NOACs in VTE
drug selection according to patient's risk profile and duration of therapy

João Morais

Head of Cardiology Division and Research Centre

Leiria Hospital Centre

Portugal

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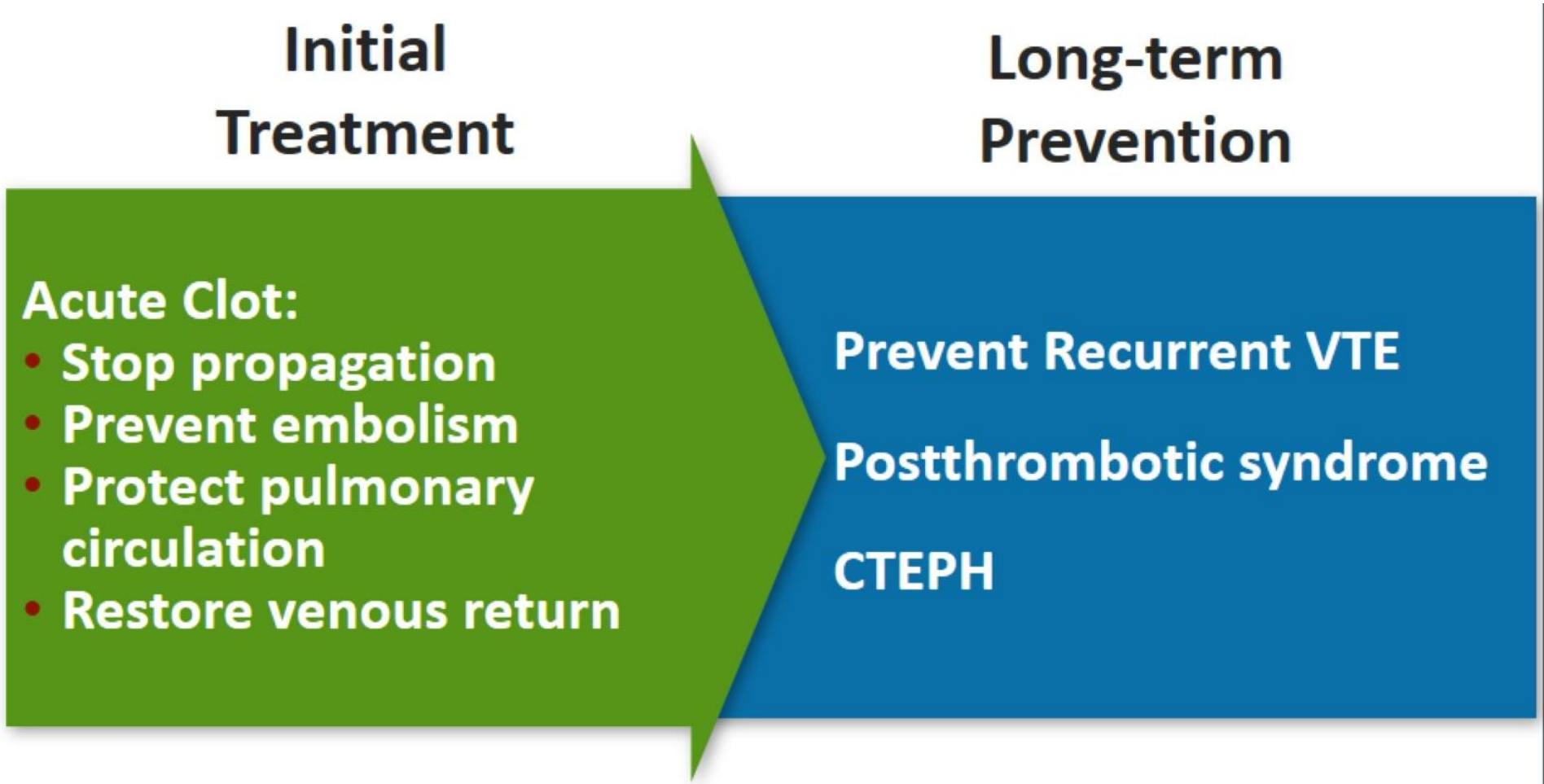
Disclosures

João Morais

On the last year JM received honoraria for consultant activities and invited speaker for pharmaceutical and device's companies

- Astra Zeneca
- Bayer Healthcare
- BMS / Pfizer
- Boehringher Ingelheim
- Boston Scientific
- Daiichi Sankyo
- Merck Sharp and Dhome

