

**Advances in Cardiac Diseases and  
Great Innovations in Cardiology**

**Anticoagulation 3.0**

**Dabigatran & Idarucizumab: New Therapeutic Standards**

Torino, Centro Congressi Unione Industriale  
13-15 Ottobre 2016

# Dabigatran: Full and Complete Safety

**Leonardo De Luca, MD, PhD, FACC, FESC, FSCAI**

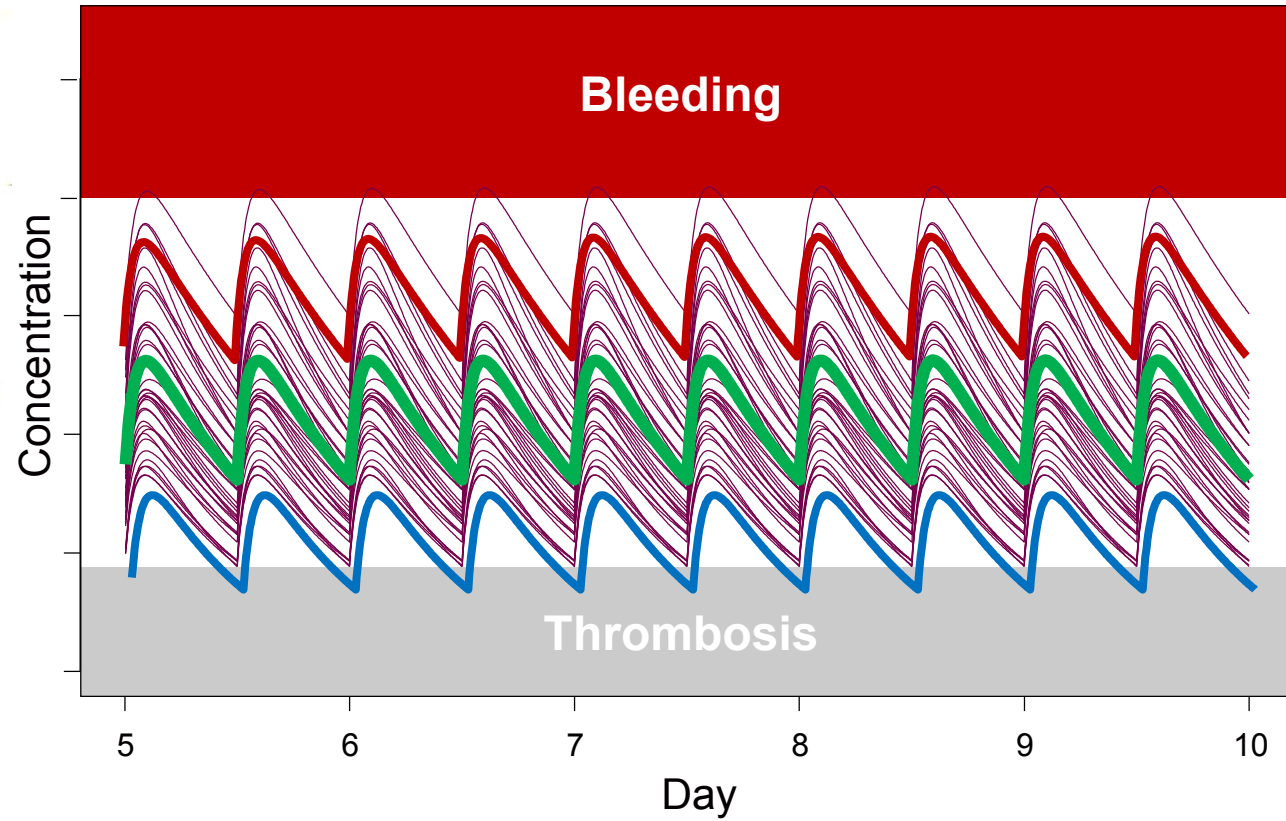
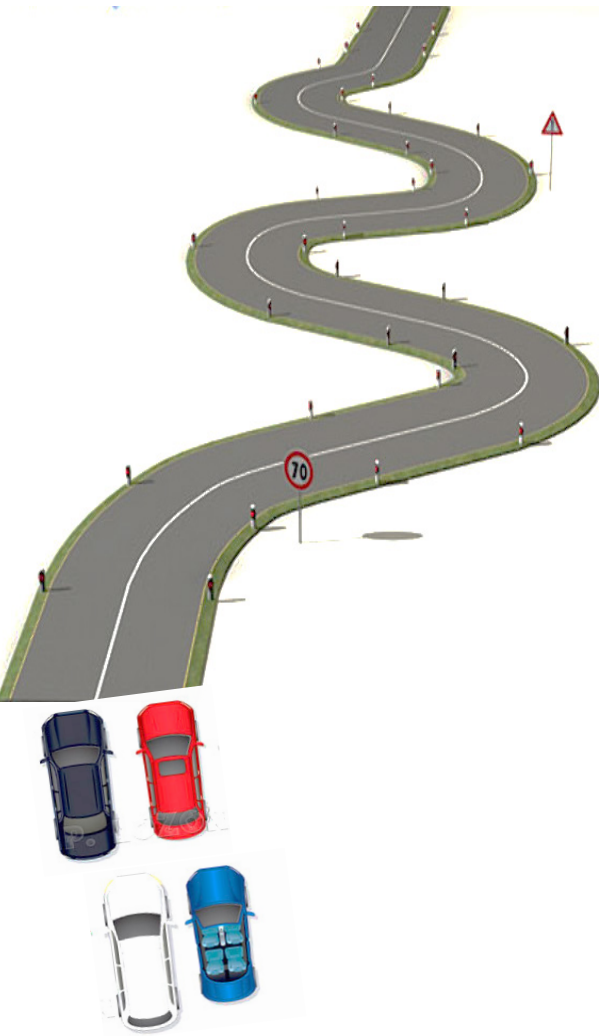
Division of Cardiology  
Interventional Cardiology Unit  
*San Giovanni Evangelista Hospital*  
Tivoli (Rome), Italy  
leo.deluca@libero.it



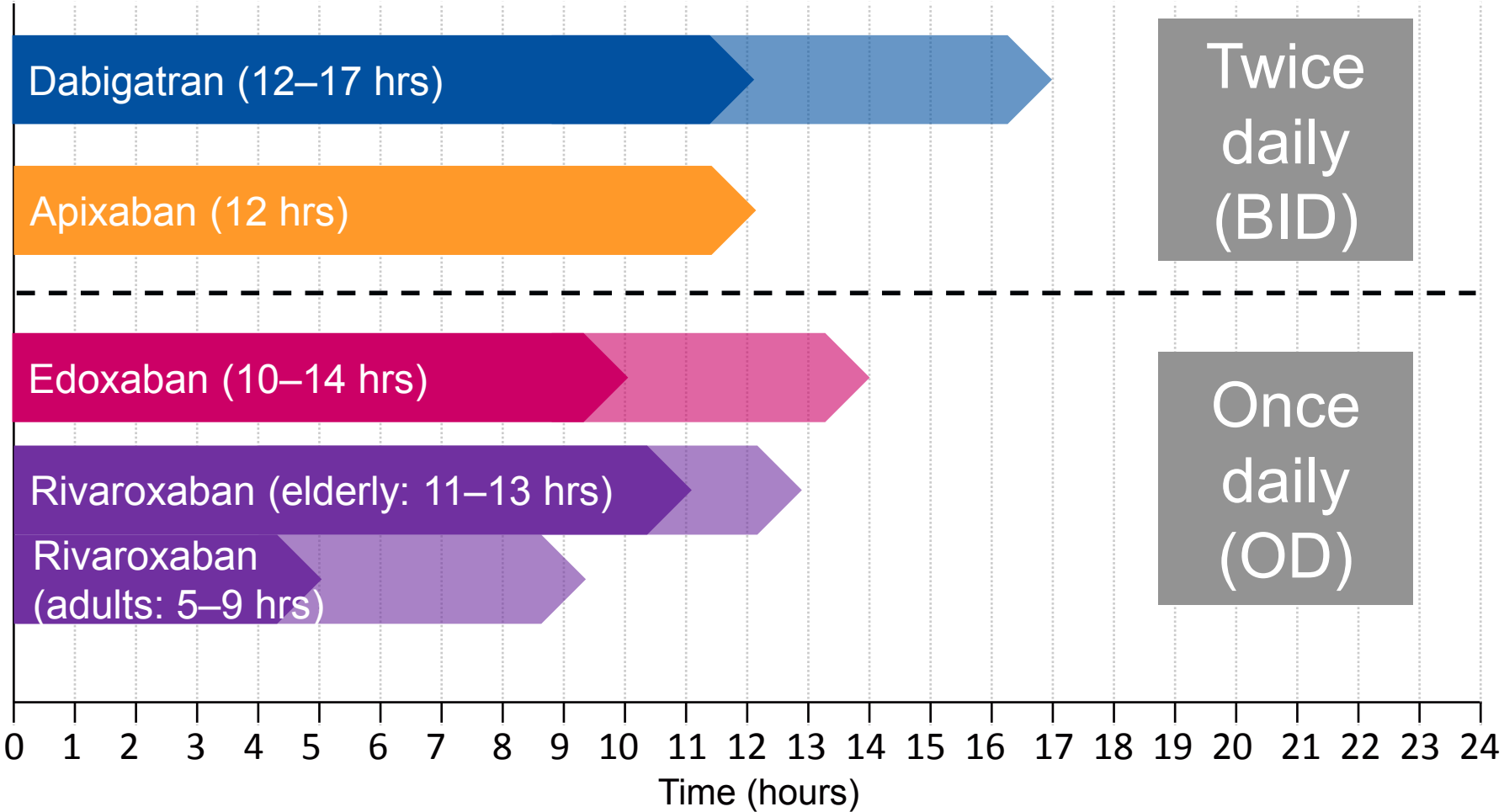
# Comparing NOACs is Like Comparing Different Cars Performance



