SIMPÓSIO DE MEDICINA
CARDIOVASCULAR DE COIMBRA 2018

11 e 12
MAIO 2018
VILA GALÉ COIMBRA

Cursos Pré-Simpósio
10 MAIO

Hipocoagulação oral, quando, a quem, com quê? Como reagir em caso de hemorragia?

Serviço de Cardiologia
Centro Hospitalar de Leiria

ESC European Society of Cardiology

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

João Morais
Centro Hospitalar de Leiria

Disclosures related with current topic

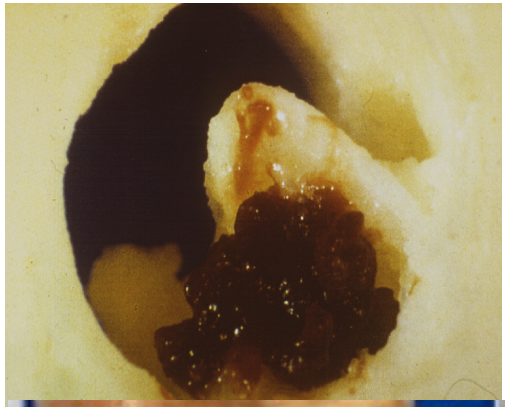
João Morais

Consulting and lecture fees (last two years)
Bayer Healthcare; Boheringer Ingelheim; Daiichi Sankyo; Pfizer/BMS

European Task Force on Anticoagulants
Member and co-author

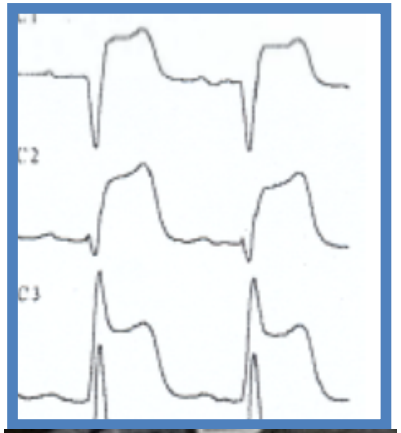
Working Group on Thrombosis (ESC)
Past-chairman

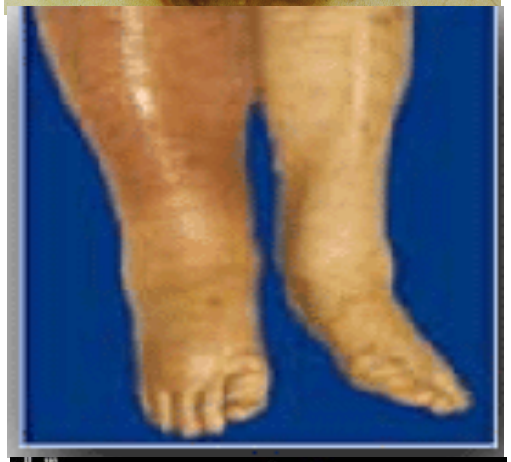
Steering Committee, clinical trials on NOACs
ATLAS-ACS 2; RE-DUAL; AUGUSTUS



Coronary thrombosis

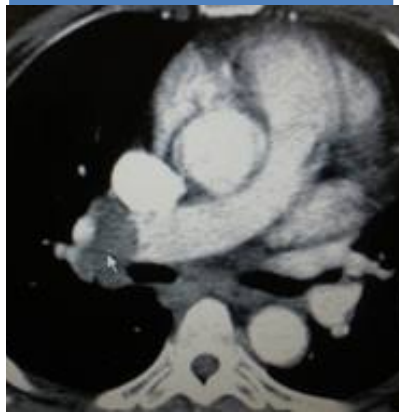
Myocardial infarction





Venous thrombosis

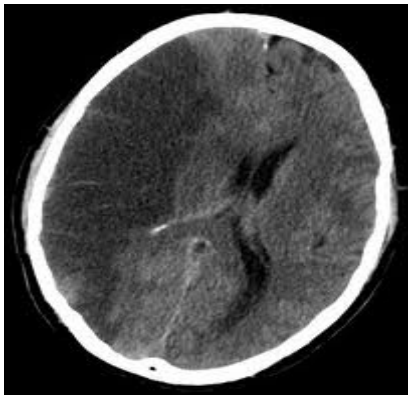
Pulmonary embolism



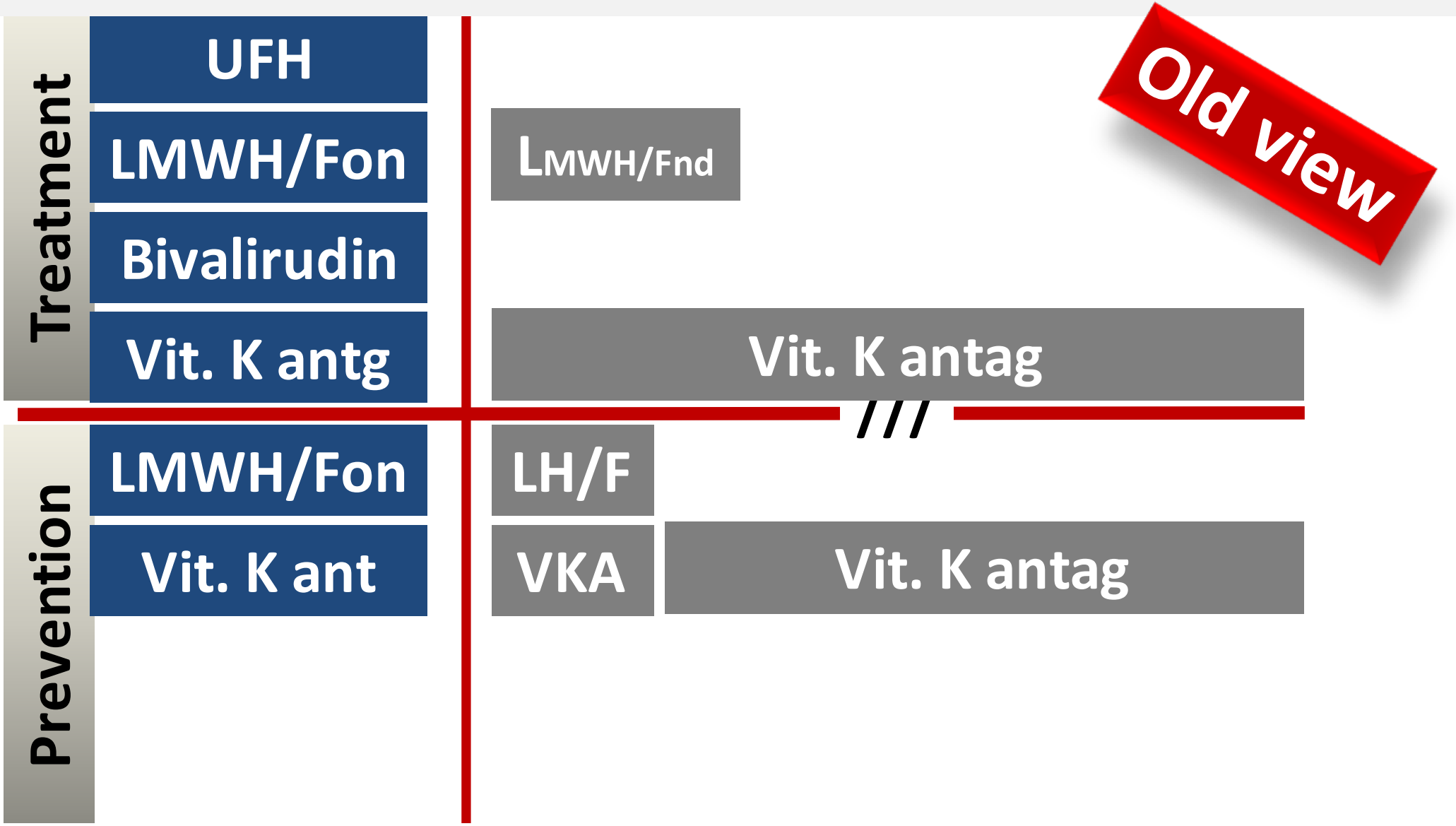
Intracardiac thrombus

Atrial fibrillation, mechanical valves

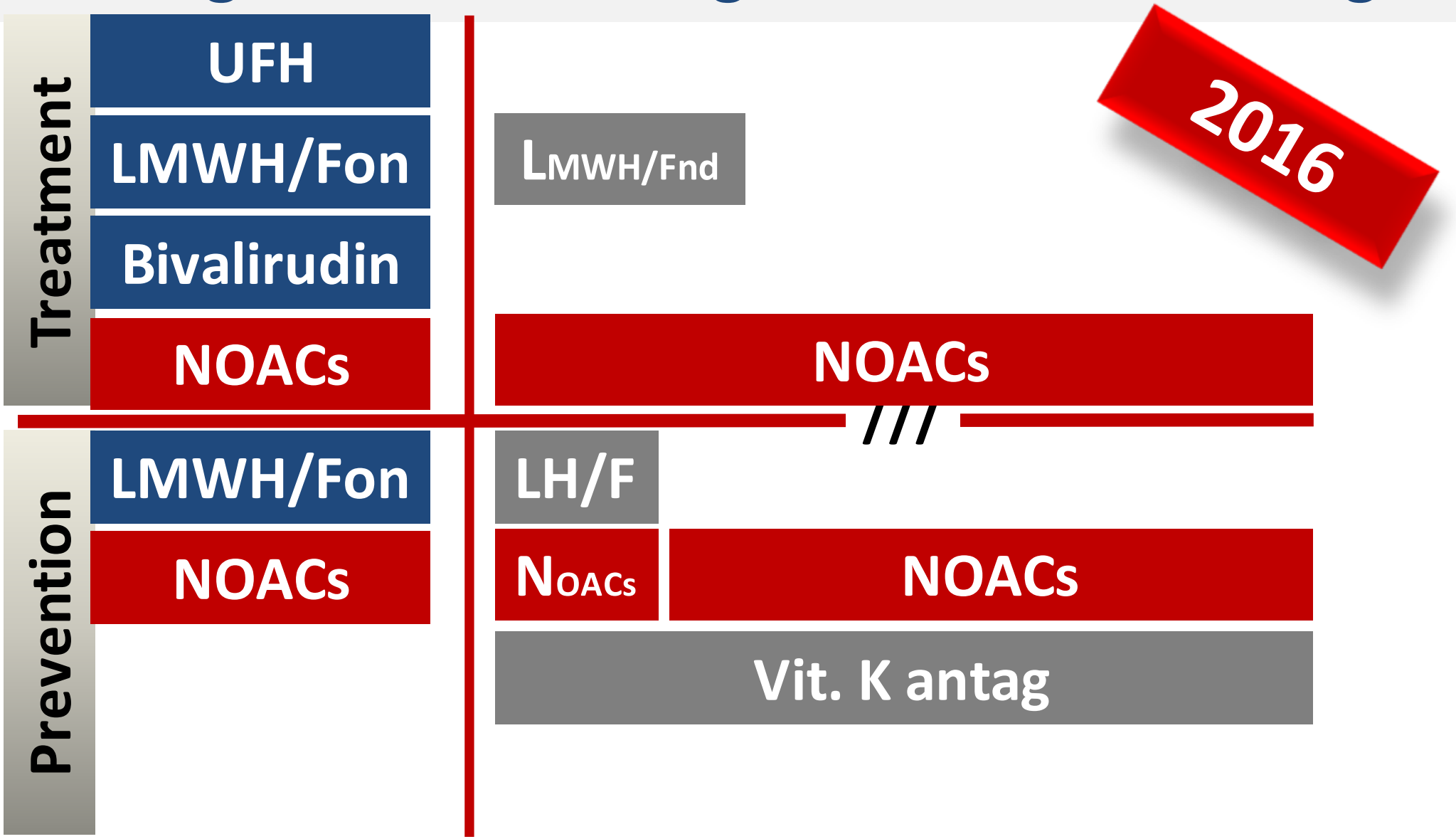
Ischaemic stroke



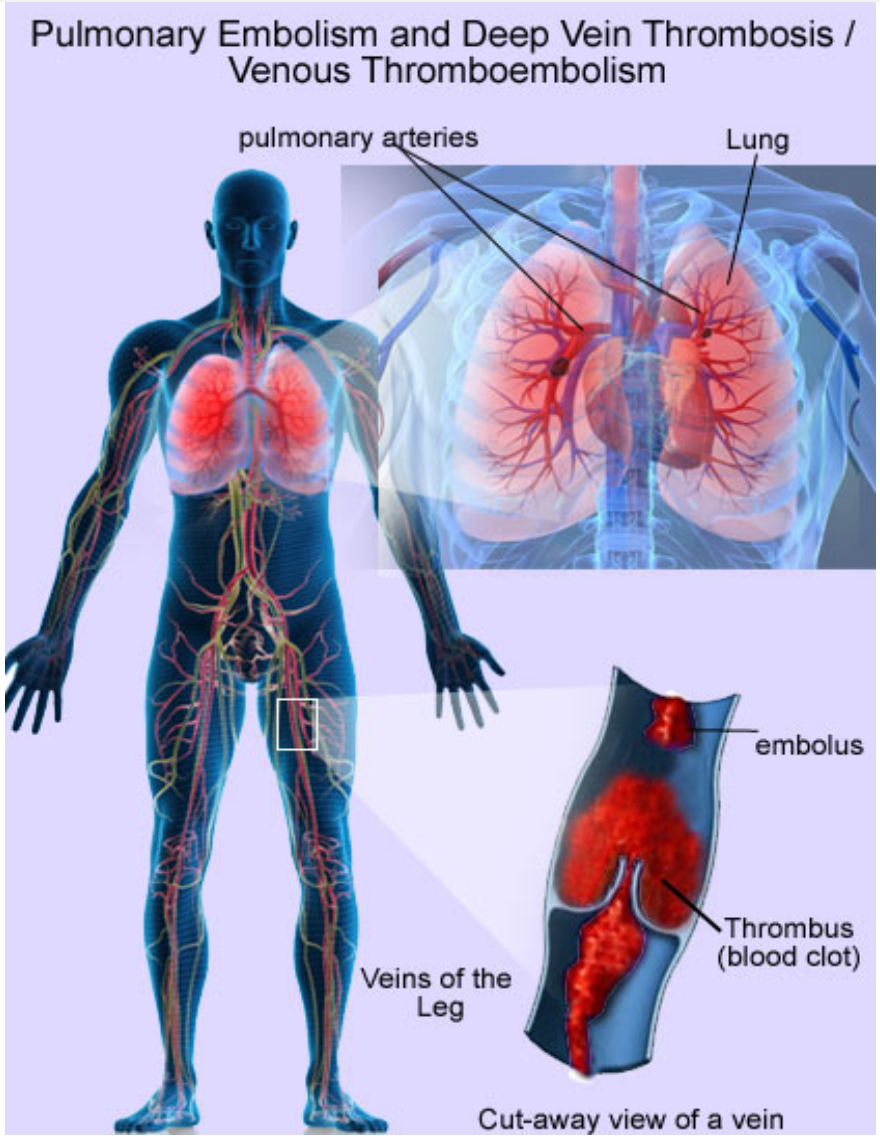
Anticoagulation according to the clinical setting



Anticoagulation according to the clinical setting



Background



Venous thrombosis

Yearly incidence
1/1000 person-years

1/3 of DVT complicate with a clot in the lungs

Recurrence at 5 years -28%

Case-fatality rate
(recurrence) 3% - 6%

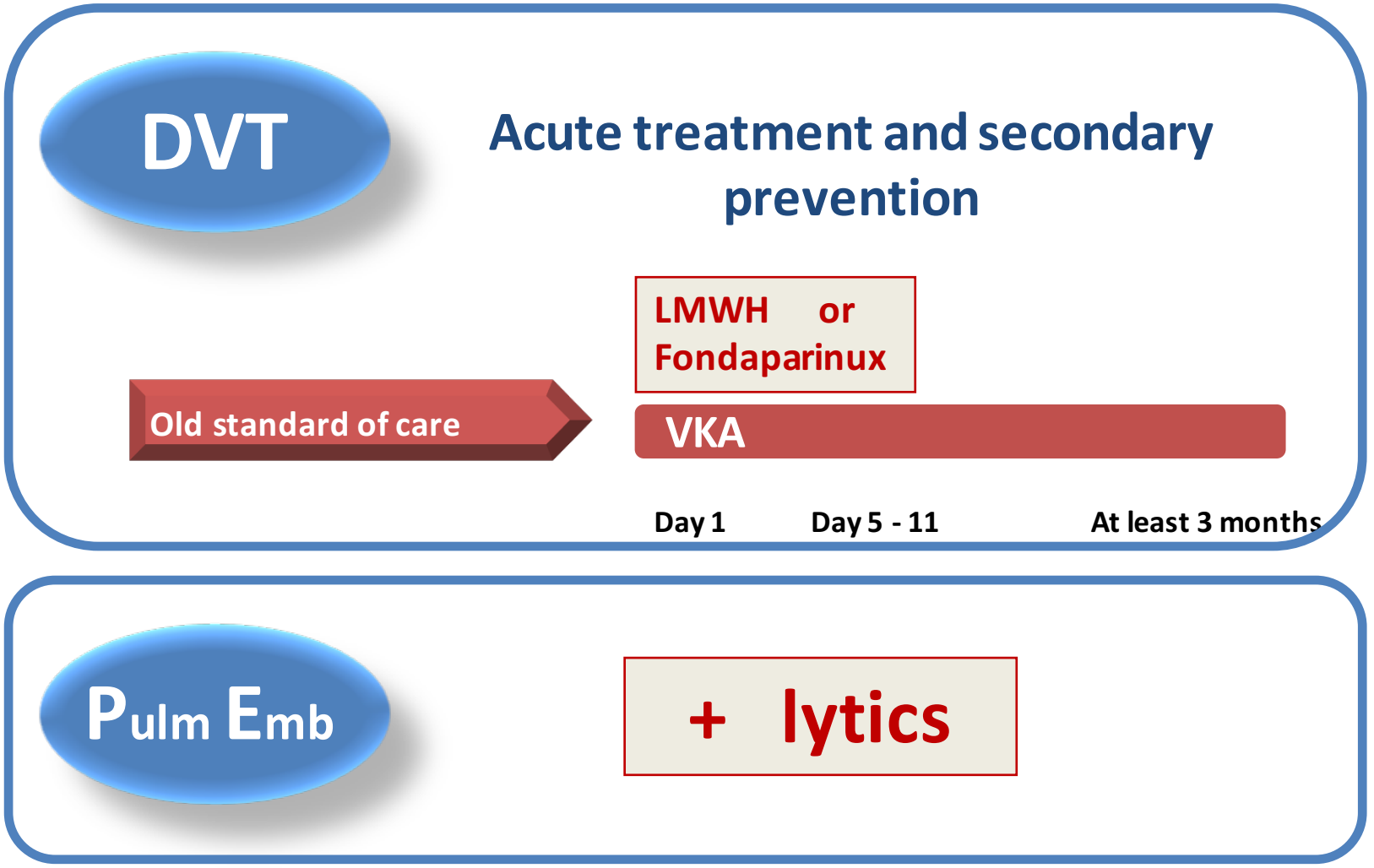
Habson PO et al. Arch Intern Med 2000;160:769
Carrier M et al. Ann Intern Med 2010;152:578

Individualized treatment of DVT ?

