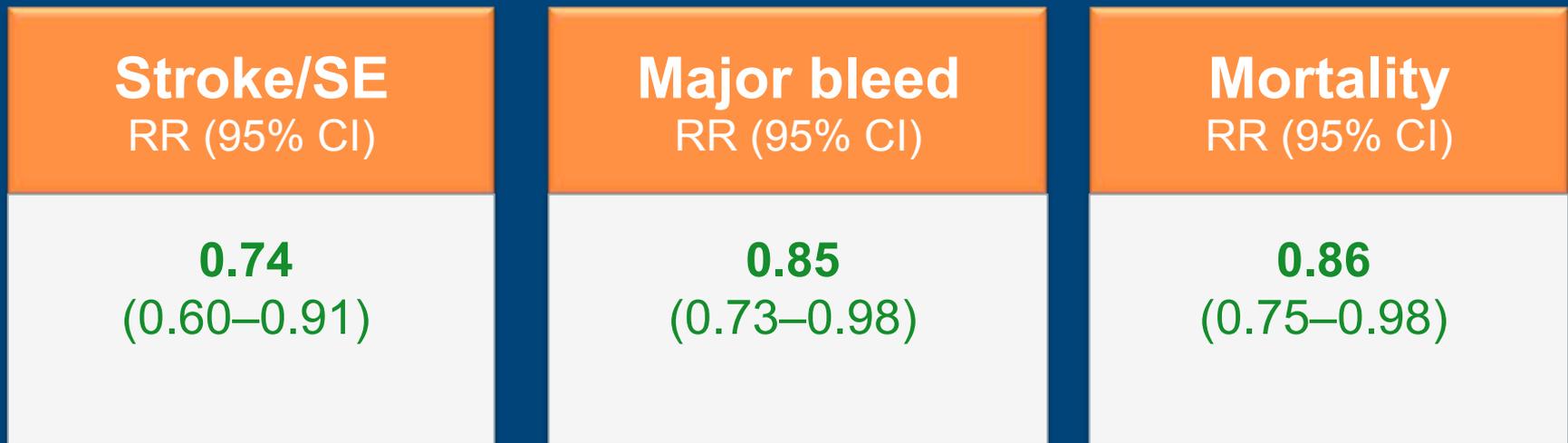


Intracranial Hemorrhage – Age



European-label dosing analysis of RE-LY

Selected dosing dabigatran treatment compared to warfarin



In clinical practice, selection of the most appropriate dabigatran dose can be used to optimize patient outcomes

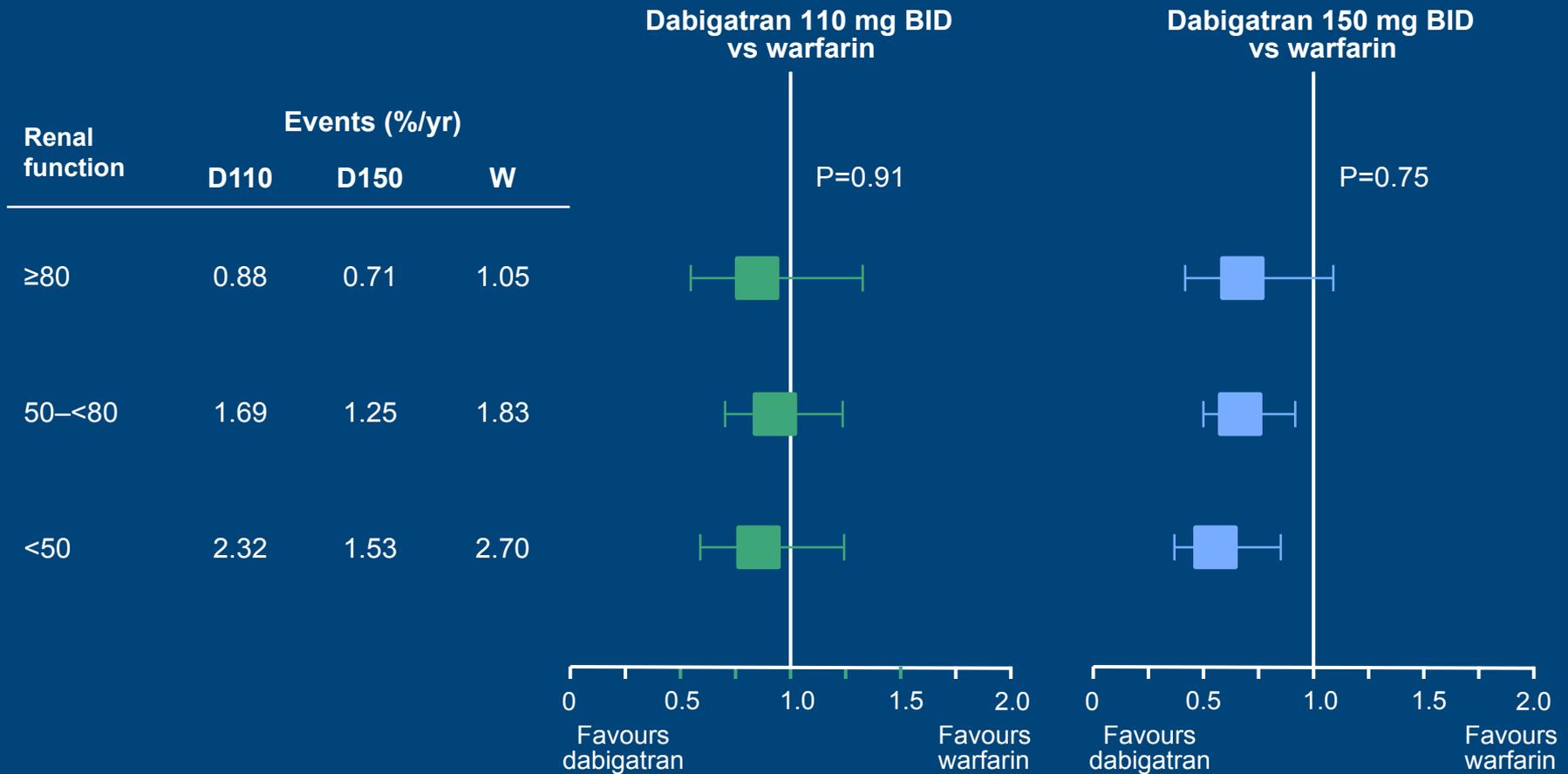
SE = systemic embolism

Connolly SJ et al. N Engl J Med 2009; Lip GYH et al. Thromb Haemost 2014;111:933–42

