Terapie con i NAO: quali vantaggi

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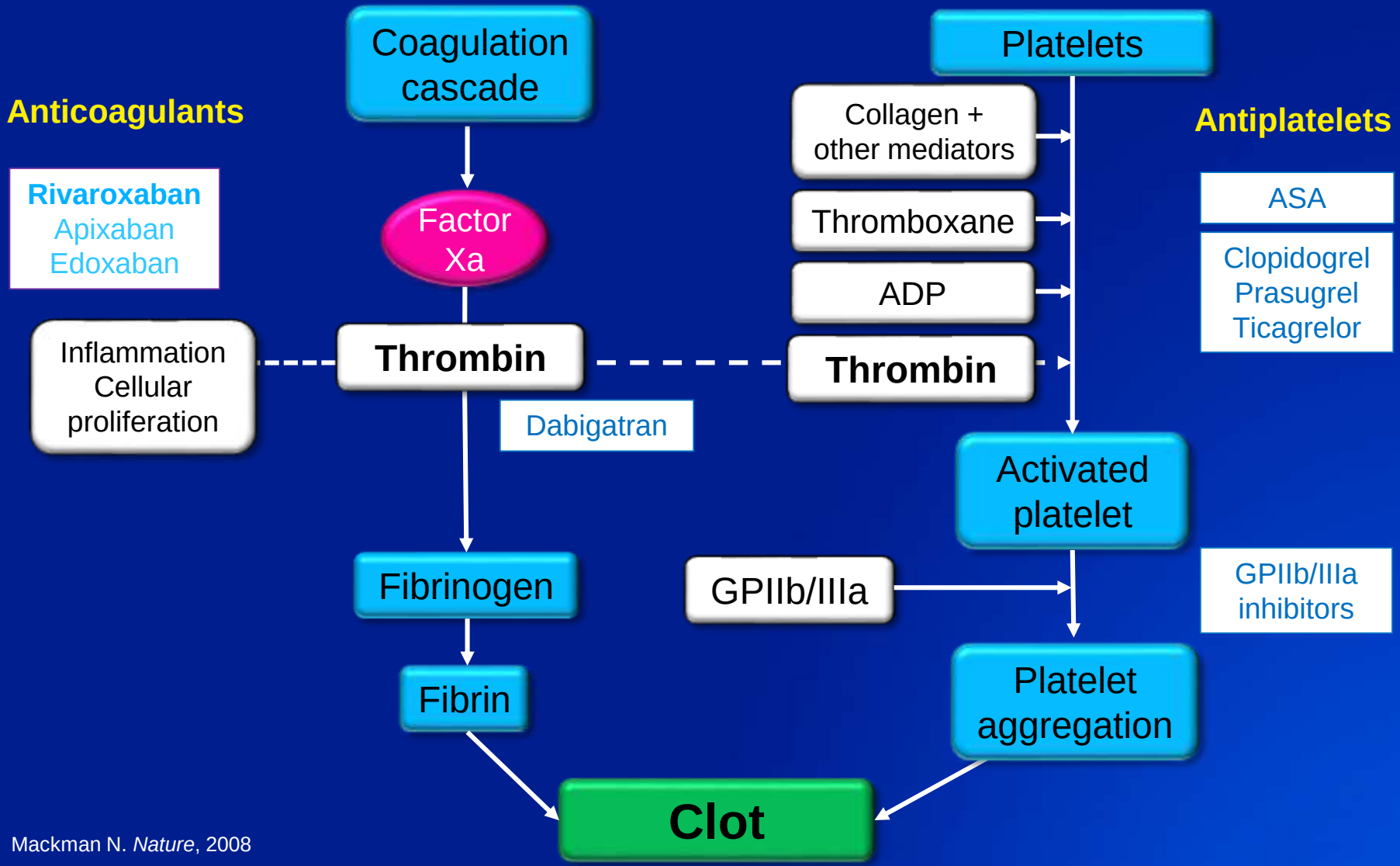
Pharmacological Profiles of Warfarin and NOACs

Drug	Bioavailability	T_{max}	$T_{1/2}$	Metabolism	Primary excretion
Warfarin	100%	72-96 h	40 h	CYP2C9	92% renal (unchanged)
Dabigatran	6.5% (prodrug)	1-2 h	12-17 h	P-gp	80% renal (unchanged)
Rivaroxaban*	80%	2.5-4 h	5-9 h	CYP3A4 CYP2J2 P-gp	33% renal (unchanged)
Apixaban	50-66%	3 h	8-15 h	CYP3A4 P-gp	27% renal (unchanged)
Edoxaban*	**62%**	**1-2 h**	**10-14 h**	**CYP3A4 (<4%) P-gp**	**50% renal (unchanged)**