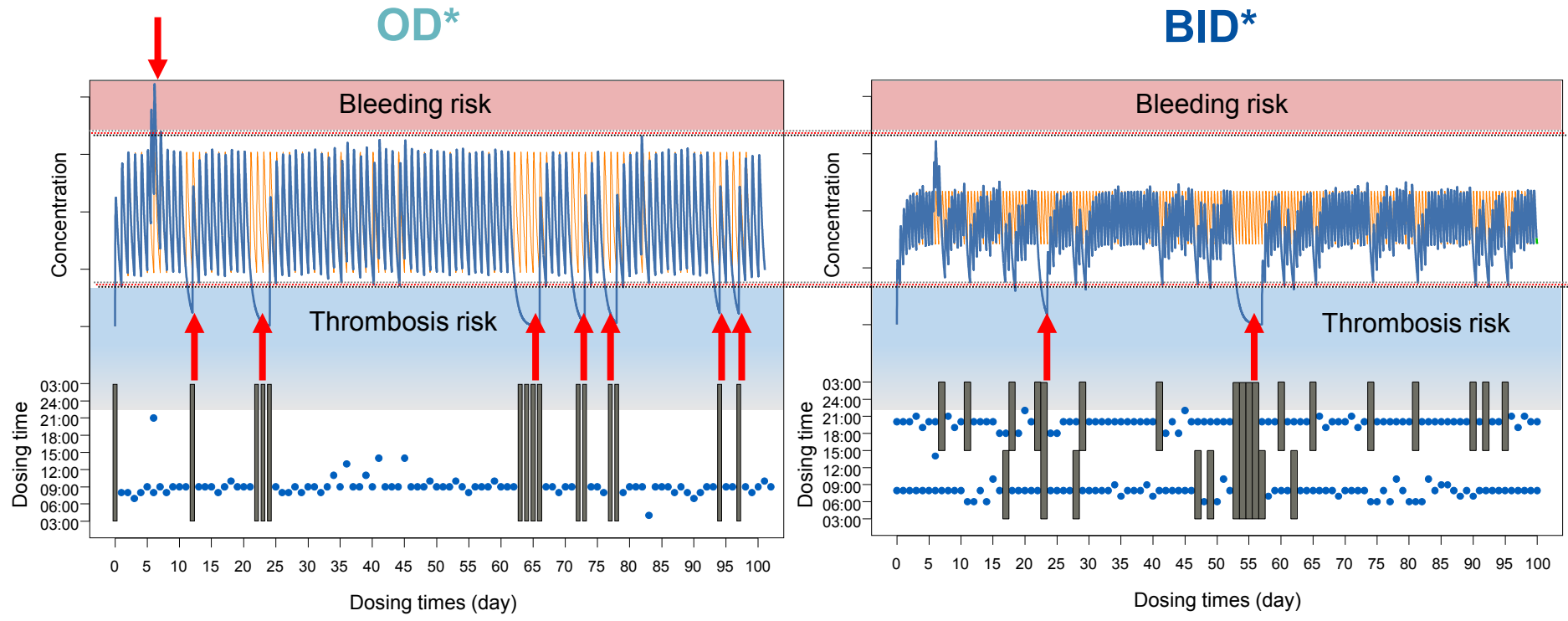
# Therapeutic Range and Biologic Variability for Anticoagulants



# Half-Lives of all NOACs are Similar, but Dosing Regimens Differ



# BID Regimen Increases Forgiveness for Similar Deviations in Adherence

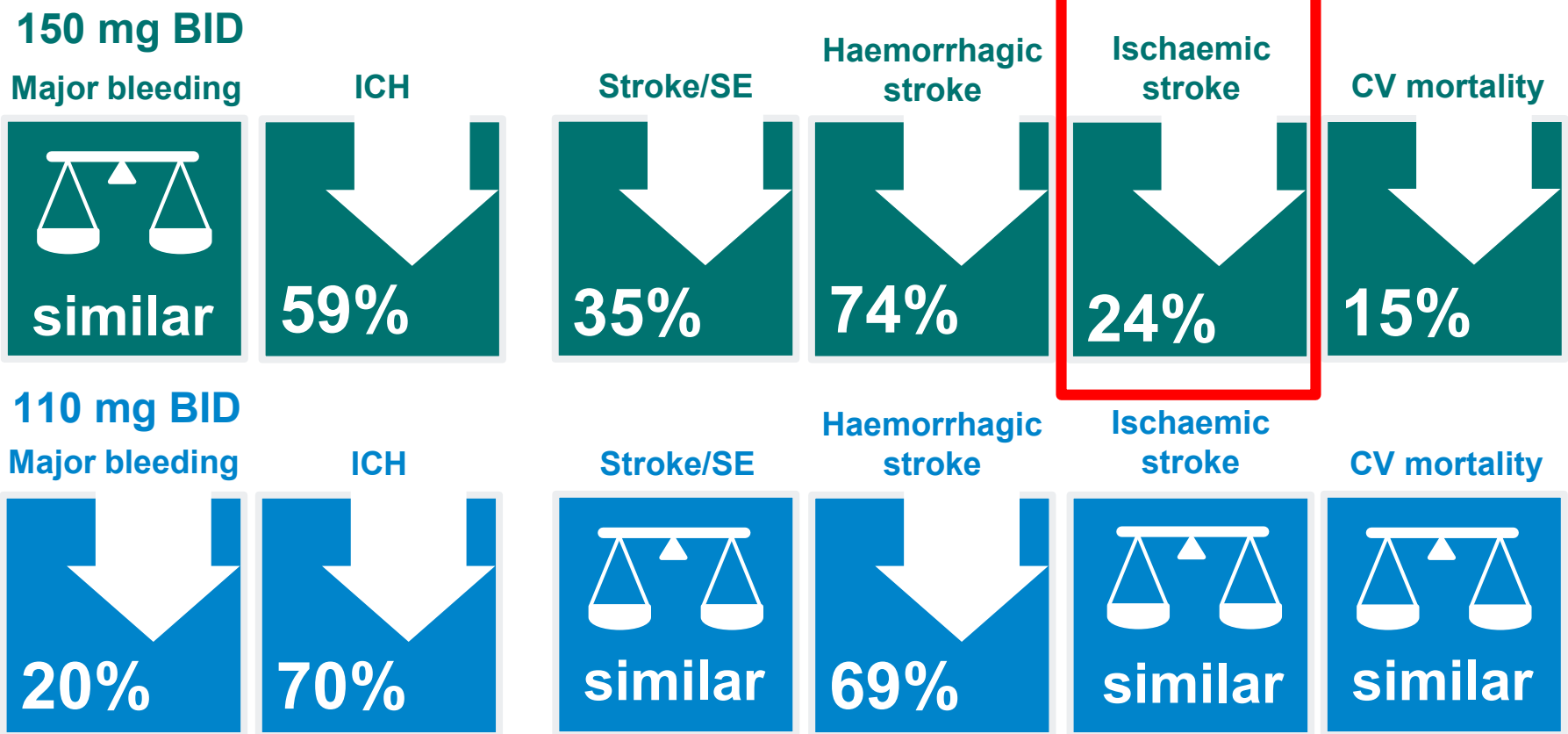


- 15% missed doses
- 15 OD missed doses vs 30 BID missed doses over 100 days

\*OD and BID dosing for same agent and the same total daily dose; assuming  $T_{1/2} = 12$  hrs;  $T_{max} = 3$  hrs  
Vrijens & Heidbuchel. Europace 2015