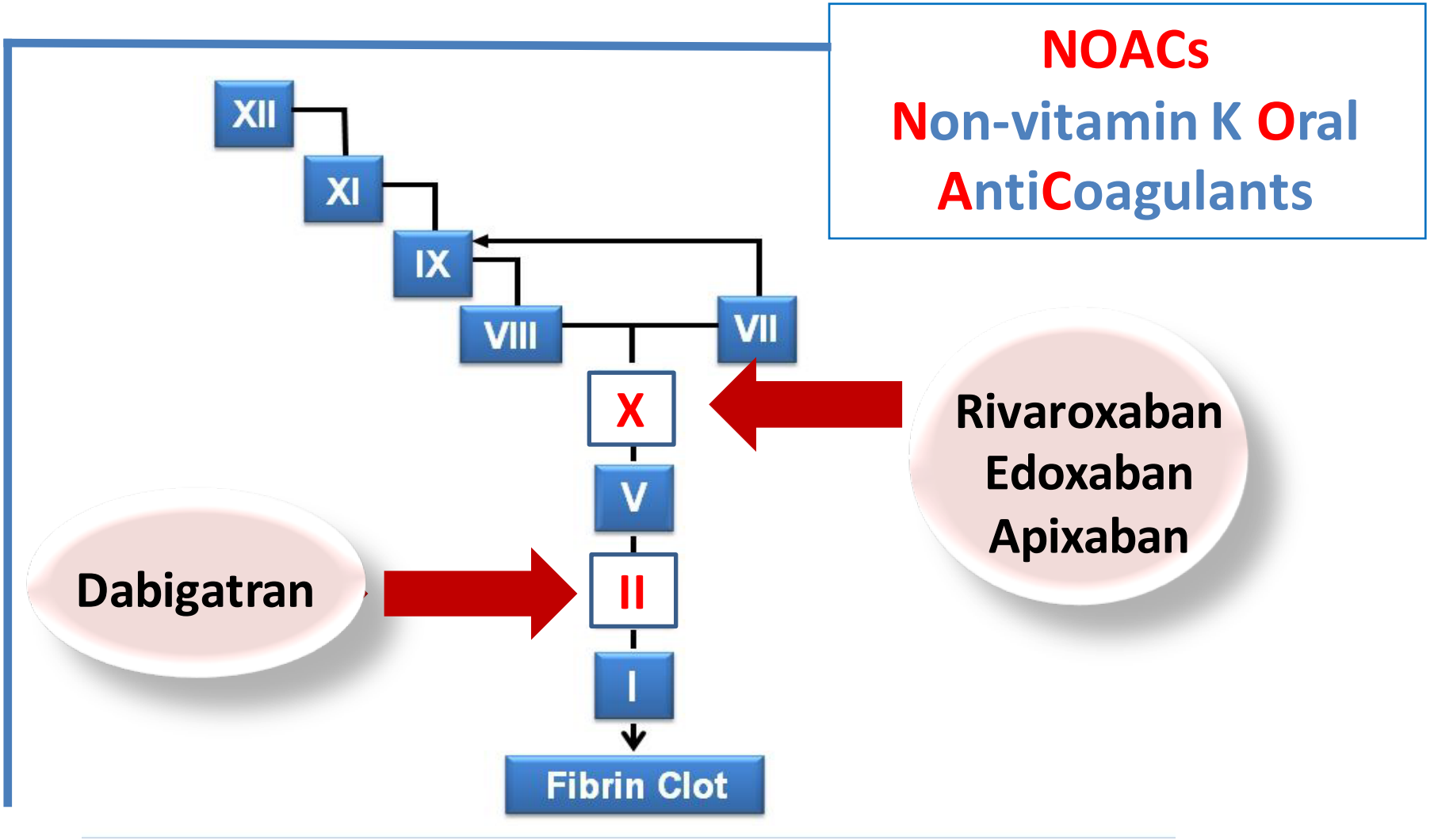
DVT treatment may be individualized based on

- ✓Thrombus location
- ✓Thrombus burden
- ✓Clinical trigger
- ✓Individual bleeding risk
- ✓Outpatient approach
- ✓Physician’s preference
- ✓Patient’s preference

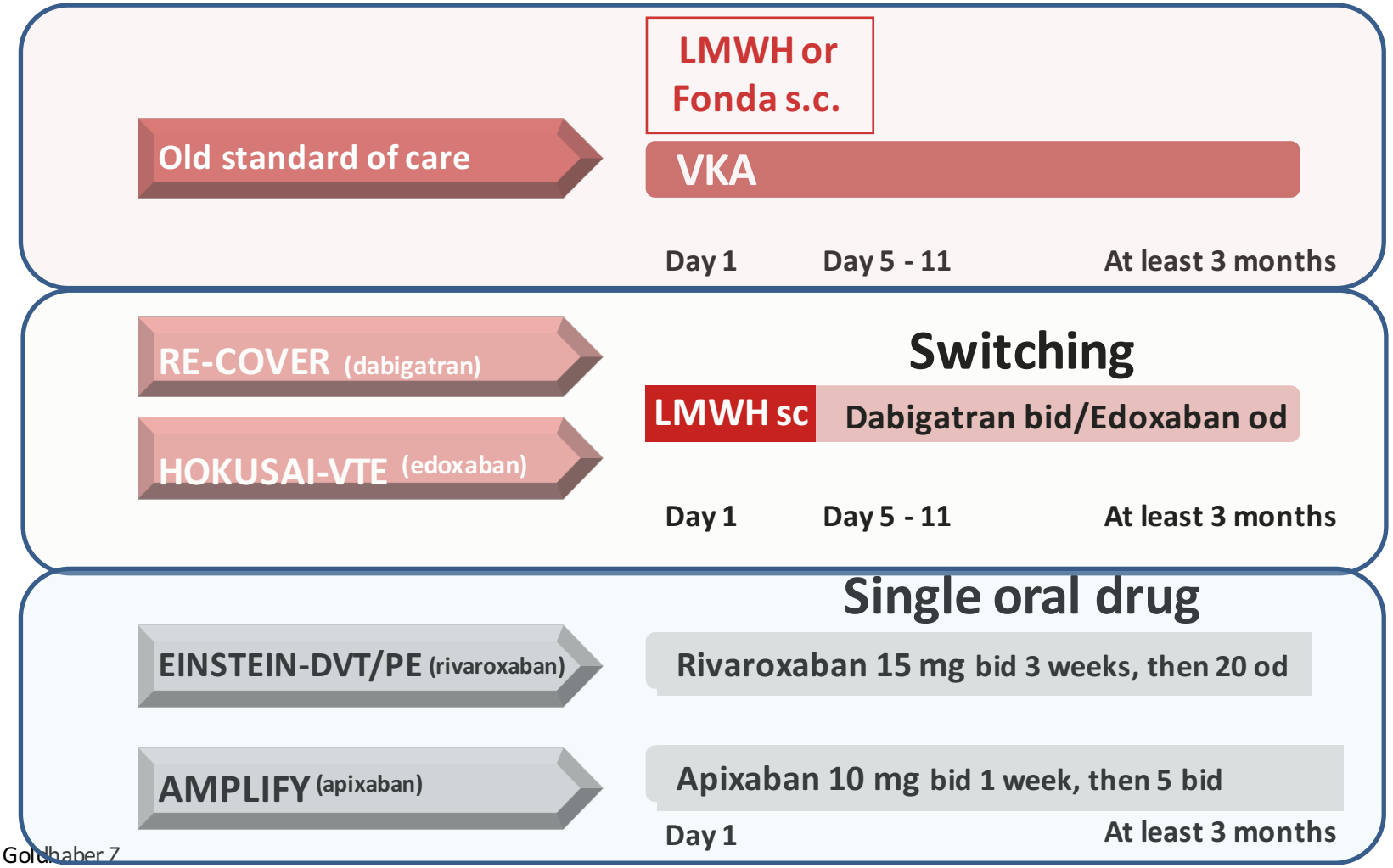
Old options for DVT treatment



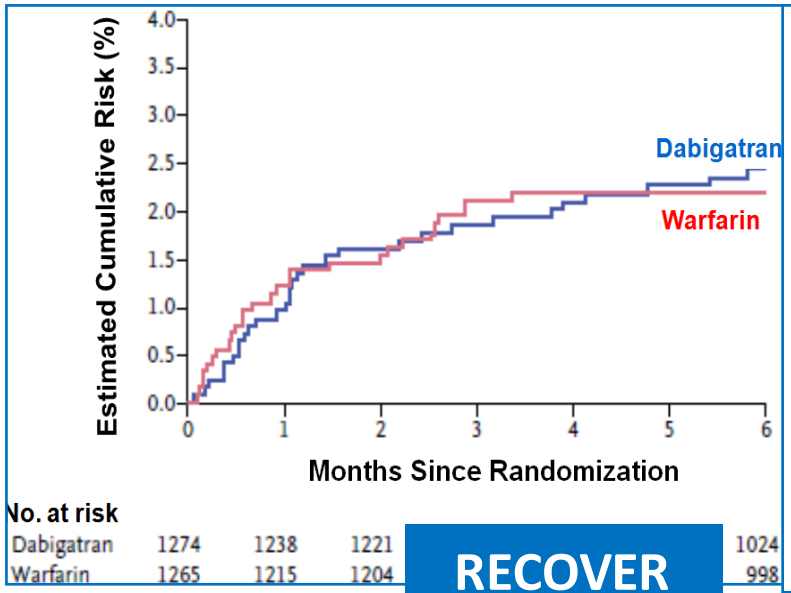
Targets for the new oral anticoagulants



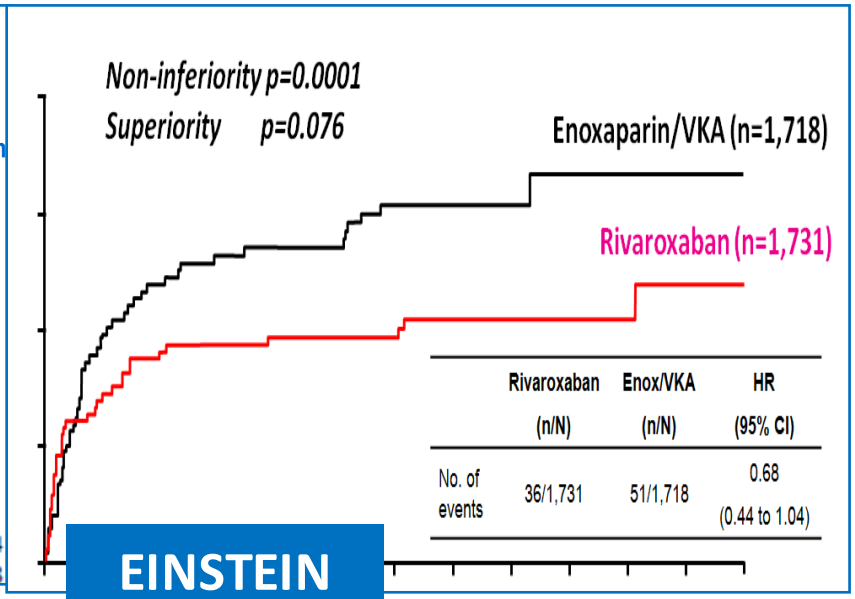
Current and evolving anticoagulant regimen



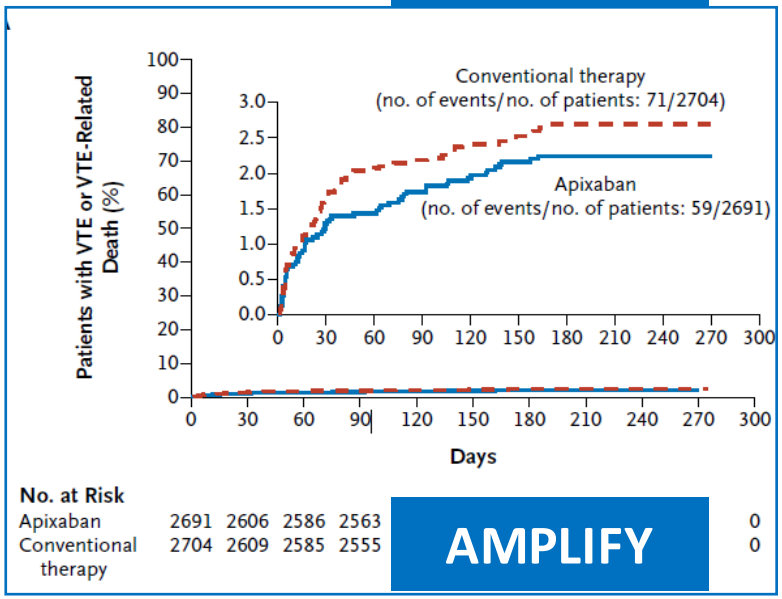
Konstantinides S and Goldhaber Z
Europ Heart J 2012 doi:10.1093/eurheartj/ehs258



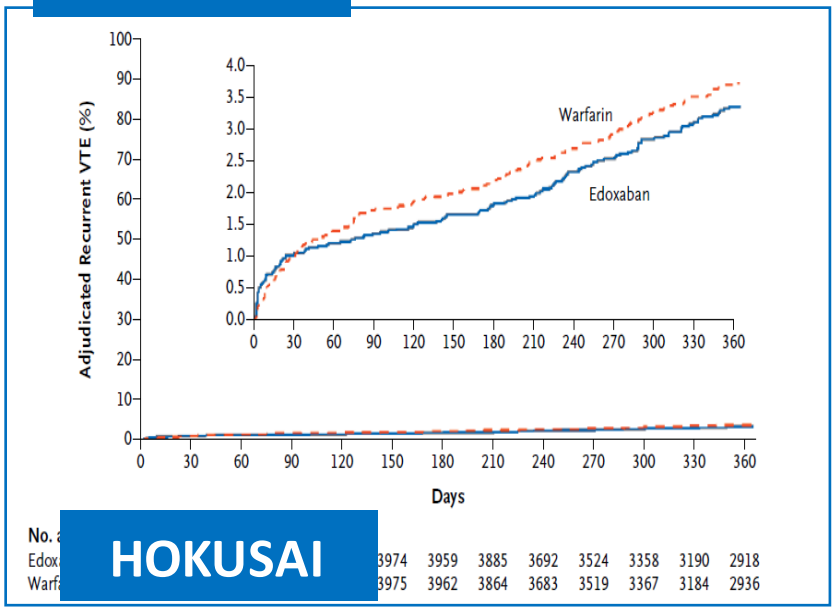
RECOVER



EINSTEIN

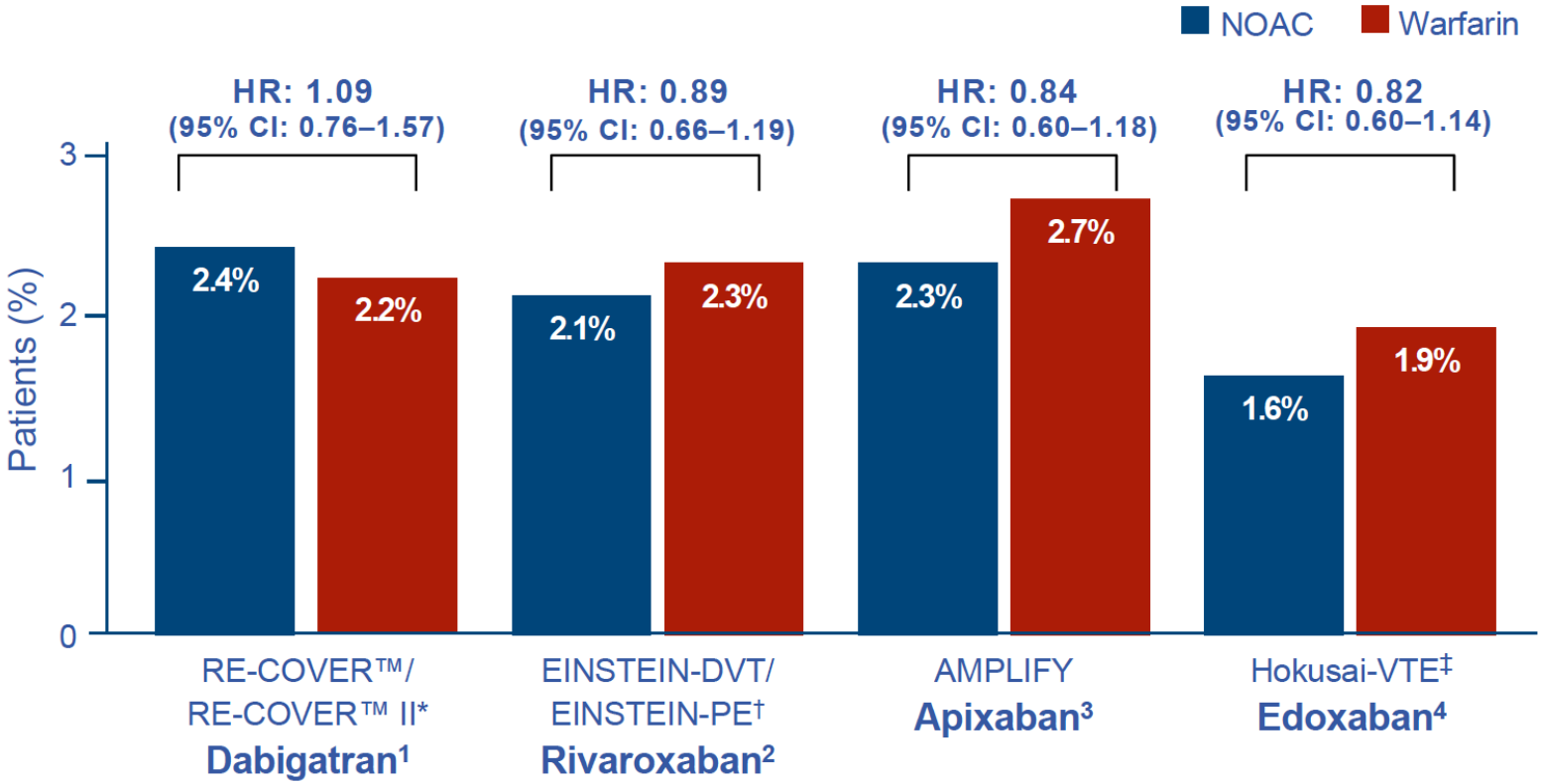


AMPLIFY



HOKUSAI

Treatment of acute DVT/PE: NOACs non-inferior to warfarin for prevention of recurrent DVT/PE in Phase III trials

