Come e perché scelgo tra i vari anticoagulanti diretti?

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Varese

Conflitti di interesse

- Supporto alla ricerca: Bayer Healthcare, Boehringer Ingelheim
- Advisory Boards: Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, BMS-Pfizer
- Fees per letture a congressi: Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, BMS-Pfizer, Stago, Aspen

Attuali indicazioni ai farmaci anticoagulanti orali diretti

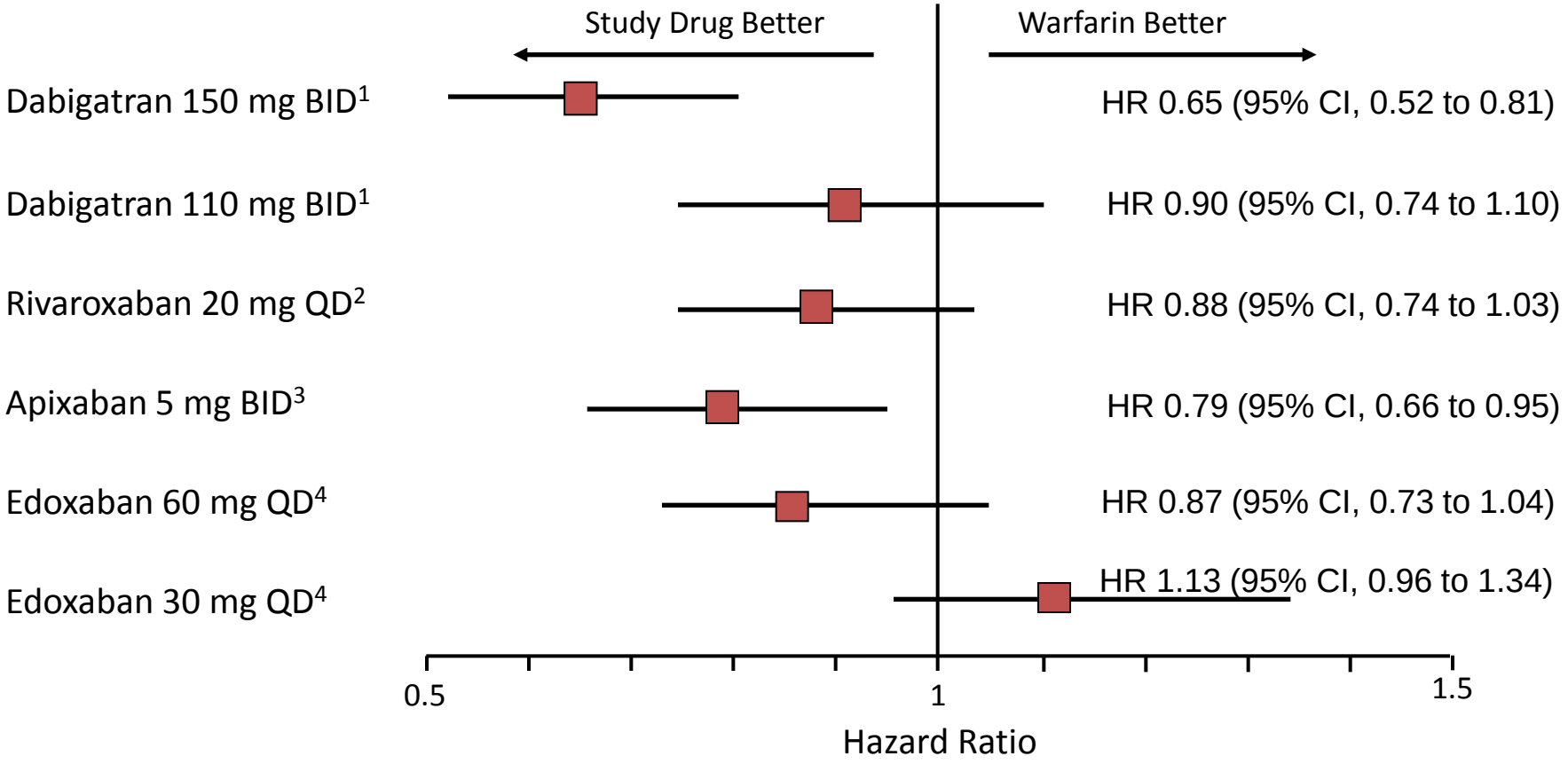
- Prevenzione dell'ictus nei pazienti con fibrillazione atriale non valvolare (tutti)
- Sindromi coronariche acute (rivaroxaban)

- Prevenzione del tromboembolismo venoso in pazienti sottoposti a chirurgia protesica di anca e ginocchio (apixaban, dabigatran, rivaroxaban)
- Terapia acuta e prevenzione secondaria di TVP ed embolia polmonare (tutti)

Come scegliere tra i vari anticoagulanti orali diretti

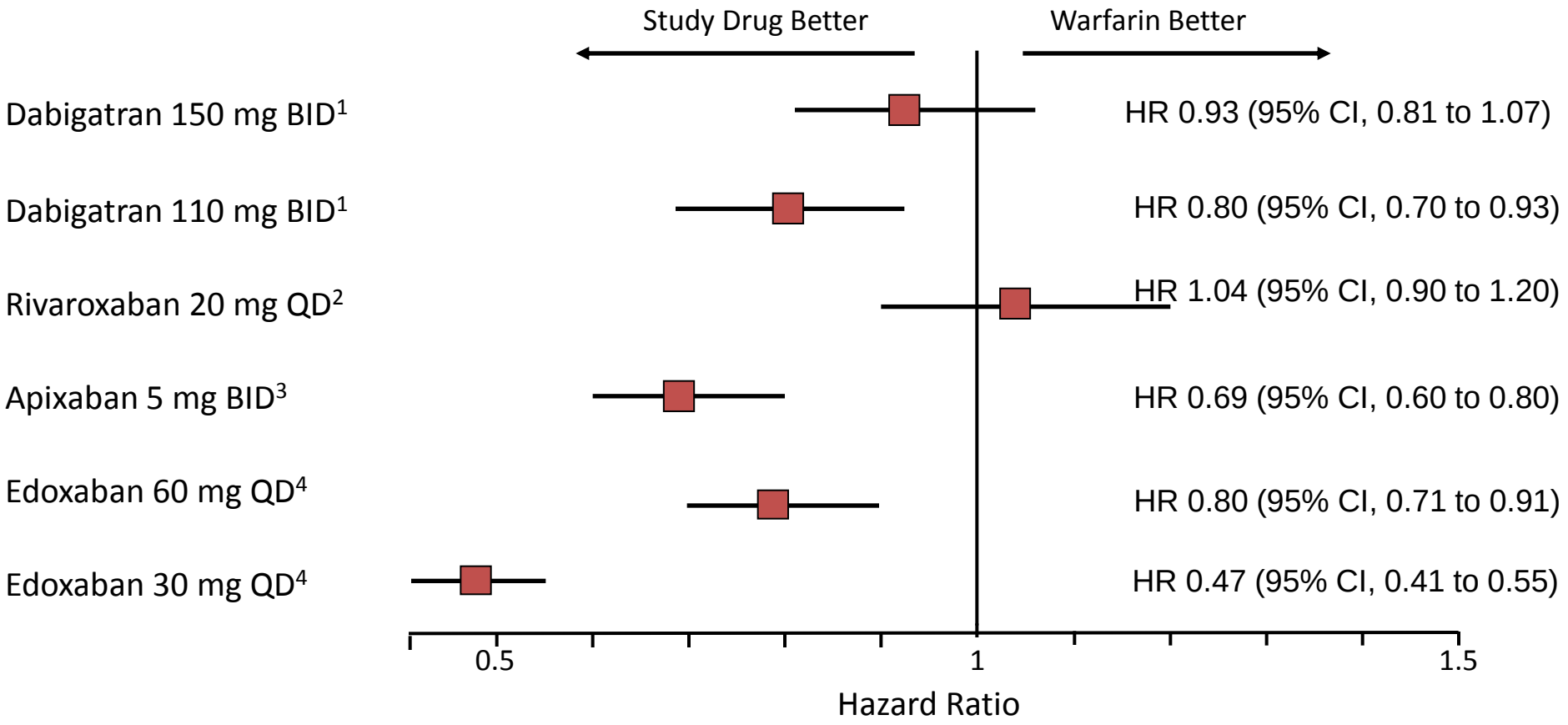
- Valutando i risultati degli studi registrativi
  - Punti di forza e punti di debolezza negli studi
- Valutando i risultati degli studi post-marketing
  - Confronti diretti e indiretti
- Valutando le caratteristiche delle molecole
  - Vie di eliminazione, interferenze, reversibilità
- Valutando aspetti pratici
  - Frequenza di somministrazione, tollerabilità