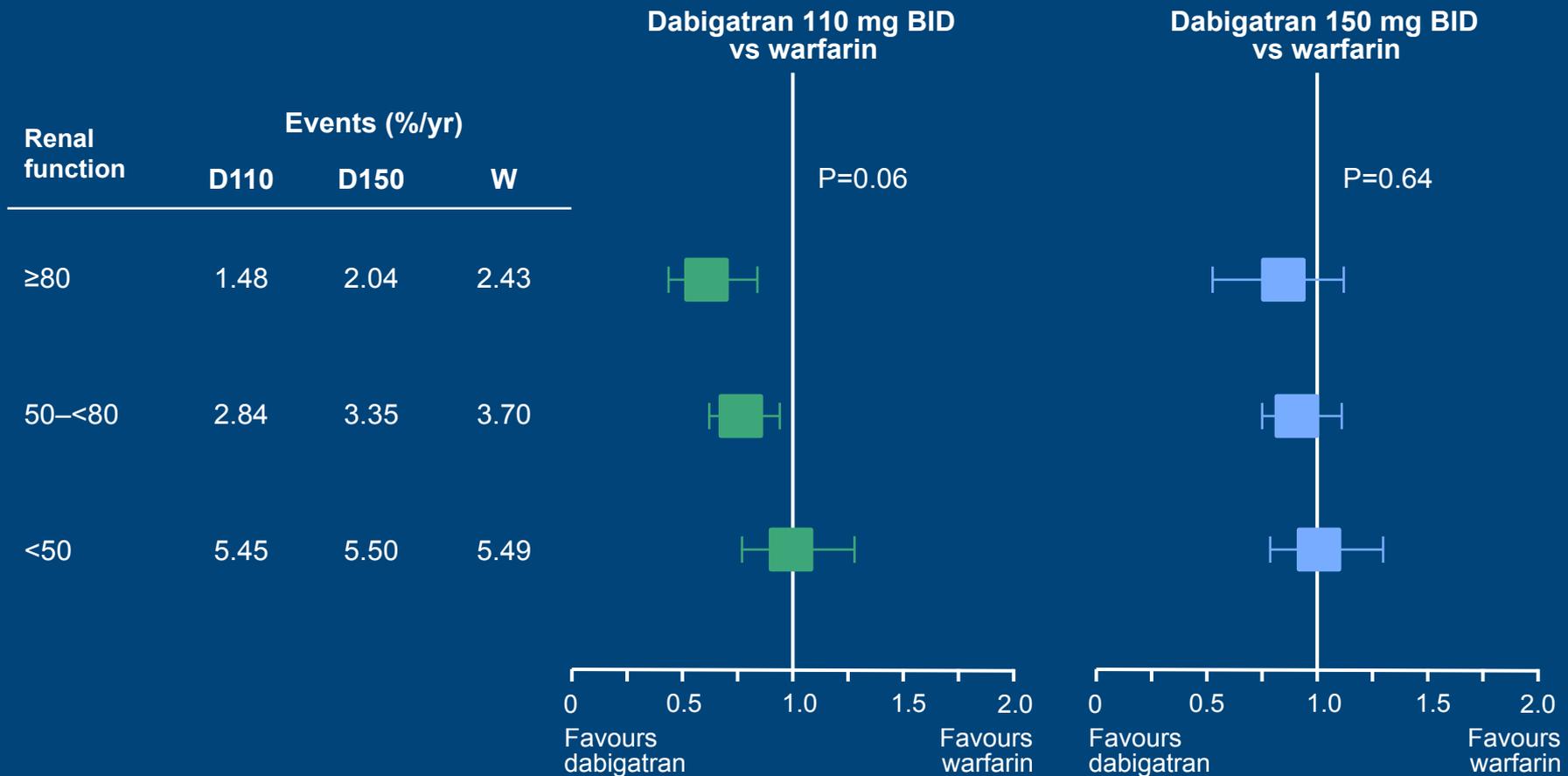
Renal Function

**Estimated Creatinine Clearance
varied from 30 to >100 ml/min in
RE-LY**

The efficacy of dabigatran was consistent with the overall trial irrespective of renal function



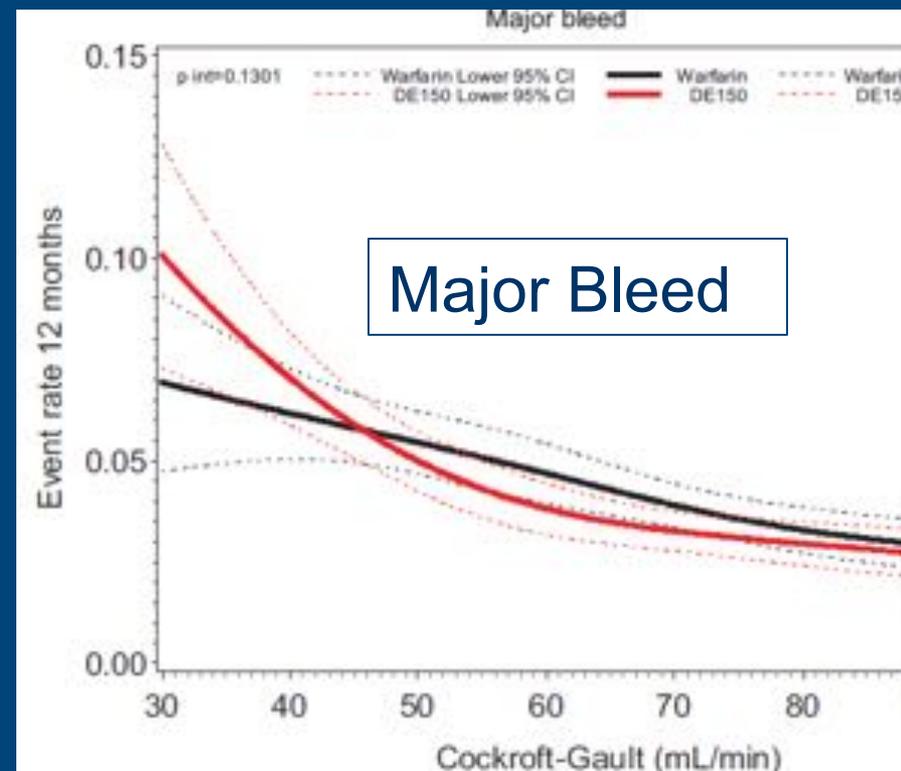
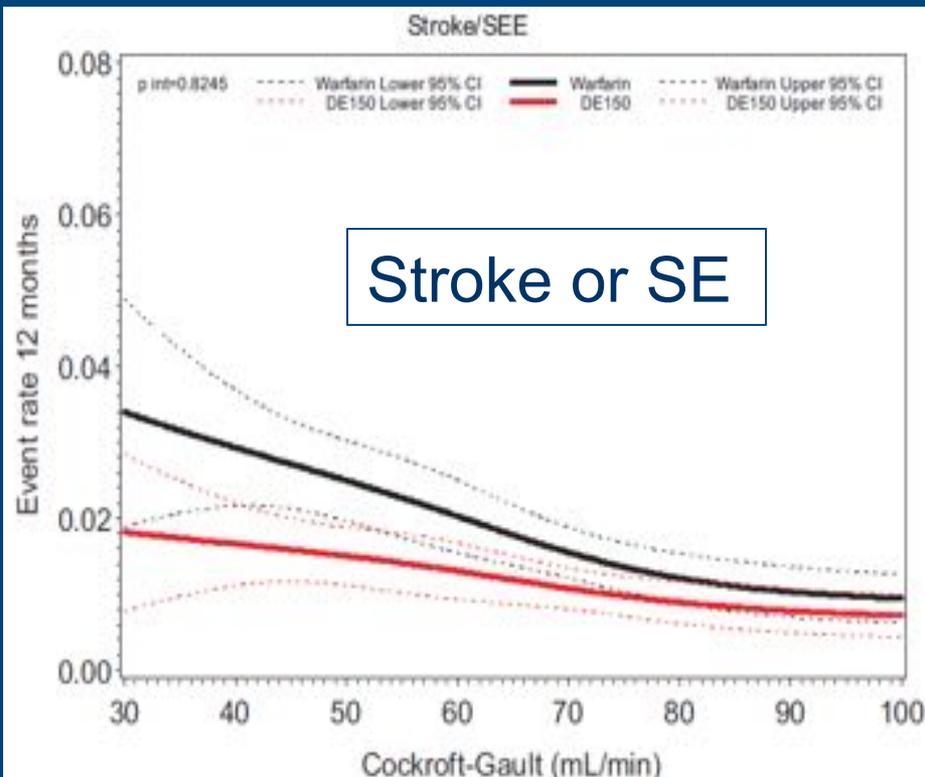
Benefits of dabigatran in terms of major bleeding are maintained in patients with moderate renal impairment



Efficacy and Safety of Dabigatran Compared With Warfarin in Relation to Baseline Renal Function in Patients With Atrial Fibrillation

A RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) Trial Analysis

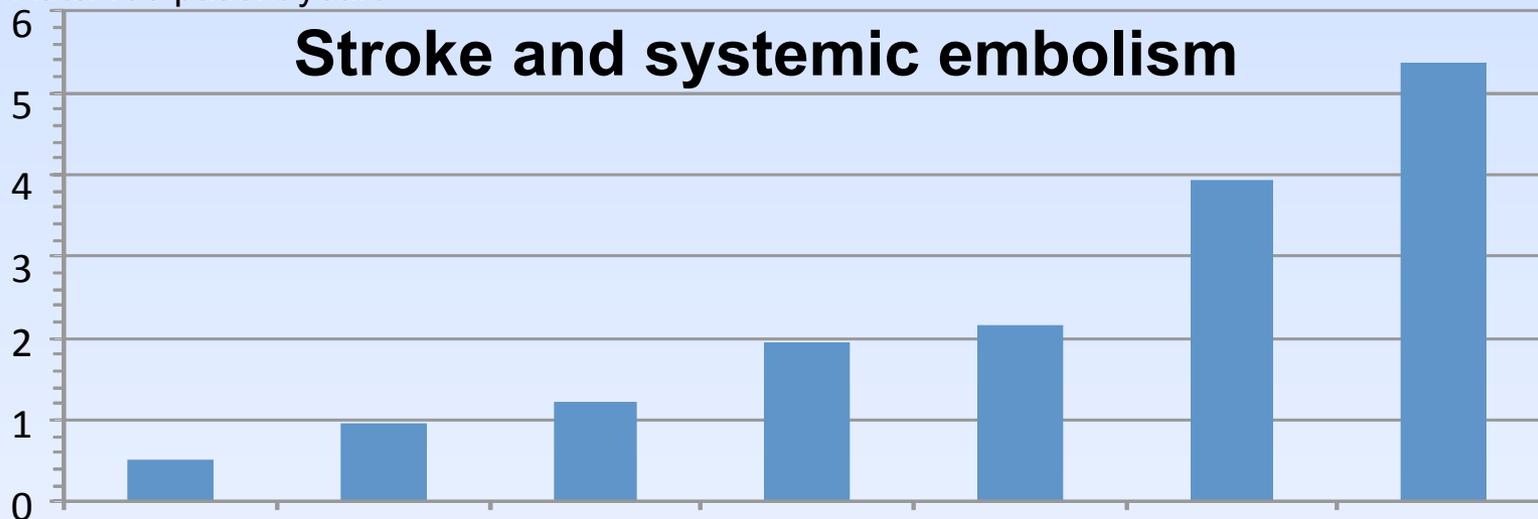
Ziad Hijazi, MD, PhD; Stefan H. Hohnloser, MD; Jonas Oldgren, MD, PhD;
Ulrika Andersson, MSc; Stuart J. Connolly, MD; John W. Eikelboom, MD;
Michael D. Ezekowitz, MB, ChB, PhD; Paul A. Reilly, PhD; Agneta Siegbahn, MD, PhD;
Salim Yusuf, MD, PhD; Lars Wallentin, MD, PhD