Goals of VTE treatment



CTEPH = chronic thromboembolic pulmonary hypertension

Conventional therapy

- Heparin plus VKA

New therapy

- Single drug approach
- Higher initial dose

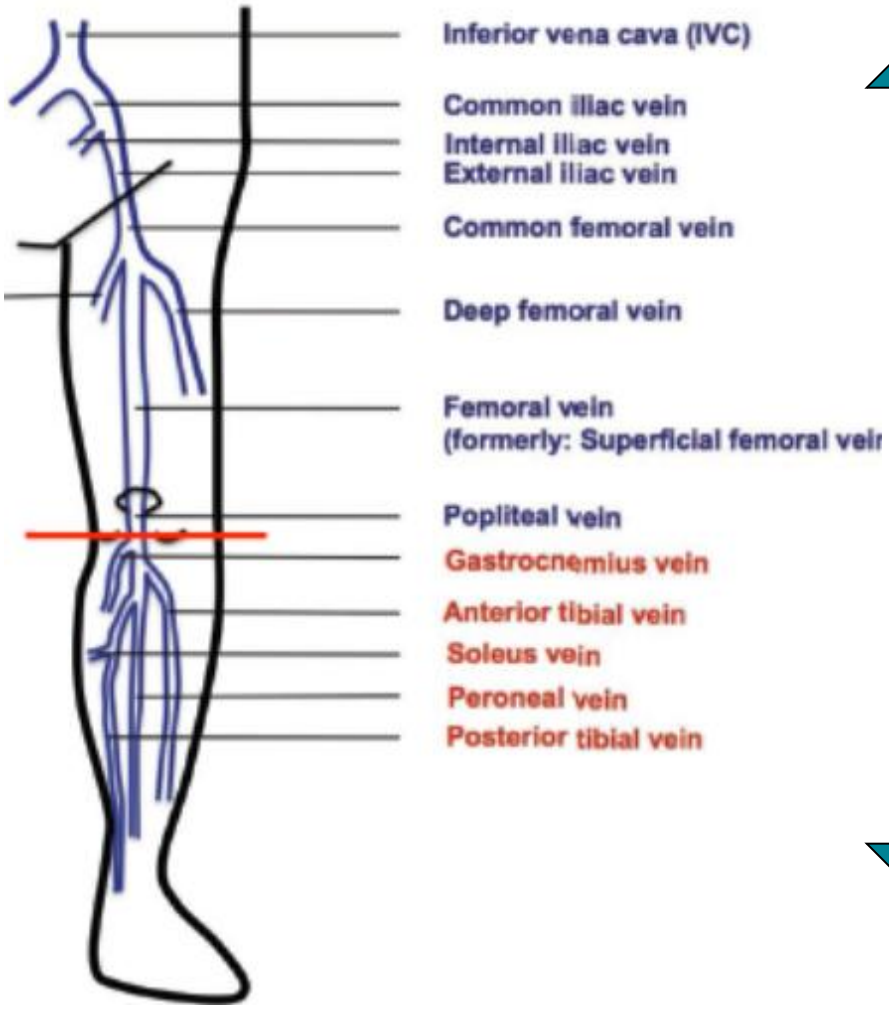
Individualized therapy

Based on the clinical setting

Based on patient's characteristics

Based on the individual prognosis

Classification of lower limb DVT



Proximal DVT

Popliteal
Femoral
Deep femoral
Common femoral
Iliac

Distal DVT

Gastrocnemius
Tibial (ant/post)
Soleus
Peroneal

Superficial vein

Great saphenous

Chest 2012;141:e419S-e494S

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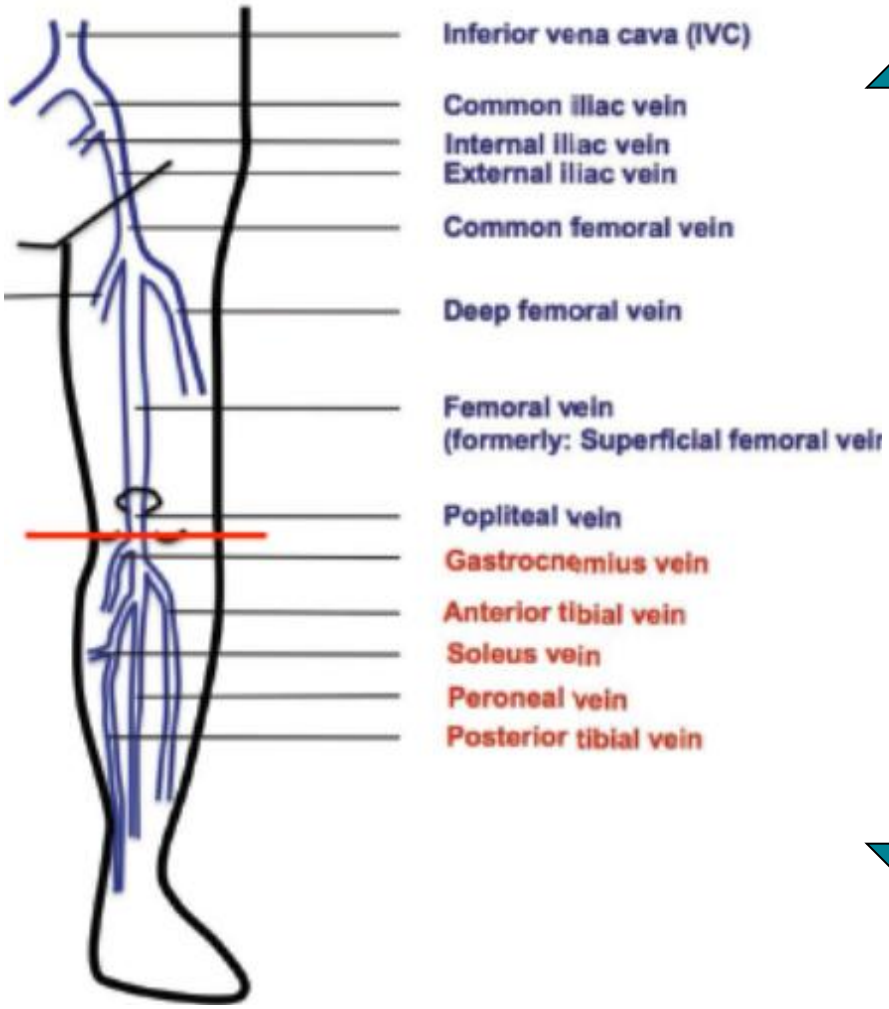
Classification of lower limb DVT



Proximal DVT

Early treatment
Anticoagulants
Agressive
Parenteral R_x

Distal DVT

Gastrocnemius
Tibial (ant/post)
Soleus
Peroneal

Superficial vein

Great saphenous

Chest 2012;141:e419S-e494S

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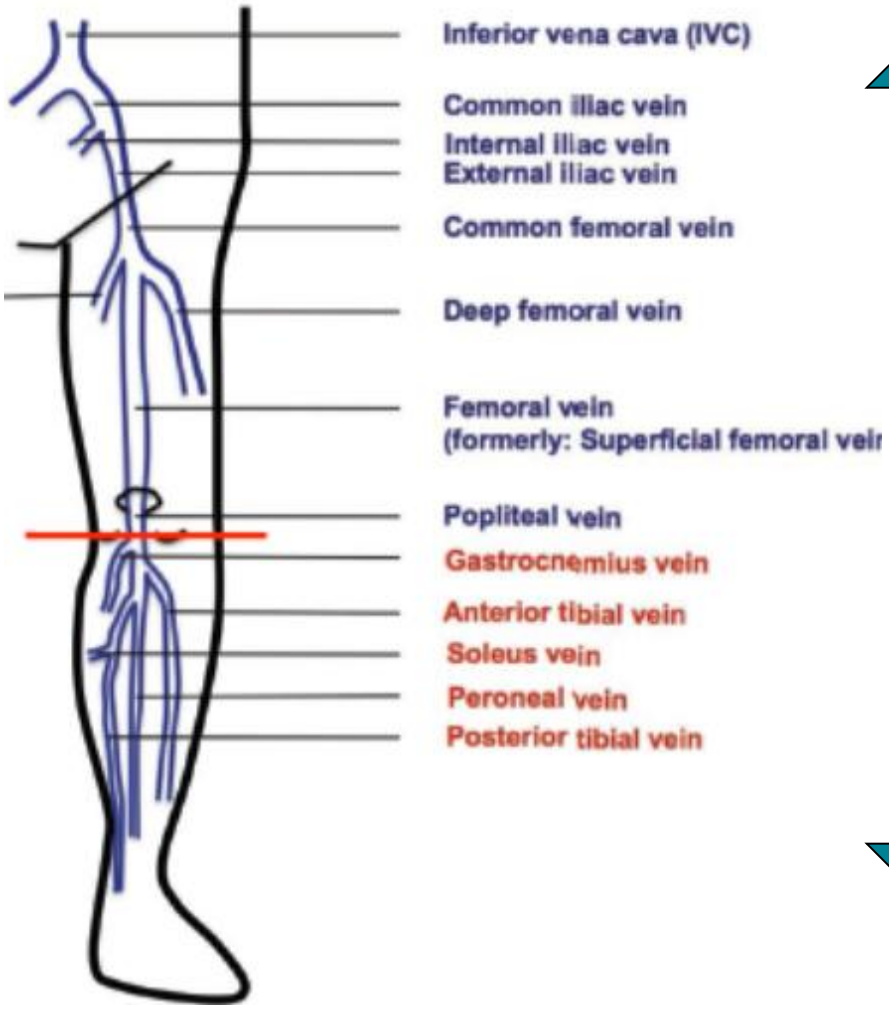
Classification of lower limb DVT