● Dose taken  
| Dose missed

# Both Doses of Dabigatran Provide Safety and Efficacy Benefits vs Warfarin in the RE-LY Population

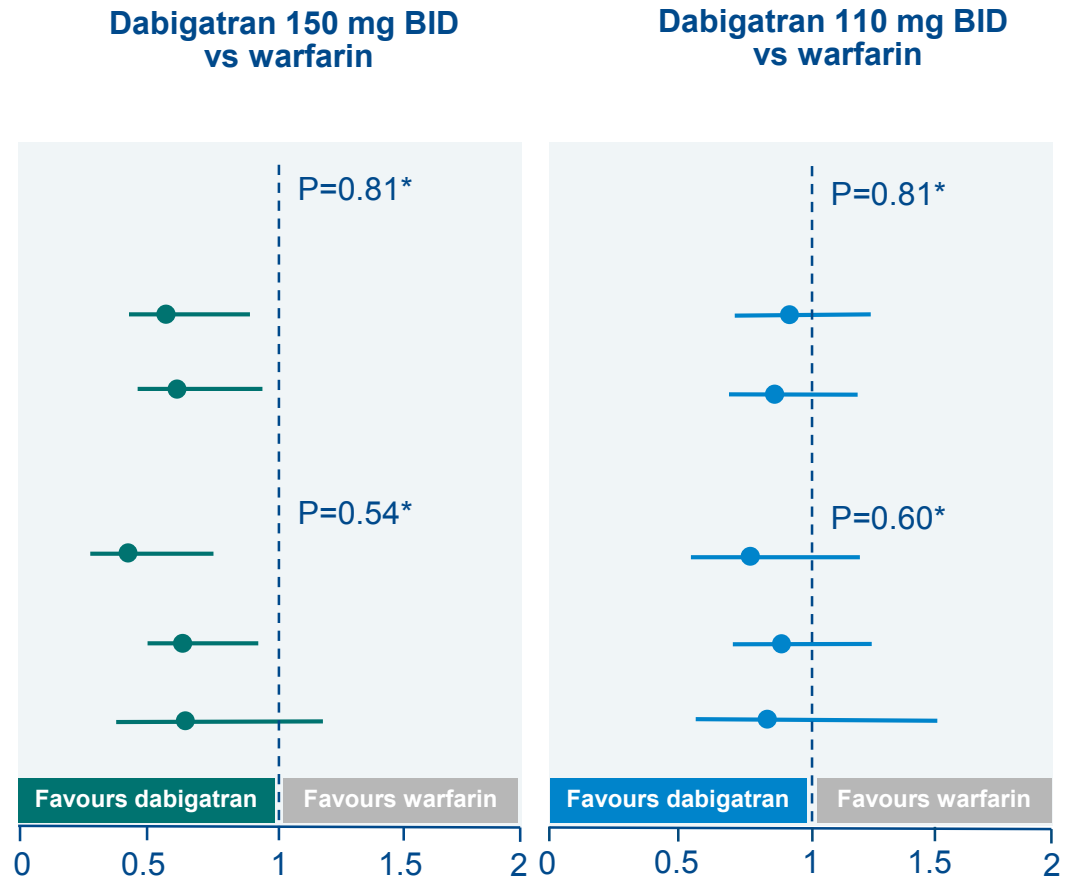


1. Connolly SJ et al. N Engl J Med 2010;  
 2. Connolly SJ et al. N Engl J Med 2014

# 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

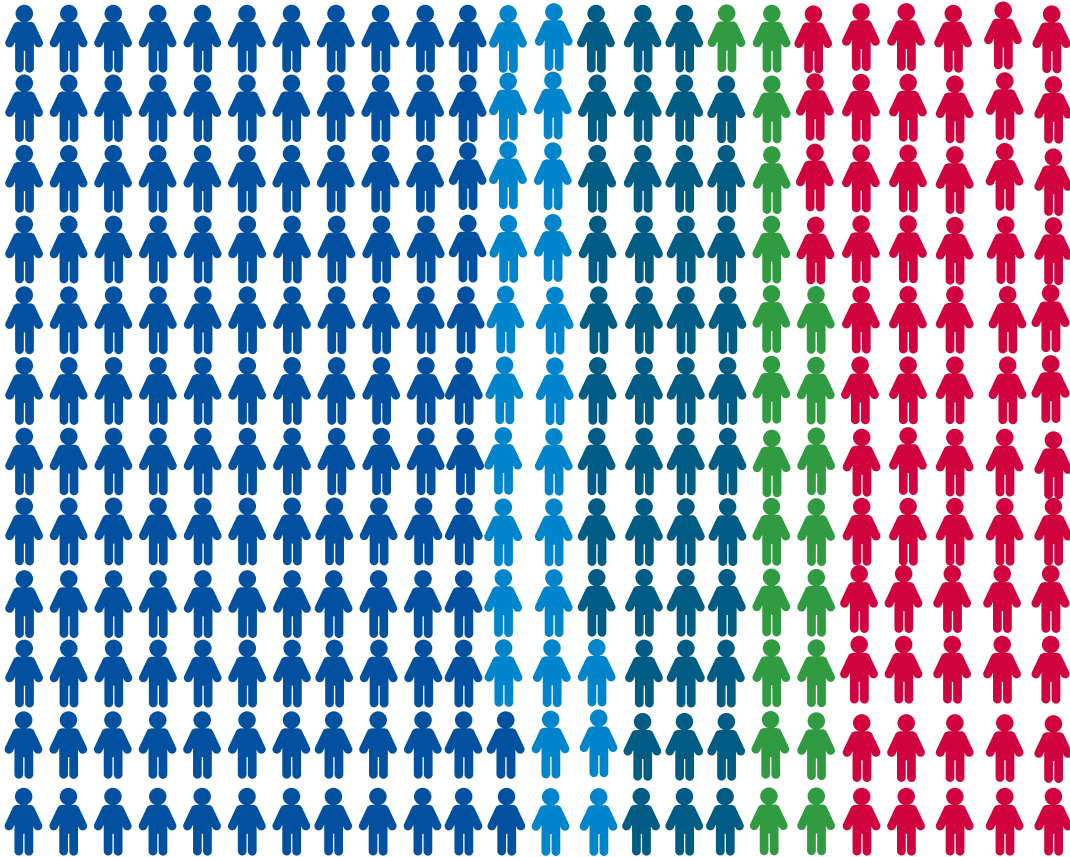







\*P values for interaction

# Real-World Experience from >250 000 Patients Confirms Positive Outcome of Dabigatran

## Clinical practice (n>250 000 patients)

**RE-LY®**  
(n>18 000 patients)



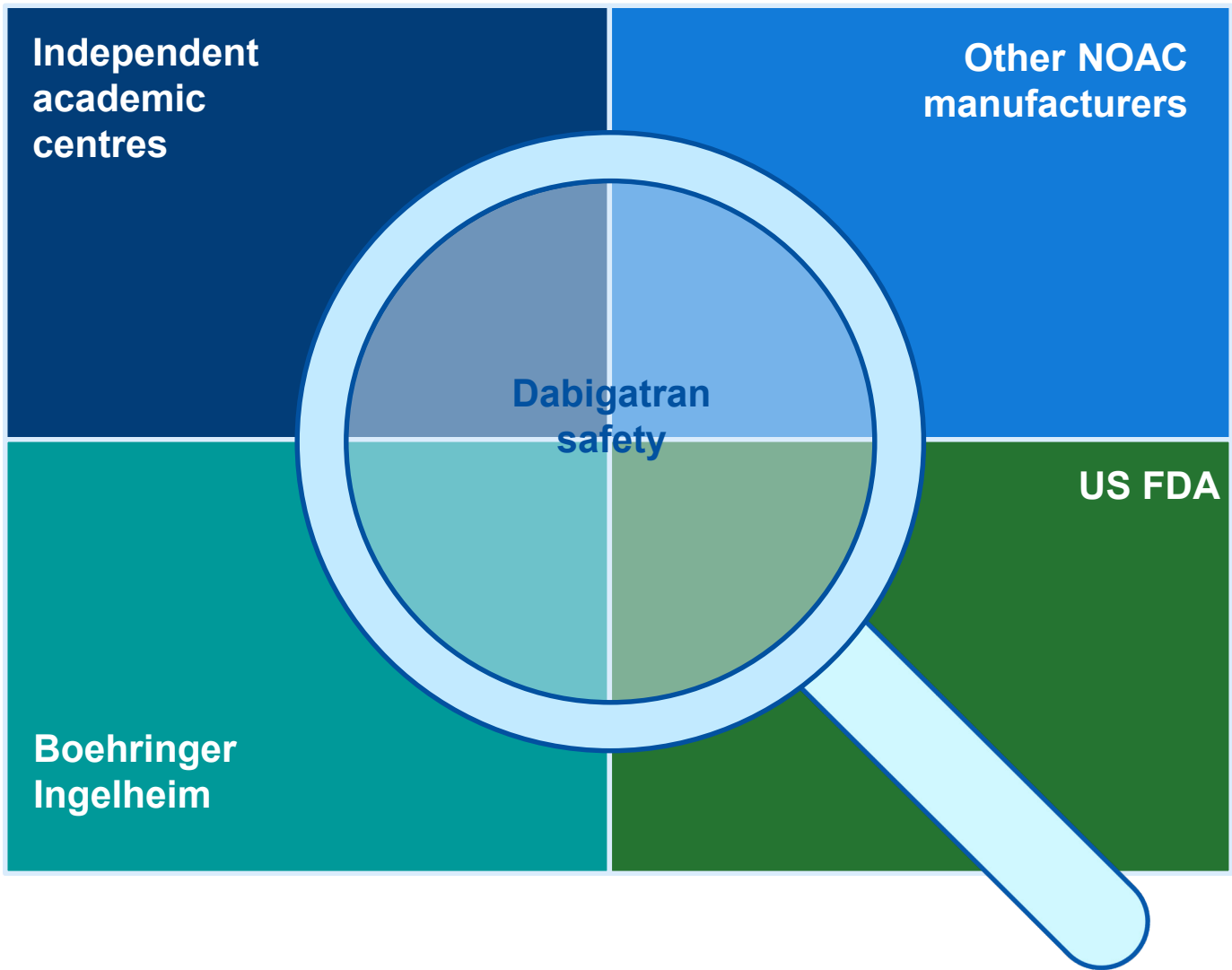
-  FDA Medicare study (n>134 000)<sup>1</sup>
-  US Dept of Defense database (n>25 000)<sup>2</sup>
-  2 US insurance databases (n>44 000)<sup>3</sup>
-  Danish observational studies (n>21 000)<sup>4,5</sup>
-  US insurance database (n>64 000)<sup>6</sup>

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 NVAf