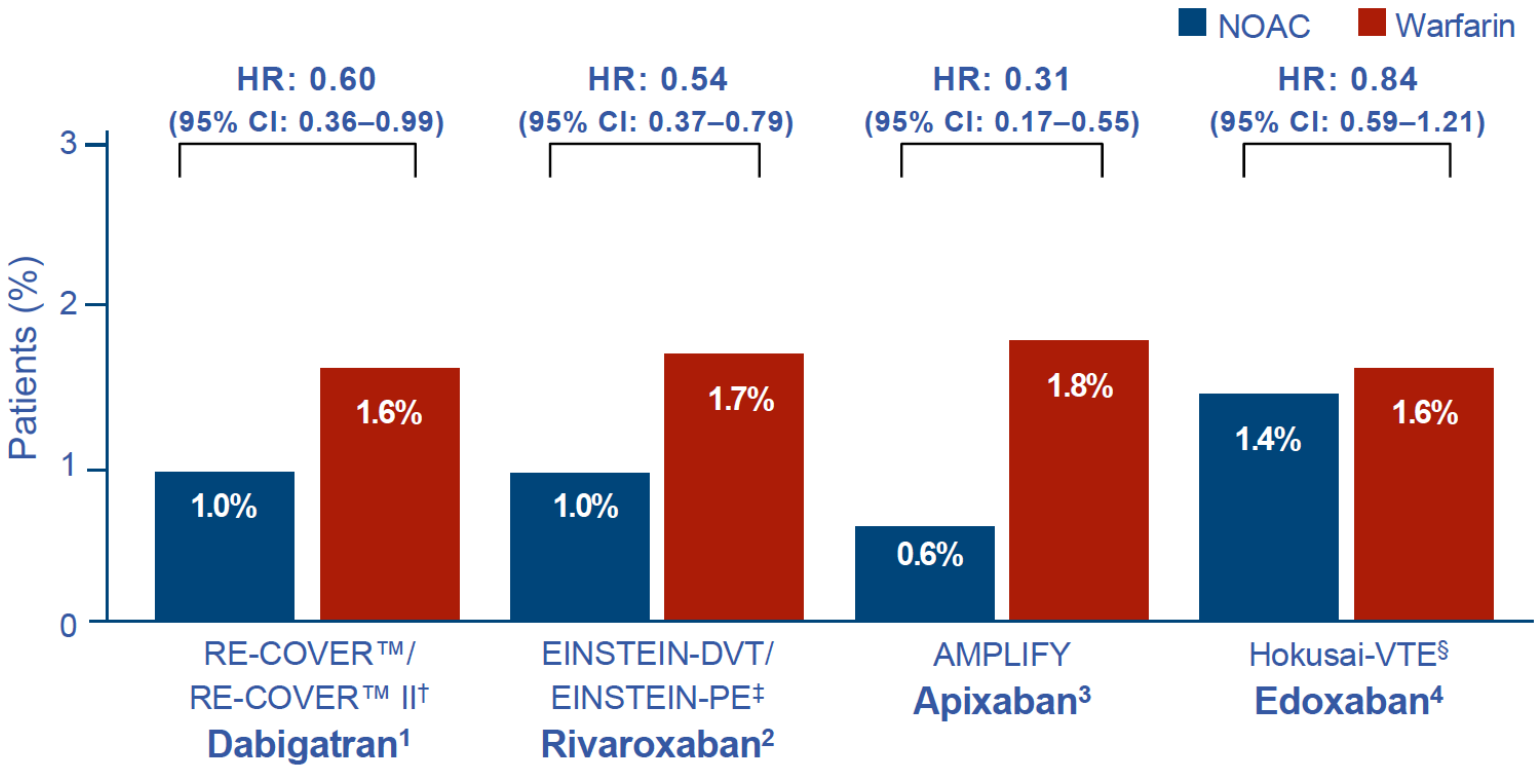


Direct comparisons cannot be made as no head-to-head data are available

*Pooled data from RE-COVER™ and RE-COVER™ II; †Pooled analysis; ‡On treatment

1. Schulman S et al. Circulation 2014;129:764–72; **2.** Prins MH et al. Thromb J 2013;11:21; **3.** Agnelli G et al. N Engl J Med 2013;369:799–808; **4.** The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406–15

Treatment of acute DVT/PE: NOACs associated with less major bleeding than warfarin in Phase III trials*



Direct comparisons cannot be made as no head-to-head data are available

*Statistically significant reductions for dabigatran, rivaroxaban, and apixaban vs warfarin, numerical reduction for edoxaban vs warfarin; †Pooled data from RE-COVER™ and RE-COVER™ II; oral drug treatment period only; ‡Pooled analysis; §On treatment

1. Schulman S et al. Circulation 2014;129:764–72; **2.** Prins MH et al. Thromb J 2013;11:21; **3.** Agnelli G et al. N Engl J Med 2013;369:799–808; **4.** The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406–15

NOACs and DVT

REVIEW

Efficacy and Safety of the New Oral Anticoagulants Dabigatran, Rivaroxaban, Apixaban, and Edoxaban in the Treatment and Secondary Prevention of Venous Thromboembolism: A Systematic Review and Meta-analysis of Phase III Trials

S.K. Kakkos *, G.I. Kirkilesis, I.A. Tsolakis

Department of Vascular Surgery, University Hospital of Patras, Patras, Greece

European Journal of Vascular and Endovascular Surgery (2014),
http://dx.doi.org/10.1016/j.ejvs.2014.05.001

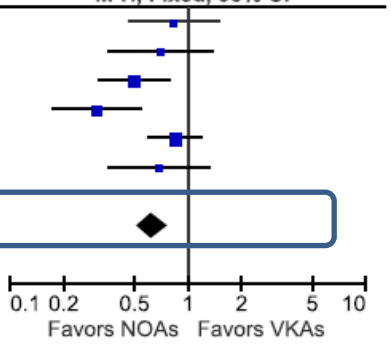
Major bleeding

a

Study or Subgroup	NOAs Events	NOAs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
RE-COVER	20	1274	24	1265	10.3%	0.83 [0.46, 1.49]	2009
EINSTEIN-DVT	14	1718	20	1711	8.6%	0.70 [0.35, 1.38]	2010
EINSTEIN-PE	26	2412	52	2405	22.4%	0.50 [0.31, 0.80]	2012
AMPLIFY	15	2676	49	2689	21.0%	0.31 [0.17, 0.55]	2013
Hokusai-VTE	56	4118	66	4122	28.3%	0.85 [0.60, 1.21]	2013
RE-COVER II	15	1280	22	1288	9.4%	0.69 [0.36, 1.32]	2014
Total (95% CI)		**13478**		**13480**	**100.0%**	**0.63 [0.51, 0.77]**	
Total events	146		233				

Heterogeneity: Chi² = 10.65, df = 5 (P = 0.06); I² = 53%

Test for overall effect: Z = 4.46 (P < 0.00001)



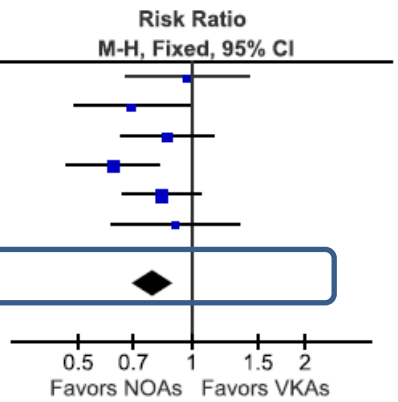
Net clinical benefit

e

Study or Subgroup	NOAs Events	NOAs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
RE-COVER	50	1274	51	1265	9.6%	0.97 [0.66, 1.43]	2009
EINSTEIN-DVT	51	1731	73	1718	13.7%	0.69 [0.49, 0.99]	2010
EINSTEIN-PE	83	2419	96	2413	18.0%	0.86 [0.65, 1.15]	2012
AMPLIFY	74	2676	120	2689	22.4%	0.62 [0.47, 0.82]	2013
Hokusai-VTE	120	4118	144	4122	27.0%	0.83 [0.66, 1.06]	2013
RE-COVER II	45	1279	50	1289	9.3%	0.91 [0.61, 1.35]	2014
Total (95% CI)		**13497**		**13496**	**100.0%**	**0.79 [0.70, 0.90]**	
Total events	423		534				

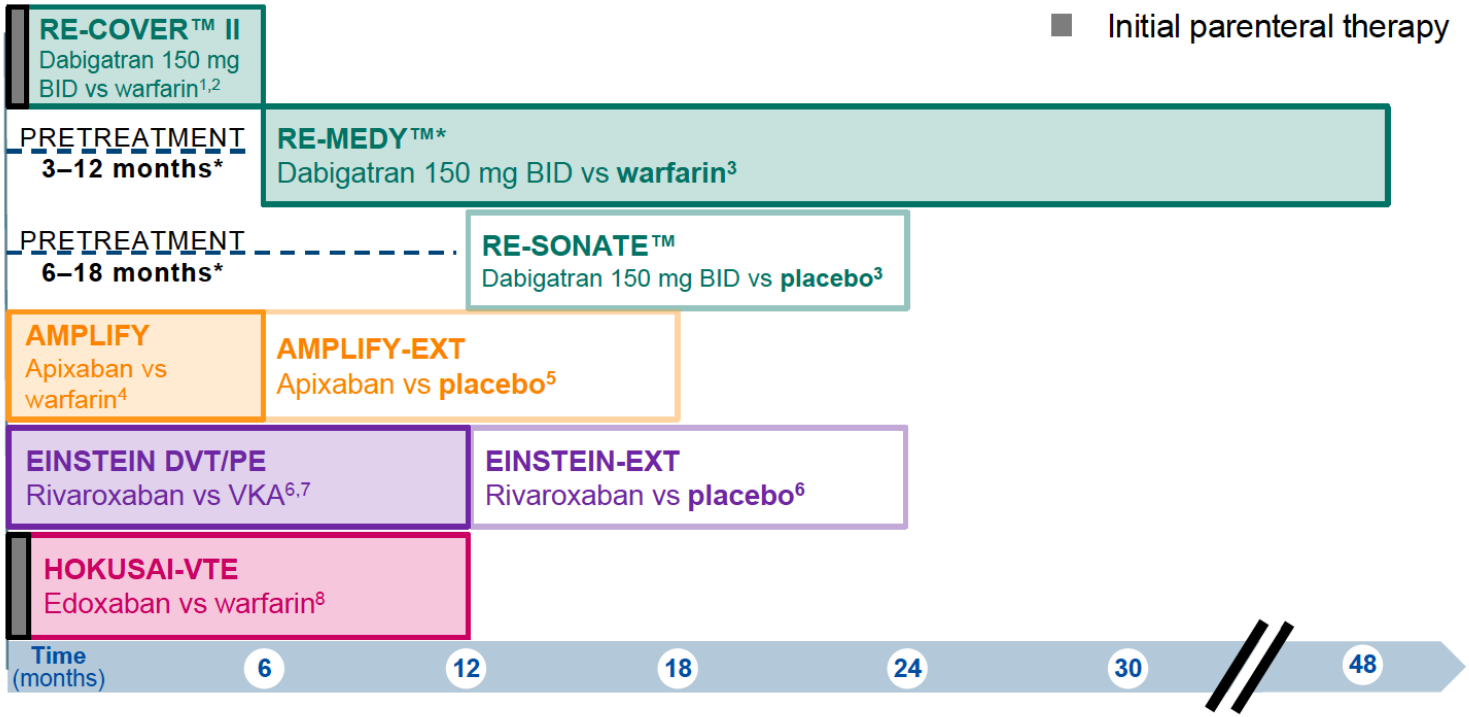
Heterogeneity: Chi² = 5.49, df = 5 (P = 0.36); I² = 9%

Test for overall effect: Z = 3.65 (P = 0.0003)



European Journal of Vascular and Endovascular Surgery (2014), http://dx.doi.org/10.1016/j.ejvs.2014.05.001

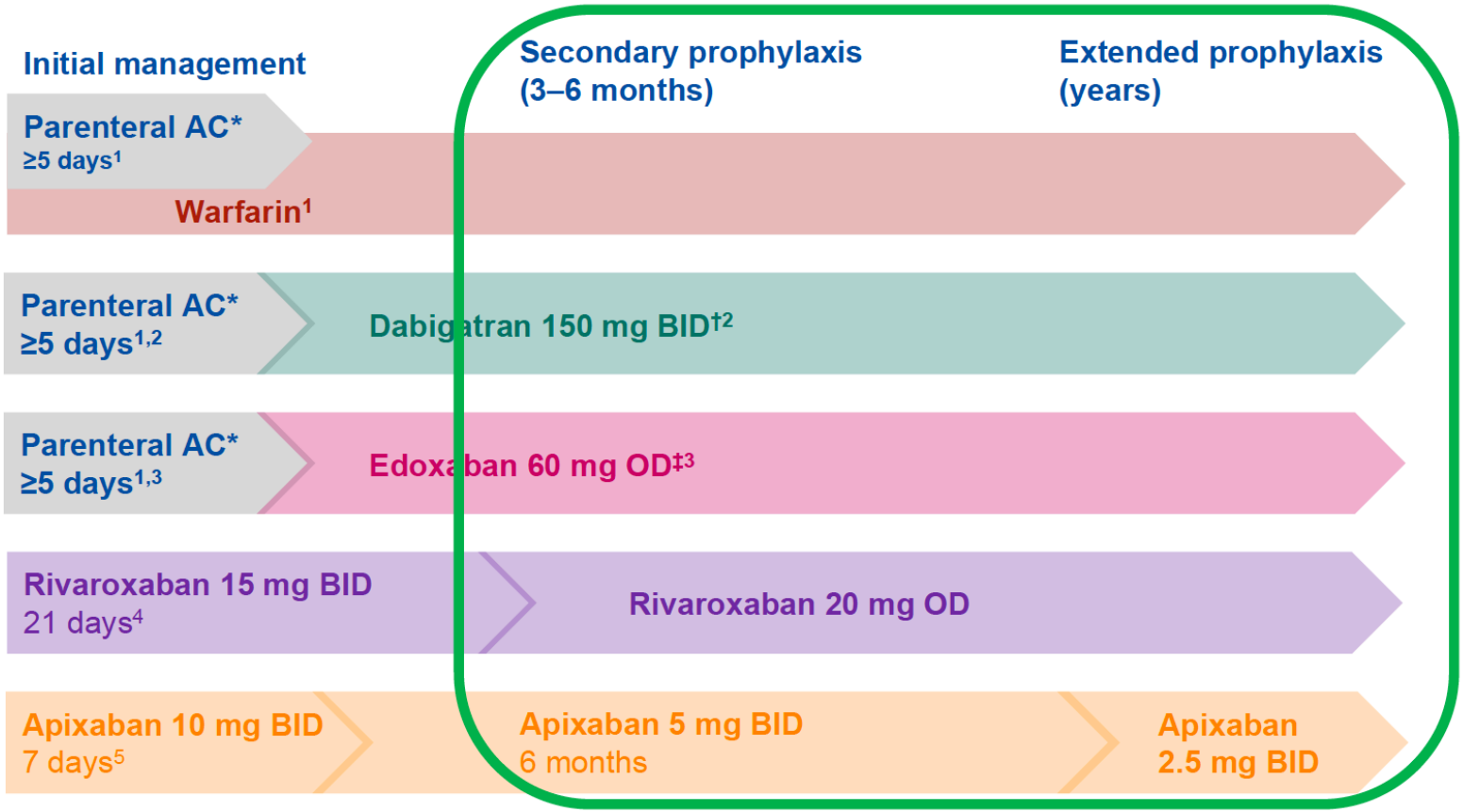
What long-term data exist for NOACs compared with warfarin in secondary prevention of VTE?



*Original protocol, 3–6 months pretreatment, 18 months on study drug; amendment allowed 3–12 months pretreatment, then up to 36 months on study drug

1. Schulman S et al. N Engl J Med 2009;361:2342–52; **2.** Schulman S et al. Circulation 2014;129:764–72;
3. Schulman S et al. N Engl J Med 2013;368:709–18; **4.** Agnelli G et al. N Engl J Med 2013;369:799–808;
5. Agnelli G et al. N Engl J Med 2013;368:699–708; **6.** The EINSTEIN Investigators. N Engl J Med 2010;363:2499–510;
7. The EINSTEIN-PE Investigators. N Engl J Med 2012;366:1287–97;
8. The Hokusai-VTE Investigators. N Engl J Med 2014;369:1406–15

VTE requires acute and extended treatment for prevention of recurrence



*LMWH, fondaparinux, or UFH; †Dabigatran 110 mg BID for aged ≥80 years, concomitant verapamil, or based on individual assessment of thromboembolic/bleeding risk; ‡Edoxaban 30 mg OD for CrCl 15–50 mL/min, weight ≤60 kg, certain concomitant P-gp inhibitors

1. Kearon C et al. Chest 2012;141(Suppl. 2):e419S-94S; **2.** Pradaxa SPC; **3.** Lixiana SPC; **4.** Xarelto SPC; **5.** Eliquis SPC. Current versions available online at: http://www.medicines.org.uk/emc/

Risk of recurrent VTE or VTE-related death: NOACs vs placebo

Study	% Patients		HR (95% CI)	P-value
	NOAC	Placebo		
RE-SONATE™ 1*	0.4	5.6	0.08 (0.02–0.25)	<0.001
EINSTEIN-EXT[2]	1.3	7.1	0.18 (0.09–0.39)	<0.001
AMPLIFY-EXT[3†]				
2.5 mg BID	1.7	8.8	0.19 (0.11–0.33)	<0.001
5 mg BID	1.7	8.8	0.20 (0.11–0.34)	<0.001

Direct comparisons cannot be made as no head-to-head data are available

*Unexplained death also included in primary efficacy outcome; †All-cause death also included in primary efficacy outcome

1. Schulman S et al. N Engl J Med 2013;368:709–18; **2.** The EINSTEIN Investigators. N Engl J Med 2010;363:2499–510; **3.** Agnelli G et al. N Engl J Med 2013;368:699–708