Slide coagulation.pptx

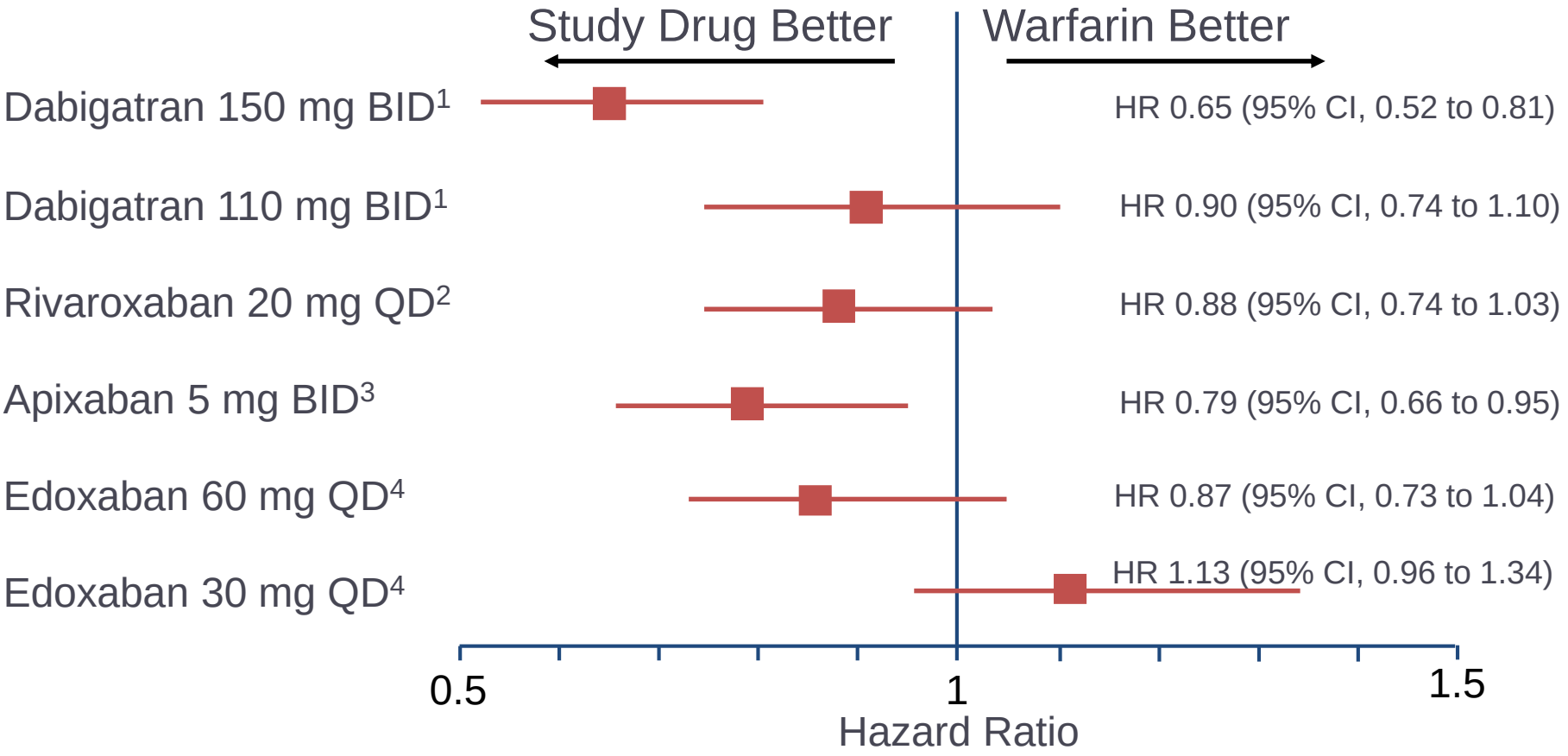
* Once Day

Thrombus formation involves both platelet activation and blood coagulation



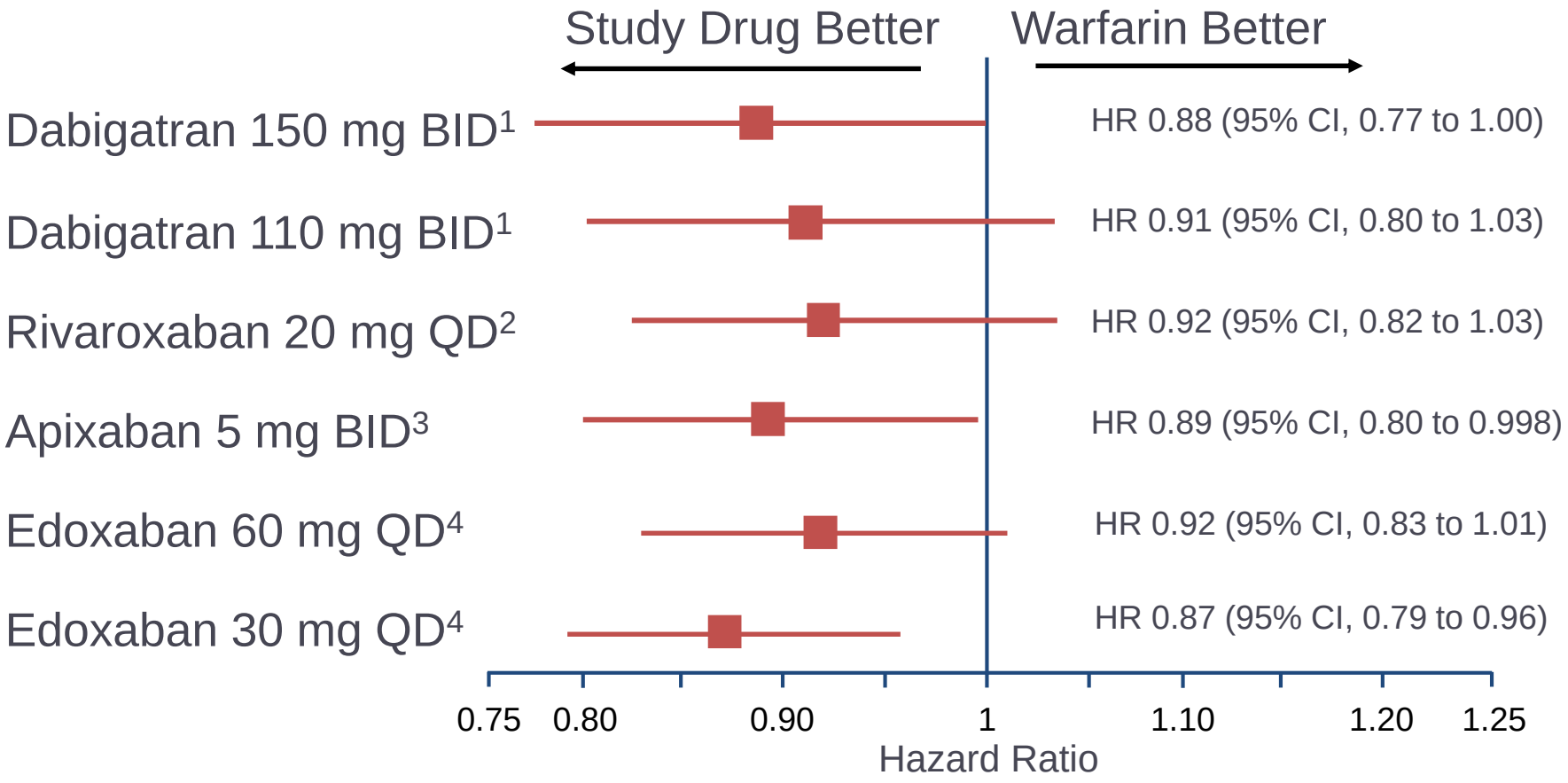
Mackman N. *Nature*, 2008

Nuovi anticoagulanti vs. Warfarin: *Stroke o Embolismo sistemico*



1. Connolly SJ et al. *N Engl J Med.* 2010;363:1875-1876.
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, for the ENGAGE-AF TIMI 48 Investigators; *N Engl J Med*. 2013

Nuovi anticoagulanti vs. Warfarin: *Mortalità per tutte le cause*



1. Connolly SJ et al. *N Engl J Med*. 2010;363:1875-1876.
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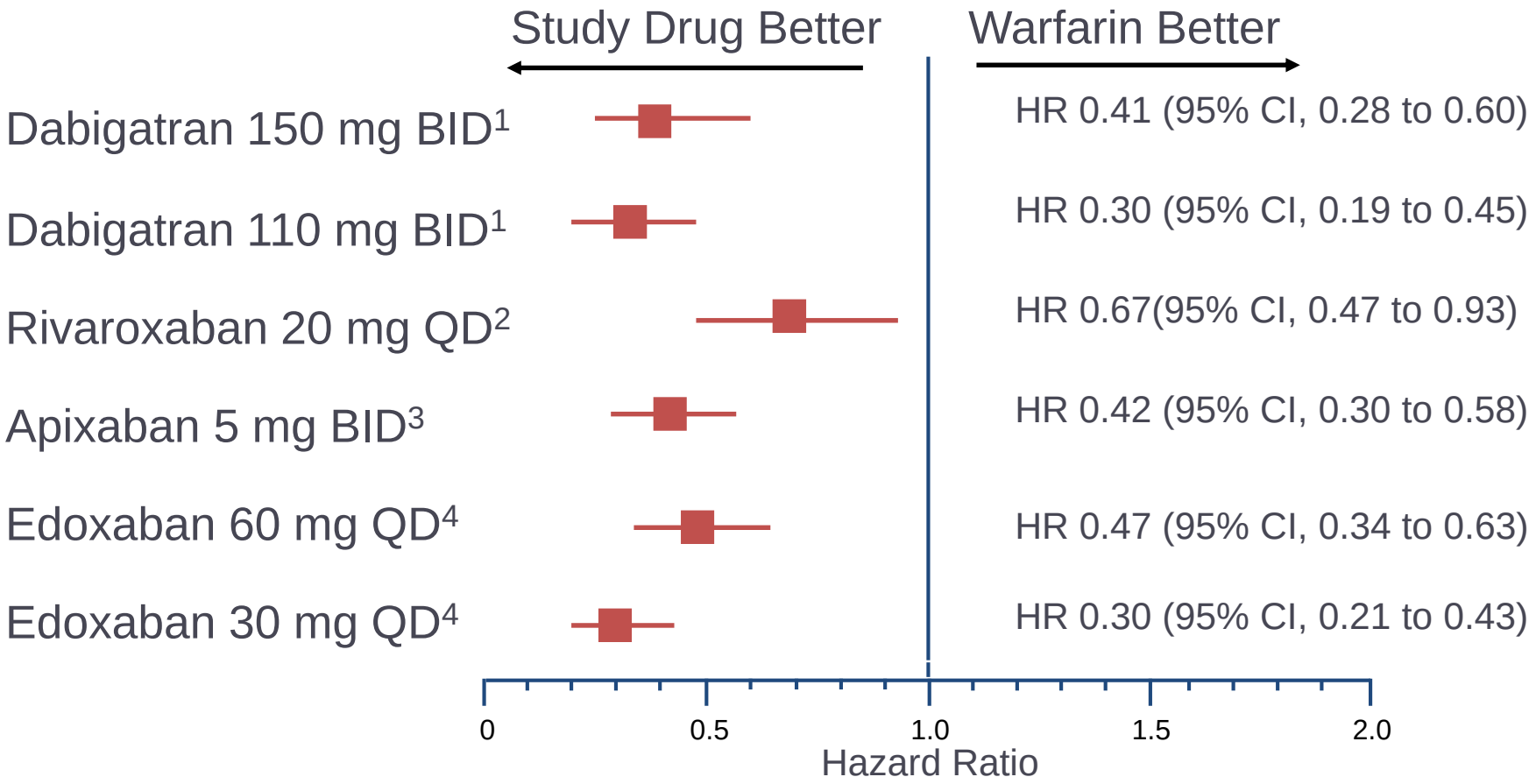
4. Giugliano RP et al, for the ENGAGE-AF TIMI 48 Investigators; . *N Engl J Med*. 2013,