1. Graham et al. Circulation 2015; 2. Villines et al. Thromb Haemost 2015; 3. Seeger et al. AHA 2015; 4. Larsen et al. Am J Med 2014a; 5. Larsen Am J Med 2014b; 6. Lauffenburger et al. J Am Heart Assoc 2015



# Studies from various sponsors and with different comparators



# US DoD

# Database Analysis

US DoD  
& Boehringer  
Ingelheim

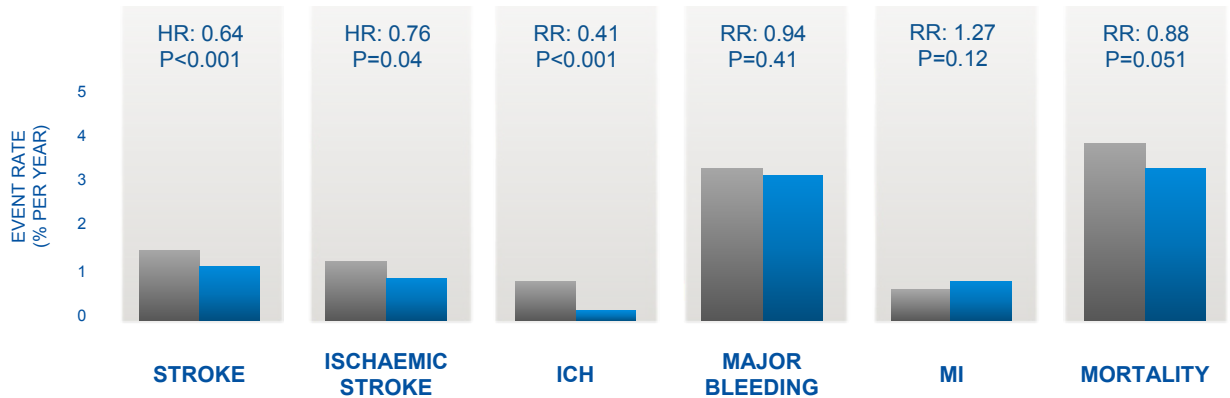
## RE-LY<sup>®</sup>1-4

■ Warfarin  
■ D150 BID



RCT

>18000 patients



## US DoD<sup>5,6</sup>

■ Warfarin  
■ D150 & D75 BID combined\*



Real-world data

>25 000 patients



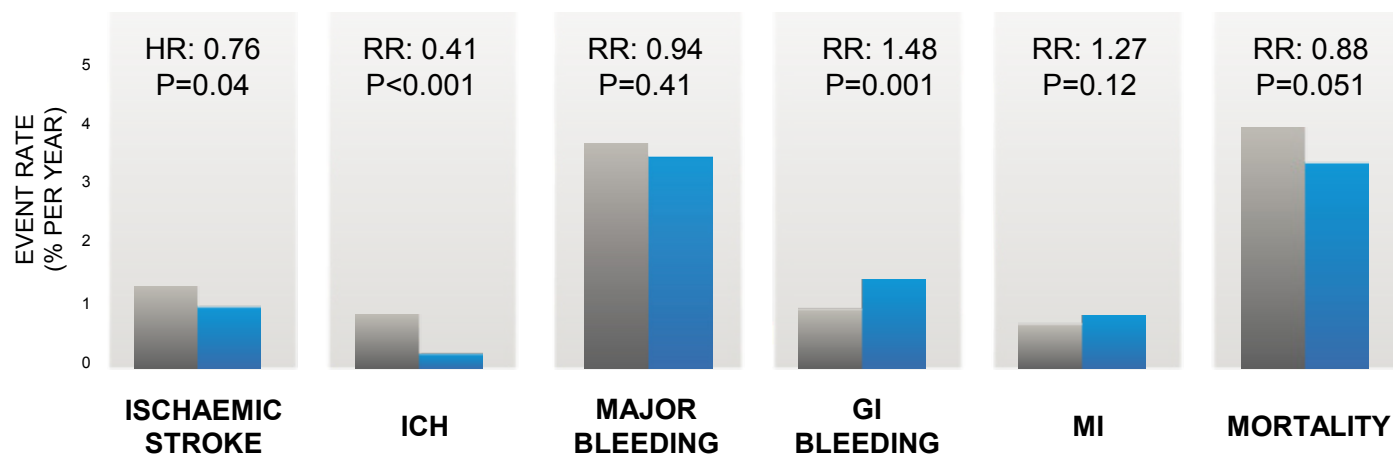
In the USA, the licensed doses for Pradaxa<sup>®</sup> are: 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with NVAf. \*88% of patients were on dabigatran 150 mg BID. DoD, Department of Defense

1. Connolly et al. N Engl J Med 2009; 2. Connolly et al. N Engl J Med 2010; 3. Connolly et al. N Engl J Med 2014; 4. Pradaxa<sup>®</sup>: EU SPC 2016; 5. Villines et al. AHA 2015; 6. Villines et al. Thromb Haemost 2015