CHADS2 risk score in RE-LY

Rate/100 patient years

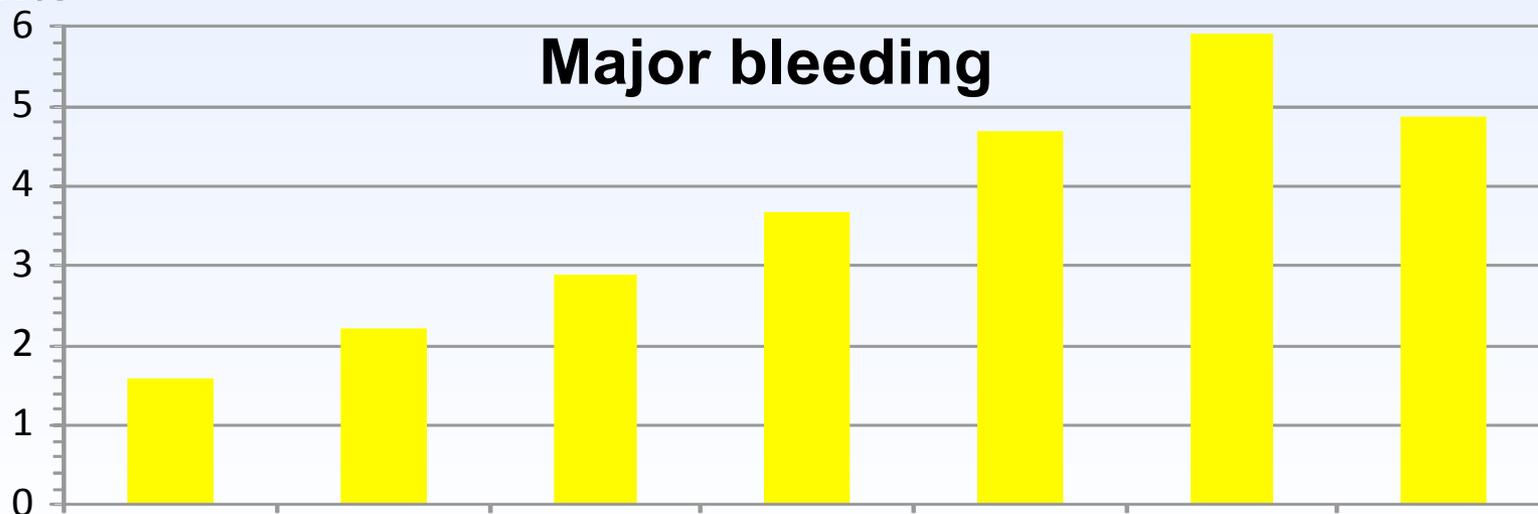
Stroke and systemic embolism



CHADS2
Patients

0	1	2	3	4	5	6
452	5323	6455	3654	1619	524	85

Major bleeding

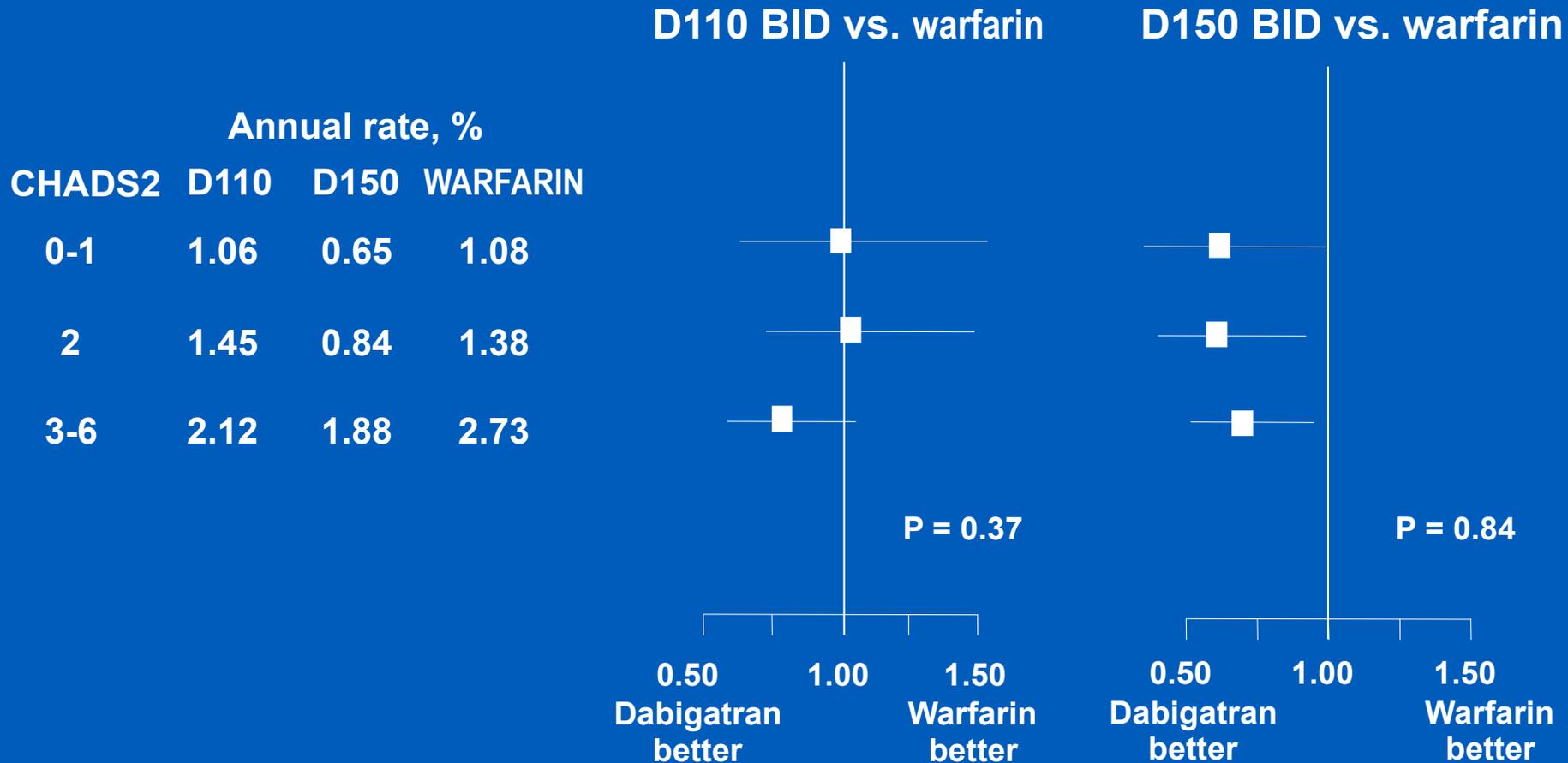


CHADS2

0	1	2	3	4	5	6
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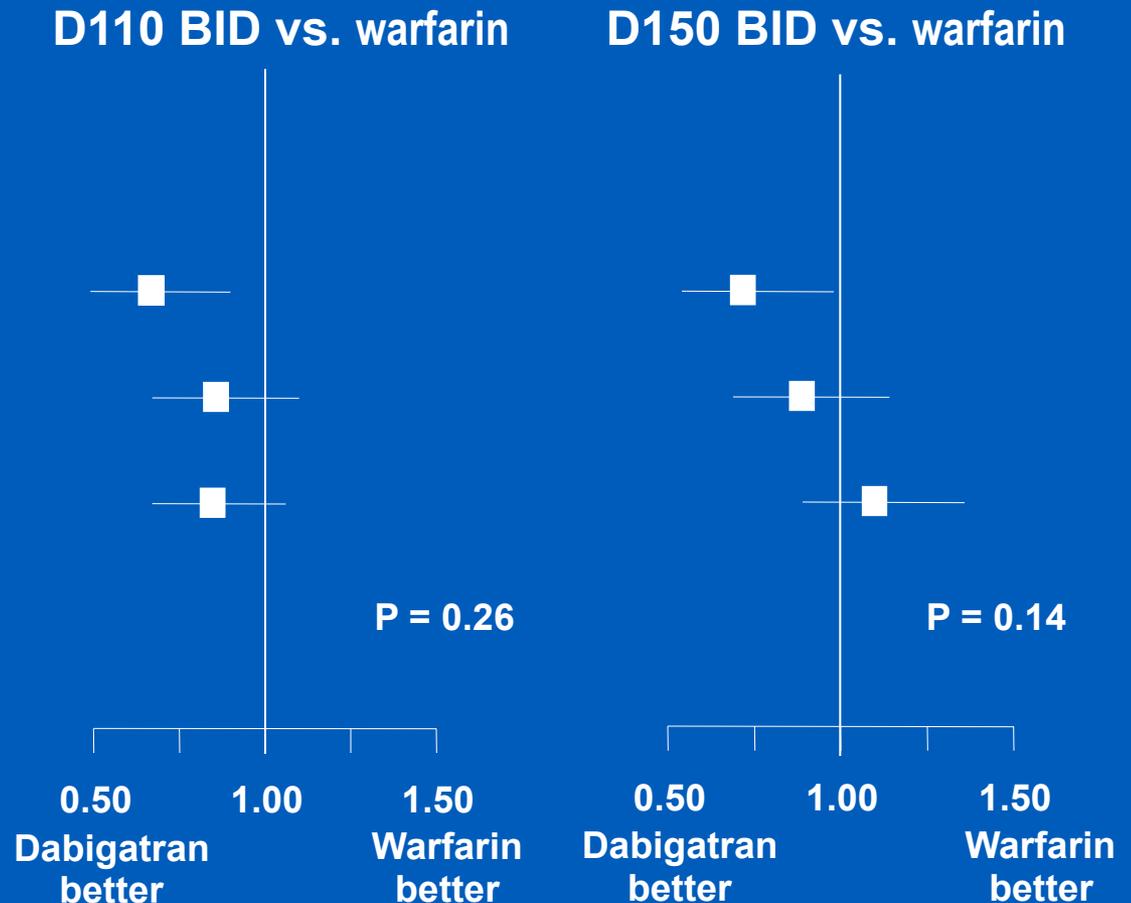
Risk Score: CHADS₂

Stroke and systemic embolism (SE)

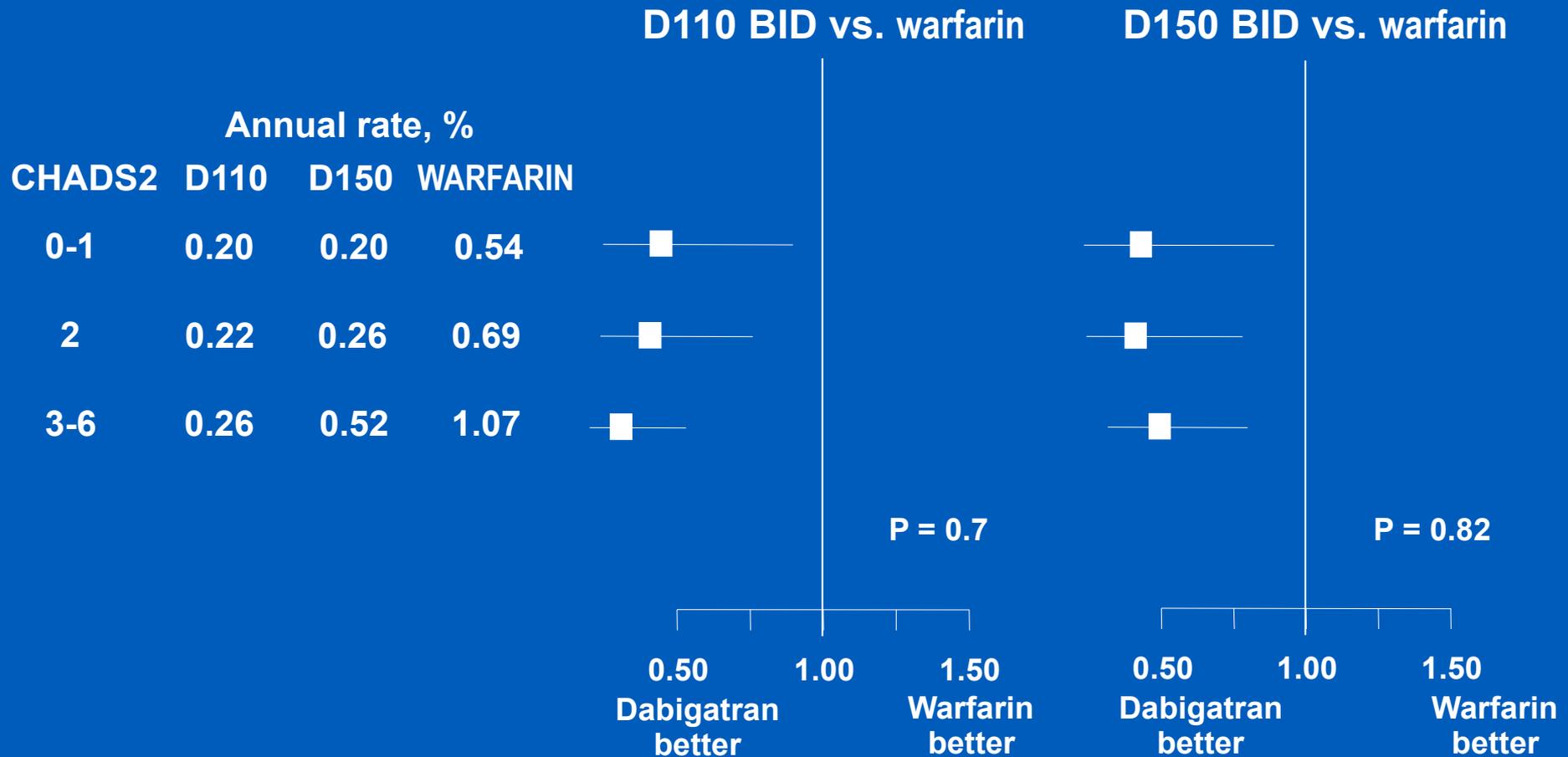


Major bleeding

	Annual rate, %		
CHADS ₂	D110	D150	WARFARIN
0-1	1.86	2.11	2.84
2	2.98	3.03	3.3
3-6	3.8	4.85	4.6



Intracranial bleeding



Cardioversions in RE-LY

	D110	D150	Warfarin
Total Randomized	6015	6076	6022
Cardioversions Performed	647	672	664
Electrical	554	550	553
Pharmacological	91	122	111
TEE Performed	165	162	88

Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation. 2011 Jan 18;123(2):131-6. Epub 2011 Jan 3.

Outcomes post-Cardioversion

	D110	D150	Warfarin	D110 vs. W	D150 vs. W
Stroke or Systemic Embolism < 30 Days Post-Cardioversion	5 (0.77%)	2 (0.30%)	4 (0.60%)	1.28 (0.35-4.76) p=0.71	0.49 (0.09-2.69) p=0.40
Major Bleeding < 30 Days Post-Cardioversion	11 (1.70%)	4 (0.60%)	4 (0.60%)	2.82 (0.90-8.82) p=0.06	0.99 (0.25-3.93) p=0.99

Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation. 2011 Jan 18;123(2):131-6. Epub 2011 Jan 3.