Direct Oral Anticoagulants Compared to Warfarin: Stroke or Systemic Embolism



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; NEJM; 2013, doi: 10.1056/NEJMoa1310907

Direct Oral Anticoagulants Compared to Warfarin: Major Bleeding

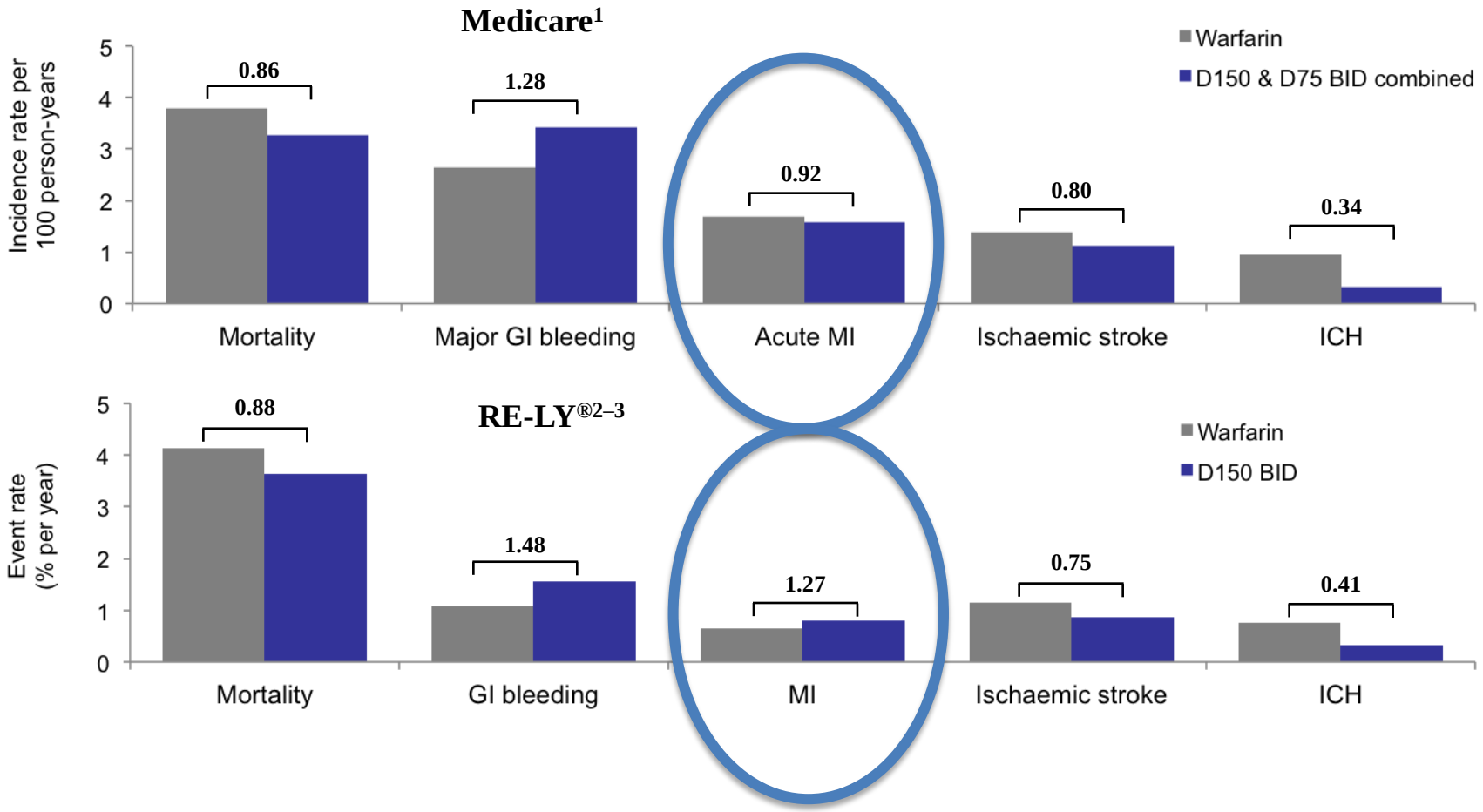


1. Connolly SJ et al. N Engl J Med. 2010;363:1875-1876.
2. Patel MR et al. N Engl J Med. 2011;365:883-891.
3. Granger CB et al. N Engl J Med. 2011;365:981-992.
4. Giugliano RP et al, for the ENGAGE-AF TIMI 48 Investigators; NEJM; 2013, doi: 10.1056/NEJMoa1310907

Principali messaggi dagli studi: fibrillazione atriale

- Superiorità/equivalenza in efficacia
- Dabigatran 150 mg bid riduce ictus ischemico
- Superiorità/equivalenza in sicurezza
- Maggior incidenza emorragie digestive (tranne apixaban)
- Aumentata incidenza cardiopatia ischemica (dabigatran)
- Significativa riduzione emorragie intracraniche
- Simile riduzione mortalità