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

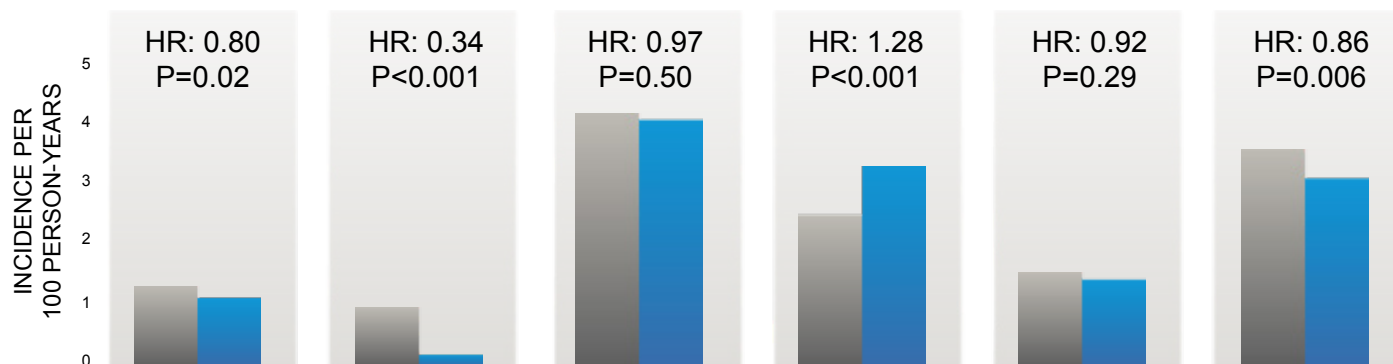
## RE-LY®<sup>1-4</sup>

■ Warfarin  
■ D150 BID



## MEDICARE<sup>\*5</sup>

■ Warfarin  
■ D150 & D75 BID combined



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 NVAF

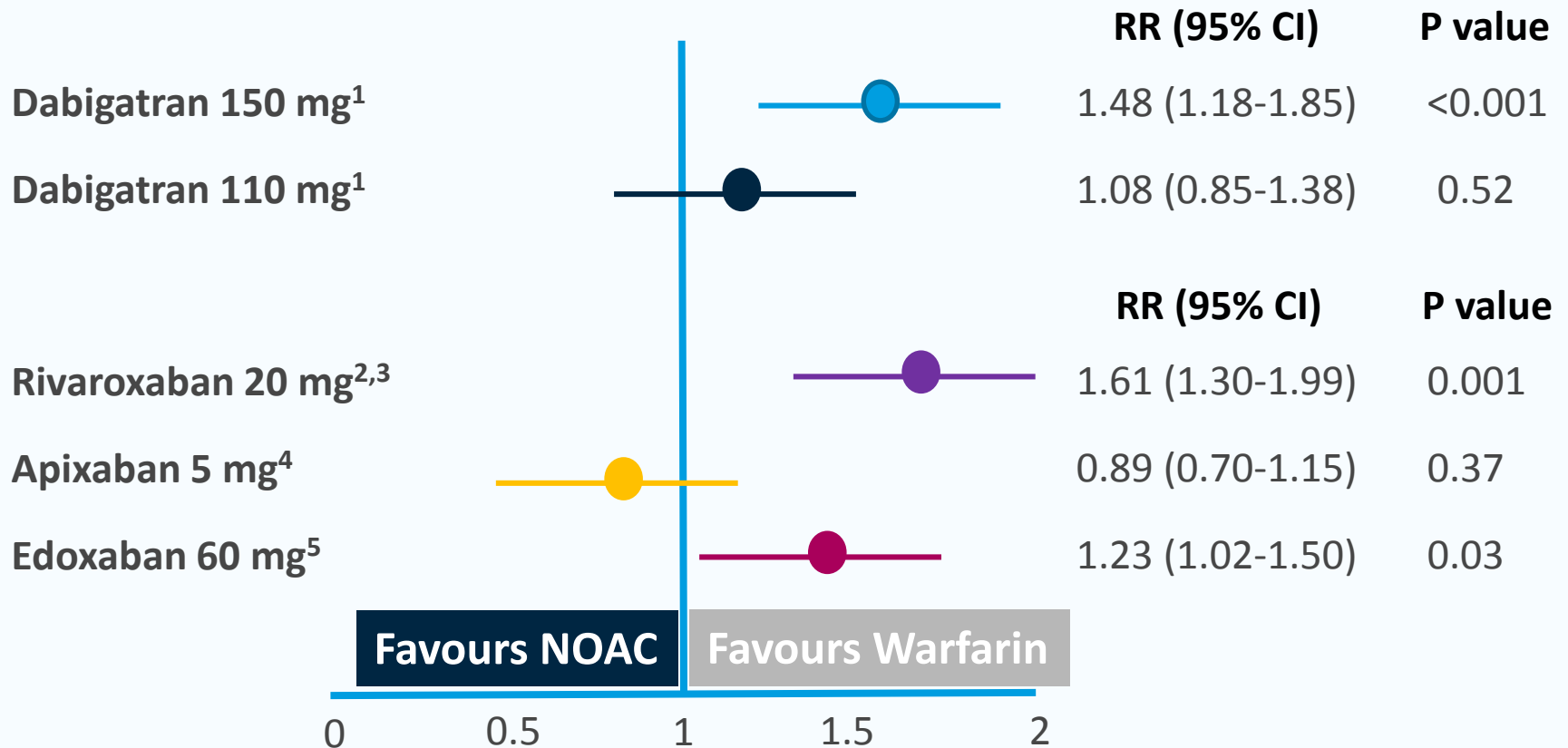
1. Connolly et al. N Engl J Med 2009; 2. Connolly et al. N Engl J Med 2010; 3. Connolly et al. N Engl J Med 2014; 4. Pradaxa®: EU SPC, 2016; 5. Graham et al. Circulation 2015

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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