Atrial fibrillation

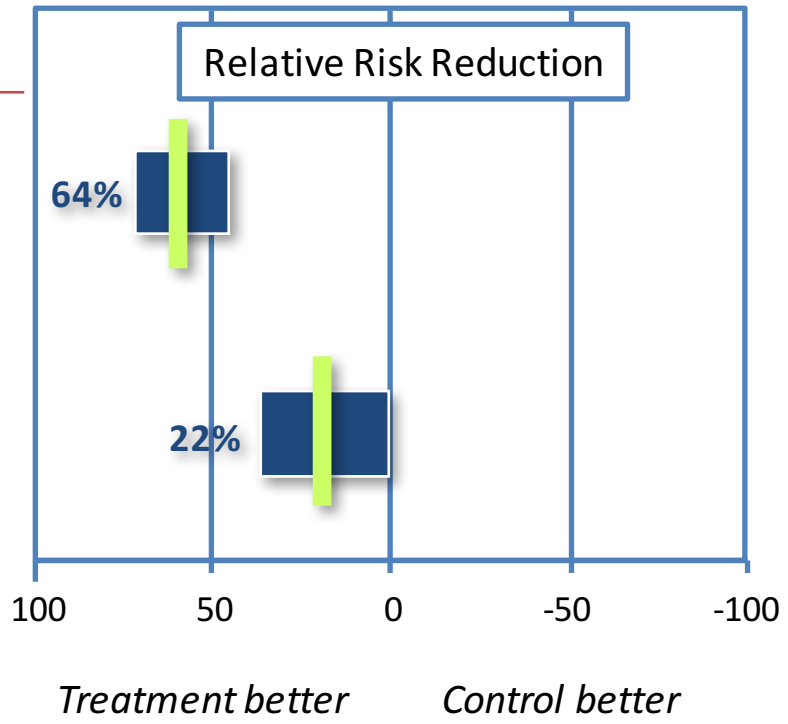
European Guidelines 2016

OACs the keystone for stroke prevention in A.Fib

Meta-analysis of Controlled Trials in Nonvalvular AF

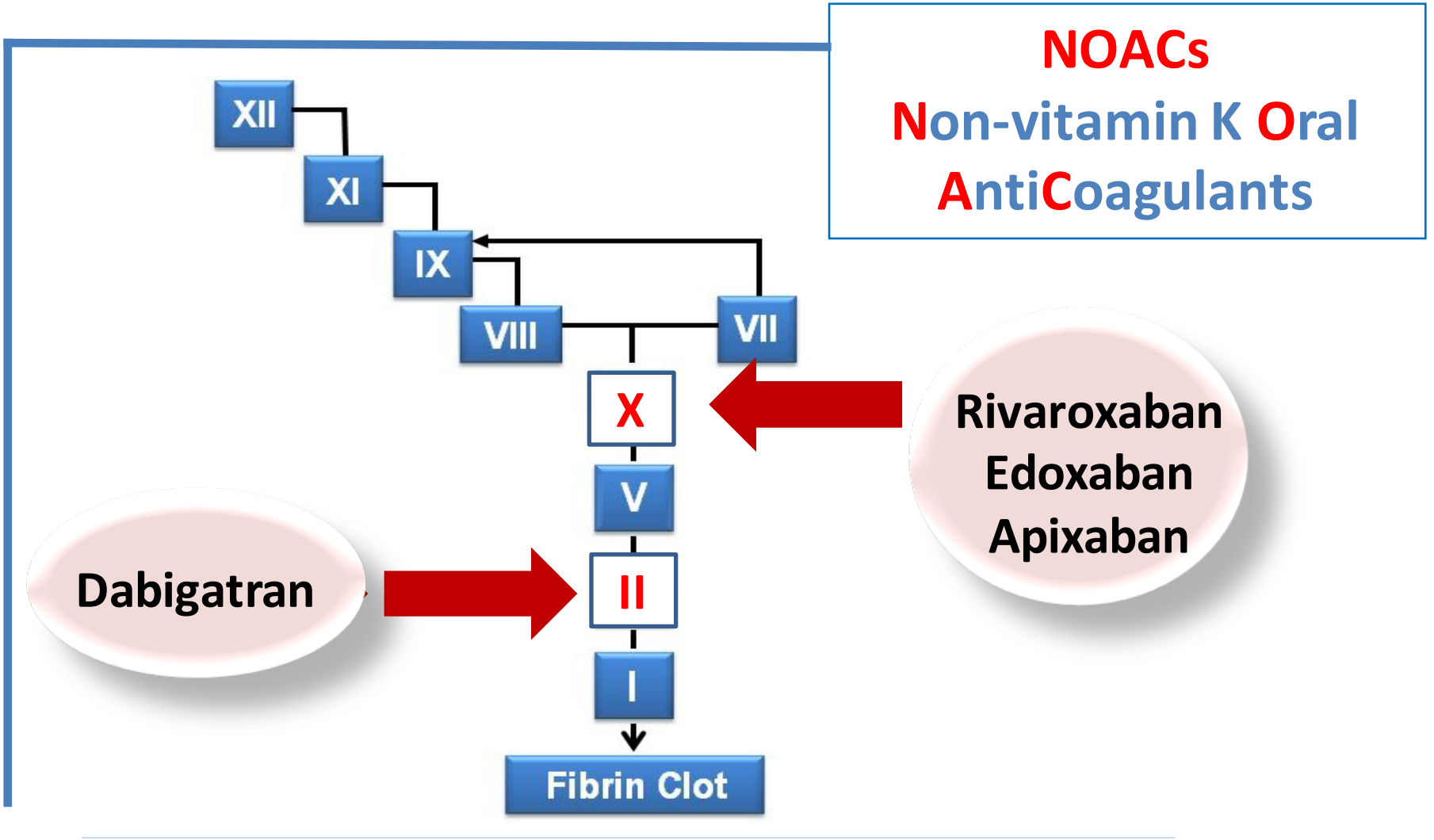
Studies	Pts n	2º Prev %	Stroke (%/yr) OAC	Contr
OAC vs Placebo/Control: 6 studies				
	2900	20	2.2	6.0
1º Prevention: NNT_1 = 37 (ARR 2.7%/yr) 2º Prevention: NNT_1 = 12 (ARR 8.4%/yr)				
Antiplatelet vs Placebo: 6 studies				
	4876	29	5.3	6.7
1º Prevention: NNT_1 = 125 (ARR 0.8%/yr) 2º Prevention: NNT_1 = 26 (ARR 3.8%/yr)				

OAC reduces all-cause mortality by 26%:
NNT_1 = 63 (ARR 1.6%/yr)



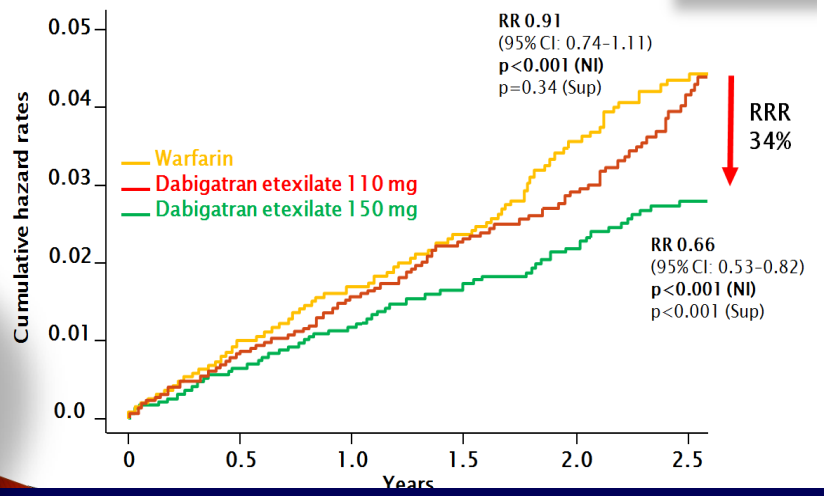
Hart RG et al. *Ann Intern Med* **2007**; 146: 857

Targets for the new oral anticoagulants

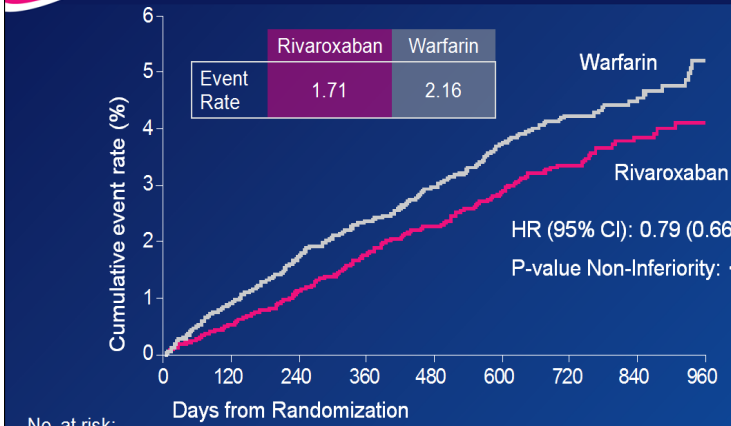


NOACs Atrial fibrillation phase III trials

RE-LY – 1y endpoint Stroke



Primary Efficacy Outcome
Stroke and non-CNS Embolism



No. at risk:

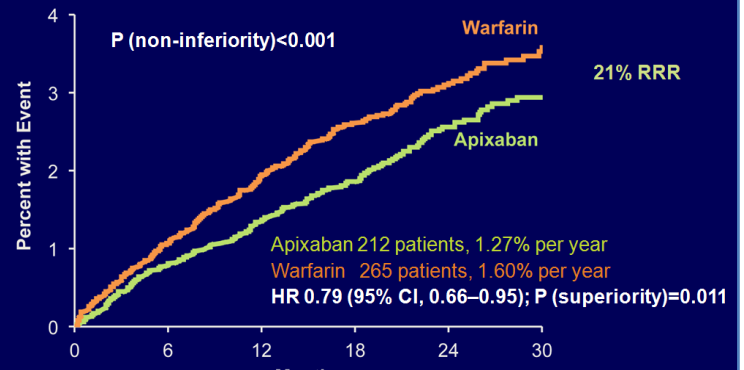
Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

ROCKET AF

Primary Outcome
Stroke (ischemic or hemorrhagic) or systemic embolism

ARISTOTLE



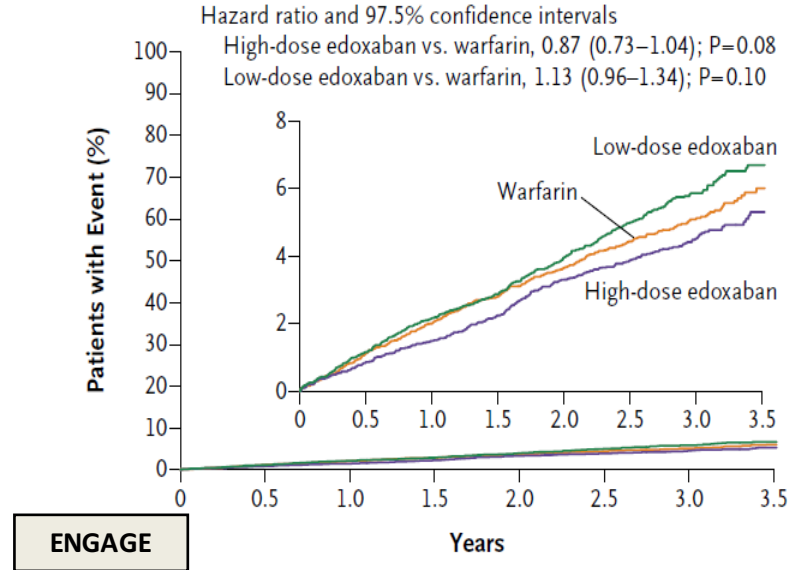
No. at Risk

Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

Duke Clinical Research Institute

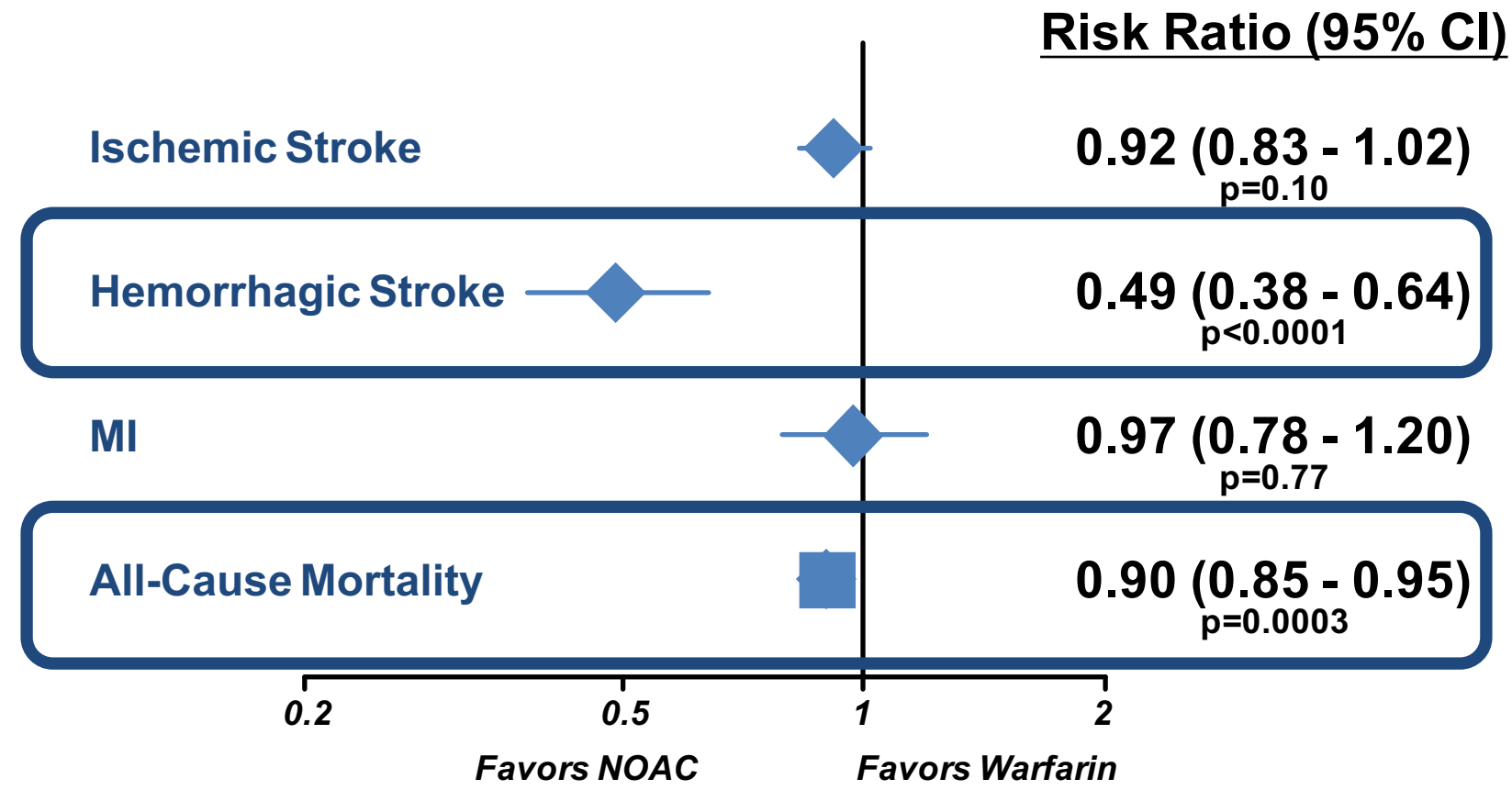
UCR UPPSALA CLINICAL RESEARCH CENTER

Stroke or Systemic Embolic Event



ENGAGE

NOACs meta-analysis (NVAF)