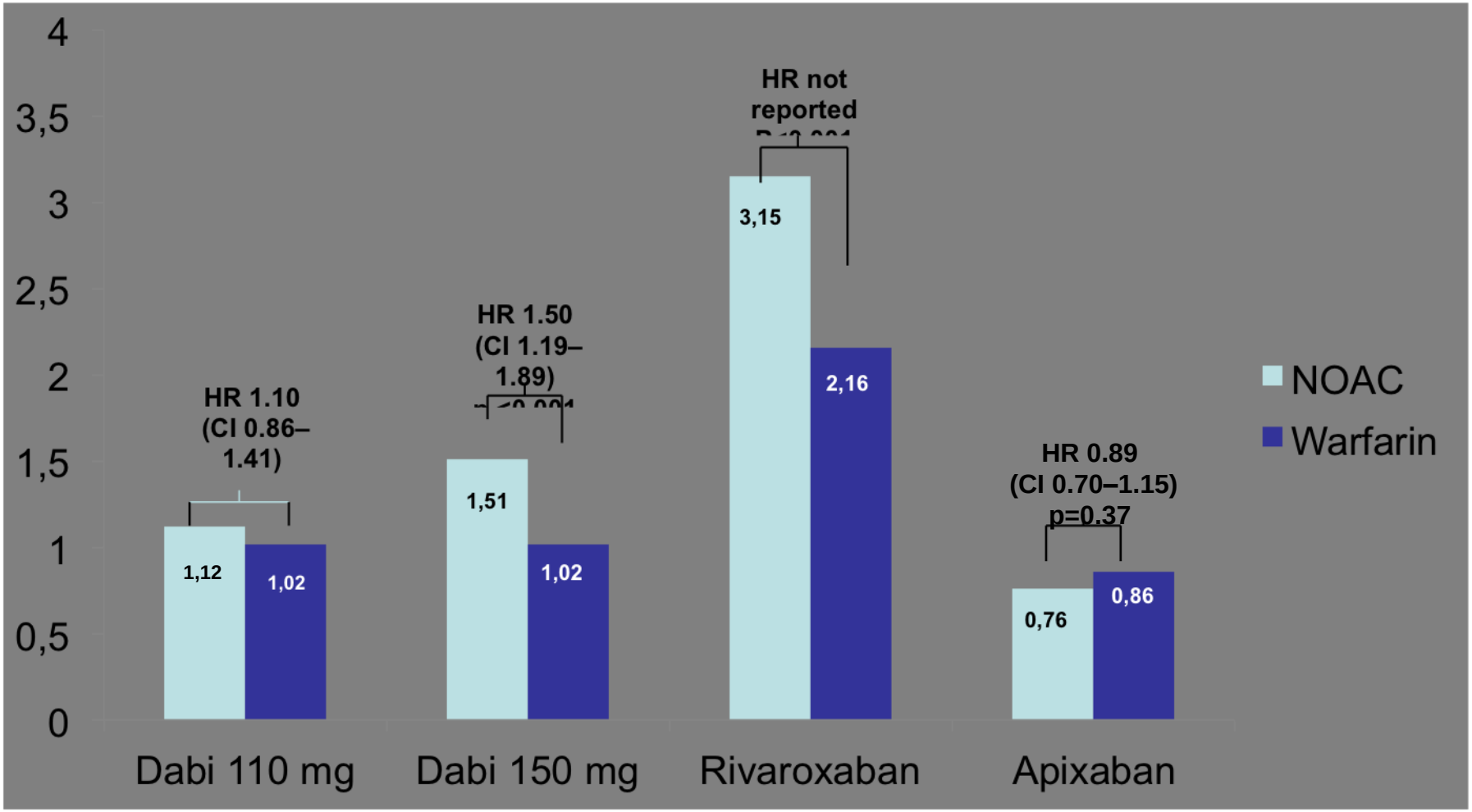
Independent FDA Medicare analysis and findings from RE-LY®



Numbers on bars denote HRs vs warfarin. D75 = dabigatran 75 mg; D150 = dabigatran 150 mg

1. Graham DJ et al Circulation 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

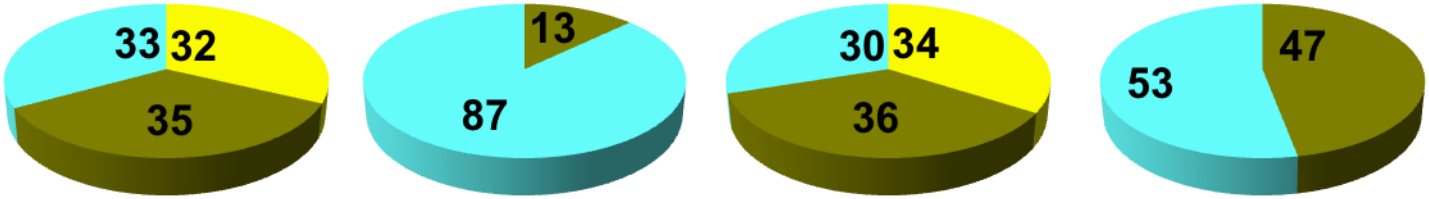
GI bleeding in NOACs clinical trial



Granger GB et al. N Engl J Med. 2011 Sep 15;365(11):981-92
Patel RM et al. N Engl J Med. 2011 Sep 8;365(10):883-91
Connolly JS et al. N Engl J Med 2009;361:1139-51

Baseline Characteristics: 4 Trials

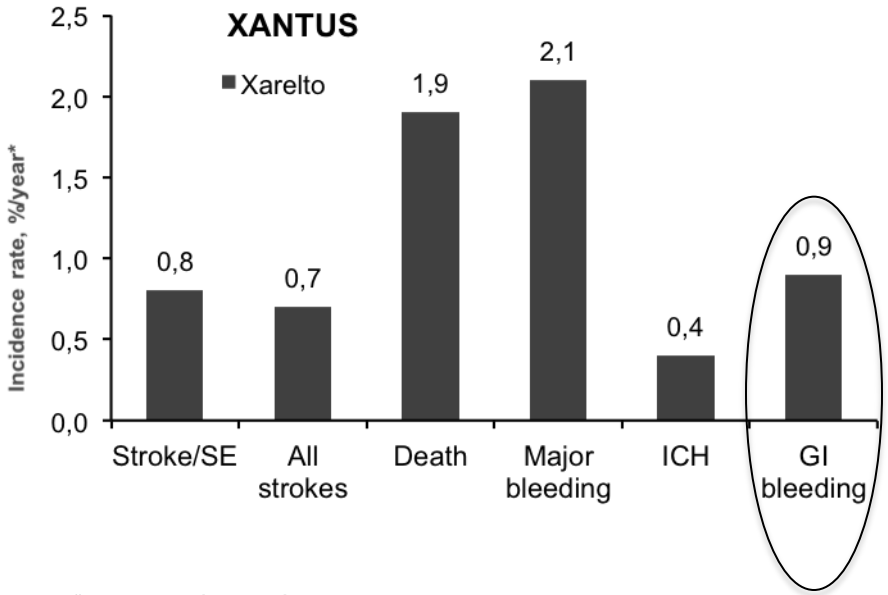
	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF (Edoxaban)
# Randomized	18,113	14,264	18,201	21,105
Age, years	72 ± 9	73 [65-78]	70 [63-76]	72 [64-78]
Female, %	37	40	35	38
Paroxysmal AF	32	18	15	25
VKA naive	50	38	43	41
Aspirin Use	40	36	31	29
$CHADS_2$				
0-1	33	13	30	47
2	32	87	34	53
3-6	35		36	
Median TTR	**66**	**58**	**66**	**68**