Proximal DVT

Early treatment
Anticoagulants
Agressive
Parenteral R_x

Distal DVT

Conservative treatment
Delayed oral R_x

Superficial vein

Great saphenous

Chest 2012;141:e419S-e494S

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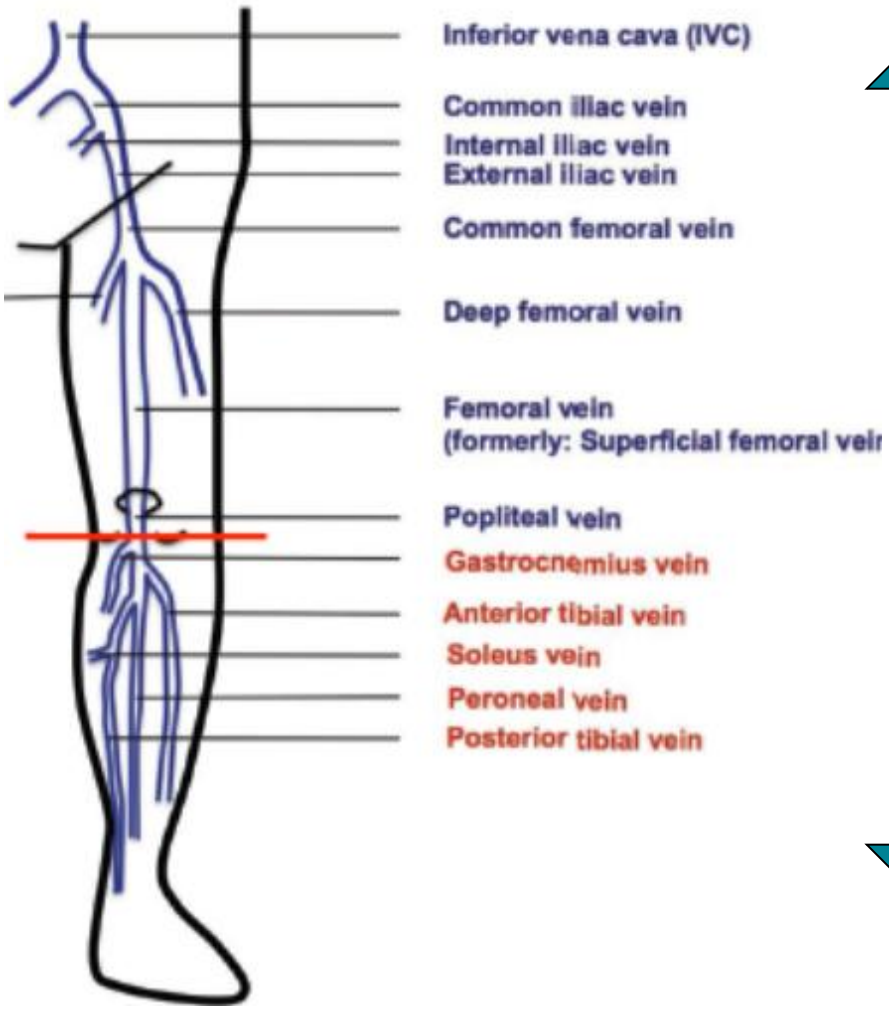
Classification of lower limb DVT



Proximal DVT

Early treatment
Anticoagulants
Agressive
Parenteral R_x

Distal DVT

Conservative treatment
Delayed oral R_x

Superficial vein

Prophylatic treatment

Chest 2012;141:e419S-e494S

Clinical trigger

Unprovoked

DVT or PE in patients with n ntly occurring major cli rs for v ism or tients with active cancer, thrombophilia or family history of DVT

Long-term treatment

Provoked

DVT or PE in patients v occurrence of al risk fact as embolism s uma, immobilization, pregnancy, oral ptive use or hormone replacement therapy

Short-term treatment

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Bleeding risk assessment

Risk factors
Age >65 y[17-25]
Age >75 y[17-21,23,25-34]
Previous bleeding[18,24,25,30,33-36]
Cancer[20,24,30,37]
Metastatic cancer[36,38,]
Renal failure[18,24,25,28,30,33]
Liver failure[19,21,27,28]
Thrombocytopenia[27,36]
Previous stroke[18,25,27,39]
Diabetes[18,19,28,32,34]
Anemia[18,21,27,30,34]
Antiplatelet therapy[19,27,28,34,40]
Poor anticoagulant control[22,28,35]
Comorbidity and reduced functional capacity[24,28,36]
Recent surgery[21,41,b]
Frequent falls[27]
Alcohol abuse[24,25,27,34]