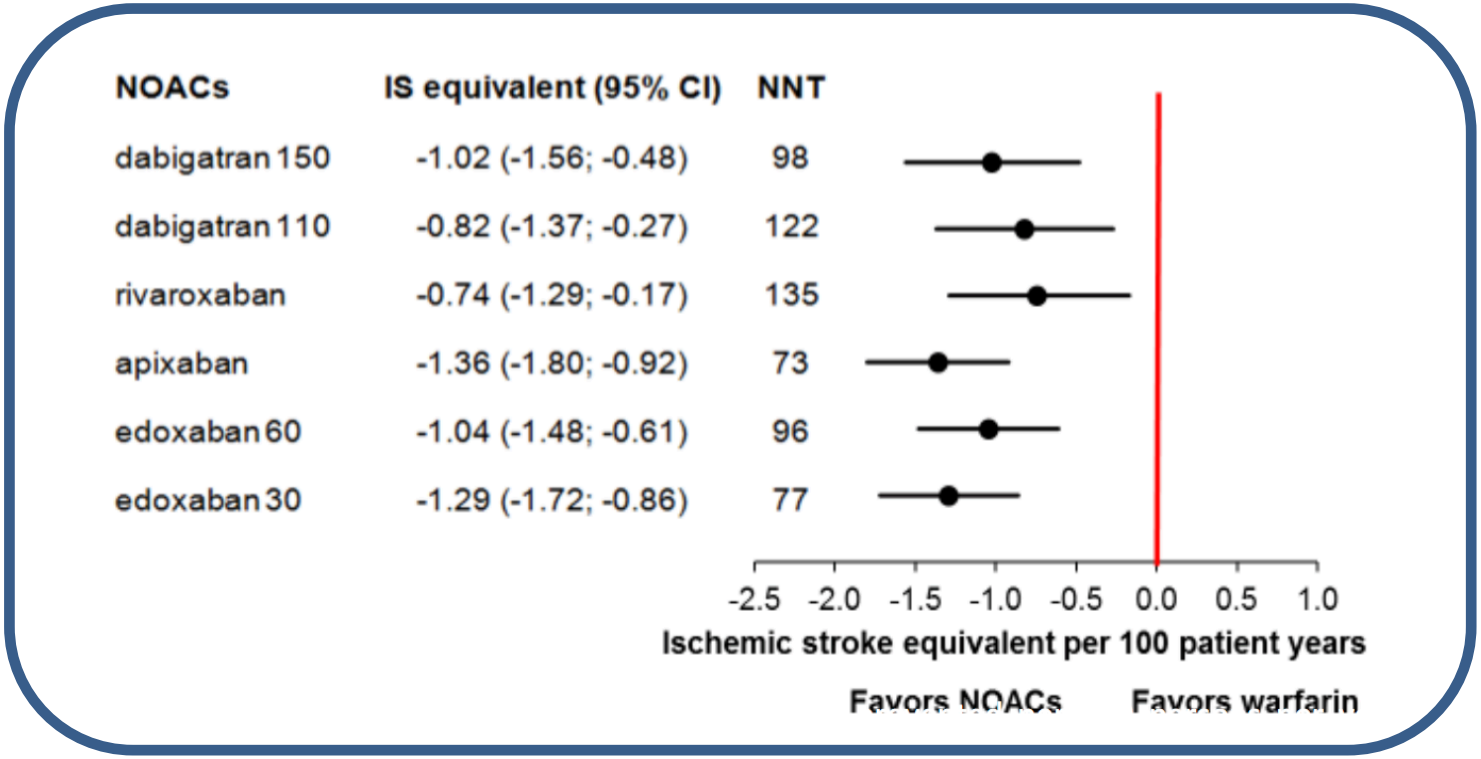


Heterogeneity p=NS for all outcomes

Ruff CT, et al. Lancet 2013;December

NOACs - the net clinical benefit

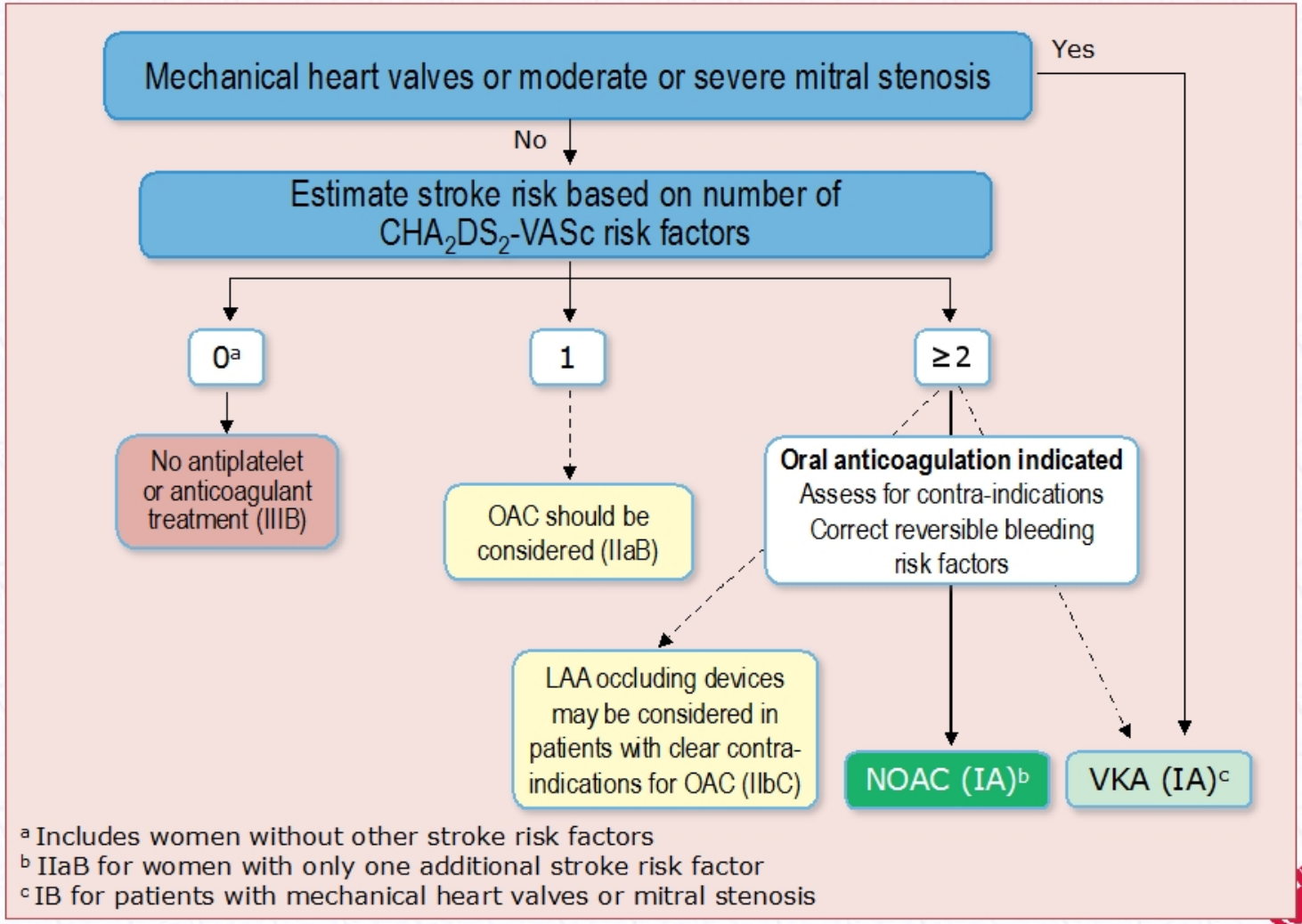
NCB (95%CI) of all treatment arms vs warfarin for the composite outcome including ischemic stroke + systemic embolism + myocardial infarction + hemorrhagic stroke + adjusted major bleeding



Renda G, et al. Am J Med 2015; 128:1007-14

2016

Stroke prevention in atrial fibrillation

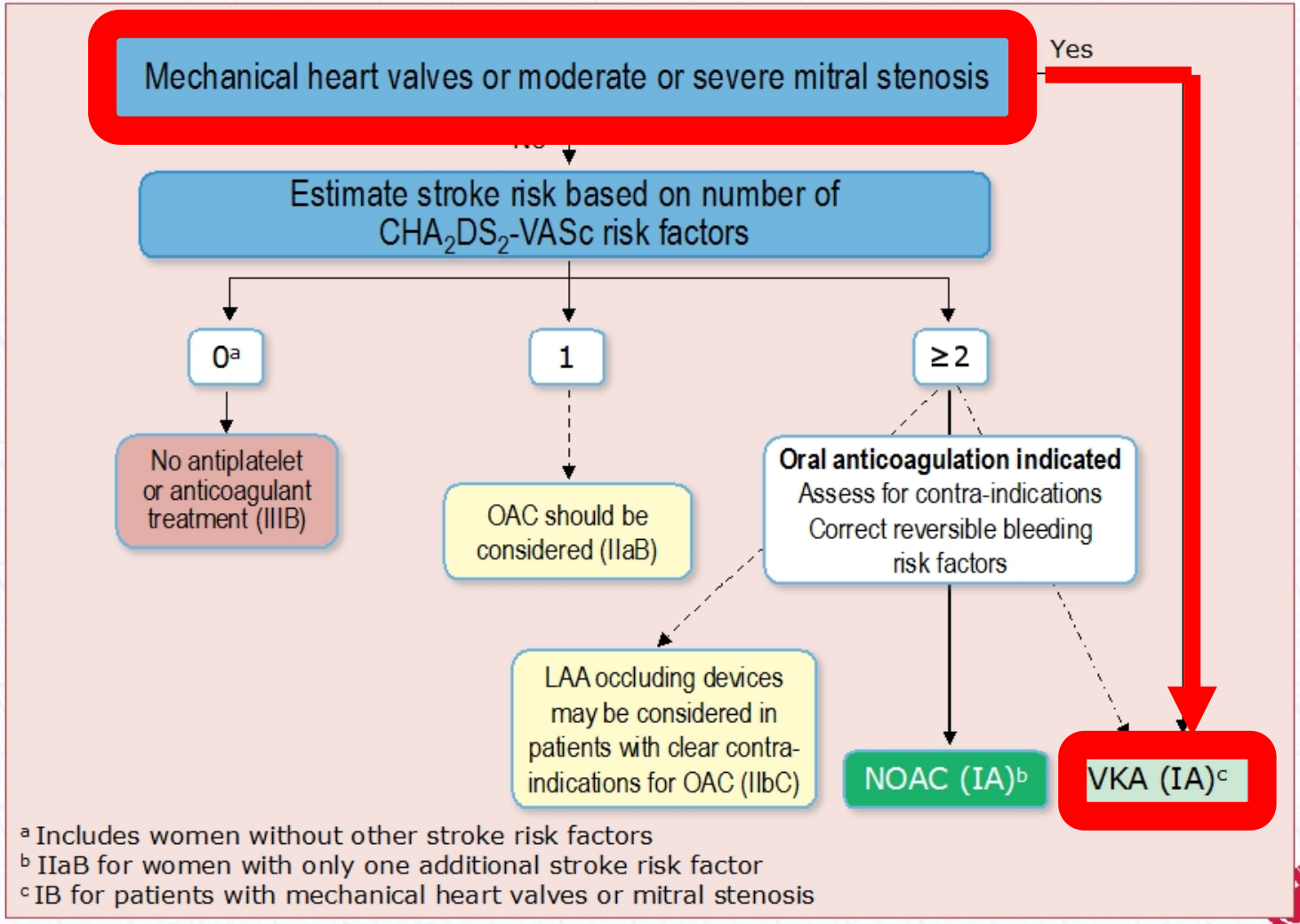


[a] Includes women without other stroke risk factors
[b] IIaB for women with only one additional stroke risk factor
[c] IB for patients with mechanical heart valves or mitral stenosis

European Heart Journal - doi:10.1093/eurheartj/ehw210

2016

Stroke prevention in atrial fibrillation



European Heart Journal - doi:10.1093/eurheartj/ehw210

European Heart Journal Advance Access published September 28, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu352

CURRENT OPINION

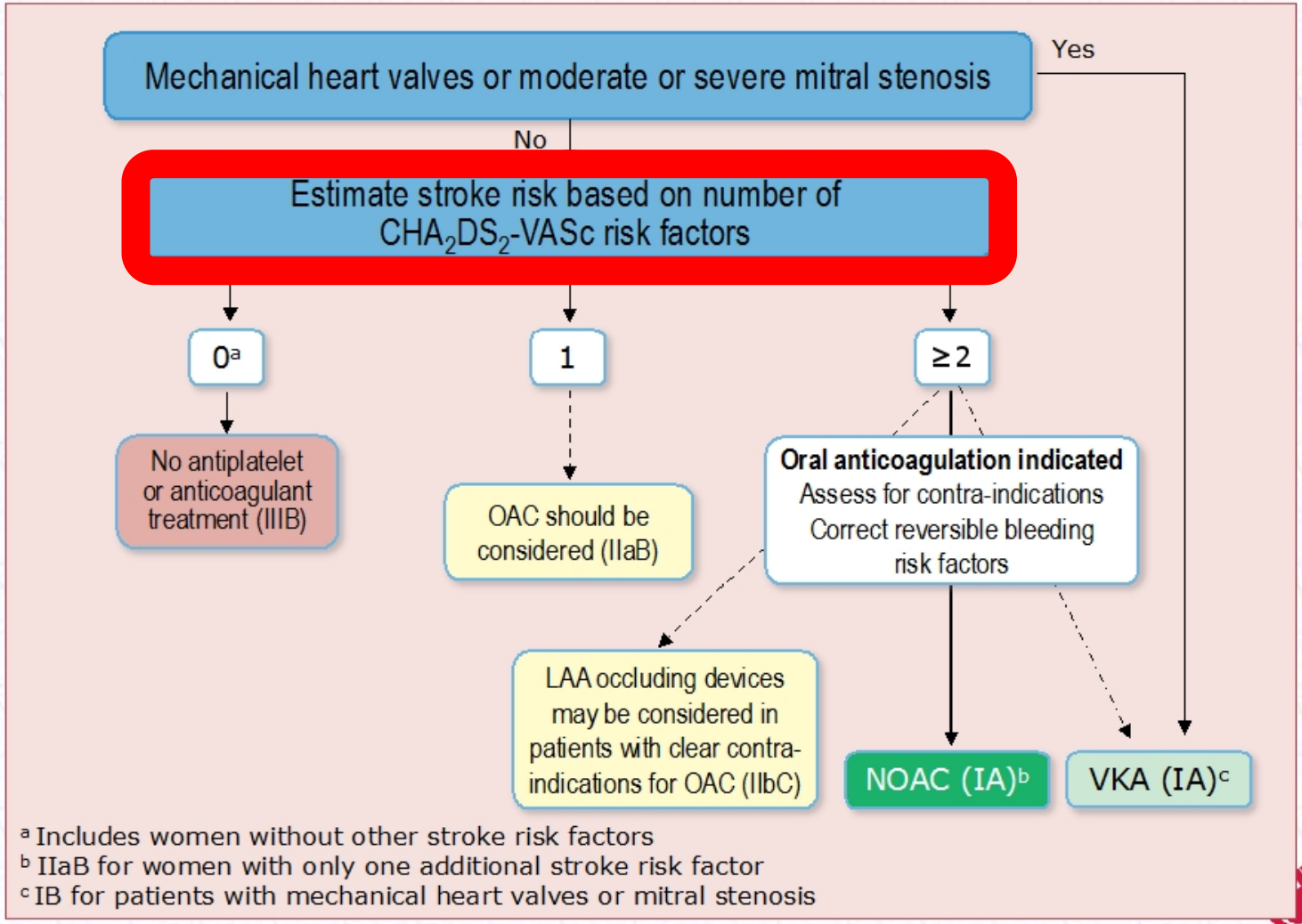
What is 'valvular' atrial fibrillation? A reappraisal

Raffaele De Caterina[1] and A. John Camm[2]*

- Rheumatic valve disease (mitral stenosis)
- Mechanical prosthesis
- Mitral valve disease with severe haemodynamic impairment

2016

Stroke prevention in atrial fibrillation



[a] Includes women without other stroke risk factors
[b] IIaB for women with only one additional stroke risk factor
[c] IB for patients with mechanical heart valves or mitral stenosis

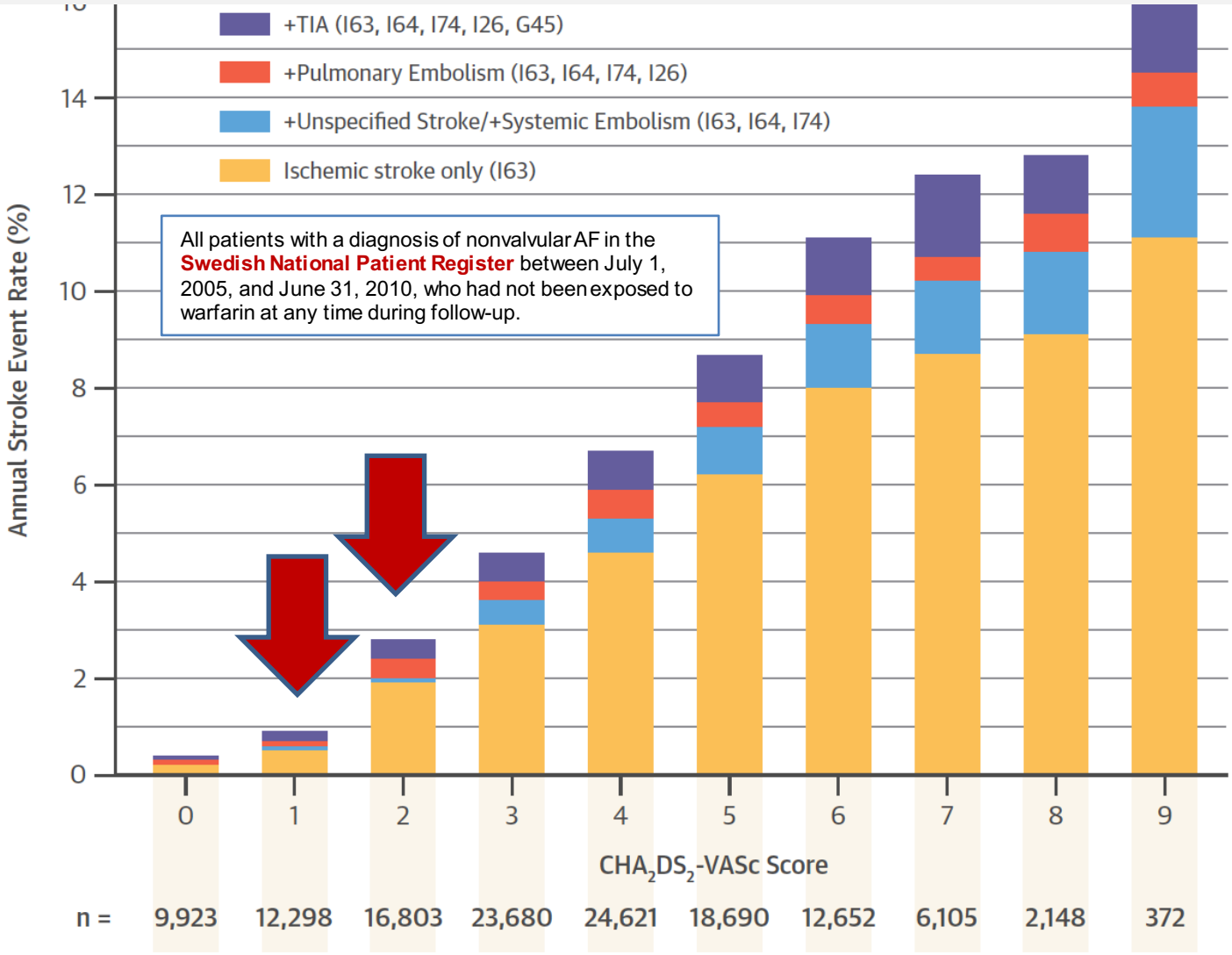
European Heart Journal - doi:10.1093/eurheartj/ehw210

Clinical risk factors for stroke, transient ischaemic attack, and systemic embolism

CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction	1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	1
Age 75 years or older	2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	1
Previous stroke, transient ischaemic attack, or thromboembolism	2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	1
Age 65–74 years	1
Sex category (female)	1

European Heart Journal - doi:10.1093/eurheartj/ehw210

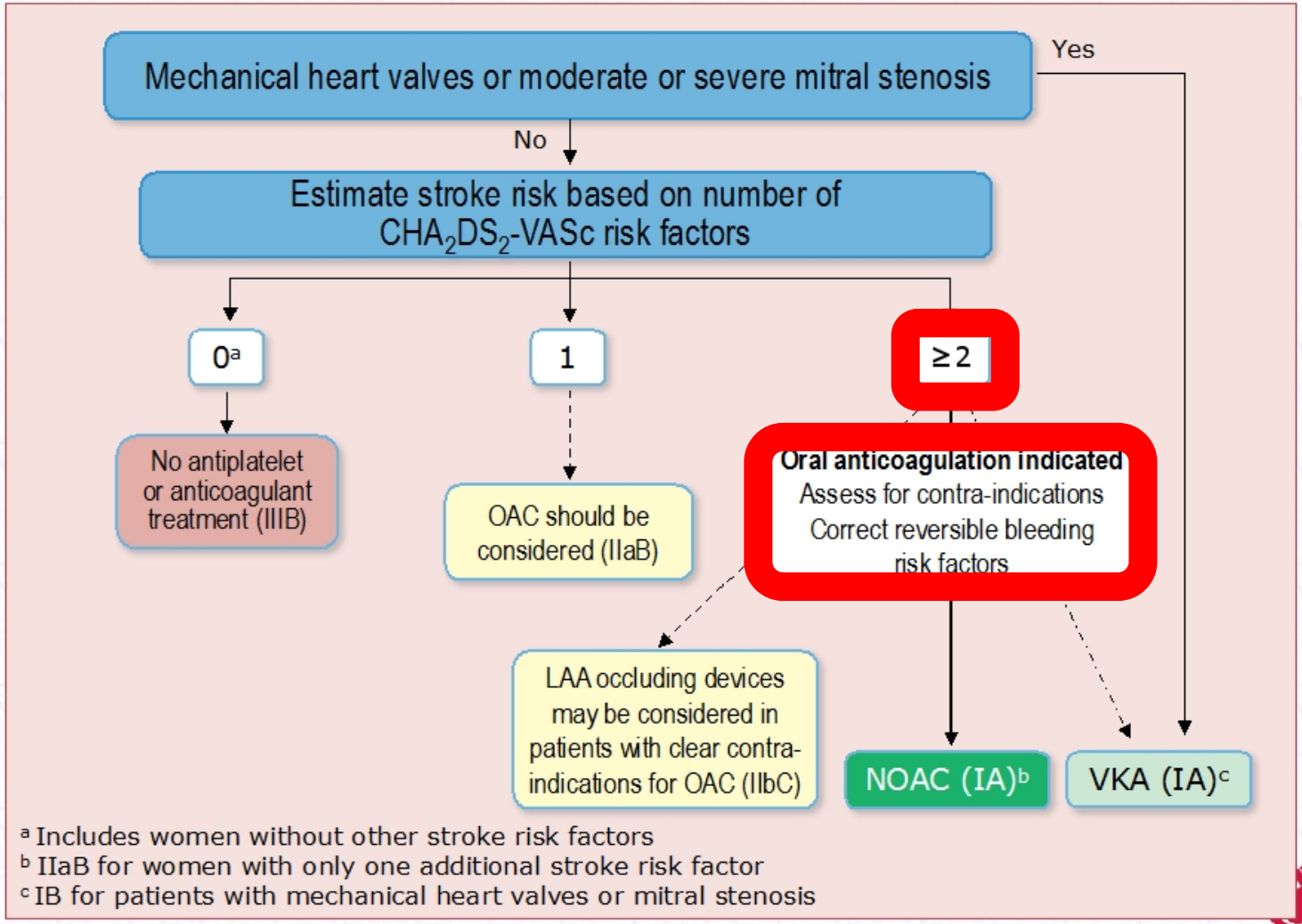
Real world data



Friberg, L. et al. J Am Coll Cardiol. 2015; 65(3):225–32.