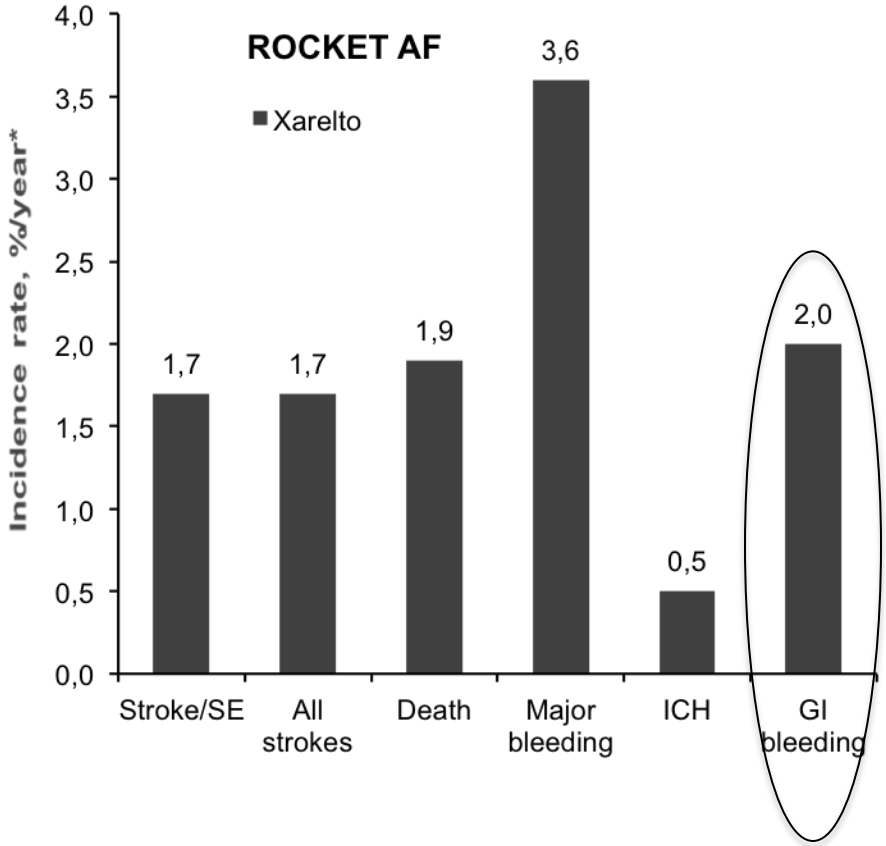


Gonzalez-Quesada CJ. Am J Cardiovasc Drugs 2014 ;14:111-27 Ruff CT,.Lancet 2014;383:955-962

Comparison of Main Outcomes: XANTUS versus ROCKET AF

	$CHADS_2$	Prior stroke#
ROCKET AF[1]	3.5	55%
XANTUS[2]	2.0	19%



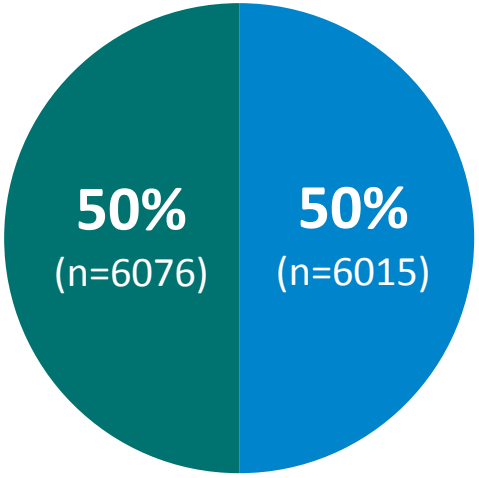


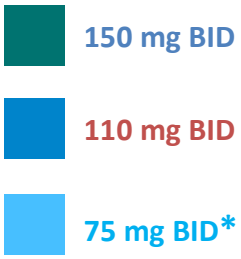
#Includes prior stroke, SE or TIA; *Events per 100 patient-years

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

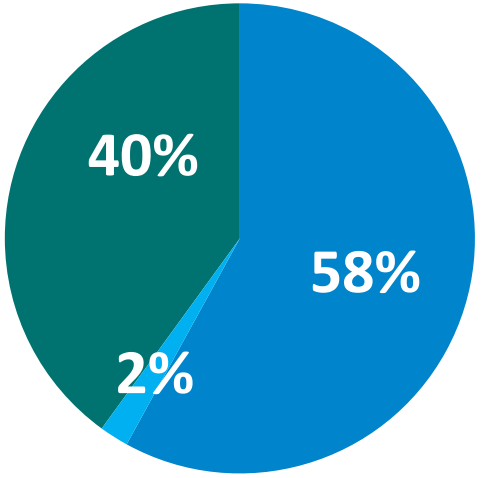
Dabigatran 110 mg BID is used more widely in clinical practice

RE-LY®[1]





Prescription data[2,3]

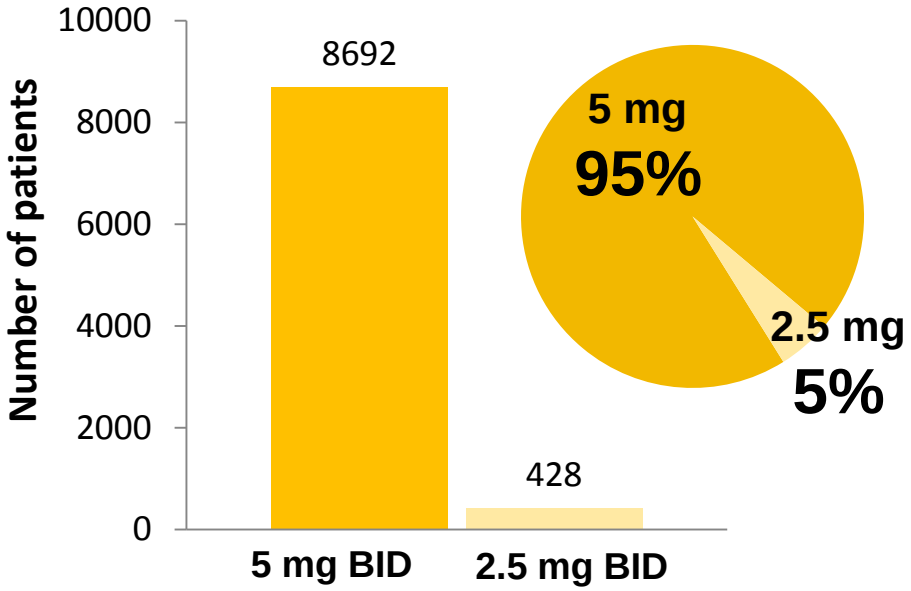


(All indications; IMS data June 2014–June 2015)

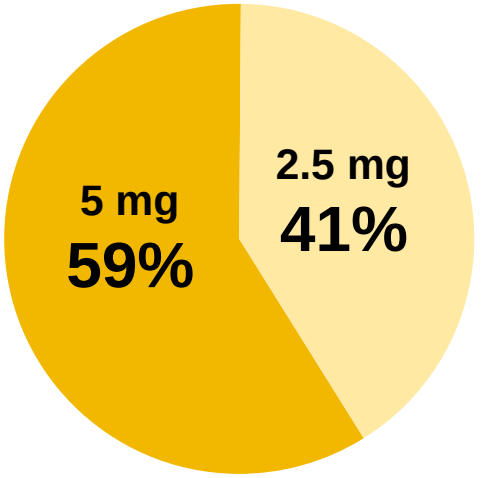
1. Connolly et al. N Engl J Med 2009; 2. BI, Data on file: DBG 15–04; 3. IMS Information Solutions UK Ltd. Patient data, June 2015

Apixaban 2.5 mg dose is used more widely in clinical practice

ARISTOTLE[1]



Prescription data[2]