Warfarin Naive

Dabigatran 110 vs. Warfarin

AC Experience

AC Naive

Non-inferiority
p-value Superiority
p-value

<0.001

0.34

<0.001

0.003

Dabigatran 150 vs. Warfarin

AC Experience

AC Naive

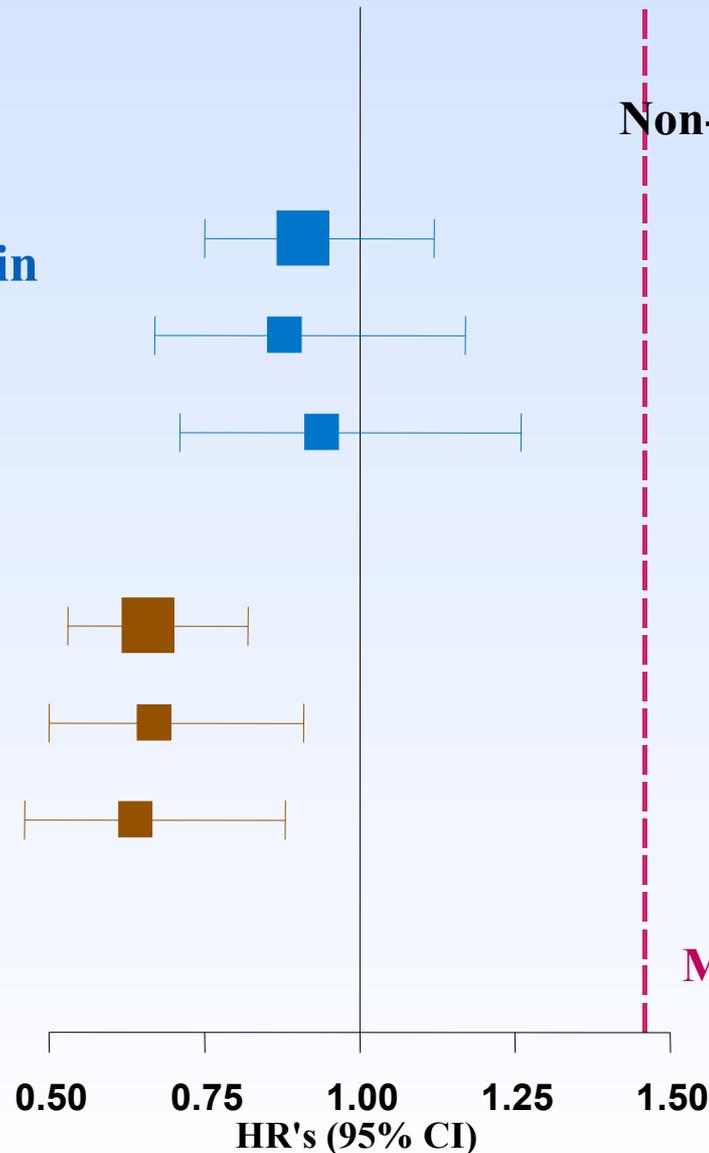
<0.001

<0.001

<0.001

<0.001

Margin = 1.46



Long term follow up data



The Long Term Multi-Center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) study

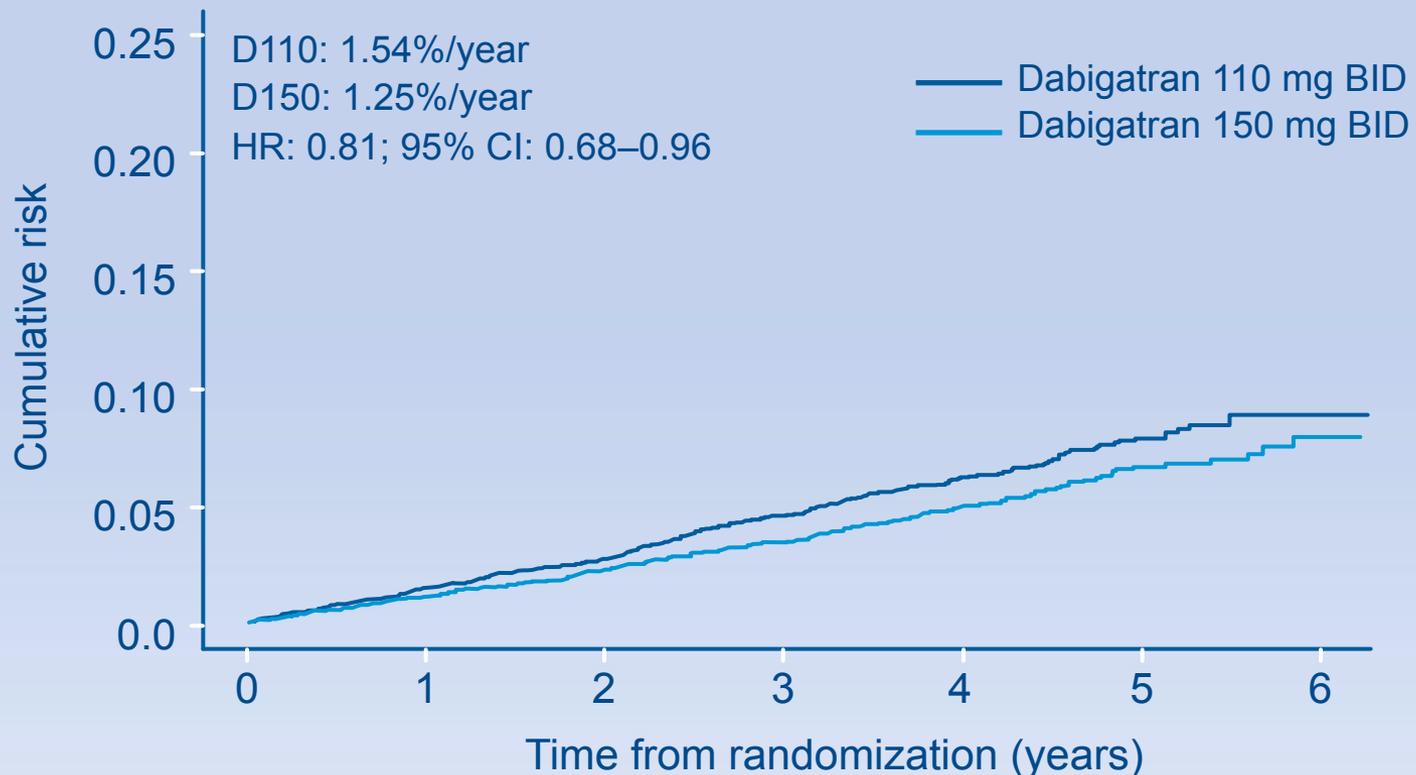
Stuart J. Connolly, Lars Wallentin, Michael Ezekowitz, John Eikelboom, Jonas Oldgren, Janice Pogue, Paul Reilly, Martina Brueckmann, Salim Yusuf; on behalf of the RELY-ABLE Steering Committee and Investigators

RELY-ABLE: benefits of dabigatran are maintained long-term



- Long-term extension of RE-LY
- Up to 6.7 years' follow-up over the two studies
- Patients were eligible if still receiving dabigatran upon completion of RE-LY®
- Confirmed the findings from RE-LY
- No new safety signals

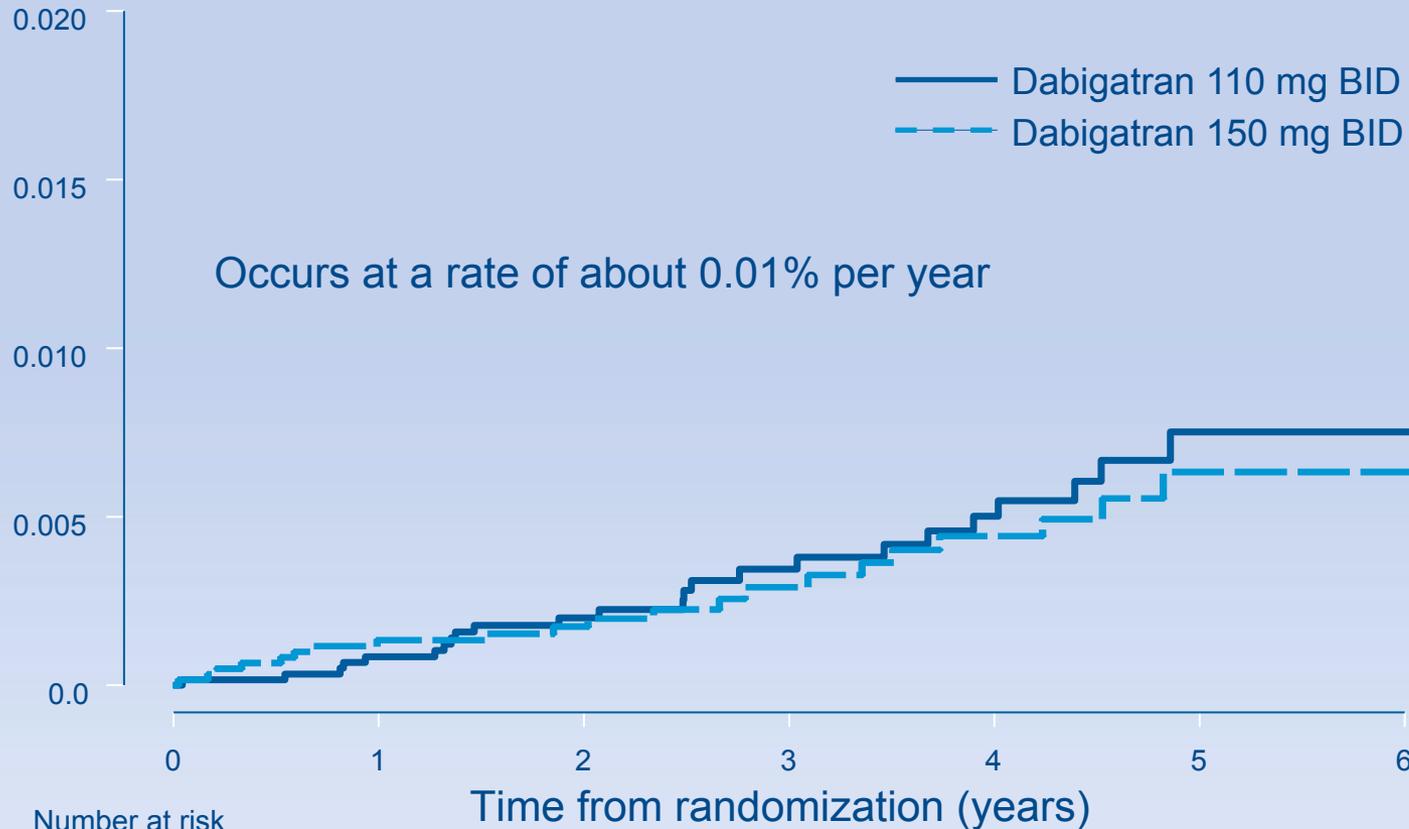
Prevention of stroke and systemic embolism RE-LY and RELY-ABLE