2016

Stroke prevention in atrial fibrillation

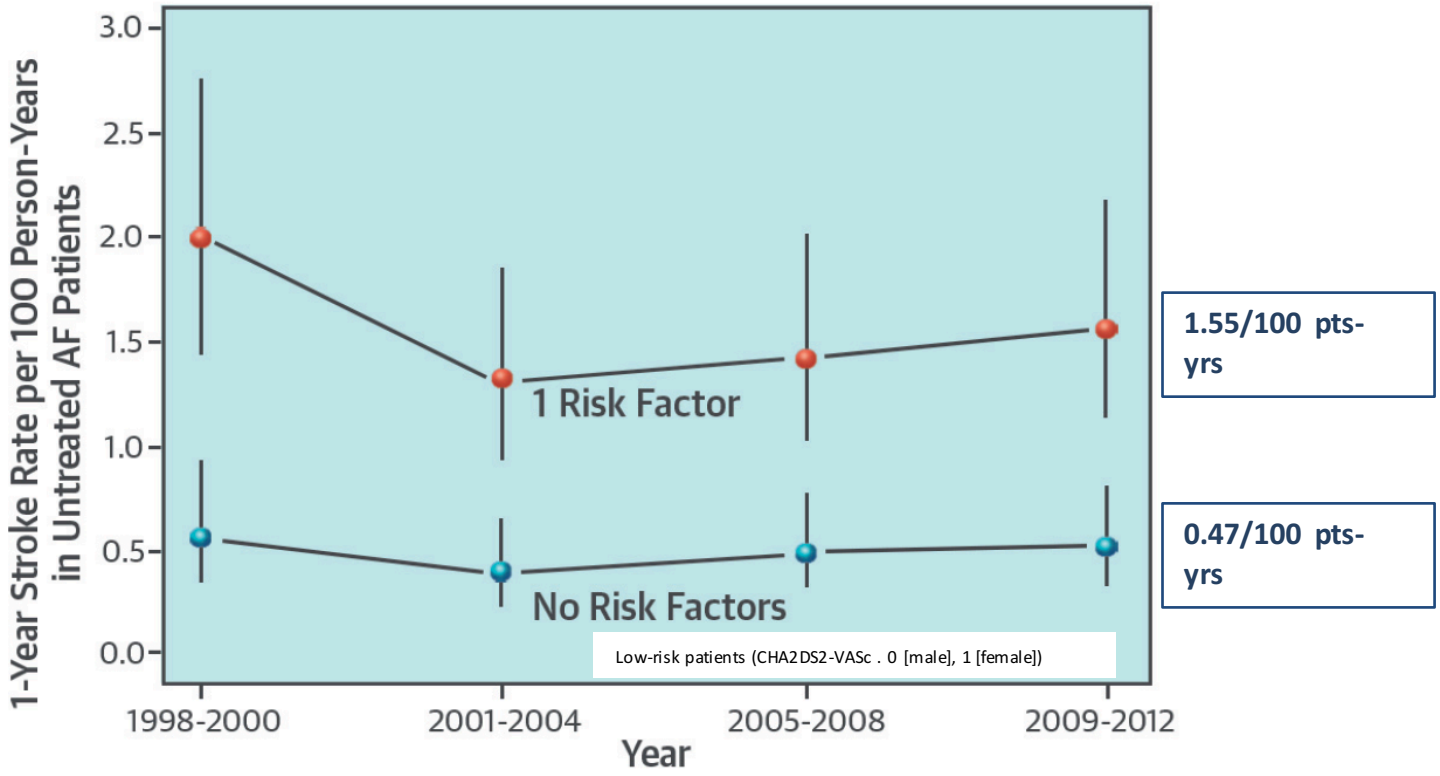


European Heart Journal - doi:10.1093/eurheartj/ehw210

Real world data

National Danish Registries

All patients with an incident hospital diagnosis of nonvalvular AF in the study period (from 1998 to the end of June 2012)



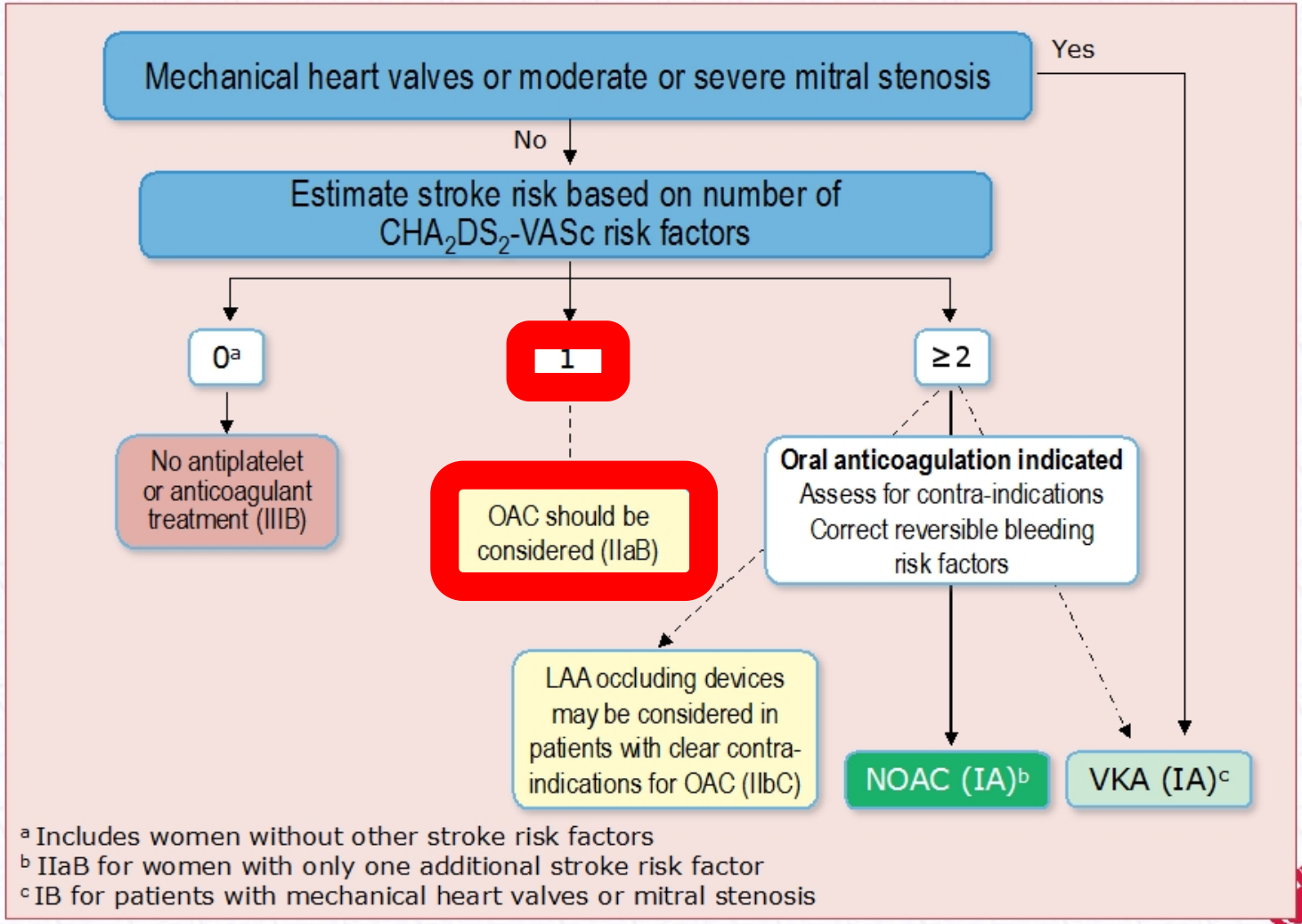
1.55/100 pts-yrs

0.47/100 pts-yrs

Lip, G.Y.H. et al. J Am Coll Cardiol. 2015; 65(14):1385–94. *(Adapted figure)*

2016

Stroke prevention in atrial fibrillation

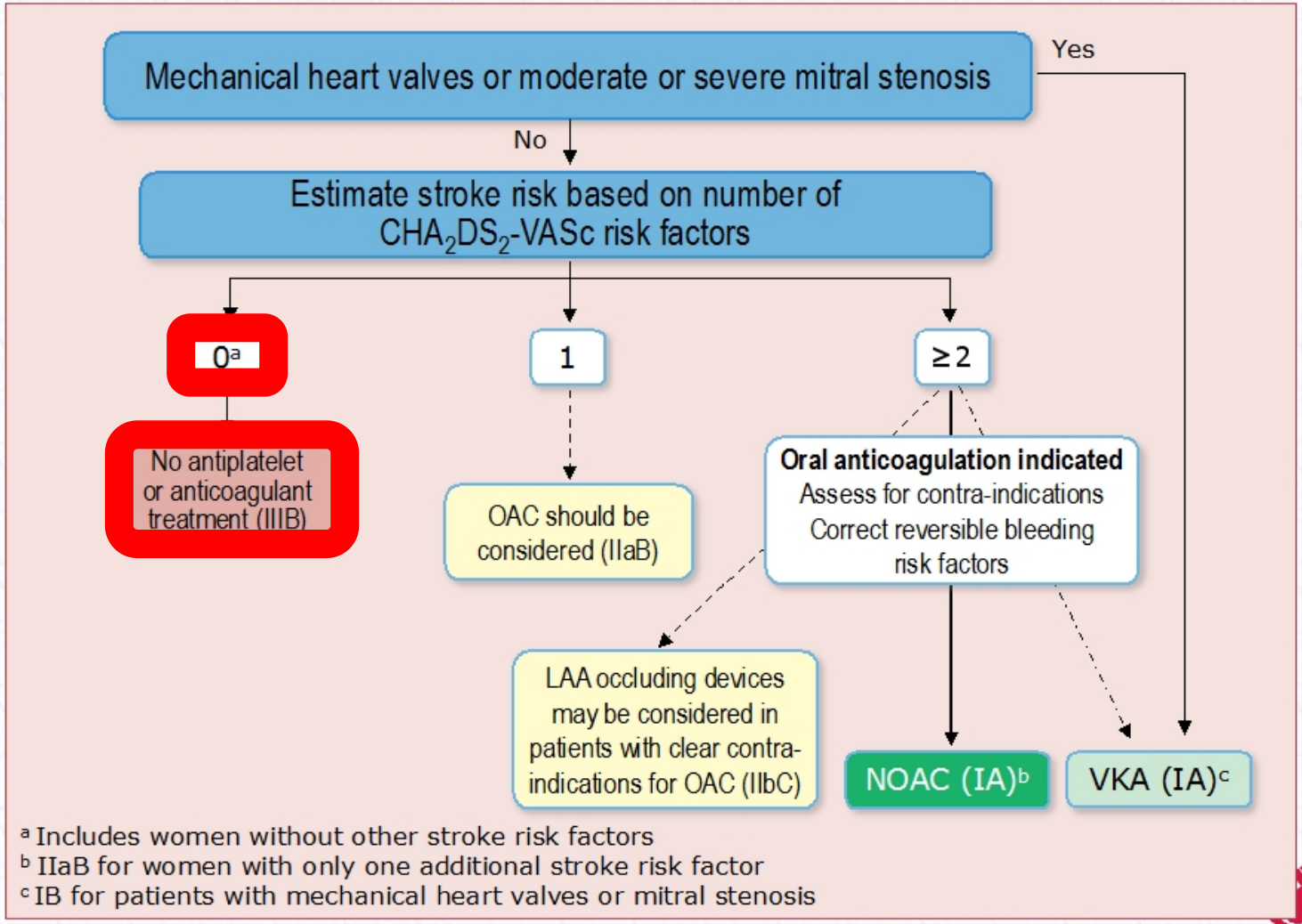


[a] Includes women without other stroke risk factors
[b] IIaB for women with only one additional stroke risk factor
[c] IB for patients with mechanical heart valves or mitral stenosis

European Heart Journal - doi:10.1093/eurheartj/ehw210

2016

Stroke prevention in atrial fibrillation



[a] Includes women without other stroke risk factors
[b] IIaB for women with only one additional stroke risk factor
[c] IB for patients with mechanical heart valves or mitral stenosis

European Heart Journal - doi:10.1093/eurheartj/ehw210

Dark side
of the Moon

Bleeding

NOACs – Bleeding rate in the four landmark trials

Table 5 Key safety results from phase III trials with novel oral anticoagulants compared with standard therapy

	RE-LY [21, 26, 27] (dabigatran)[a]		ROCKET AF [22, 30] (rivaroxaban)	ARISTOTLE [23] (apixaban)	ENGAGE AF [25] (edoxaban)	
	110 mg bid	150 mg bid			30 mg od	60 mg od
Major bleeding (%/year)	2.92 vs 3.61**	3.40 vs 3.61†	3.60 vs 3.40†	2.13 vs 3.09***	1.61 vs 3.43***	2.75 vs 3.43***
Major and NMCR bleeding (%/year)	N/A	N/A	14.90 vs 14.50†	4.07 vs 6.01***	7.97 vs 13.02***	11.10 vs 13.02***
Major GI bleeding (%/year)	1.15 vs 1.07†	1.56 vs 1.07***	2.00 vs 1.24***	0.76 vs 0.86†	0.82 vs 1.23***	1.51 vs 1.23*
Intracranial hemorrhage (%/year)	0.23 vs 0.76***	0.32 vs 0.76***	0.50 vs 0.70*	0.33 vs 0.80***	0.26 vs 0.85***	0.39 vs 0.85***
All-cause mortality (%/year)	3.75 vs 4.13†	3.64 vs 4.13†	4.50 vs 4.90†	3.52 vs 3.94*	3.80 vs 4.35**	3.99 vs 4.35†
Myocardial infarction (%/year)	0.82 vs 0.64†	0.81 vs 0.64†	0.91 vs 1.12†	0.53 vs 0.61†	0.89 vs 0.75†	0.70 vs 0.75†

bid twice daily, *GI* gastrointestinal, *N/A* not applicable, *NMCR* non-major clinically relevant, *od* once daily

† p = not significant; * $p < 0.05$; ** $p < 0.01$; *** $p \leq 0.001$

[a] Updated data (2010 and 2014) after identification of additional events post-publication (2009)

João Morais and Raffaele De Caterina

Cardiovasc Drugs Ther
DOI 10.1007/s10557-015-6632-3,

Bleeding and outcomes in AF

probability of dying in case of bleeding

Tabela 2 de hemorragia, numa população portadora de fibrilhação auricular, no contexto do estudo ACTIVE-W[10].

Tipo de hemorragia*	N.º de doentes	HR para morte (IC a 95%)	Valor de p
Todas	593	2,5 (1,8-3,5)	< 0,0001
Minor	412	1,6 (1,0-2,5)	0,036
Major	181	4,2 (2,8-6,4)	< 0,0001
Major não severa	58	1,7 (0,64-4,7)	0,28
Major severa	123	5,7 (3,6-9,1)	< 0,0001

*Cada tipo de hemorragia foi definido por protocolo.