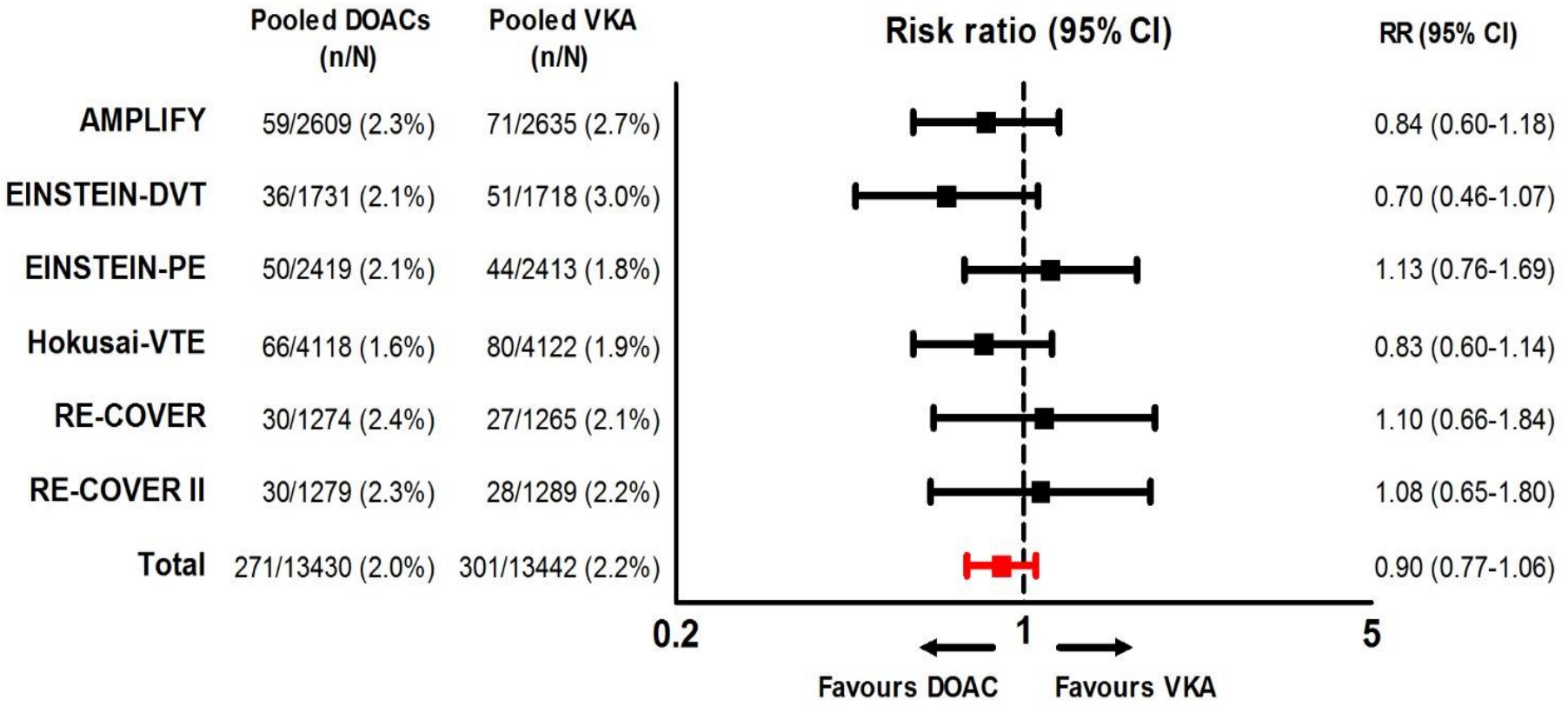


(All indications; IMS data June 2014–June 2015)

*Dose reduction to 2.5 mg BID if ≥2 criteria: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL (133 µmol /L).

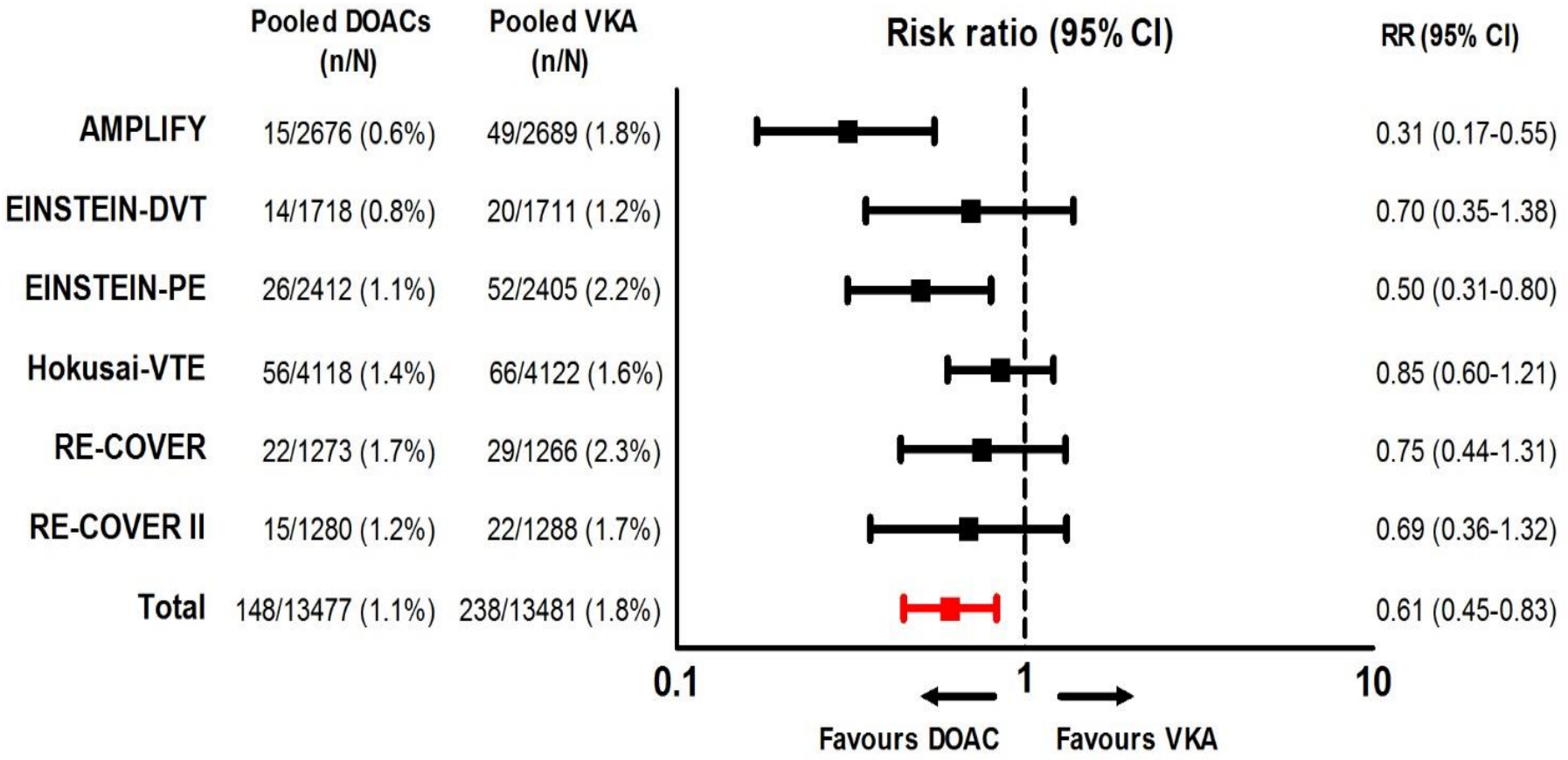
1. Granger et al. N Engl J Med 2011; 2. IMS Information Solutions UK Ltd. Patient data, June 2015; 3. Halvorsen et al. Eur Heart J 2014