Low risk

0 risk factors

Moderate risk

1 risk factor

High risk

≥ 2 risk factors

Chest 2012;141:e419S-e494S

Bleeding risk assessment

Anticoagulation 0 - 3 months

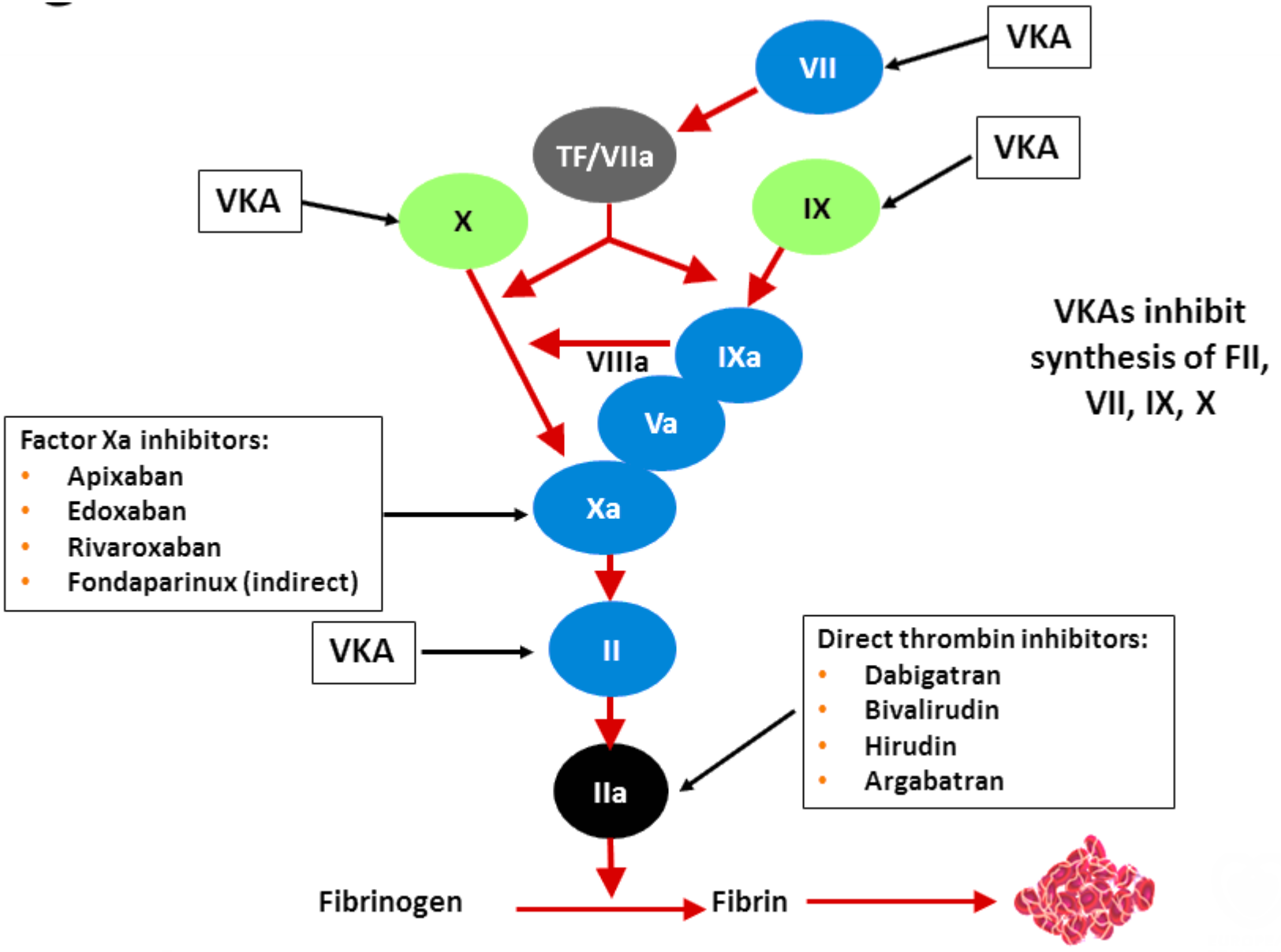
Categorization of Risk of Bleeding[c]	Estimated Absolute Risk of Major Bleeding, %		
	Low Risk[d] (0 Risk Factors)	Moderate Risk[d] (1 Risk Factor)	High Risk[d] (≥2 Risk Factors)
Anticoagulation 0-3 mo[e]			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6[e]	3.2	12.8[f]

Anticoagulation after 3 months

Baseline risk (%/y)	0.3[h]	0.6	≥2.5
Increased risk (%/y)	0.5	1.0	≥4.0
Total risk (%/y)	0.8[i]	1.6[i]	≥6.5

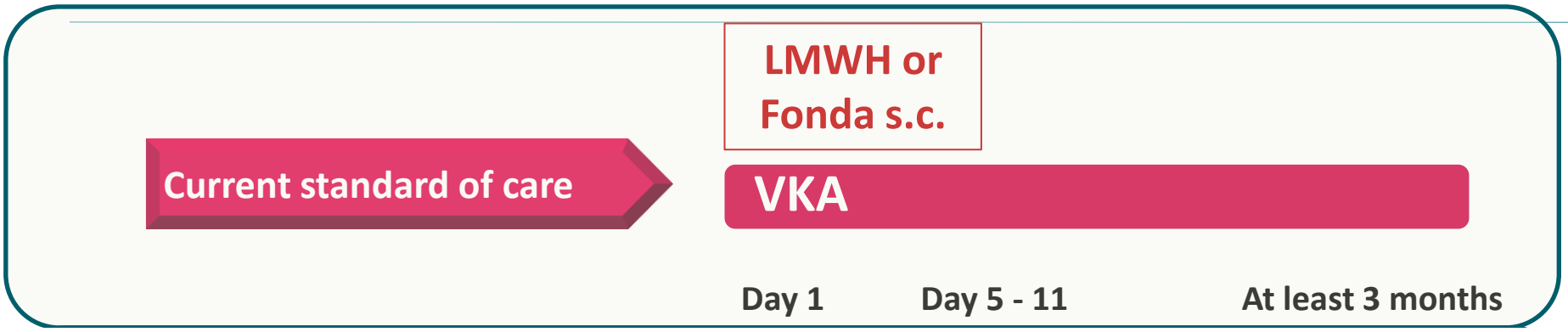
Chest 2012;141:e419S-e494S

Targets for anticoagulants

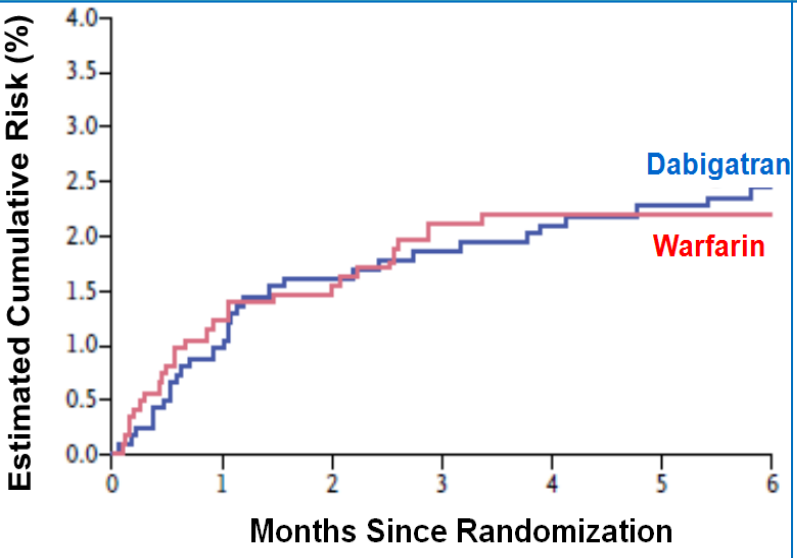


Adapted from Weitz JI, et al.[1]

Current and evolving anticoagulant regimen



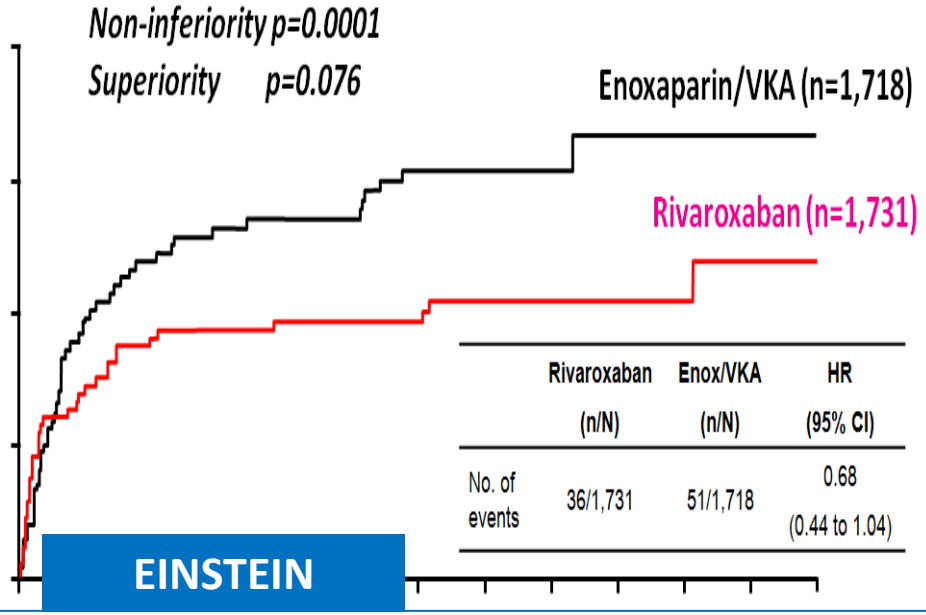
Konstantinides S and Goldhaber Z Eur Heart J 2012 doi:10.1093/eurheartj/ehs258