# Risk of Major GI Bleeding in Phase III Trials on NOACs



**Meta-analysis showed increased risk of GI bleeding for NOACs as a group<sup>6</sup>**

1. Connolly 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

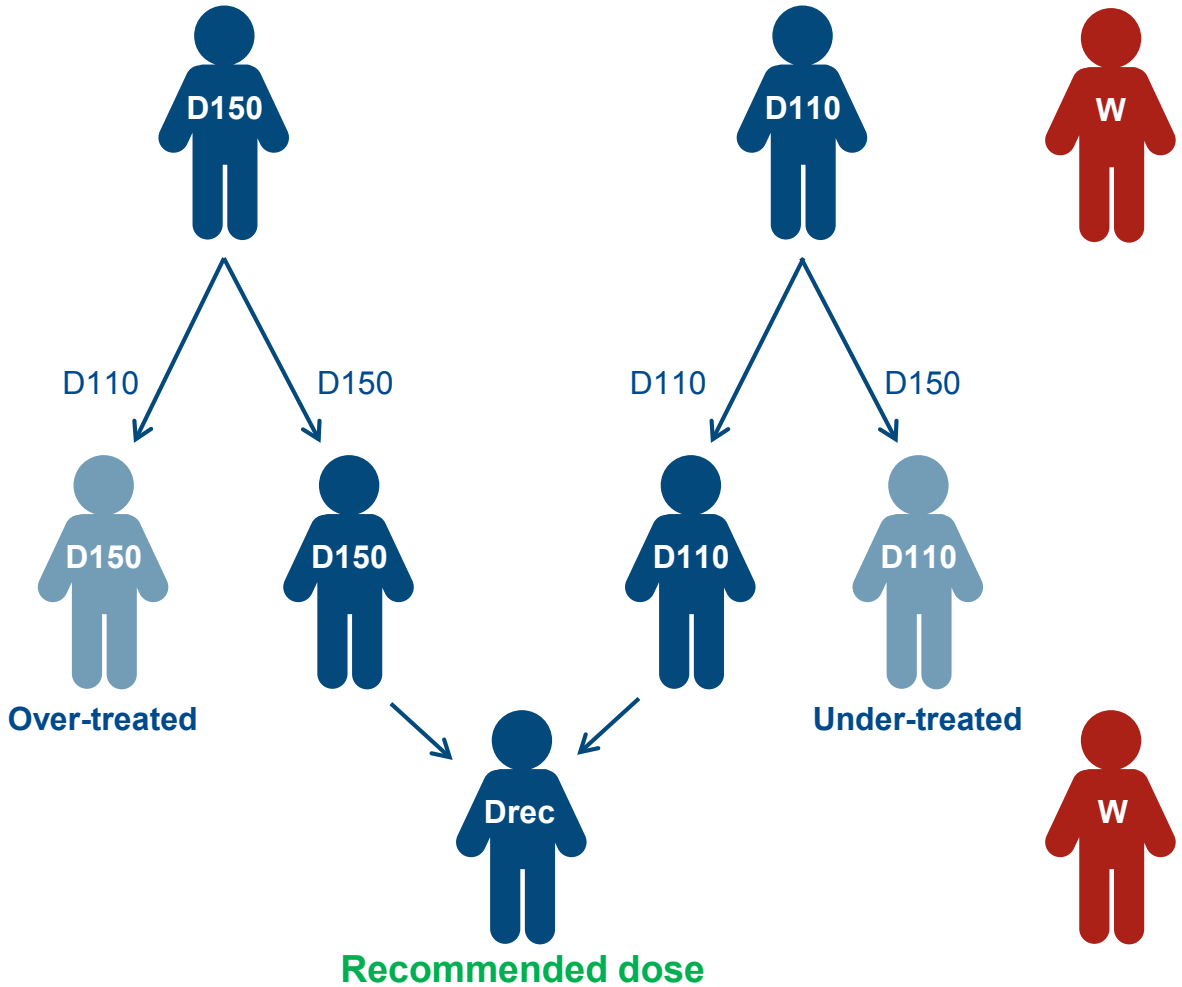
Full RE-LY population

Post hoc analysis of patients' baseline characteristics

Recommended dose\*

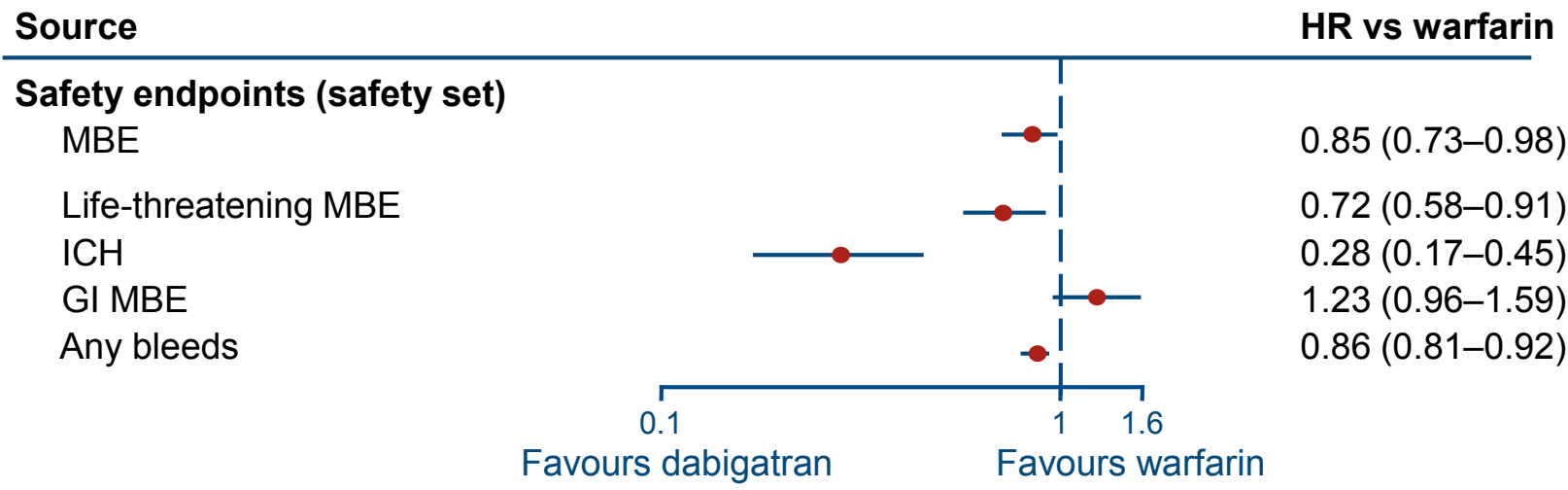
Dose received

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

# 'EU Label-Compliant' Dabigatran Rx Provides a Meaningful and Clinically Relevant Benefit

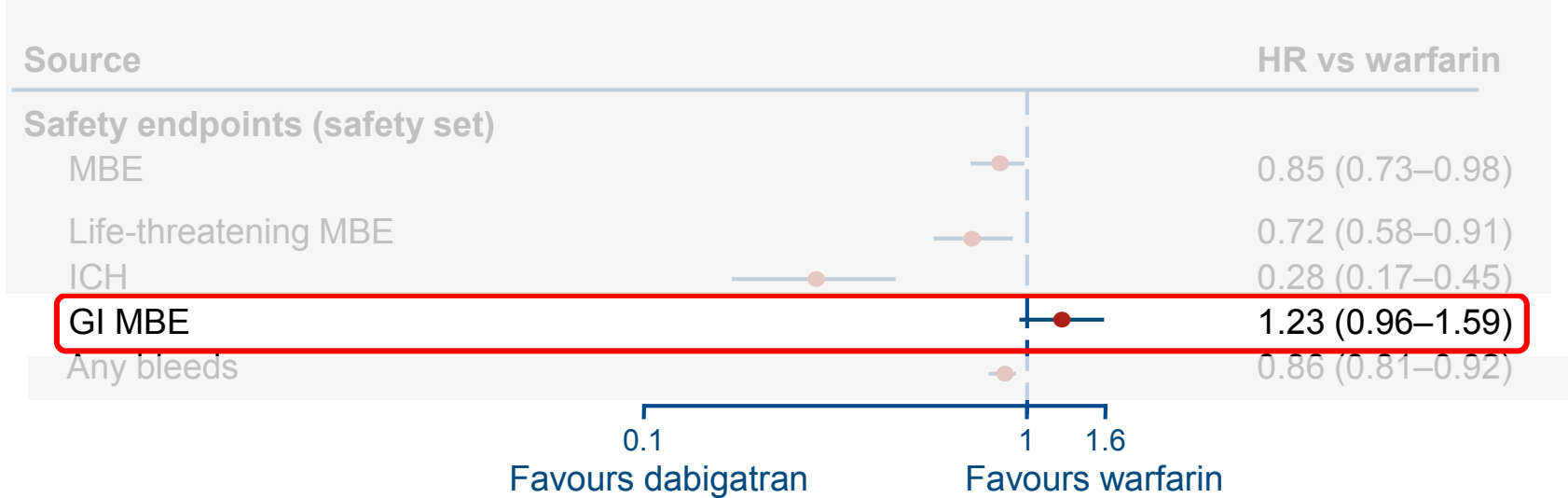


**ICH**  
RR (95% CI)  
**0.28**  
(0.17–0.45)

**Major bleed**  
RR (95% CI)  
**0.85**  
(0.73–0.98)

**GI MBE**  
RR (95% CI)  
**1.23**  
(0.96–1.59)

# 'EU Label-Compliant' Dabigatran Rx Provides a Meaningful and Clinically Relevant Benefit



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**GI MBE**  
RR (95% CI)  
**1.23**  
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# Are all NOACs the Same?

## Risk reductions vs warfarin

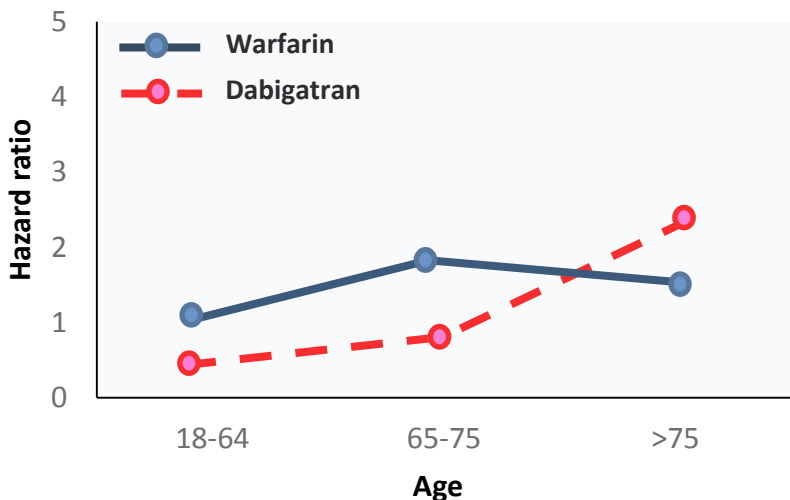
	Dabigatran <sup>1</sup>	Apixaban <sup>2</sup>	Rivaroxaban <sup>3</sup>	Edoxaban <sup>4</sup>
ICH	72%	58%	33%	53%
Major bleeding	15%	31%	No sig. diff.	20%
Major GI bleeding	No sig. diff.	No sig. diff.	66%	23%
Stroke/SE	26%	21%	No sig. diff.	No sig. diff.
Total mortality	14%	11%	No sig. diff.	No sig. diff.