DOAC Phase III VTE trials
Primary efficacy endpoint



van Es et al Blood 2014

DOAC Phase III VTE trials
Major bleeding

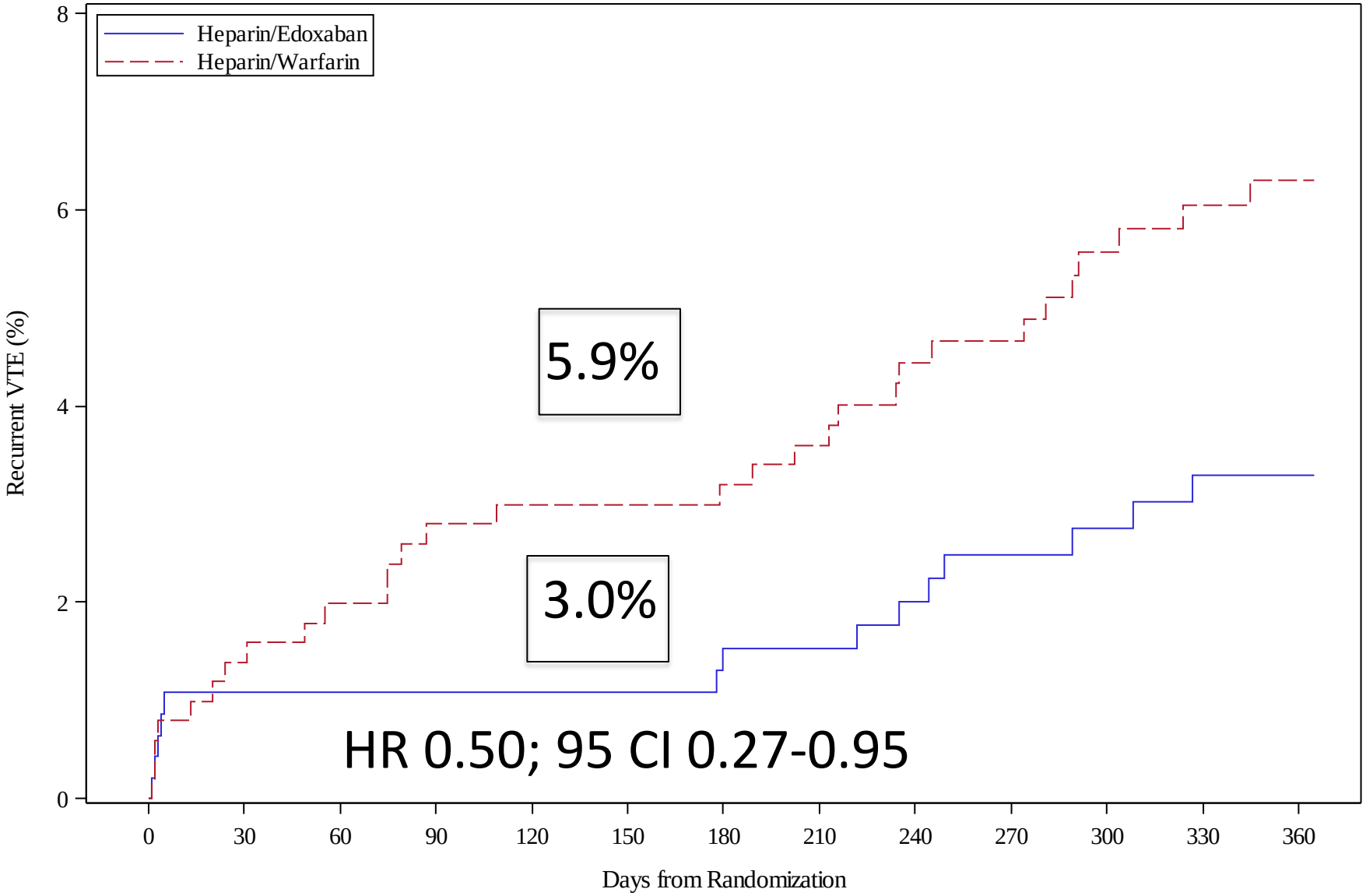


van Es et al Blood 2014

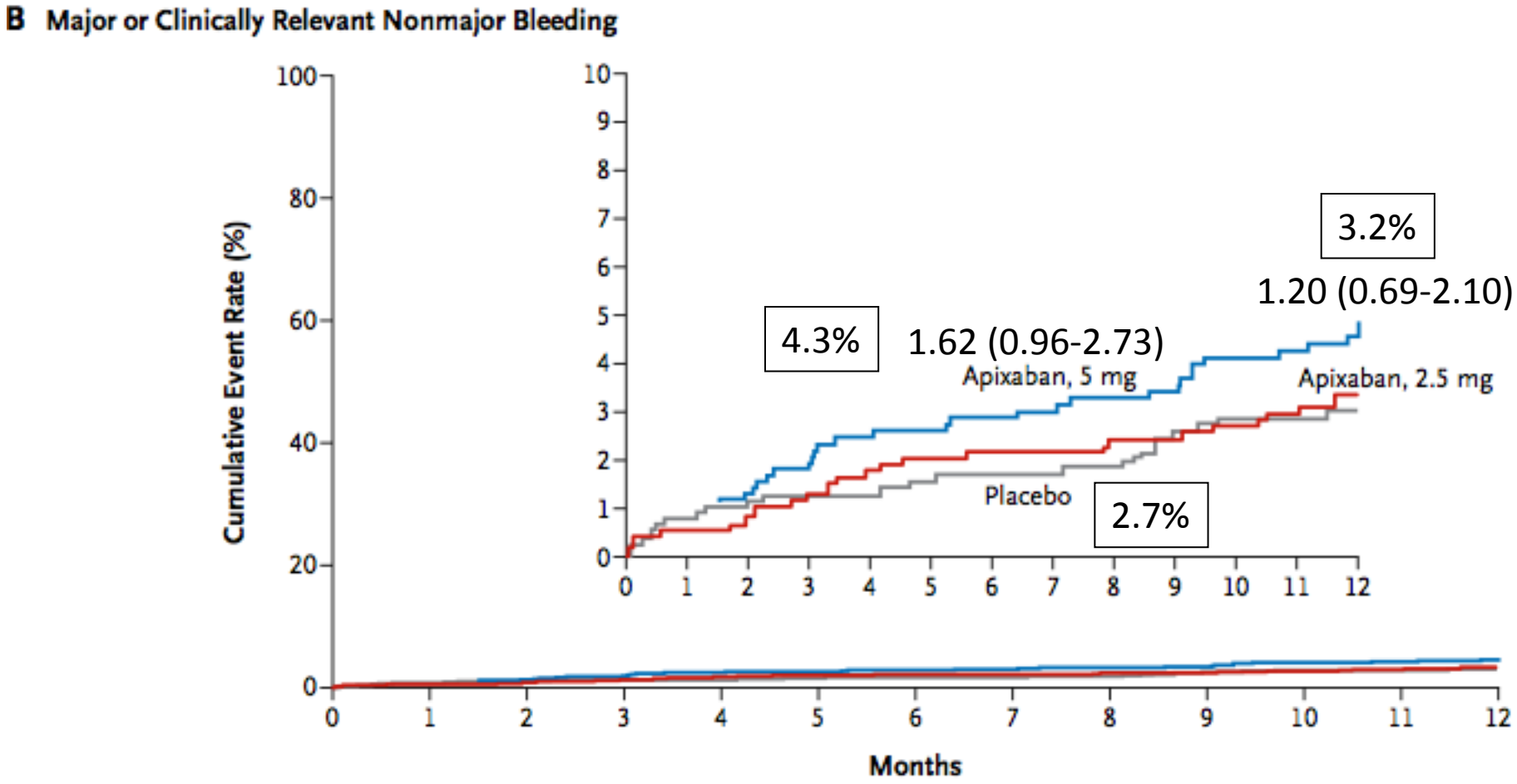
Principali messaggio dagli studi: tromboembolismo venoso

- Disegni diversi: eparina nei primi 5-7 giorni (dabigatran-edoxaban) vs terapia orale da subito (rivaroxaban-apixaban)
- Difficile valutazione dei pazienti con embolia polmonare: livello di rischio?
- Pazienti candidati ad una prevenzione secondaria a lungo termine: riduzione del dosaggio?