No. at risk

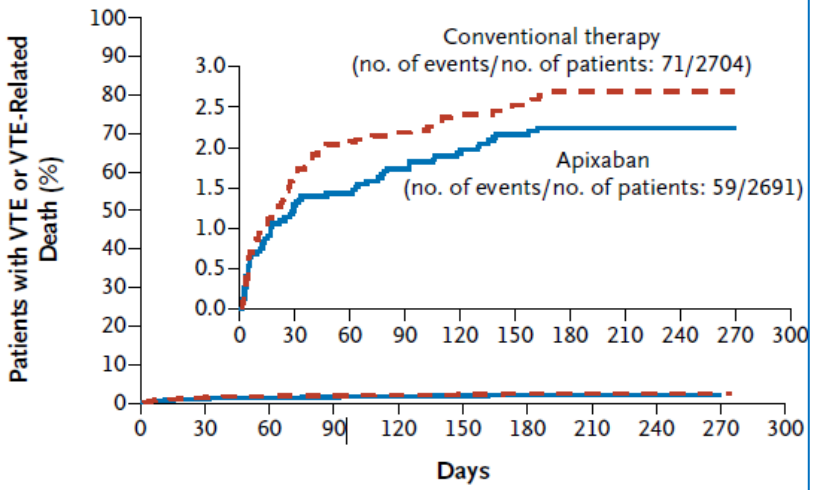
Dabigatran	1274	1238	1221	1024
Warfarin	1265	1215	1204	998

RECOVER



	Rivaroxaban (n/N)	Enox/VKA (n/N)	HR (95% CI)
No. of events	36/1,731	51/1,718	0.68 (0.44 to 1.04)