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

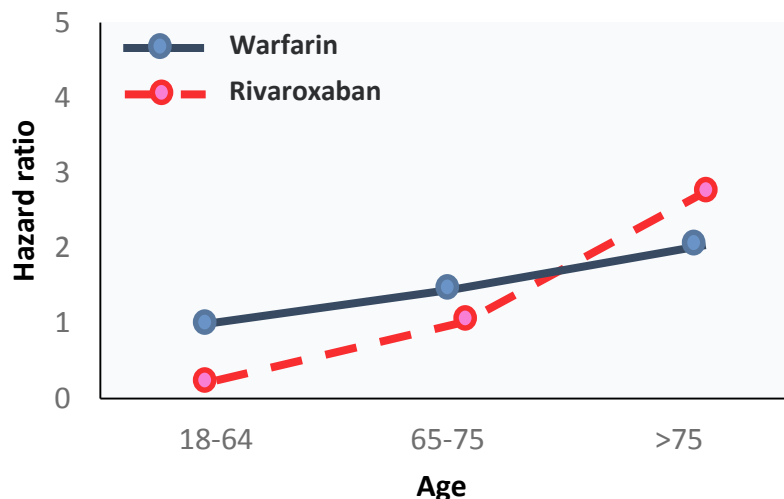


- Optum Labs Data Warehouse
- Administrative claims data on privately insured and Medicare Advantage enrollees
- Propensity matched cohort study
- 7749 matched AF pts

**Dabigatran vs Warfarin**



**Rivaroxaban vs Warfarin**



# GI Bleeding in the FDA Study of Medicare Patients

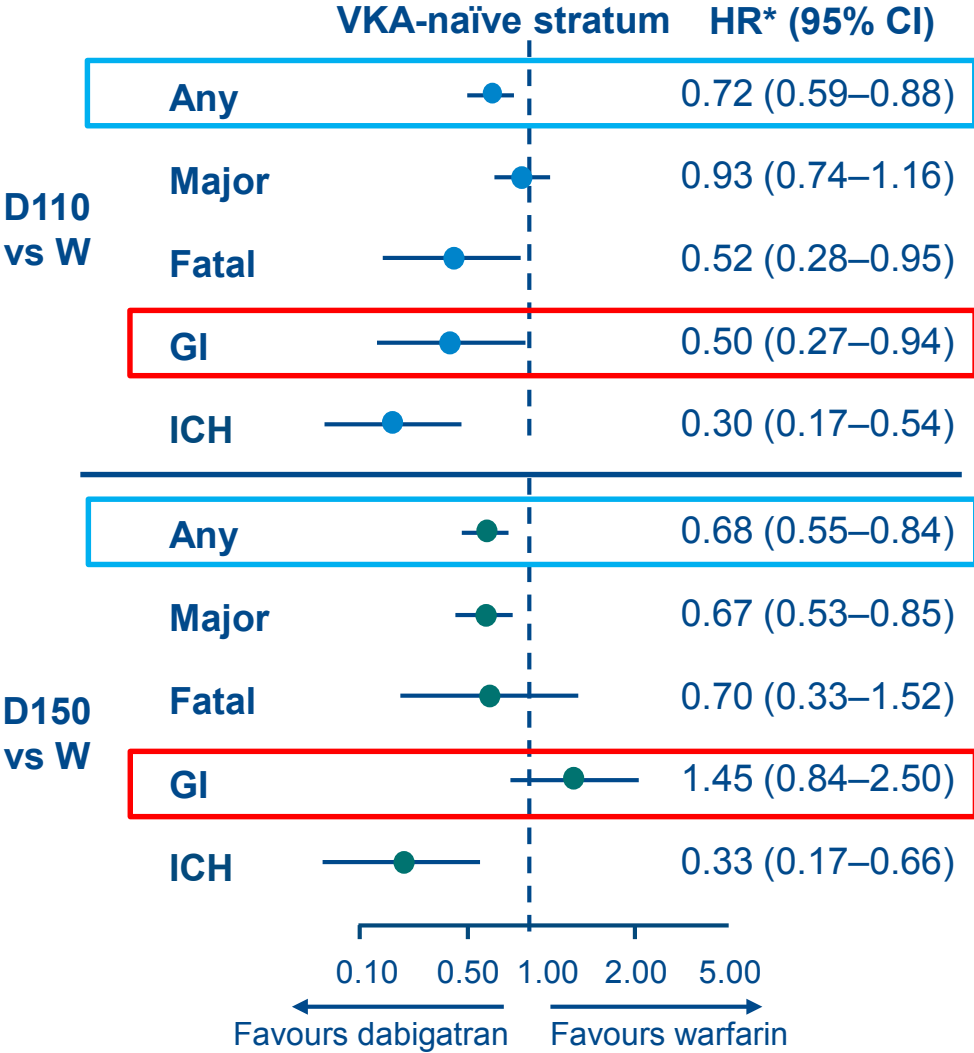
Age group (n)	Men HR (95% CI)	Women HR (95% CI)
65-74 (55.761)	0.83 (0.60-1.14)	0.99 (0.72-1.37)
75-84 (57.345)	1.02 (0.79-1.31)	1.50 (1.20-1.88)
≥85 (21.308)	1.55 (1.04-2.32)	2.18 (1.61-2.97)

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

# 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

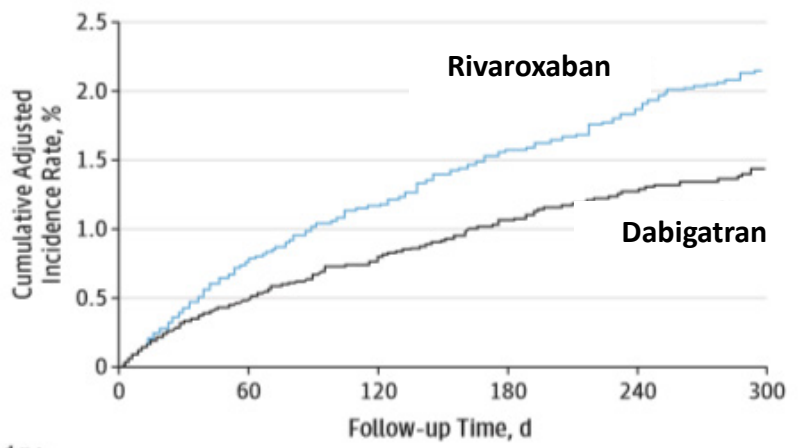


\*Adjusted HR: age, components of CHA<sub>2</sub>DS<sub>2</sub>-VASc, HAS-BLED, months since August 2011, time since initiation of VKA therapy

# Bleeding Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban

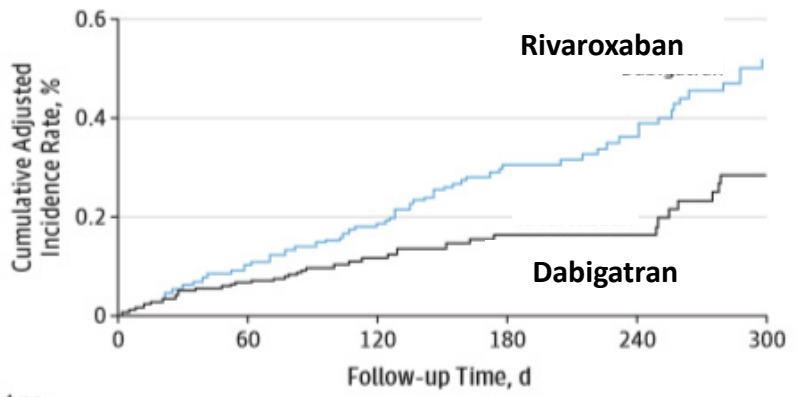
118891 patients with nonvalvular AF >65 yrs, enrolled in Medicare, and who initiated treatment with dabigatran 150 mg/BID or rivaroxaban 20 mg/od from Nov 2011 through June 2014

**C** Major gastrointestinal bleeding



Weighted no. at risk	0	60	120	180	240	300
Dabigatran	52 264	26 729	13 355	9 236	6 156	4 384
Rivaroxaban	66 630	35 707	19 527	12 947	8 511	5 753