Hokusai study: Subgroup analysis in PE patients with NT-proBNP ≥500 pg/mL



AMPLIFY-Extension safety results

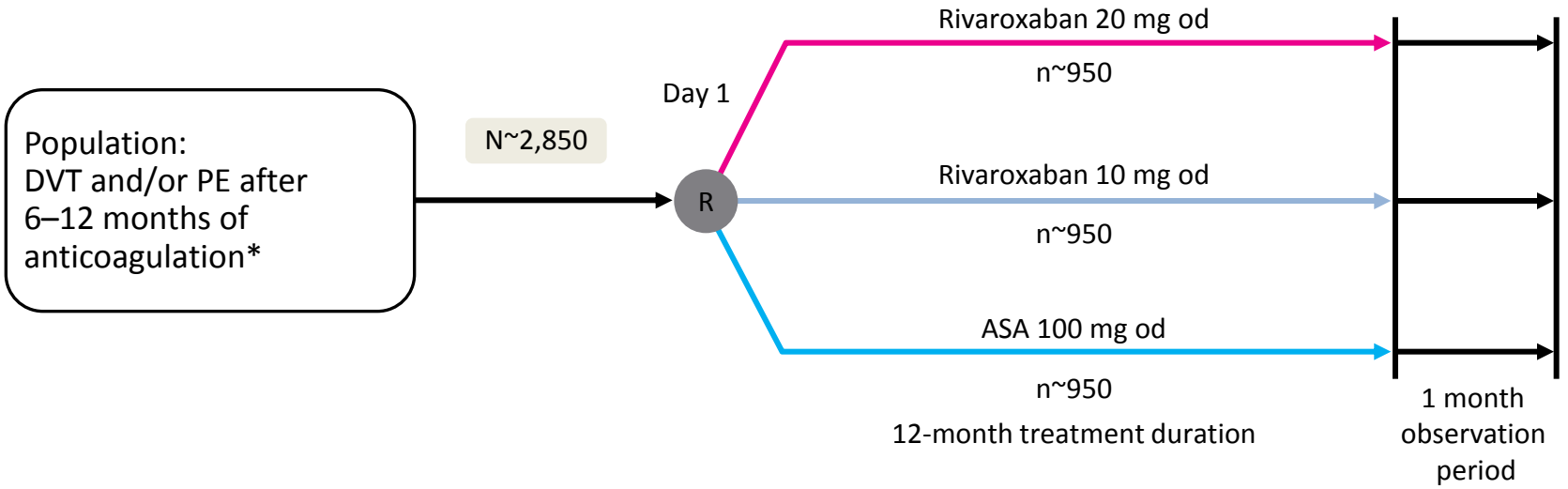


Agnelli et al N Engl J Med 2012

EINSTEIN CHOICE
Long-Term Secondary VTE Prevention Study

Official study title: Reduced-dosed Rivaroxaban and Standard-dosed Rivaroxaban Versus ASA in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-vein Thrombosis and/or Pulmonary Embolism

Objective: efficacy and safety of reduced-dosed rivaroxaban, standard-dosed rivaroxaban versus ASA for the long-term secondary prevention of recurrent symptomatic VTE in patients with symptomatic DVT and/or PE



Short design: Multicentre, randomized, double-blind, active-controlled, event-driven, superiority study

Indication: VTEx

FPFV: Q1-14
LPLV: Q4-16

*Completed 6–12 months (±1 month) with interruption of anticoagulation ≤1 week at randomization

www.clinicaltrials.gov/ct2/show/NCT02064439 Weitz JI et al. Thromb Haemost 2015

EINSTEIN CHOICE

PK/PD of the 4 DOACs

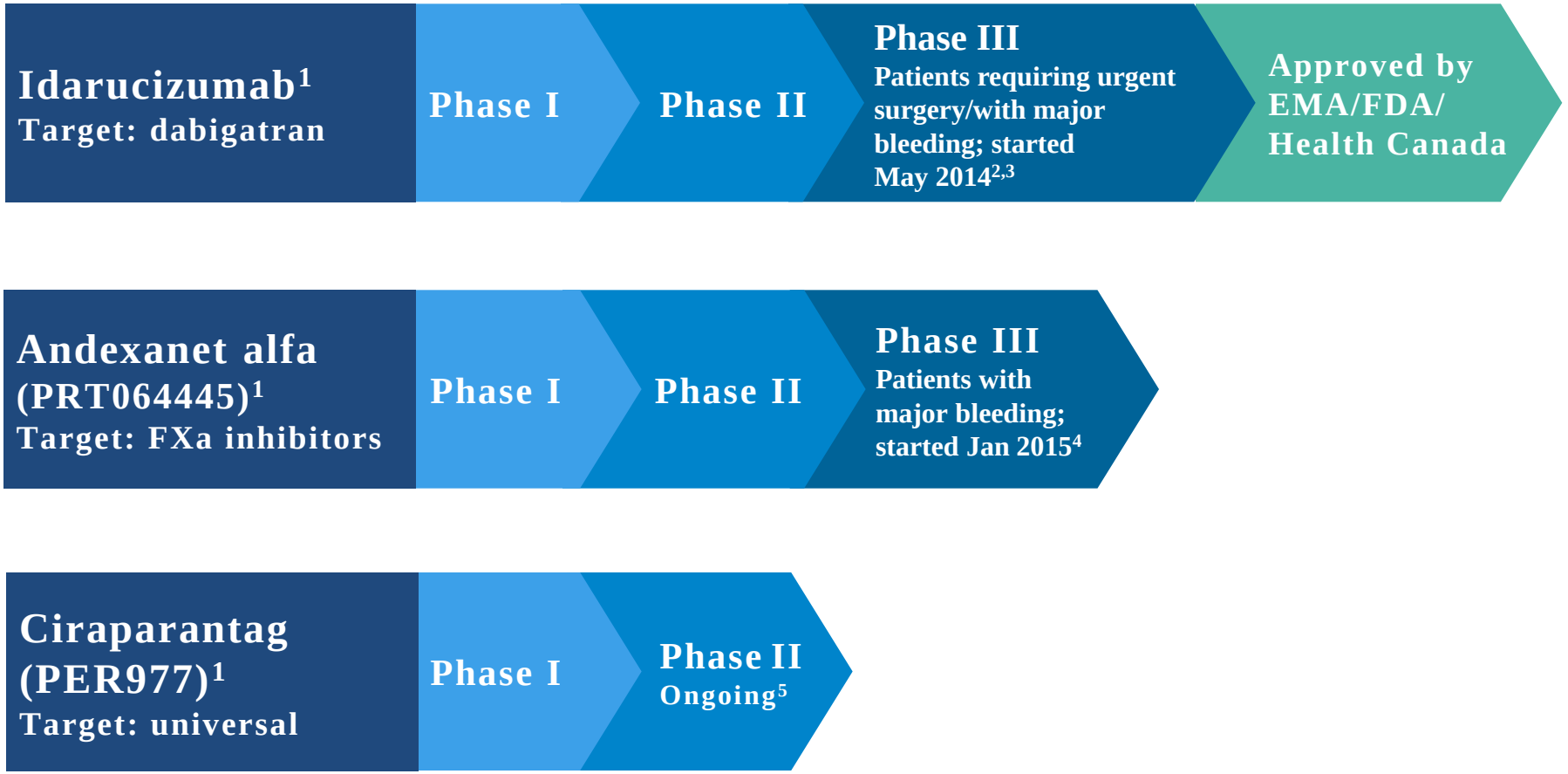
	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)
Target	IIa (thrombin)	Xa	Xa	Xa
Hrs to Cmax	2	2-4	1-3	1-2
CYP metabolism	None	32%	15%	<4%
Bioavailability	7%	80%	66%	62%
Transporters	P-gp	P-gp/BCRP	P-gp	P-gp
Protein binding	35%	>90%	87%	55%
Half-life	12-14h	9-13h	8-15h	10-14h
Renal elimination	80%	66%*	27%	50%