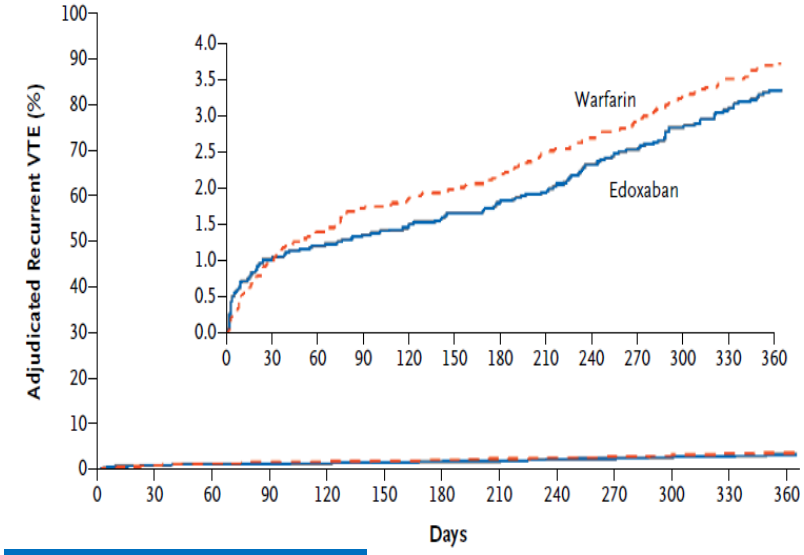
EINSTEIN



No. at Risk

Apixaban	2691	2606	2586	2563	0
Conventional therapy	2704	2609	2585	2555	0

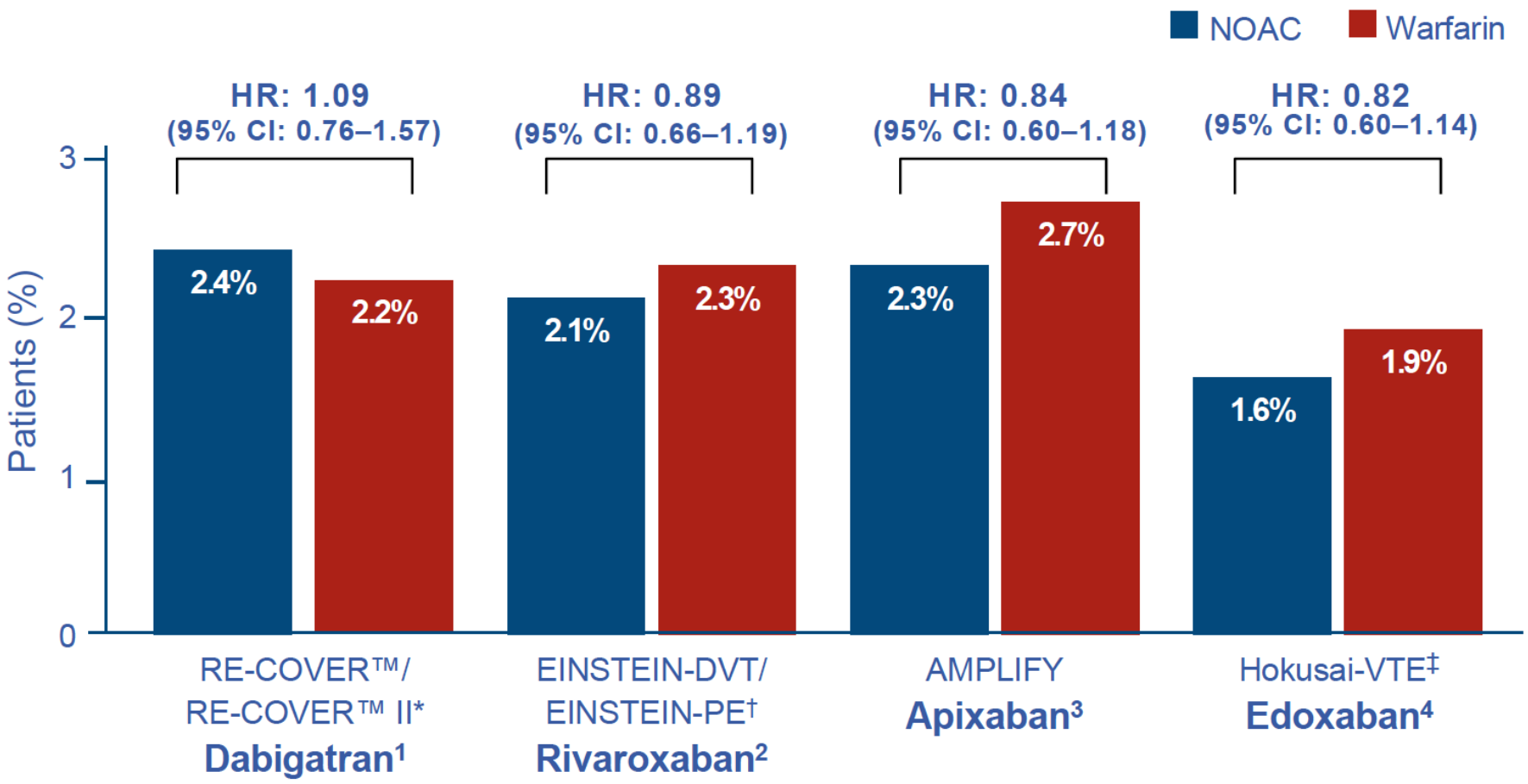
AMPLIFY



Edox						3974	3959	3885	3692	3524	3358	3190	2918
Warfarin	4112	4055	4023	4001	3992	3975	3962	3864	3683	3519	3367	3184	2936

HOKUSAI

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

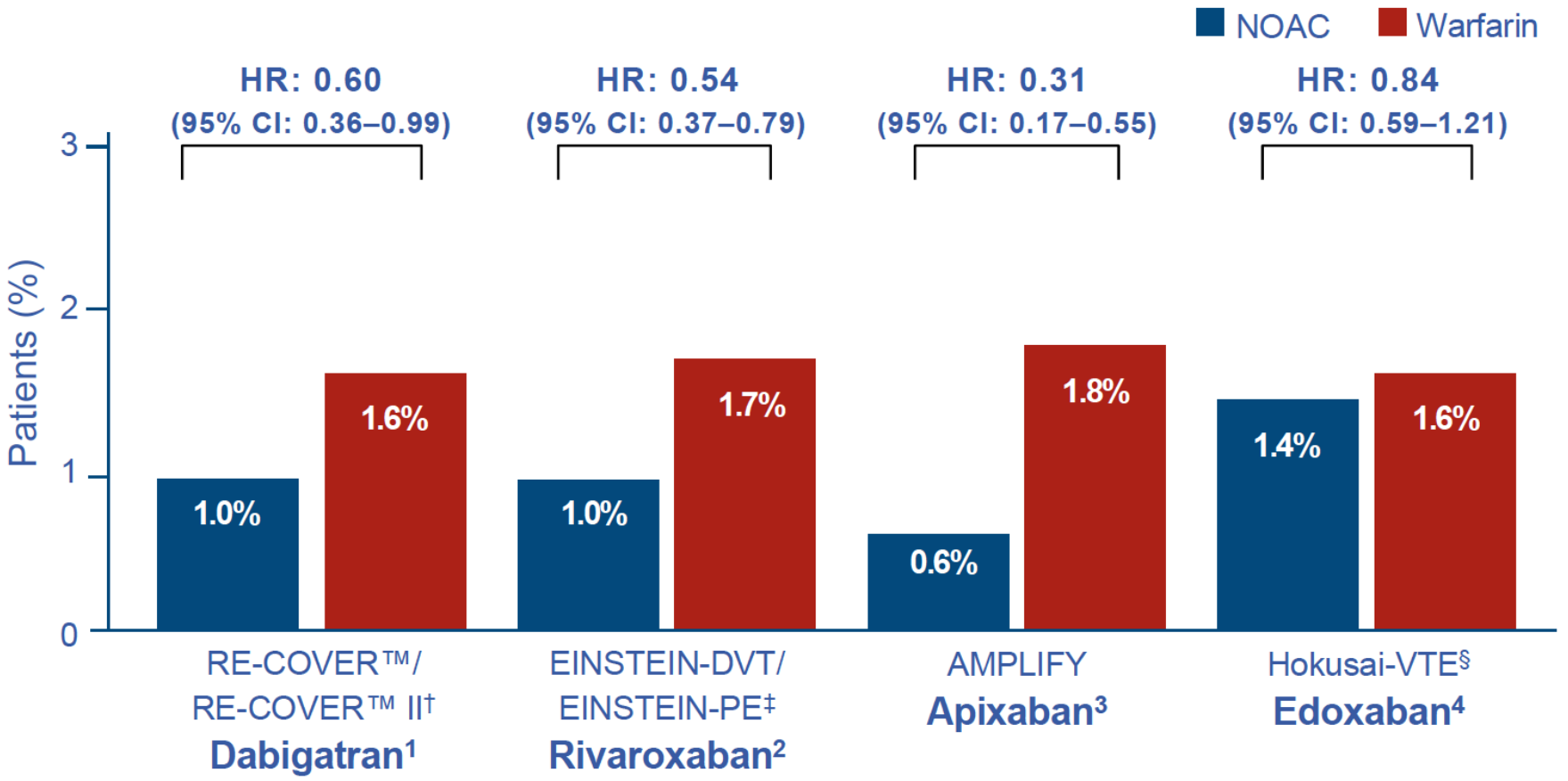


Direct comparisons cannot be made as no head-to-head data are available

*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

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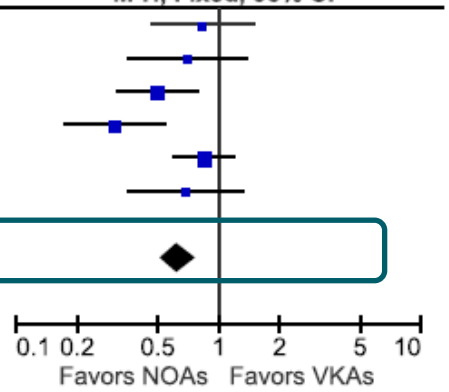
Major bleeding

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)