Nuovi anticoagulanti vs. Warfarin: *Emorrragie intracraniche*



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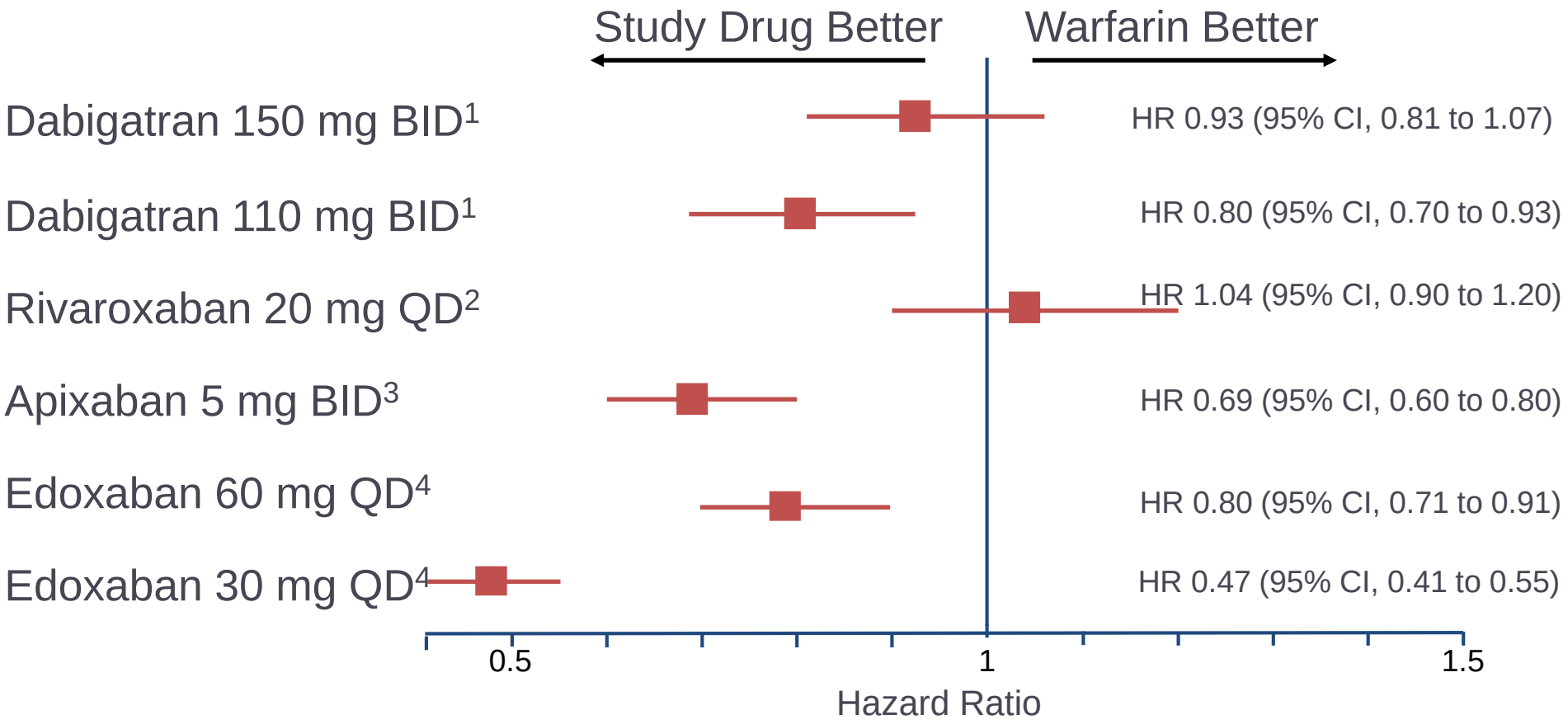
Nuovi anticoagulanti vs. Warfarin: *Sanguinamenti maggiori*



1. Connolly SJ et al. *N Engl J Med.* 2010;363:1875-1876.
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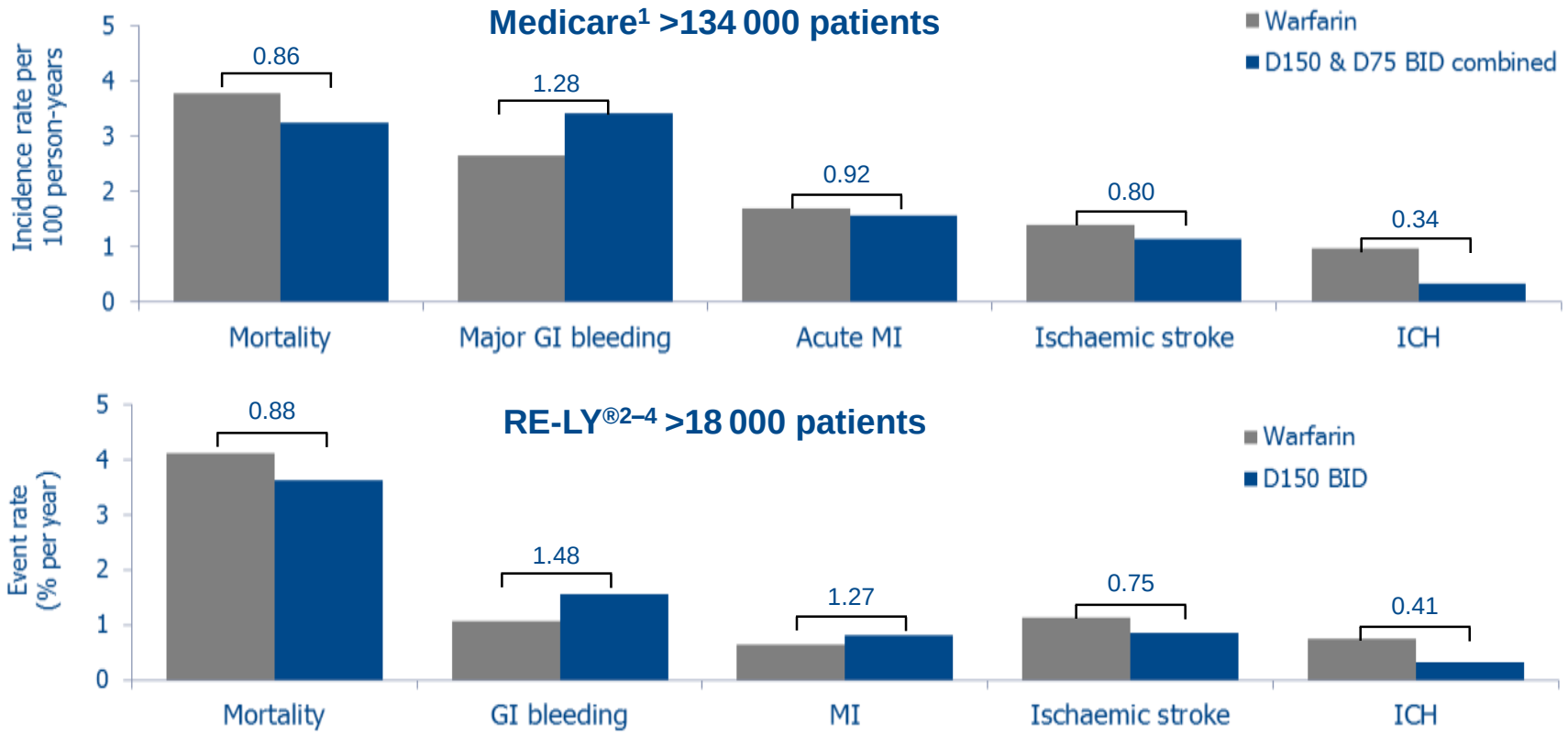
4. Giugliano RP et al, for the ENGAGE-AF TIMI 48 Investigators; *N Engl J Med*. 2013