*Approximately half of which s excreted unchanged in the urine

BCRP = breast cancer resistance protein; CYP = cytochrome P450; NR = not reported; P-gp = P-glycoprotein

Gonzalez-Quesada CJ. Am J Cardiovasc Drugs 2014 ;14:111-27
Plitt A. JCPT 2014 (on-line doi: 10.1177/1074248414523675)
Grip LT. Hot Topics 2013:31:7-18
Ericksson BI. Clin Pharmacokinet 2009; 48: 1-22

DOAC reversal agents in development



DOAC reversal agents are investigational compounds under development and have not been approved for use in the EU.

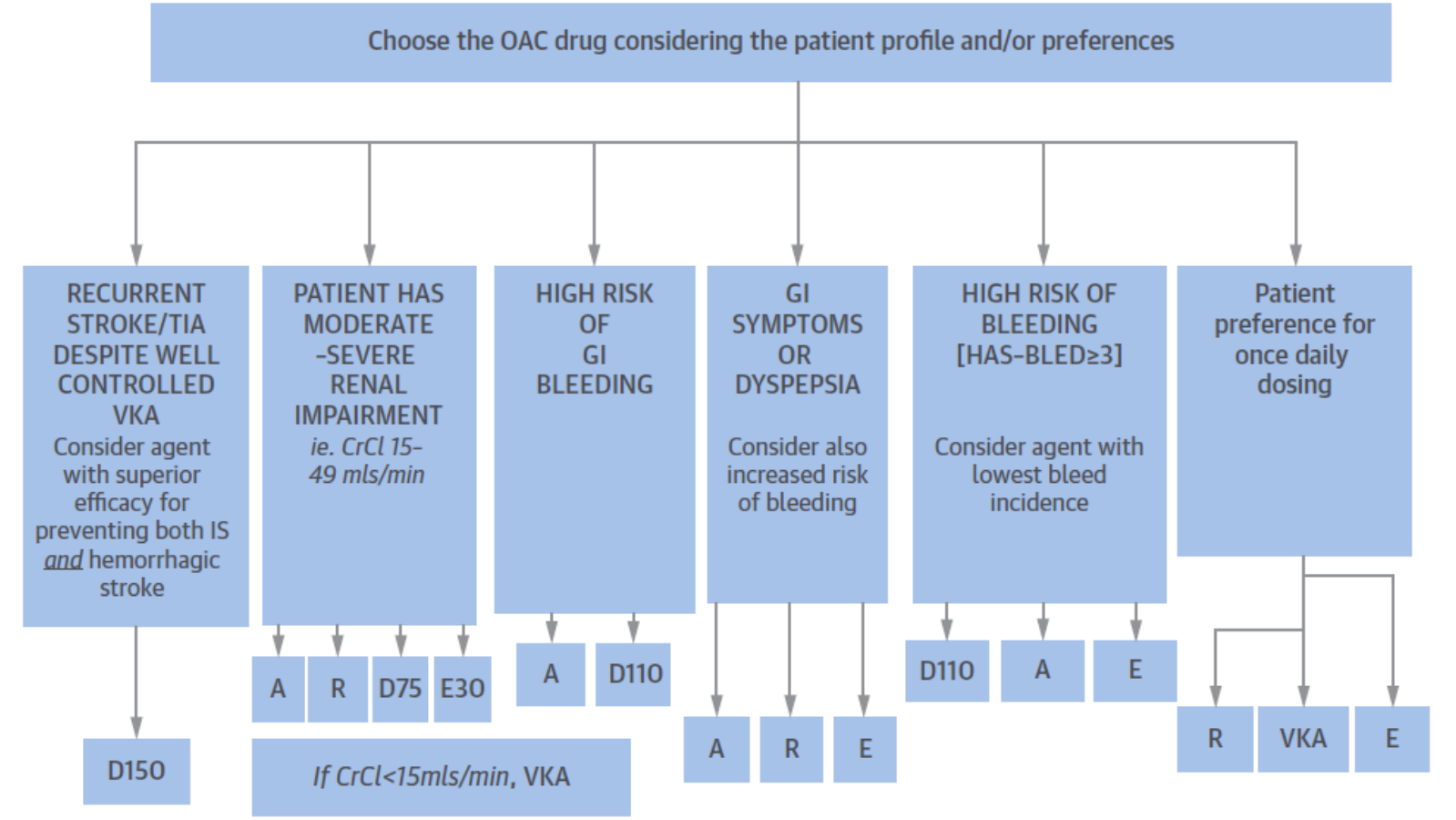
1. Adapted from Greinacher A et al. Thromb Haemost 2015;113:931–42;
2. Clinicaltrials.gov: NCT02104947; 3. Pollack CV et al. Thromb Haemost. 2015;114:198–205;
4. ClinicalTrials.gov Identifier: NCT02329327; 5. ClinicalTrials.gov Identifier: NCT02207257

Altri aspetti nella scelta del farmaco

- Monosomministrazione vs doppia somministrazione (praticità vs stabilità?)
- Intolleranza gastrica con dabigatran
- Aumento sanguinamenti vaginali con rivaroxaban (e gli altri?)

Impatto sull'aderenza al trattamento?

Selecting the Optimal Oral Anticoagulant for Stroke Prevention in Atrial Fibrillation: some suggestion for Initial Treatment Options



A = apixaban; CrCl = creatinine clearance; D = dabigatran (D75, 75 mg bid does in United States only; D110 = 110 mg bid dose, not in the United States); E = edoxaban; E30 = edoxaban 30 mg; GI = gastrointestinal; IS = ischemic stroke; OAC = oral anticoagulation; R = rivaroxaban; TIA = transient ischemic attack; VKA = vitamin K antagonist.

Lip GYH and Lane J Am Coll Cardiol 2015 Dec 1;66(21):2282-4