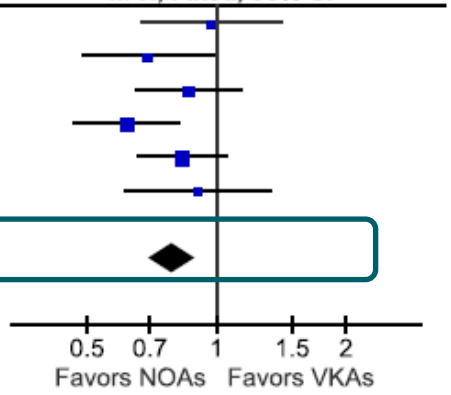
Net clinical benefit

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				

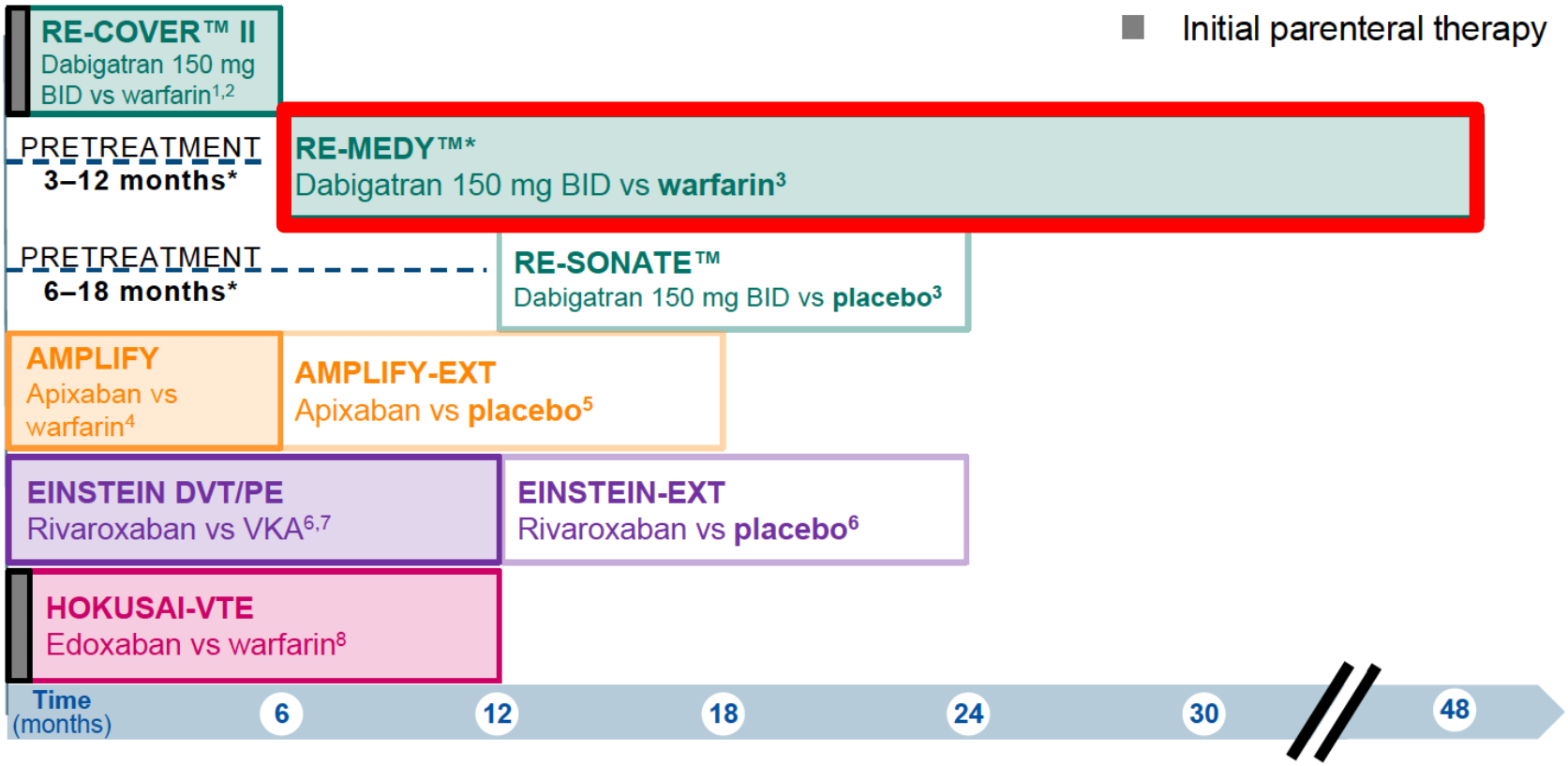
Heterogeneity: Chi² = 5.49, df = 5 (P = 0.36); I² = 9%

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

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

REMEDY: efficacy and safety of long-term treatment

Outcome	Dabigatran (N = 1430)	Warfarin (N =1426)	HR (95% CI)	*P* Value
	no. of patients (%)			
Primary endpoint of recurrent or fatal VTE	26 (1.8)	18 (1.3)	1.44 (0.78-2.64)	.01*
Secondary endpoints				
Symptomatic DVT	17 (1.2)	13 (0.9)	1.32 (0.64-2.71)	.46
Symptomatic nonfatal PE	10 (0.7)	5 (0.4)	2.04 (0.70-5.98)	.19
Major bleeding event	13 (0.9)	25 (1.8)	0.52 (0.27-1.02)	.06
Major or clinically relevant bleeding event	80 (5.6)	145 (10.2)	0.54 (0.41-0.71)	<.001

*The *P* value for the primary outcome is for noninferiority

Schulman S, et al. *N Engl J Med*. 2013;368:709-718.

VTE trials: proportions of patients with PE

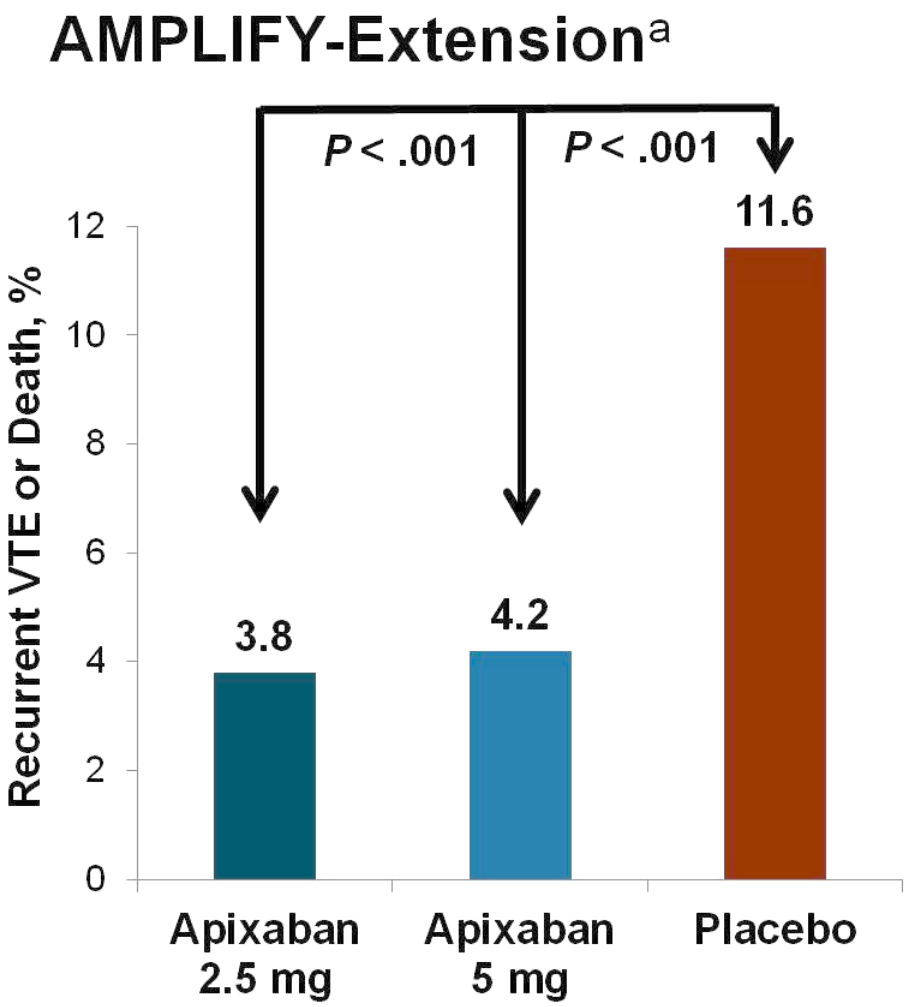
Study	Study Drug/Control, %
Rivaroxaban	
• EINSTEIN-PE	100/100
Dabigatran	
• RE-COVER	21.2/21.4
• RE-MEDY	22.7/23.5
• RE-SONATE	26.9/26.9
Apixaban	
• AMPLIFY	25.2/25.2
• AMPLIFY-Extension	35.2/33.5
Edoxaban	
• Hokusai-VTE	40/40