No at risk:

D110	6015	5706	4190	2737	2147	929	157
D150	6076	5774	4276	2753	2181	953	149

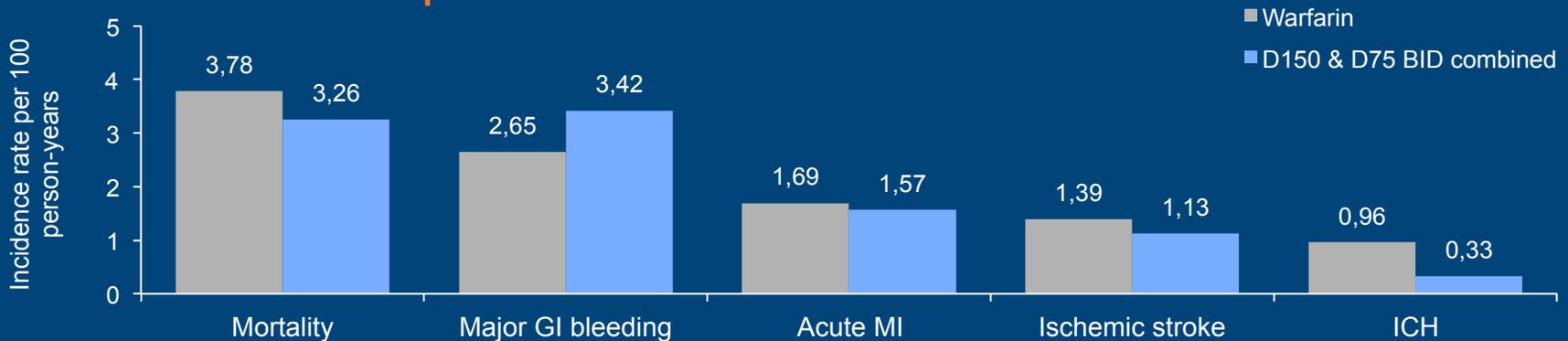
Prevention of haemorrhagic stroke confirmed in the long term



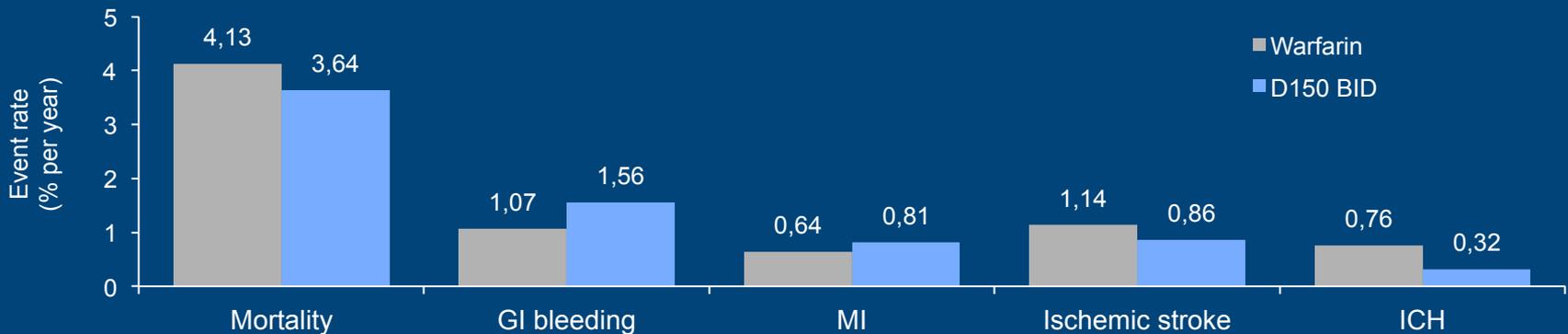
Number at risk		Time from randomization (years)					
	0	1	2	3	4	5	6
DE 110	6015	5771	4264	2796	2209	956	0
DE 150	6076	5821	4338	2785	2226	979	0

Independent FDA analysis confirmed the positive safety and efficacy of dabigatran in clinical practice

Medicare¹ > 134 000 patients



RE-LY^{2,3} >18 000 patients



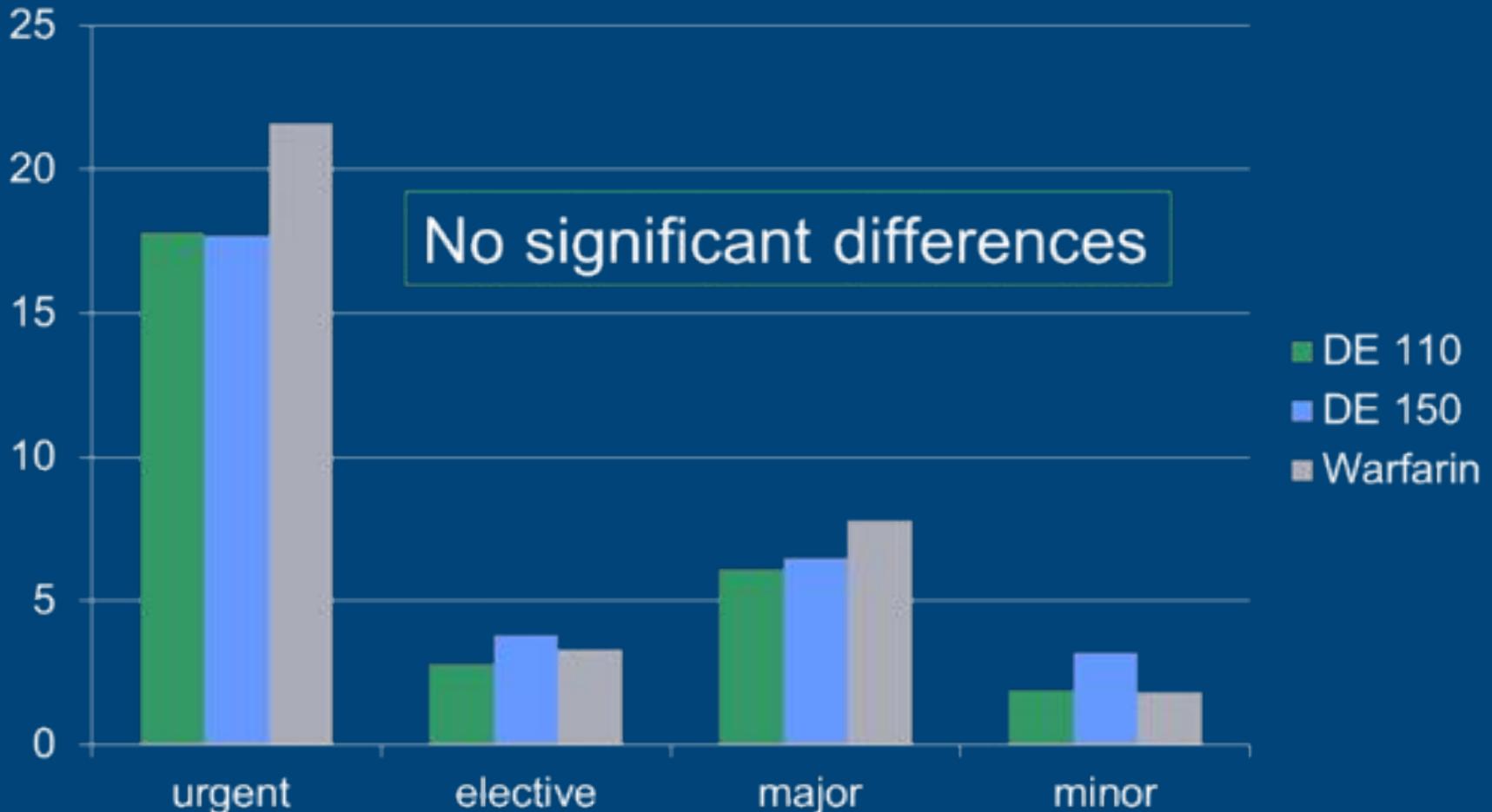
In the US, the licensed doses for dabigatran etexilate are 150mg BID and 75mg BID for the prevention of stroke and systemic embolism in adult patients with non valvular AF

1. <http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm>. Accessed on 14 May 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.