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

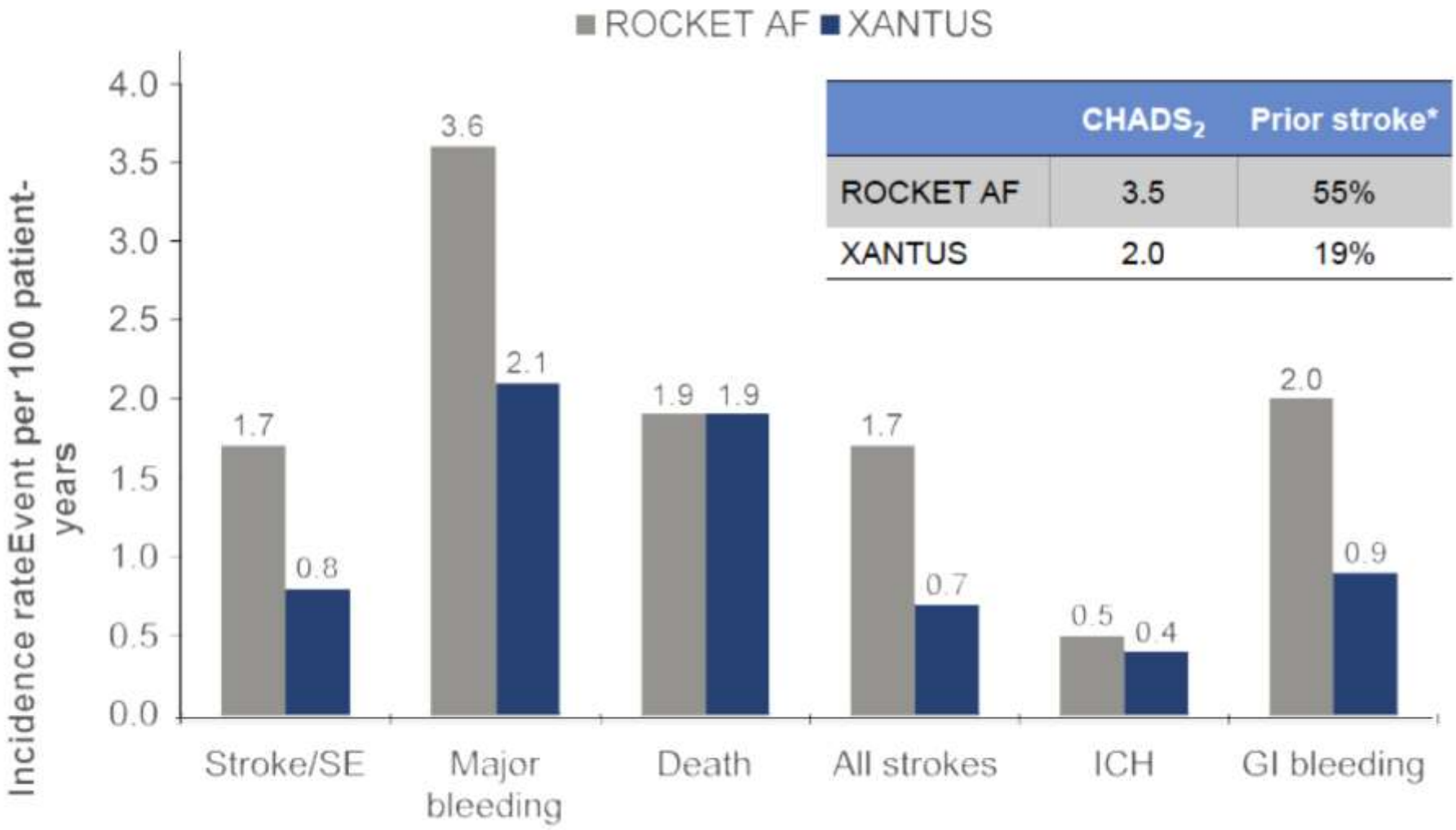
In the USA, the licensed doses for Pradaxa ® are: Pradaxa® 150 mg BID and Pradaxa ® 75 mg BID for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF

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

Comparison of Main Outcomes: XANTUS versus ROCKET AF

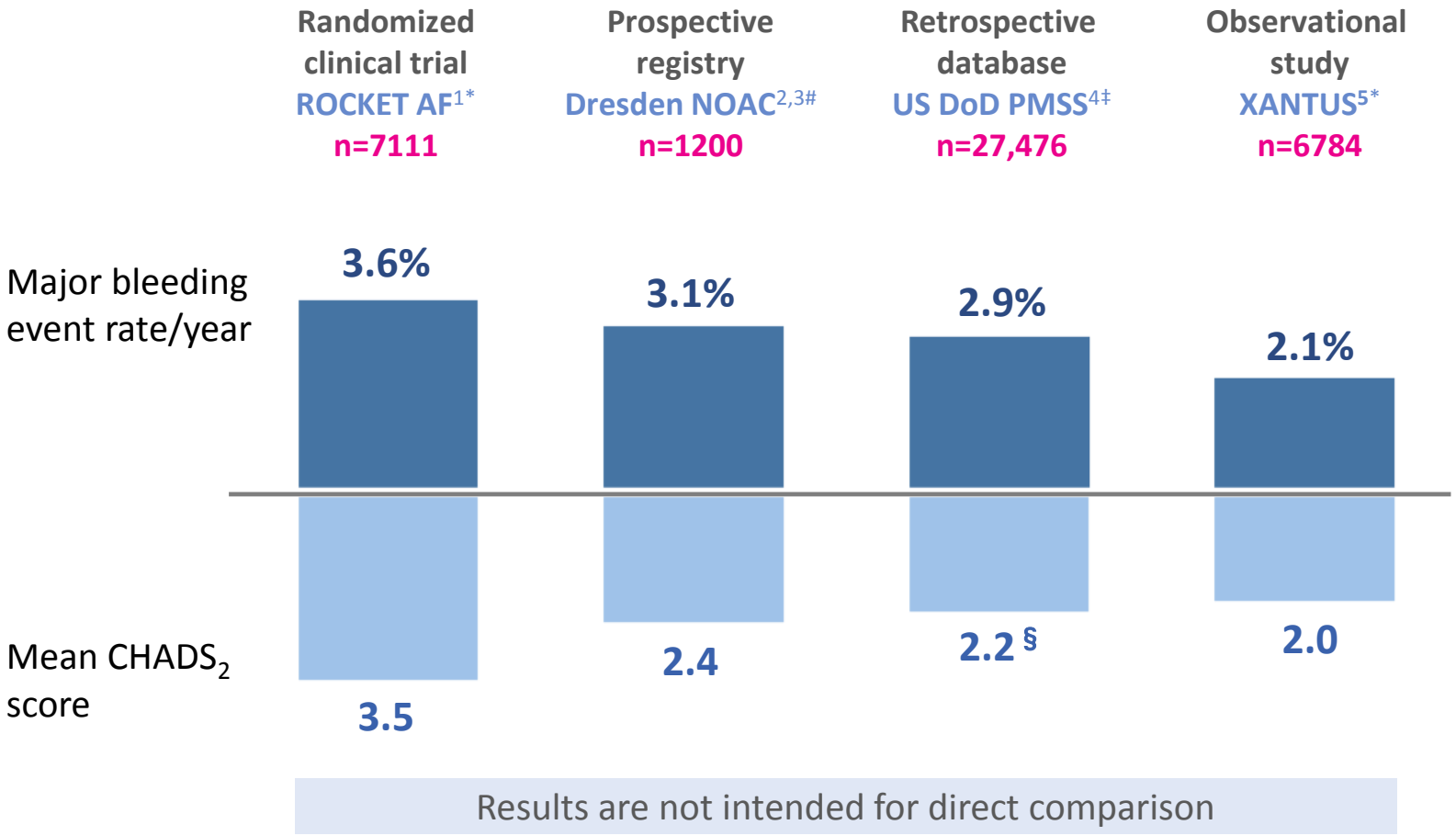
6784 patients



	$CHADS_2$	Prior stroke*
ROCKET AF	3.5	55%
XANTUS	2.0	19%

*Includes prior stroke, SE or TIA

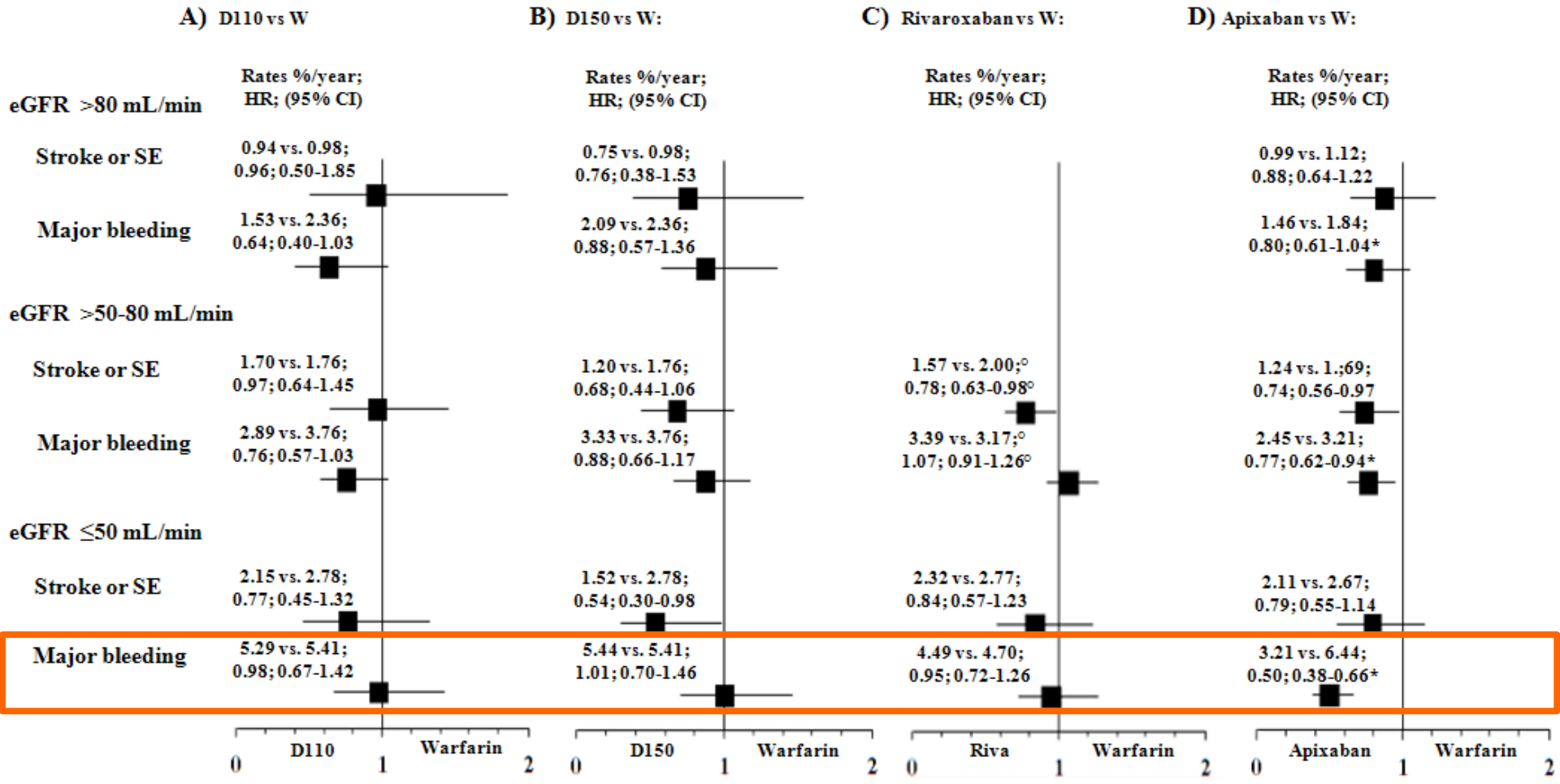
Safety Profile of Rivaroxaban Confirmed Through Real-World Evidence Regardless of Data Source



*Major bleeding definition according to ISTH; #modified ISTH definition (additionally included surgical revision from bleeding);
‡major bleeding defined by the Cunningham algorithm[6]; § No major bleeding cohort (representative of >98% of the patient population)

1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Beyer-Westendorf J *et al*, *Blood* 2014;124;955–962; 3. Beyer-Westendorf J *et al.* Presented at ESC 2013: abstract P4870; 4. Tamayo S *et al*, *Clin Cardiol* 2015;38:63–68; 5. Camm AJ *et al*, *Eur Heart J* 2015;doi:10.1093/eurheartj/ehv466;
6. Cunningham A *et al*, *Pharmacoepidemiol Drug Saf* 2011;20:560–566

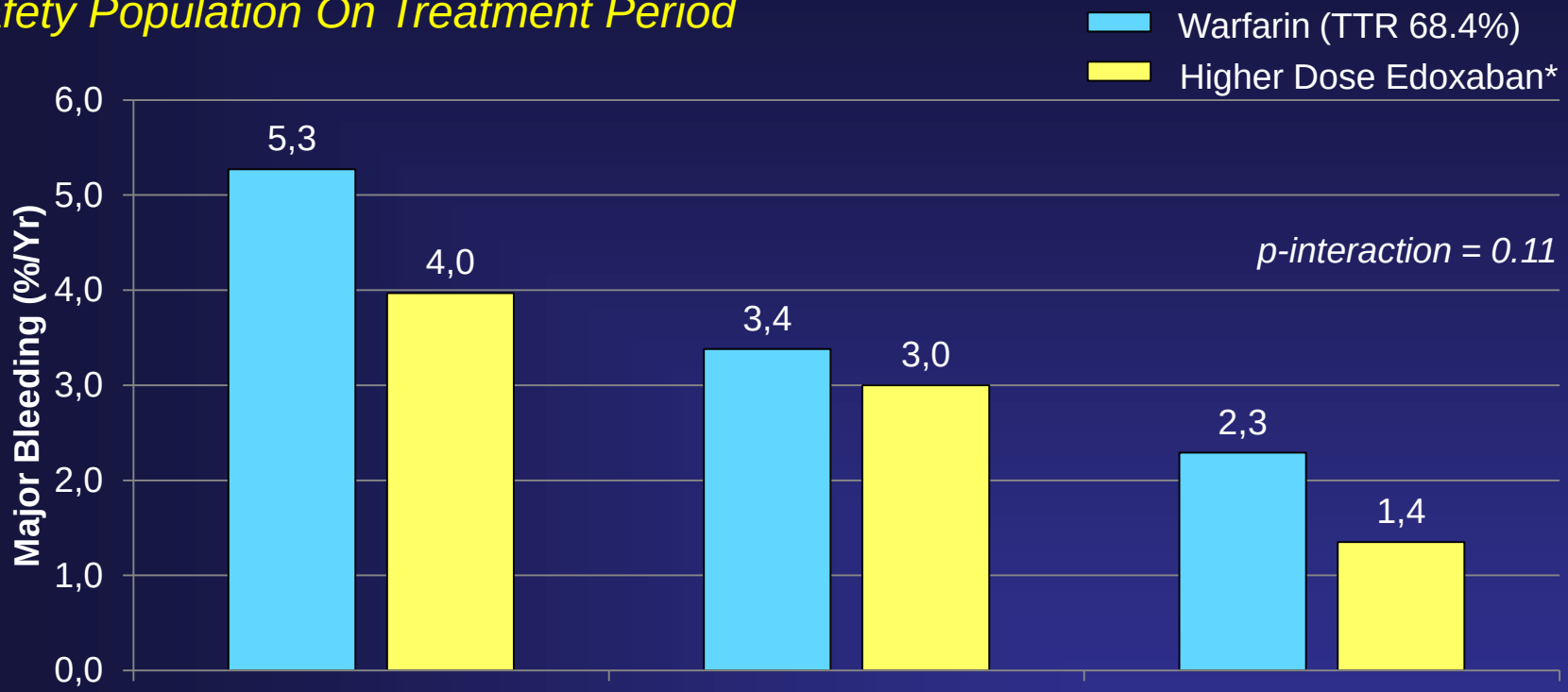
Efficacy and safety of NOACs vs W across levels of GRF