Morais J
Rev Port Cardiol. 2012;31(Supl. I):28-33

Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients with AF

Modifiable bleeding risk factors:
Hypertension (especially when systolic blood pressure is >160 mmHg)
Labile INR or time in therapeutic range <60% in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs
Excess alcohol (≥8 drinks/week)
Potentially modifiable bleeding risk factors:
Anaemia
Impaired renal function
Impaired liver function
Reduced platelet count or function

Non-modifiable bleeding risk factors:
Age (>65 years) (≥75 years)
History of major bleeding
Previous stroke
Dialysis-dependent kidney disease or renal transplant
Cirrhotic liver disease
Malignancy
Genetic factors
Biomarker-based bleeding risk factors:
High-sensitivity troponin
Growth differentiation factor-15
Serum creatinine/estimated CrCl

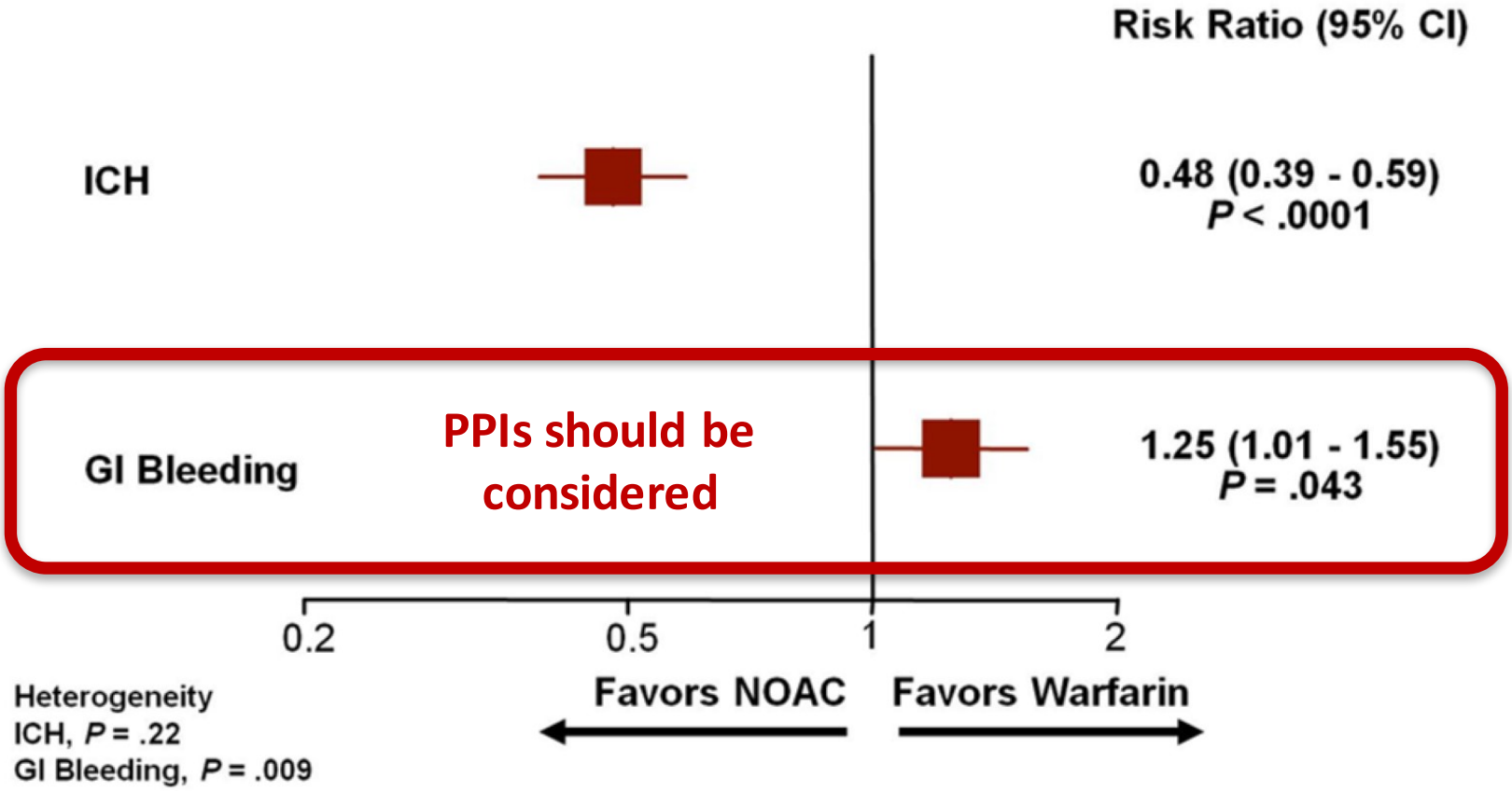
European Heart Journal - doi:10.1093/eurheartj/ehw210

Discontinuation of NOACs Pre-Procedure

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Temporary interruption of NOAC for surgery and other invasive procedures	If CrCl ≥ 50 mL/min: discontinue at least 1-2 days prior to surgery or invasive procedure If CrCl < 50 mL/min: discontinue at least 3-5 days prior to surgery or invasive procedure	Moderate-High-Risk Bleeding: discontinue at least 48 hours prior to surgery or invasive procedure Low-Risk Bleeding: discontinue at least 24 hours prior to surgery or invasive procedure	Discontinue at least 24 hours prior to surgery or invasive procedure	Discontinue at least 24 hours prior to surgery or invasive procedure

Kovacs RJ, et al. *J Am Coll Cardiol.* 2015;65:1340-1360.[12]

GI bleeding the Achilles heel



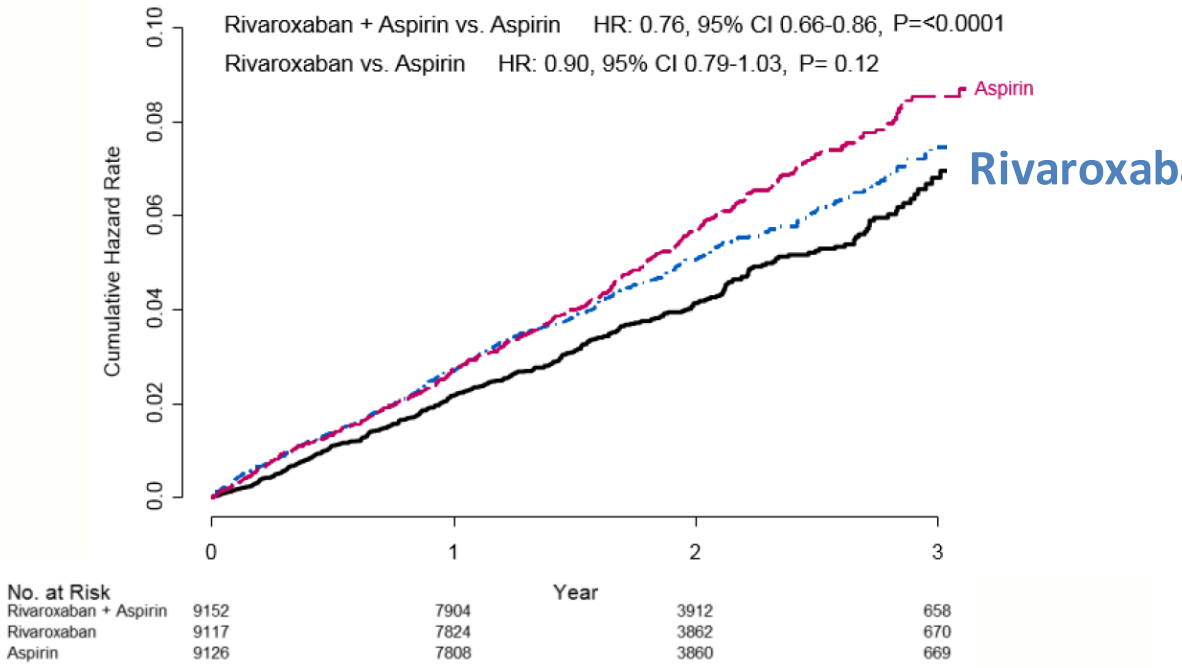
Ruff CT, et al. *Lancet.* 2014;383:955-962.

Key questions to reduce the bleeding risk

- When do you stop antiplatelet therapy?
- When do you start anticoagulant therapy?
- When do you reduce the anticoagulant dose?
- When do you avoid anticoagulation?

NOAC plus aspirin (COMPASS experience)

Primary: CV death, stroke, MI



Major bleeding

Rivaroxaban + Aspirin vs. Aspirin	
HR (95% CI)	**P**
1.70 (1.40-2.05)	<0.0001

NOACs and renal function

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran Etexilate
Target Enzyme	Factor Xa	Factor Xa	Factor Xa	Thrombin
T_{max}, h	1-4	2-4	1-2	2
Elimination $t_{½}$, h	12	5-9 (young); 11-13 (elderly)	9-11	12-17
Nonrenal/renal clearance of adsorbed dose, %	73/27	65/35*	50/50	20/80

Heidbuchel H, et al. *Europace*. 2013;15:625-651.[20]

NOACs dose reduction

RE-LY[a]	ROCKET-AF[b]	ARISTOTLE[c]	ENGAGE-AF[d]
• None	• 20→15 mg QD for: – Creatinine clearance < 30-49 mL/min	• 5→2.5 mg BID for ANY TWO of: – Age ≥ 80 years – body weight ≤ 60 kg – Serum creatinine ≥ 1.5 mg/dL	• 60→30 mg QD or 30→15 mg QD for: – Creatinine clearance 30-50 mL/min – body weight ≤ 60 kg – Use of quinidine, verapamil, or dronedarone

a. Connolly SJ,et al. *N Engl J Med*. 2009;361:1139-1151[18]
b. Patel MR, et al. *N Engl J Med*. 2011;365:883-891[19];
c. Granger CB, et al. *N Engl J Med*. 2011;365:981-992[20];
d. Giugliano RP, et al. *N Engl J Med*. 2013;369:2093-2104.[21]

Reversal of Warfarin and the VKAs: Time to Effect

Product	Time to Effect (After Administration)	Duration of Effect
Oral vitamin K	24 hours	Days
Intravenous vitamin K	8-12 hours	Days
FFP	Immediate	12-24 hours
PCCs	Immediate	12-24 hours
Recombinant factor VIIa	Immediate	2-6 hours

Garcia DA, et al. *Circulation*. 2012;125(23):2944-2947.

European Heart Journal Advance Access published December 24, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv676

CURRENT OPINION

Reversal strategies for non-vitamin K antagonist oral anticoagulants: a critical appraisal of available evidence and recommendations for clinical management—a joint position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Working Group on Thrombosis

Niessner A, ... Morais J... et al. EHJ 2015

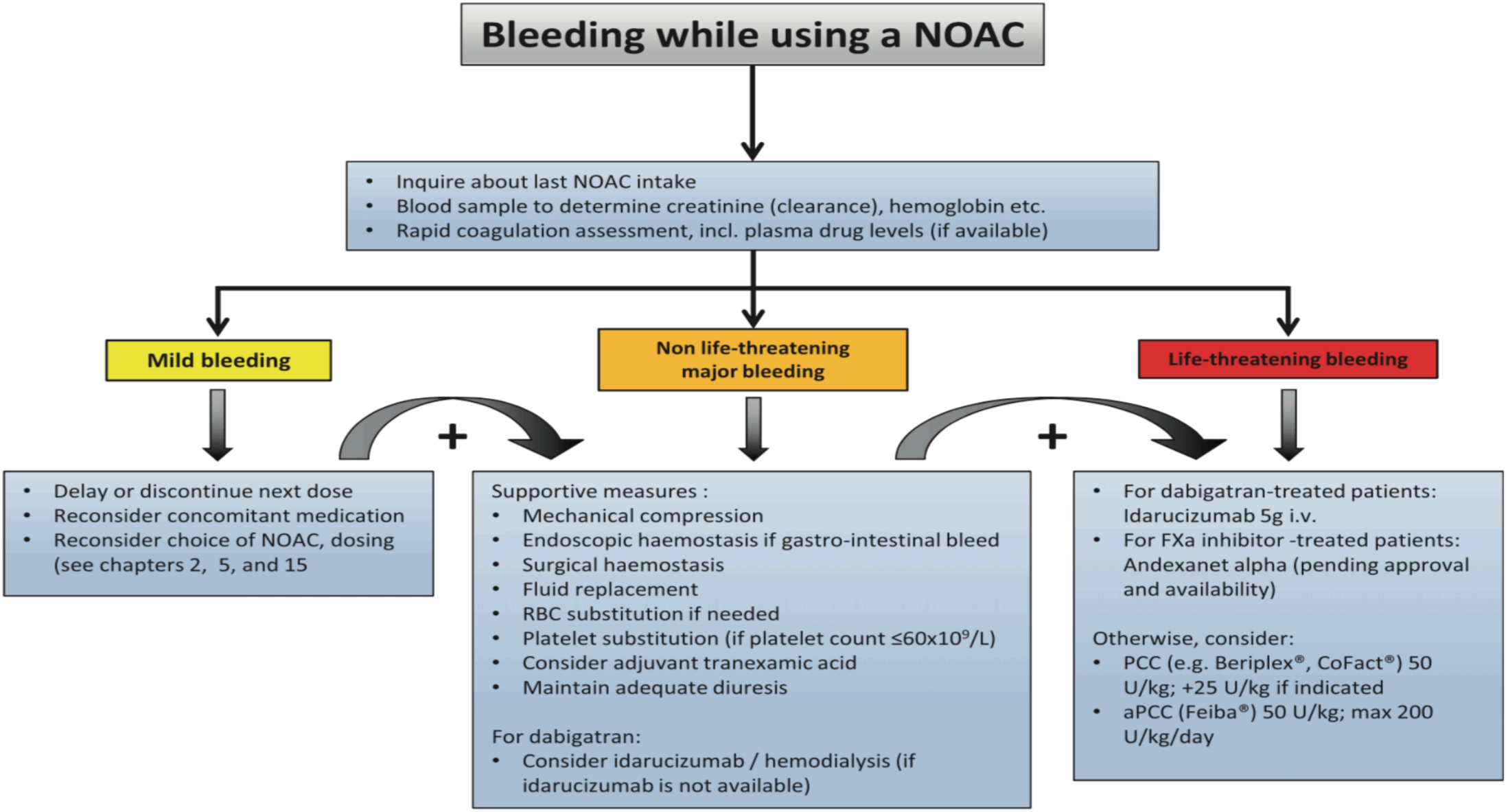
European Heart Journal Advance Access published October 27, 2016

European Heart Journal (2016) **0**, 1–11
doi:10.1093/eurheartj/ehw454

CURRENT OPINION

Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European Society of Cardiology Working Group on Thrombosis

Halvorsen S , ... Morais J... et al. EHJ 2016


Bleeding while using a NOAC
• Inquire about last NOAC intake
• Blood sample to determine creatinine (clearance), hemoglobin etc.
• Rapid coagulation assessment, incl. plasma drug levels (if available)
Mild bleeding
Non life-threatening major bleeding
Life-threatening bleeding
+
+
• Delay or discontinue next dose
• Reconsider concomitant medication
• Reconsider choice of NOAC, dosing (see chapters 2, 5, and 15
Supportive measures :
• Mechanical compression
• Endoscopic haemostasis if gastro-intestinal bleed
• Surgical haemostasis
• Fluid replacement
• RBC substitution if needed
• Platelet substitution (if platelet count ≤60x10^9/L)
• Consider adjuvant tranexamic acid
• Maintain adequate diuresis
For dabigatran:
• Consider idarucizumab / hemodialysis (if idarucizumab is not available)
• For dabigatran-treated patients: Idarucizumab 5g i.v.
• For FXa inhibitor -treated patients: Andexanet alpha (pending approval and availability)
Otherwise, consider:
• PCC (e.g. Beriplex®, CoFact®) 50 U/kg; +25 U/kg if indicated
• aPCC (Feiba®) 50 U/kg; max 200 U/kg/day

There is a need for a specific reversal agent in clinical situations where rapid reversal of NOACs is required

Emergency surgery or urgent intervention

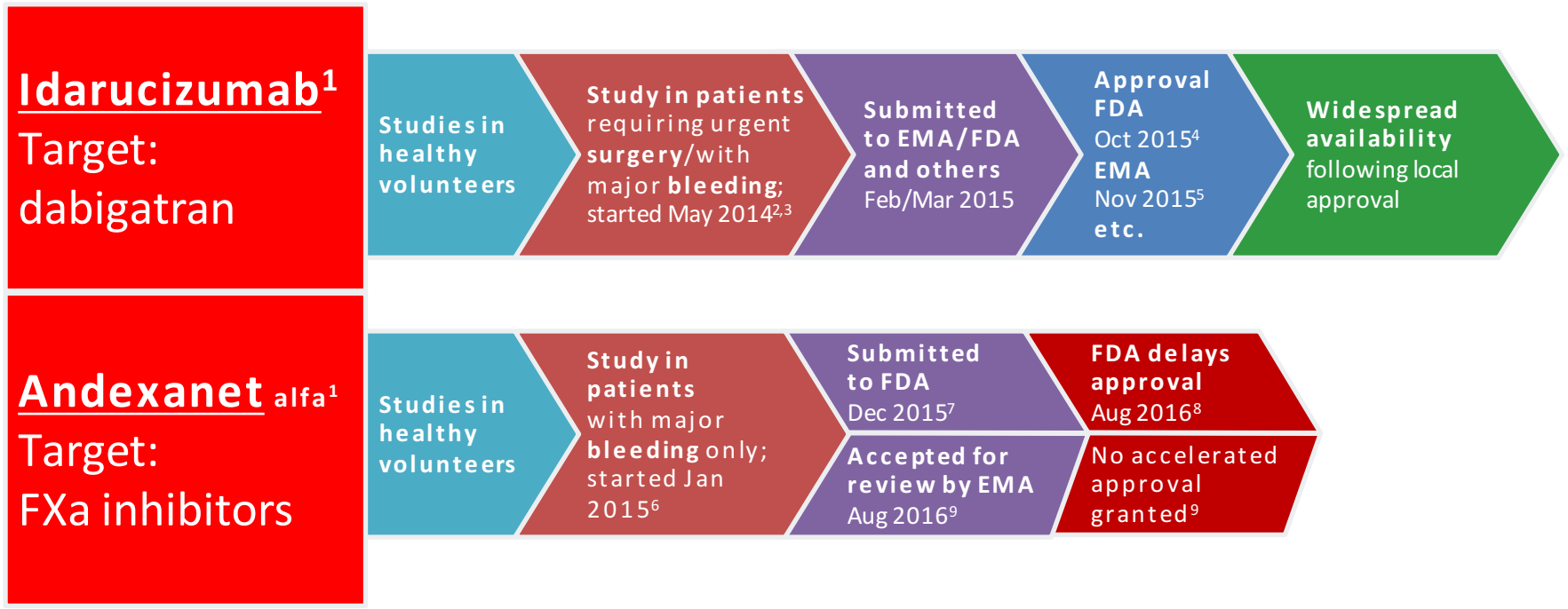
Life-threatening or uncontrolled bleeding

A specific reversal agent could take the NOAC out of the equation in these situations

While a specific reversal agent could remove the anticoagulant effect, other measures (e.g. surgery, fluid replacement) would still be required to correct the underlying cause of the bleed (e.g. vessel rupture) and its consequences (e.g. shock)

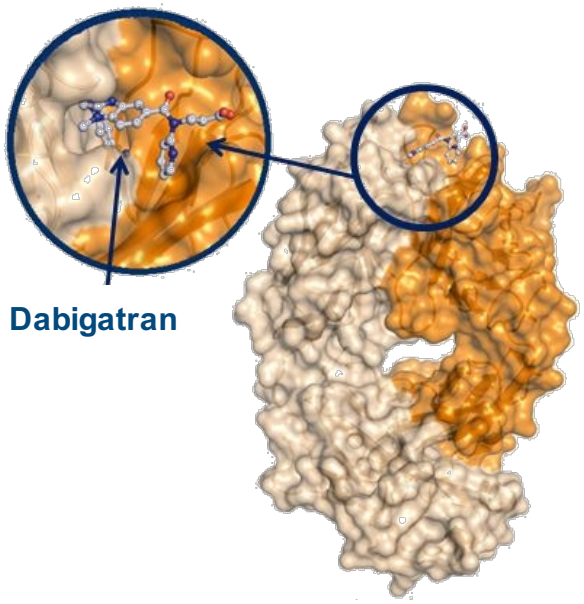
Levy JH et al. J Thromb Haemost 2016

What specific reversal agents for NOACs are available or in development?