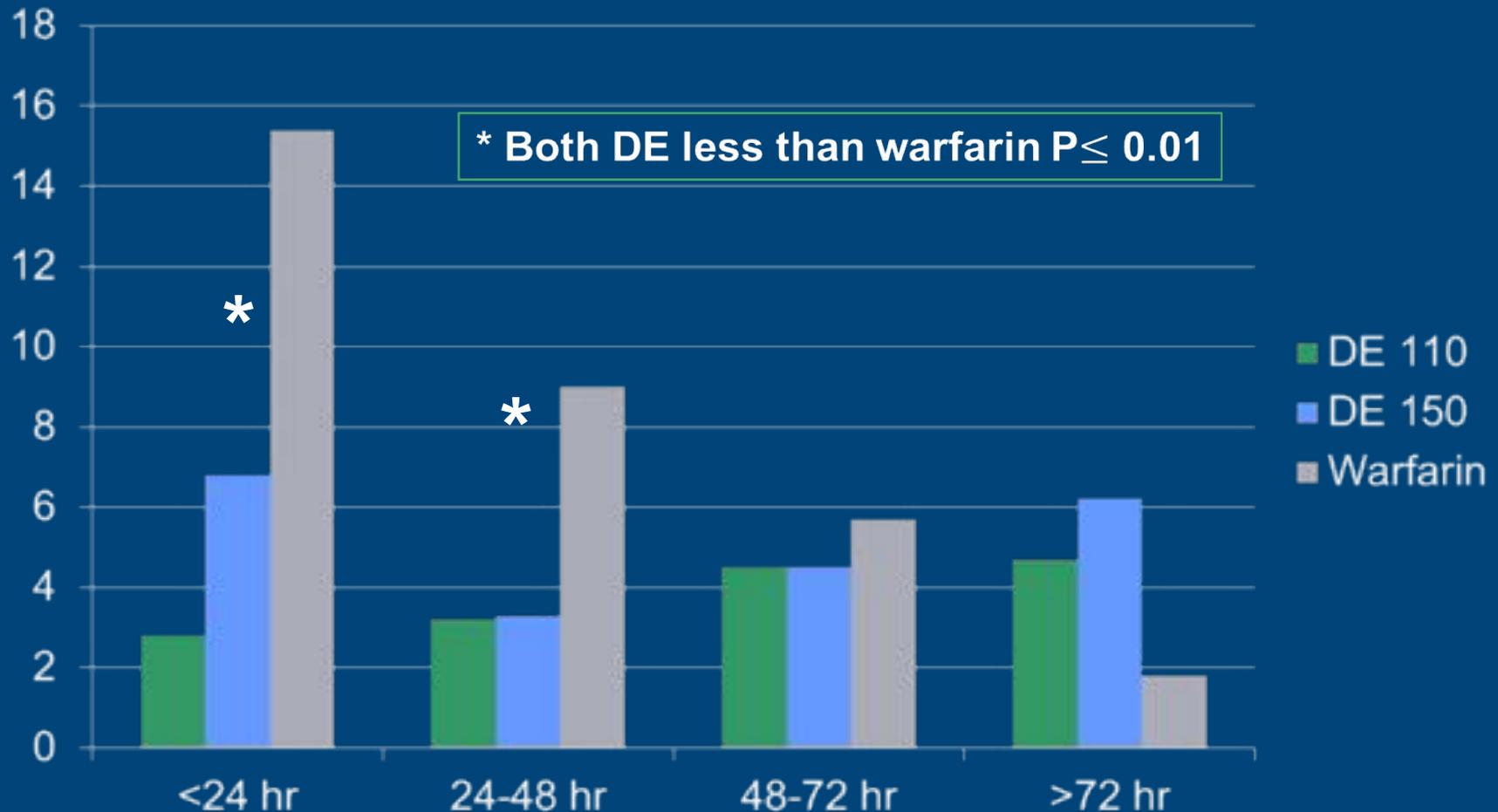
There were >7500 procedures or surgeries during RE-LY

CrCl (mL/min)	Estimated half-life (hrs)	Stop dabigatran	
		High bleeding risk or major surgery	Standard risk
≥80	~13	2 days before	24 hours before
≥50–<80	~15	2–3 days before	2–3 days before
≥30–<50	~18	4 days before	2–3 days before (>48 hours)

Rates of Major Hemorrhage (4591 patients)



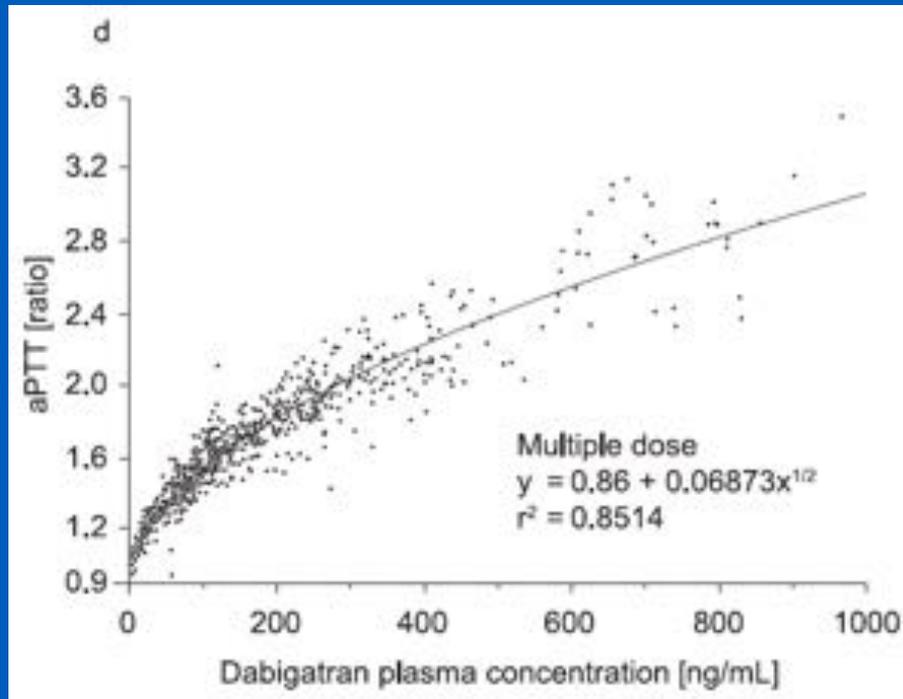
Timing of Surgery after Last Dabigatran or Warfarin Dose (4037 patients)