Capranzano P et al. Expert Rev Cardiovasc Ther. 2013;11:959-73

Major Bleeding by Exploratory CrCl Subgroup

Safety Population On Treatment Period

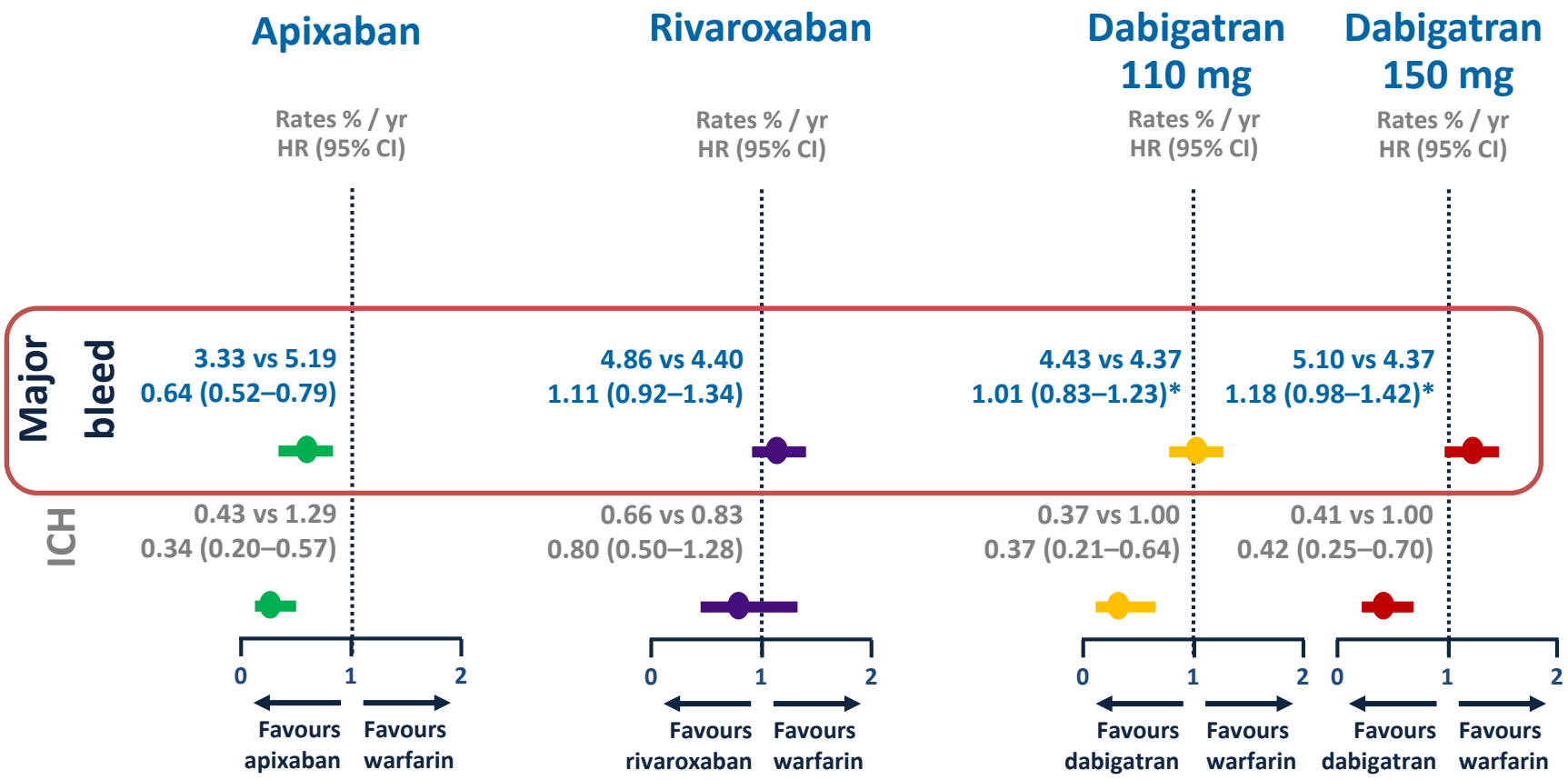


CrCl (mL/min)	≤50	>50-95	>95
N (%)	2728(20)	8177 (58)	3119 (22)
Warf Events	132	309	83
HD Edox Events	100	267	51
HR (95% CI)	0.76 (0.58, 0.98)	0.89 (0.75, 1.04)	0.60 (0.42, 0.85)

**60mg daily or 30mg if dose-reduced for CrCl≤50, weight ≤60kg or P-gp use*

Bohula et al., presented at AHA 2015

Safety of NOACs in elderly (> 75 years)

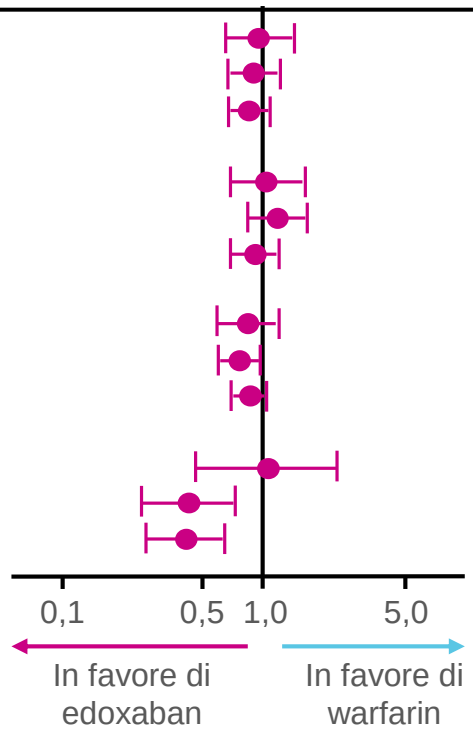


Capranzano P et al. Expert Rev Cardiovasc Ther 2013;11:959-73.