Idarucizumab is not approved in all countries. Please check your local prescribing information for details. Andexanet alfa is an investigational compound and is not approved in any country. 1. Adapted from Greinacher A et al. Thromb Haemost 2015; 2. Pollack C et al. N Engl J Med 2015; 3. Pollack C et al. Thromb Haemost 2015; 4. US FDA 2015 press release, 16 October 2015; 5. European Commission Community Register of Medicinal Products for Human Use 2015; 6. ClinicalTrials.gov Identifier: NCT02329327; 7. Portola Pharmaceuticals press release, 18 Dec 2015; 8. Portola Pharmaceuticals press release 17 August 2016; 9. Portola Pharmaceuticals press release 19 August 2016

Idarucizumab was designed as a specific reversal agent for the anticoagulant activity of dabigatran



- Humanized antibody (Fab) fragment
- Specific to dabigatran
- Binding affinity for dabigatran ~350 × higher than dabigatran to thrombin, resulting in essentially irreversible binding
- Ready to use solutions for IV administration, immediate onset of action
- No intrinsic procoagulant or anticoagulant activity
- No endogenous targets
- Idarucizumab–dabigatran complex is eliminated quickly (within a few hours)

Idarucizumab is not approved in all countries. Please check your local prescribing information for details.

Adapted from Schiele F et al. Blood 2013; Stangier J et al. ISTH 2015; Pradaxa® EU SPC, 2016; Schmohl M et al. Thromb Haemost 2016 [accepted manuscript]

RE-VERSE AD™: idarucizumab is effective in patients

Endpoints	Outcomes
Primary endpoint: Reversal of dabigatran anticoagulation with idarucizumab based on dTT and ECT	**dTT was normalized in 98% and 93% of Group A and B patients, respectively*** **ECT was normalized in 89% and 88% of Group A and B patients, respectively***
Secondary endpoint (Group A): Time to cessation of bleeding (as judged by the investigator)	**Median local investigator-determined time to bleeding cessation was 11.4 hours†**
Secondary endpoint (Group B): normal haemostasis during procedure	**Intraoperative haemostasis was normal in 33 patients (92%)**

5/90 patients (6%) had thromboembolic events
16/90 patients (18%) died in 90-day follow up

*Calculated for patients with elevated levels at baseline; †Assessable in 35 patients. Assessment of bleeding cessation may be difficult in internal bleeding into confined space such as intramuscular or intracranial bleeding.
dTT, diluted thrombin time; ECT, ecarin clotting time; Pollack et al. N Engl J Med 2015

Key messages

- The paradigm of oral anticoagulation just changed and NOACs are the preferred drugs whenever they are indicated.
- NOACs are adequate to expand the prevention of thromboembolism
  (to apparently low risk AF patients; to extend secondary prevention of DVT)
- In spite of a clear class effect of NOACs one size doesn't fit all. For a single patient a single drug and an adequate dosage.
- The counterpart of thrombus prevention is bleeding, always potentially present but also potentially preventable

SIMPÓSIO DE MEDICINA
CARDIOVASCULAR DE COIMBRA 2018

11 e 12
MAIO 2018
VILA GALÉ COIMBRA

Cursos Pré-Simpósio
10 MAIO

Hipocoagulação oral [illegible], a quem, com quê?
Como rea[illegible]so de hemorragia?

Muito obrigado

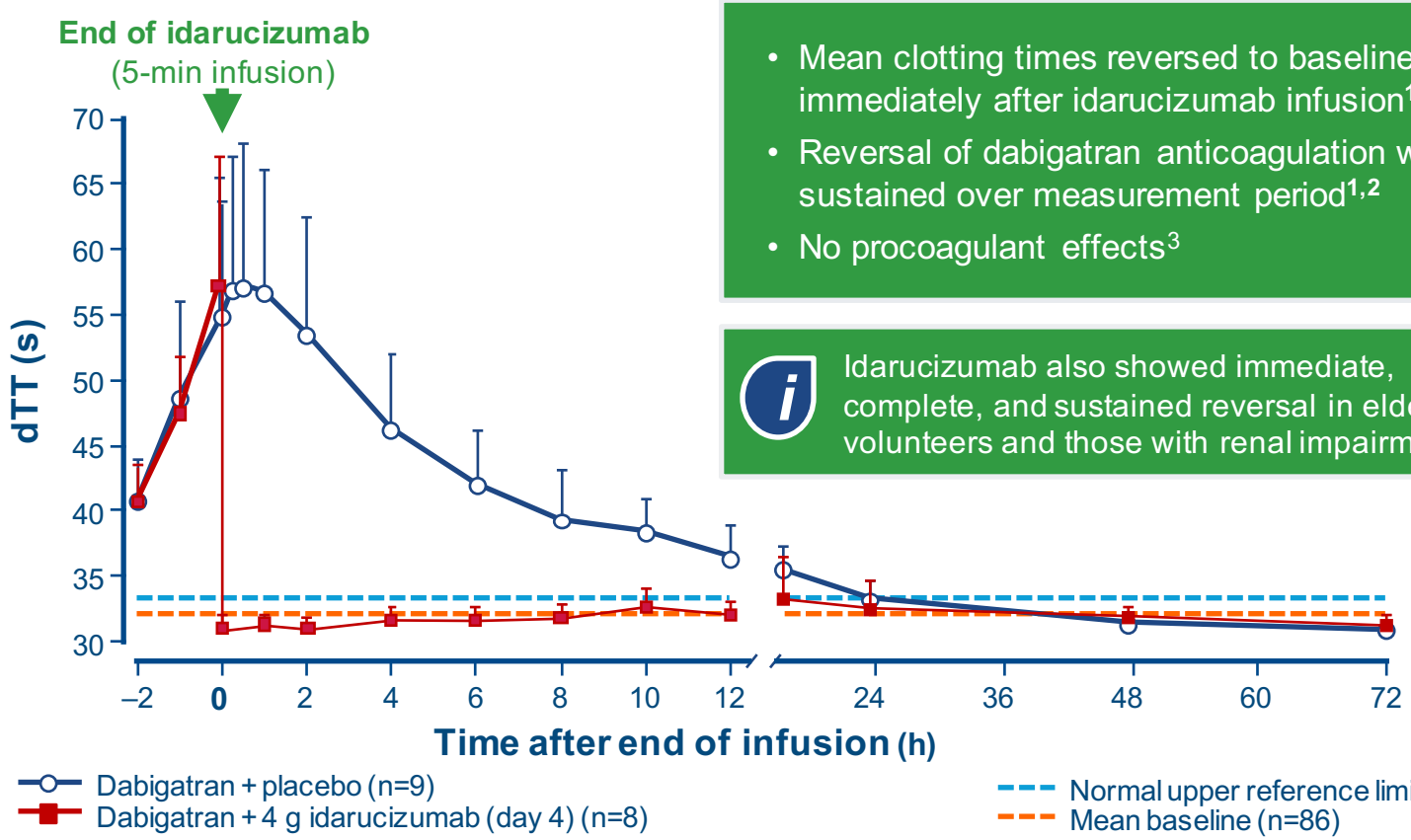
João Morais
Centro Hospitalar de Leiria

Serviço de Cardiologia
Centro Hospitalar de Leiria

ESC European Society of Cardiology

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Idarucizumab provided immediate, complete, and sustained reversal of dabigatran anticoagulation in healthy volunteers



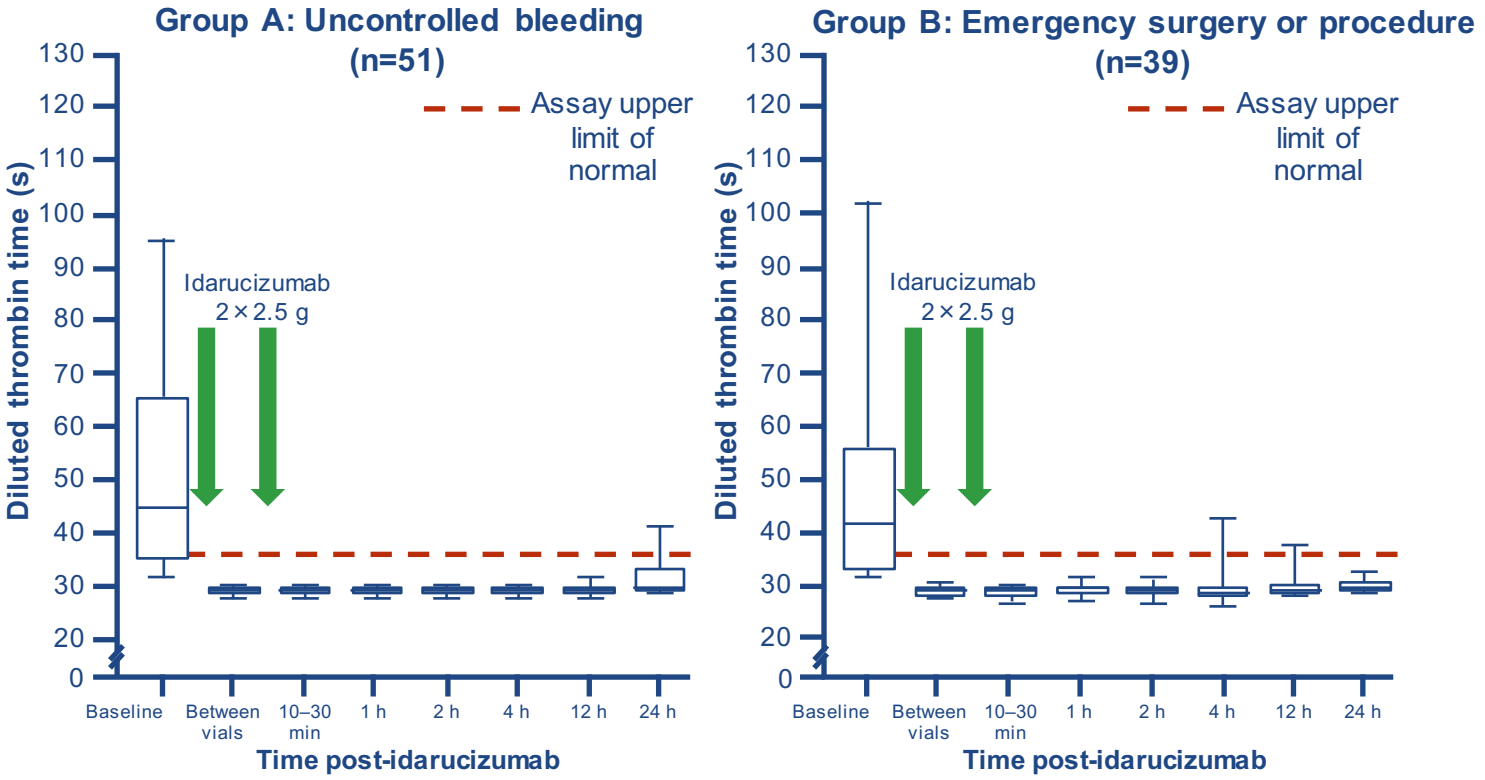
- Mean clotting times reversed to baseline immediately after idarucizumab infusion[1,2]
- Reversal of dabigatran anticoagulation was sustained over measurement period[1,2]
- No procoagulant effects[3]

Idarucizumab also showed immediate, complete, and sustained reversal in elderly volunteers and those with renal impairment

Idarucizumab is not approved in all countries. Please check your local prescribing information for details.

dTT, diluted thrombin time. 1. Glund S et al. Lancet 2015; 2. Glund S et al. Thromb Haemost 2015; 3. Glund S et al. ASH 2014

RE-VERSE AD™ interim results: idarucizumab provided sustained reversal of dabigatran in patients with bleeding or requiring surgery

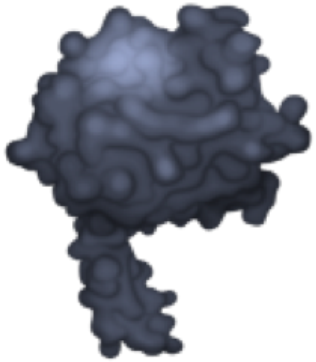


Idarucizumab is not approved in all countries. Please check your local prescribing information for details.

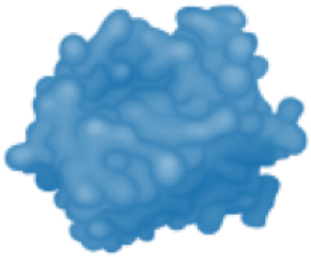
Interim analysis includes data for the first 90 patients. Adapted from Pollack CV et al. N Engl J Med 2015

Andexanet alfa acts as a reversal agent for all direct specific FXa inhibitors, plus LMWHs and fondaparinux

Andexanet alfa



Factor Xa



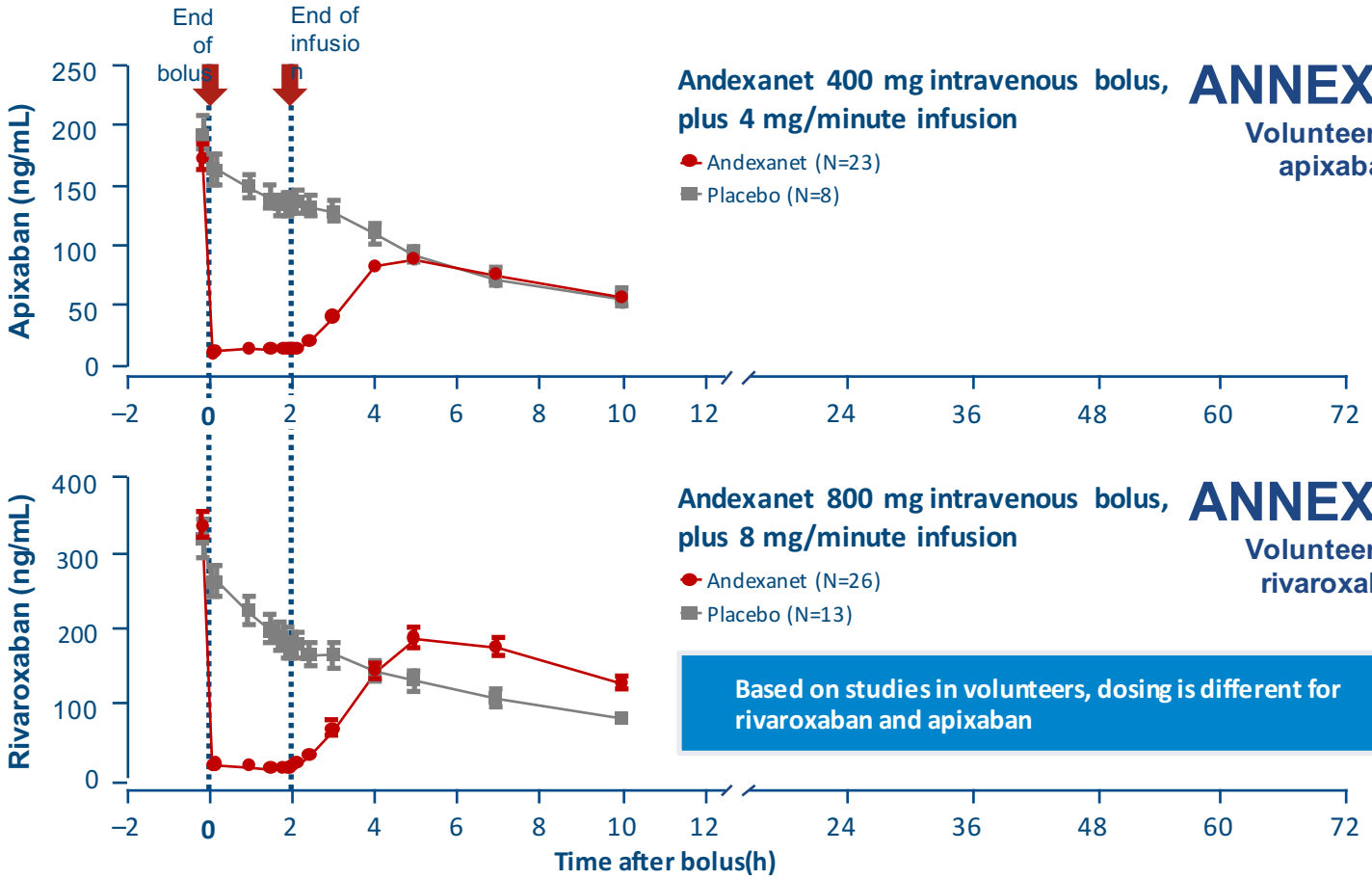
Andexanet alfa

- Recombinant modified FXa
- Targets direct and indirect FXa inhibitors, acting as a decoy by competitively binding with direct FXa inhibitors
- Similar binding affinities to FXa, leading to only temporary inactivation of FXa inhibitor and limiting potential for sustained effect
- Requires reconstitution prior to IV administration by bolus AND continuous infusion
- Transient procoagulant signals observed[1,2]
- Short half-life (30–60 min)

Andexanet alfa is an investigational compound and is not approved in any country.

LMWH, low-molecular-weight heparin. 1. Lu G et al. ISTH 2015; 2. Connolly SJ et al. N Engl J Med 2016

In healthy volunteers, the reversal effects of andexanet alfa were not sustained beyond the 2-hour infusion



Andexanet alfa is an investigational compound and is not approved in any country.

1. Siegal DM et al. N Engl J Med 2015

ANNEXA-4: andexanet alfa was associated with effective haemostasis and a high rate of thromboembolic events

Andexanet alfa

Endpoints	Outcomes
Co-primary endpoint 1: percentage change in anti-FXa activity	**In patients taking rivaroxaban and apixaban, the percentage change was 89% and 93%, respectively***
Co-primary endpoint 2: proportion of patients with excellent or good haemostasis 12 hours after the infusion	**Clinical haemostasis was adjudicated as excellent or good in 79% of patients†** Unclear if reversal occurred in those patients with poor/no haemostasis

12/67 patients (18%) had thromboembolic events
10/67 patients (15%) died in 30-day follow-up

Andexanet alfa is an investigational compound and is not approved in any country.

*Calculated for 26 patients on rivaroxaban and 20 patients on apixaban in the efficacy analysis; †Calculated for 47 patients in efficacy analysis; Connolly SJ et al. N Engl J Med 2016

Unlike RE-VERSE AD™, ANNEXA-4 does not evaluate andexanet alfa in patients requiring urgent surgery or procedures

	RE-VERSE AD™[1,2]	ANNEXA-4[3]
Reversal agent	**Idarucizumab**	**Andexanet alfa**
Indications	Life-threatening **bleeding** AND urgent **surgery**	**Major bleeding**
Endpoints	**Primary endpoint** Maximum reversal of dabigatran activity, based on central laboratory measurements of dTT or ECT from idarucizumab administration to 4 hrs after administration **Secondary endpoint** Time to recorded cessation of bleeding in Group A, normalization of haemostasis in Group B	**Co-primary endpoints** Percentage change in anti-FXa activity AND proportion of patients with excellent or good haemostasis 12 hours after the infusion
Dosing	5 g dose given as a bolus injection	15–30 minute bolus plus a 2-hr infusion

Idarucizumab is not approved in all countries. Please check your local prescribing information for details.
Andexanet alfa is an investigational compound and is not approved in any country. dTT, diluted thrombin time; ECT, ecarin clotting time; PCC, prothrombin complex concentrate. 1. Pollack CV et al. Thromb Haemost 2015; 2. ClinicalTrials.gov Identifier: NCT02104947; 3. Connolly SJ et al. N Engl J Med 2016