**B** Intracranial hemorrhage

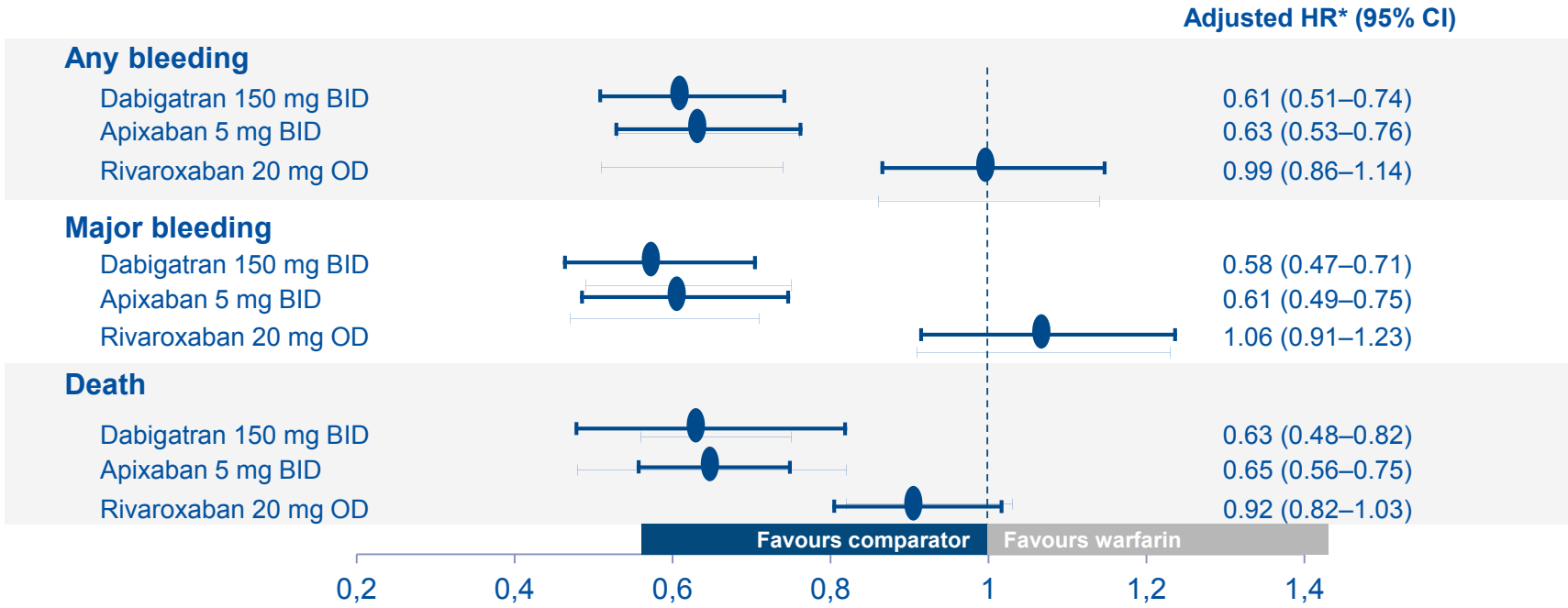


Weighted no. at risk	0	60	120	180	240	300
Dabigatran	52 264	26 729	13 355	9 236	6 156	4 384
Rivaroxaban	66 630	35 707	19 527	12 947	8 511	5 753

# Risk of any bleeding, major bleeding, or death significantly lower for dabigatran vs warfarin

Independent academic centre

61 678 patients with AF (OAC-naïve)

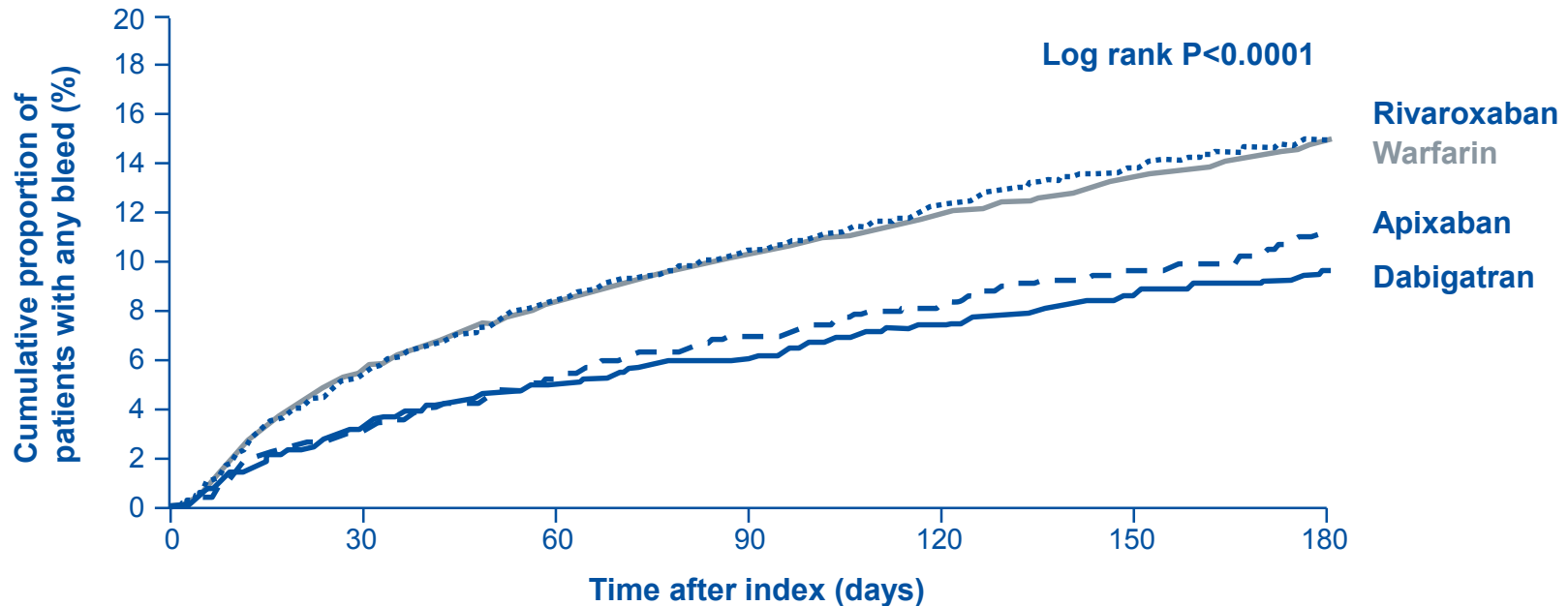


Analysis of prospective cohort from three nationwide Danish registries (Aug 2011–Oct 2015)  
 12 701 dabigatran 150 mg BID, 7 192 rivaroxaban 20 mg OD, 6 349 apixaban 5 mg BID, 35 436 warfarin  
 \*Propensity-adjusted Cox hazard ratios; Larsen et al. BMJ 2016

# Bleeding risk with dabigatran lower than with warfarin and similar to that with apixaban

Other NOAC  
manufacturer

35757 patients with AF (OAC-naïve)



Curves unadjusted for differences in baseline characteristics. Any bleed is a combination of major and clinically relevant non-major bleeding. Retrospective analysis of US Humedica electronic health record database (Jan 2013–Jun 2014): 2440 dabigatran, 6407 rivaroxaban, 2038 apixaban, 24 872 warfarin  
Lin et al. ESC 2015 (study sponsored by Pfizer/BMS)

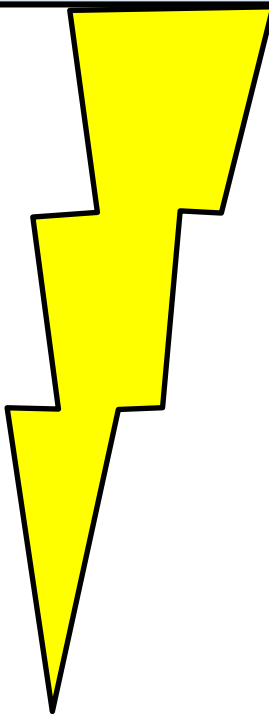
For when life happens: immediate anticoagulant reversal, if it is ever needed





# Accidents are Rare. But.. Would You Buy a Car Without Airbags?

**2.396 lives saved  
in 2014 in US**



# Patient Values and Preferences when Choosing Anticoagulants for AF

Cross-sectional study of Veterans in the primary care clinics and the international normalized ratio (INR) laboratory