Caratteristiche dei pazienti nel trial ENGAGE AF - EDOXABAN

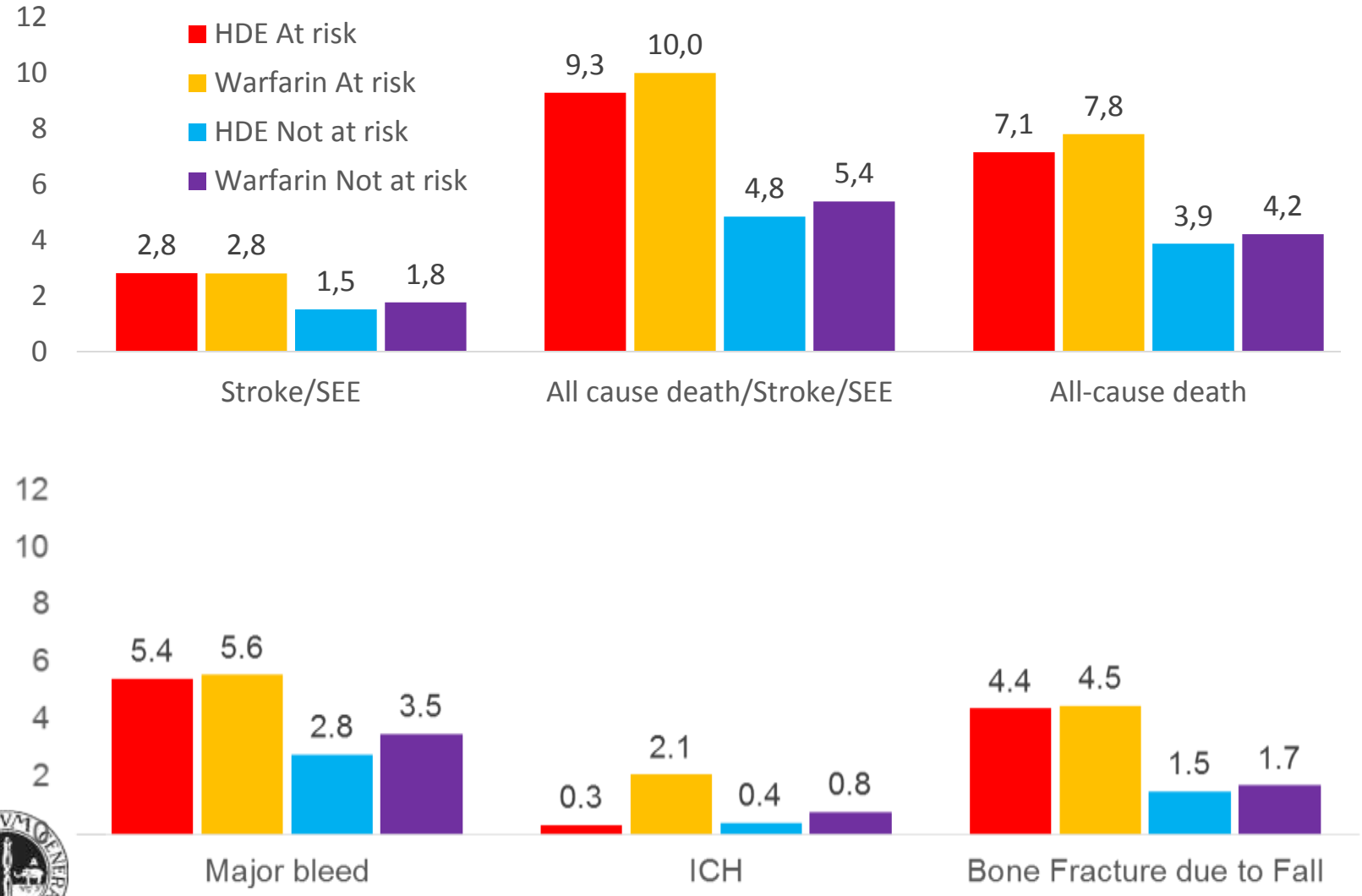
	<65 anni (N=5.497)	65–74 anni (N=7.134)	≥75 anni (N=8.474)
Sesso femminile (%)	27	39	45
Dislipidemia (%)	51	54	52
TTR con warfarin (%)	67	69	70
Punteggio $CHADS_2$ (medio)	2,6	2,7	3,2
Scompenso cardiaco congestizio (%)	70	63	45
Ipertensione (%)	94	94	93
Età media (anni)	59	70	79
Diabete (%)	41	43	28
Pregresso ictus o TIA (%)	28	33	25
Punteggio HAS - BLED ≥3 (%)	16	57	56
CrCl mediana (ml/min)	98	74	56
Peso mediano (kg)	91	83	76
Riduzione dose a randomizzazione (%)	10	18	41

Sicurezza ed efficacia di Edoxaban nei pazienti anziani



		Edoxaban 60 mg*	Warfarin
		Tasso di eventi (%/pz-anno)	
Ictus/SEE	<65 anni	1,1	1,1
	65–74 anni	16	1,8
	≥75 anni	1,9	2,3
Ischemico	<65 anni	0,9	0,9
	65–74 anni	1,3	1,1
	≥75 anni	1,5	1,7
Sanguinamento maggiore	<65 anni	1,5	1,8
	65–74 anni	2,5	3,3
	≥75 anni	4,0	4,8
ICH	<65 anni	0,3	0,3
	65–74 anni	0,4	0,96
	≥75 anni	0,5	1,2

Edoxaban versus Warfarin in Patients with an Increased Risk of Falls



Steffel et al., presented at AHA 2015

ESC AF guidelines 2016

When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.	IA
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).	IIb A
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III

NOACs outcomes

Study	Treatment	Major Bleeding	Emorragic Stroke	Discontinuation during the study
RE-LY	Dabigatran (110 mg)	2.71%	0.12%	20,7%
	Dabigatran (150 mg)	3.11%	0.10%	21,2%
	Warfarin	3.36%	0.38%	16,6%
ROCKET-AF	Rivaroxaban	3.6%	0.5%	23.7%
	Warfarin	3.4%	0.7%	22,2%
ARISTOTLE	Apixaban	2.13%	0.24%	25.3%
	Warfarin	3.09%	0.47%	nc

In elderly or in patients with moderate renal insufficiency major bleeding rate per year ranging from 3 to 5%

Strategies to minimize the risk of bleeding

- Adjusted dosage in high risk patients
- Preference of one NOAC over another in specific subgroups.
- Definition of specific follow-up management, especially in high-risk subgroups

Valutazione del rischio di sanguinamento in pazienti con FA

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Aged ≥80 years	Increased plasma level				
Aged ≥75 years	Increased plasma level				
Weight ≤60 kg	Increased plasma level				
Renal function	Increased plasma level				

Other increased bleeding risk

Pharmacodynamic interactions – antiplatelet drugs, NSAIDs

Systemic steroid therapy

Recent surgery on critical organ (brain, eye)

Thrombocytopenia (e.g. chemotherapy)

HAS-BLED ≥3 (Dabigatran 110 e Rivaroxaban 15 mg)

Red = contraindicated; Orange = adapt dose; Yellow = consider dose reduction if two concomitant yellow interactions present

Heidbuchel H et al. Europace 2015;

Underdosing and Thrombosis Risk

Analysis of claims in ~13,000 patients with NVAF within the Optum Labs Data Warehouse without any renal indication for dose adjustment.

NOAC*	Reduced Dose† Stroke/SE Rate (events/100 pt-y)	Standard Dose Stroke/SE Rate (events/100 pt-y)	HR (*P* Value) Standard Dose Is Reference
Apixaban (N = 550/dose)	2.57	0.54	4.87 (*P* = .02)
Dabigatran (N = 412/dose)	1.64	1.75	0.92 (*P* = .89)
Rivaroxaban (N = 815/dose)	1.23	1.65	0.71 (*P* = .54)

Patients more likely to receive a reduced dose (of any NOAC) were older, female, had higher stroke and bleeding risk.

*1:1 propensity-score matched reduced to standard-dose patients within each NOAC on 50 baseline characteristics.
†Renal dose adjustment (dabigatran users with GFR < 30 mL/min/1.73 m^2, rivaroxaban users with GFR < 50 mL/min/1.73 m^2, and apixaban users with Cr ≥ 1.5 mg/dL.

Yao X, et al. ISPOR 2016; Yao X, et al. *Value in Health.* 2016;19:A2.

Dose reduction in NOACs Trial

	RE-LY (Dabigatran)	ARISTOTLE (Apixaban)	ENGAGE AF-TIMI 48 (Edoxaban)	ROCKET-AF (Rivaroxaban)
Study Drug Dosage	150 and 110 mg	5 mg	21,105	14,266
Adjusted dose	No adjustment	2.5 mg BID	60/30	20/15
Characteristics requiring dose adjustment	-	If at least two of these conditions: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL	• CrCl 30–50 mL/min, • body weight ≤60 kg • patient receiving verapamil, quinidine or dronedarone	CrCl 30–49 mL/min
Patients with dose reduction	-	N=428	N=1784	N=1474

All NOACs are contraindicated when CrCl < 30 mL/min according to guidelines

Preference of one NOAC

- No reliable comparisons can be done. However it appears that apixaban and edoxaban are the safest in elderly and in patients with moderate renal insufficiency.

- With Edoxaban there are more possibilities to adjust dosage and this could turn useful in higher-risk patients.

- No specific guidelines recommendations regarding preference.