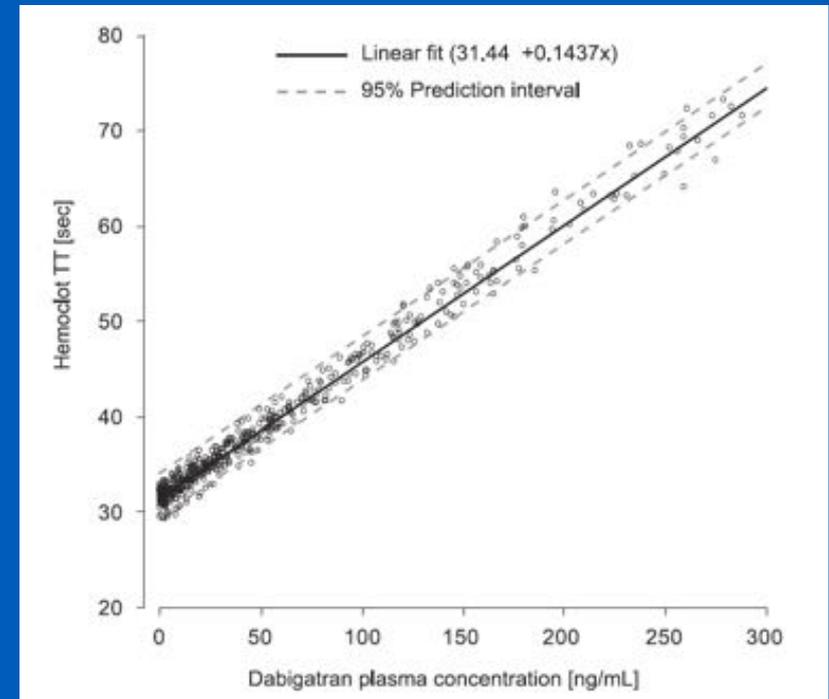
Healey et al; Circulation 2012

Measurement of Dabigatran levels

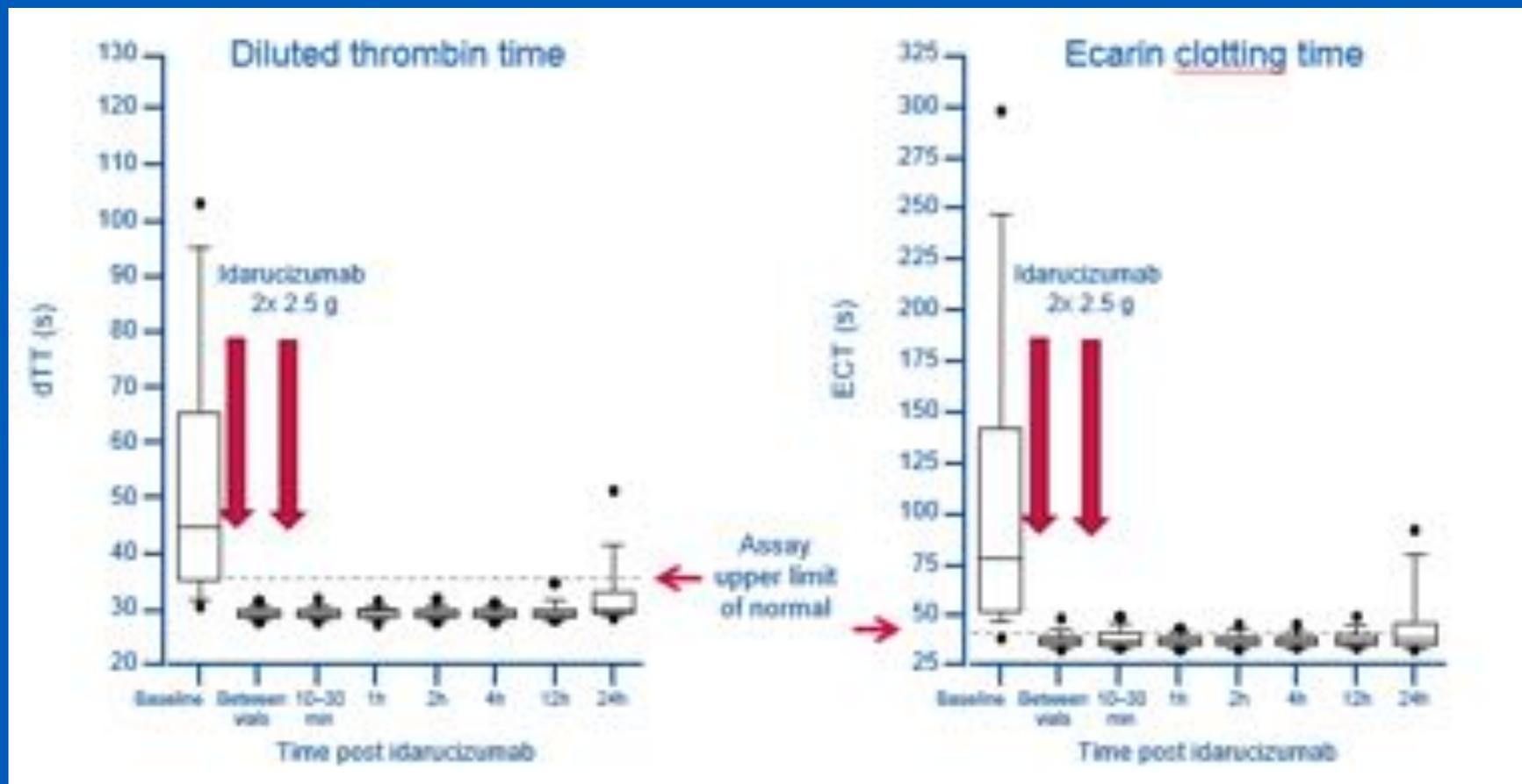
aPTT



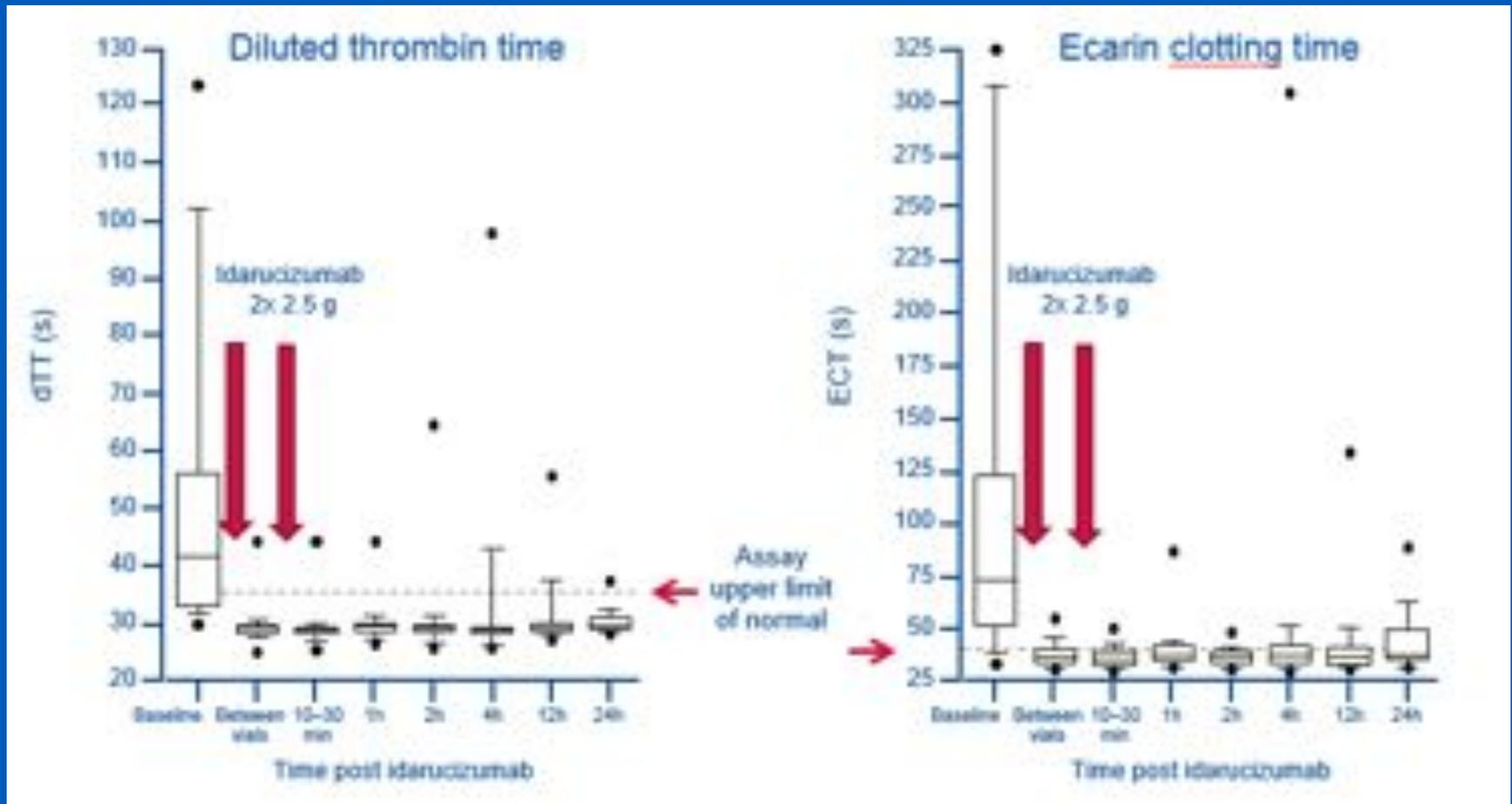
Hemoclot Test



Idarucizumab for reversal of anticoagulant effect of dabigatran



Idarucizumab: Urgent surgery patients



Conclusions

- **Dabigatran is highly effective and safe**
- **It can be used in most patients with AF**
- **Both doses are useful and well studied**
- **Long term follow up studies confirm clinical trial results**