Checklist during follow-up contacts of AF patients on NOACs

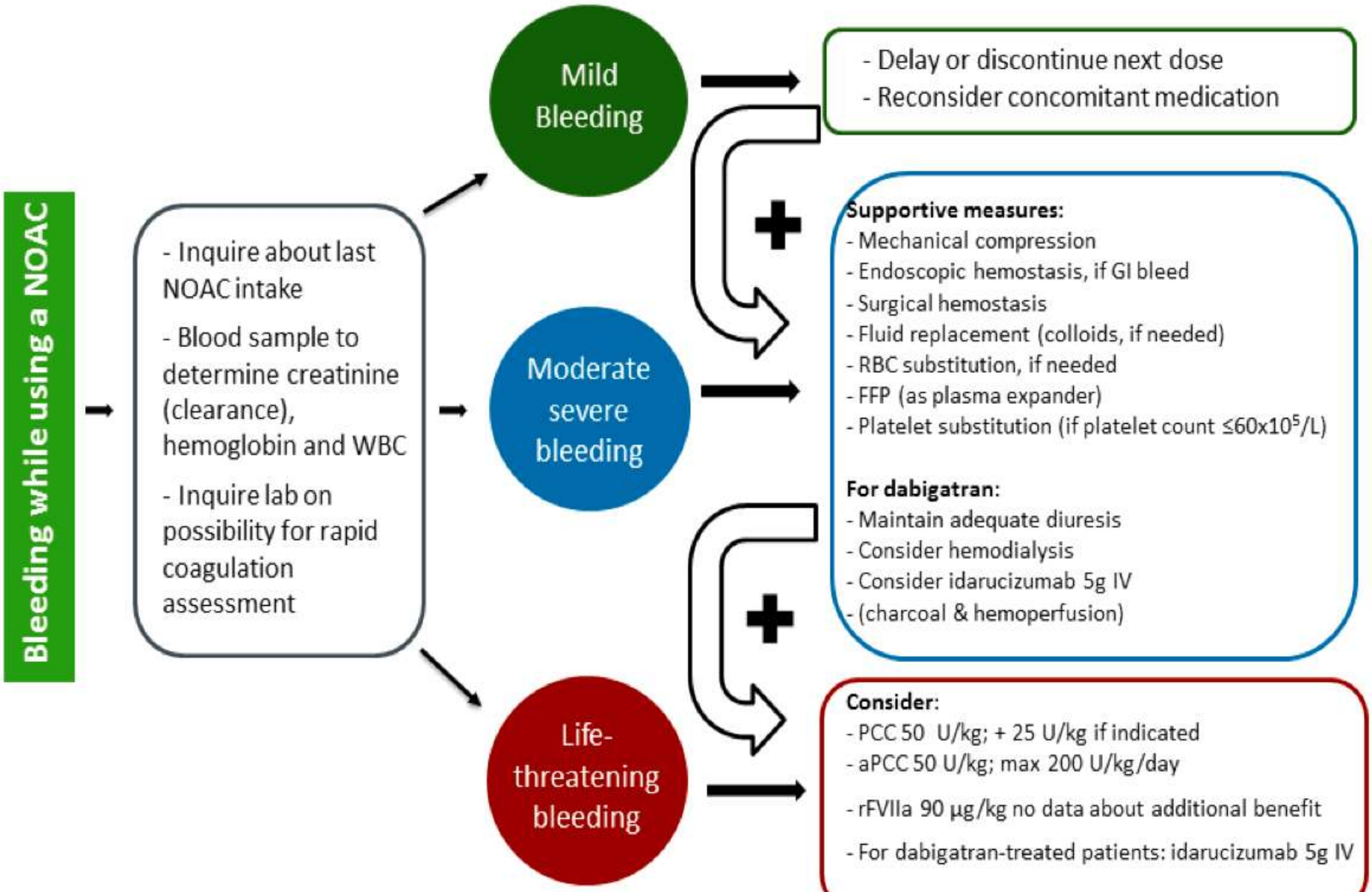
Adherence	
Side effects	
Co-medications	NSAID, antiplatelet, amiodarone, verapamil
Blood sampling	
Yearly	Haemoglobin, renal and liver function
6-monthly	≥75–80 years (especially if on dabigatran), or frail
X-monthly	If renal function ≤60 mL/min: recheck interval = CrCl/10
On indication	If intercurrent condition that may impact renal or hepatic function

ESC Guidelines 2016

In patients at high-risk of gastrointestinal bleeding, a VKA or another NOAC preparation should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily.	IIa	B

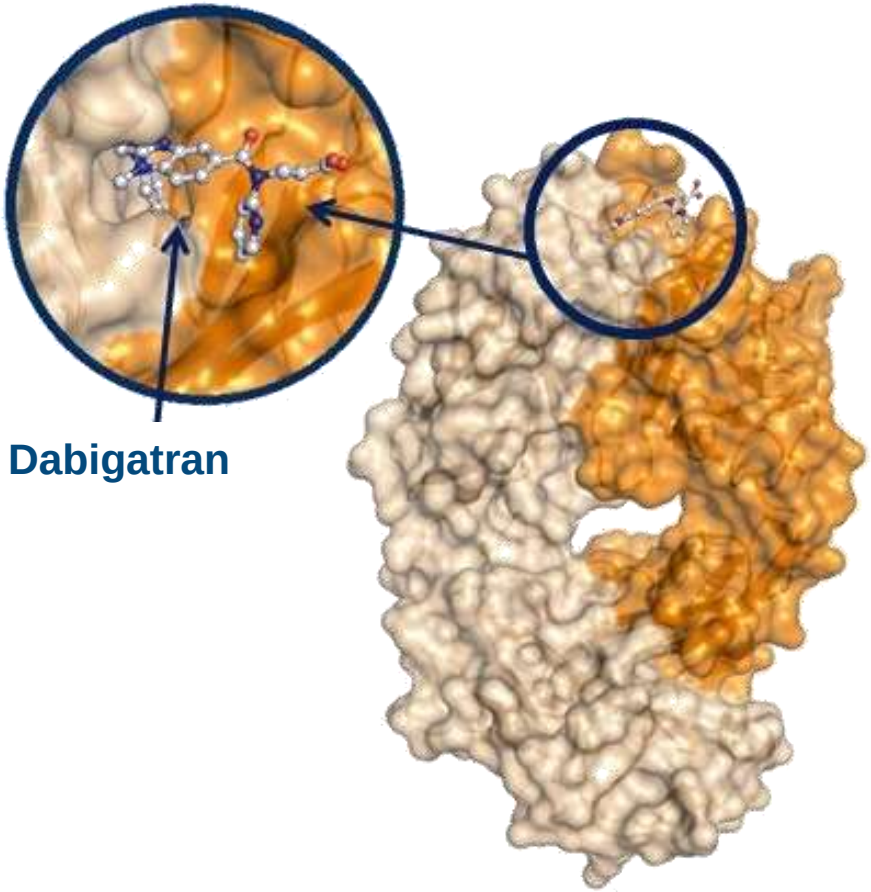
Prefer Dabigatran 110 or Apixaban 5

NOACs management of bleeding



Heidbuchel H, et al. *Europace*.2015. [Epub ahead of print]

Idarucizumab: a specific reversal agent for dabigatran



- Humanized Fab fragment
- Binding affinity for dabigatran **~350 × higher** than dabigatran to thrombin
- IV administration, immediate onset of action
- Short half-life
- No intrinsic procoagulant or anticoagulant activity

•Adapted from Schiele F et al. Blood 2013;
•Stangier J et al. ISTH 2015, OR320

Idarucizumab: EMA approved indications

- for emergency surgery/urgent procedures.
- In life-threatening or uncontrolled bleeding.

Pollack C et al. N Engl J Med 2015; 373:511-20.

Management of bleeding in dabigatran and W

	Dabigatran* (16775 pz)	Warfarin (10002 pz)	P value
Patients with major bleeds, n (%)	741 (4)	421 (4.2)	
Blood transfusion, n (%)	439 (59.2)	210 (49.9)	0.002
Fresh frozen plasma, n (%)	147 (19.8)	127 (30.2)	<0.001
Vitamin K, n (%)	70 (9.4)	115 (27.3)	<0.001
Prothrombin complex concentrate, n (%)	5 (0.7)	5 (1.2)	0.36
Recombinant Factor VIIa, n (%)	8 (1.1) (0.04)	3 (0.7) (0.03)	0.53

Conclusions

- NOACs offers important clinical benefits, also in more vulnerable patients.
- NOACs allowed to treat more risky patients.
- Bleeding and thrombotic risk still persist with NOACs.
- Several strategies could be useful to optimize outcomes with NOACs, but they are still not established.
- Compliance to NOACs remains an important issue to be addressed.