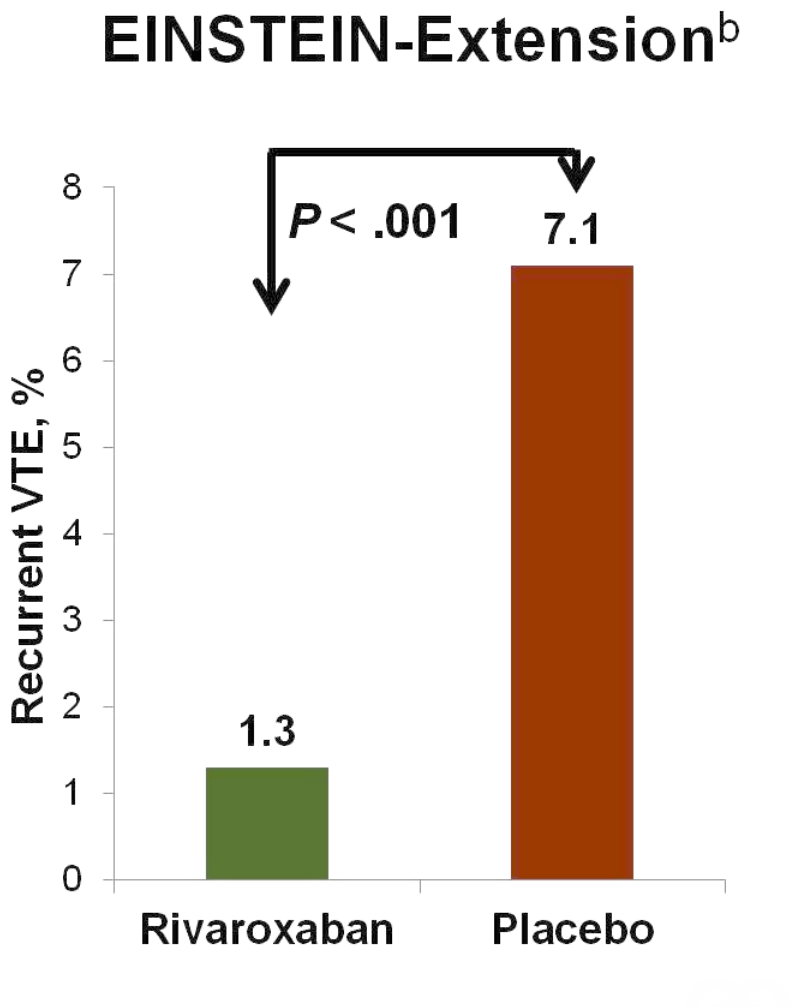
EINSTEIN Investigators. *N Engl J Med* 2012;366:1287-1297[11]; Schulman S, et al. *N Engl J Med* 2009;361:2342-2352[6]; Schulman S, et al. *N Engl J Med* 2013;368:709-718[7]; Agnelli G, et al. *N Engl J Med* 2013;369:799-808[8]; Agnelli G, et al. *N Engl J Med* 2013;368:699-708[9]; Hokusai-VTE Investigators. *N Engl J Med.* 2013;369:1406-1415.[10]

Extensive pulmonary embolism
> 25% of entire pulmonary vasculature

EINSTEIN-PE	24.7% rivarox group 23.9% control group
AMPLIFY	38.4 % apixa group 36.0% control group

VTE extension studies





a. Agnelli G, et al. *N Engl J Med*. 2013;368:699-708[4]; b. EINSTEIN Investigators. *N Engl J Med*. 2010;363:2499-2510.[9]

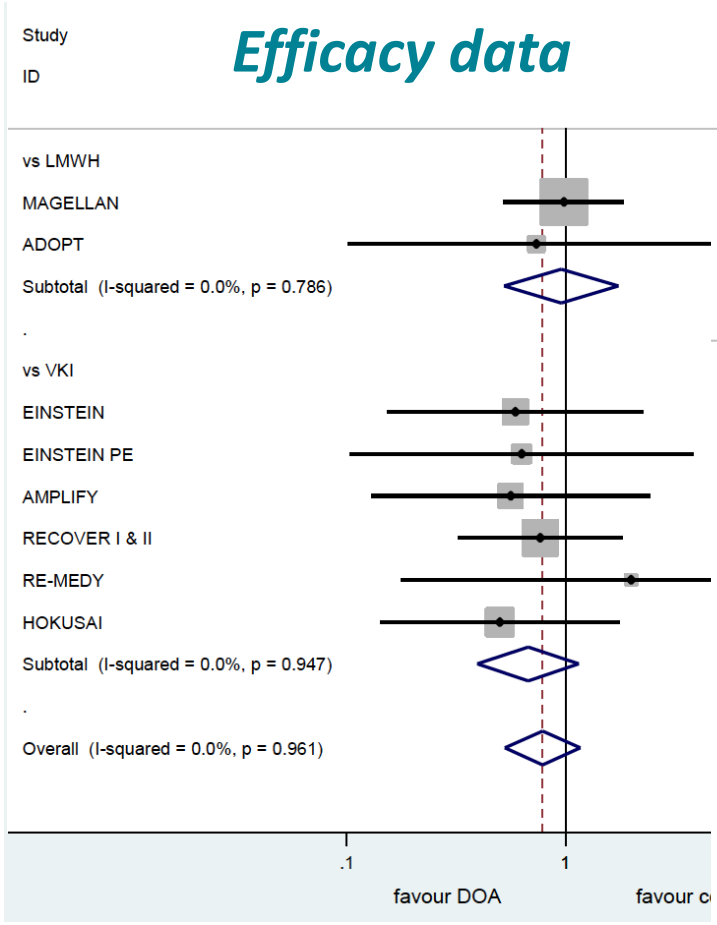
NOACs in cancer patients (limitations)

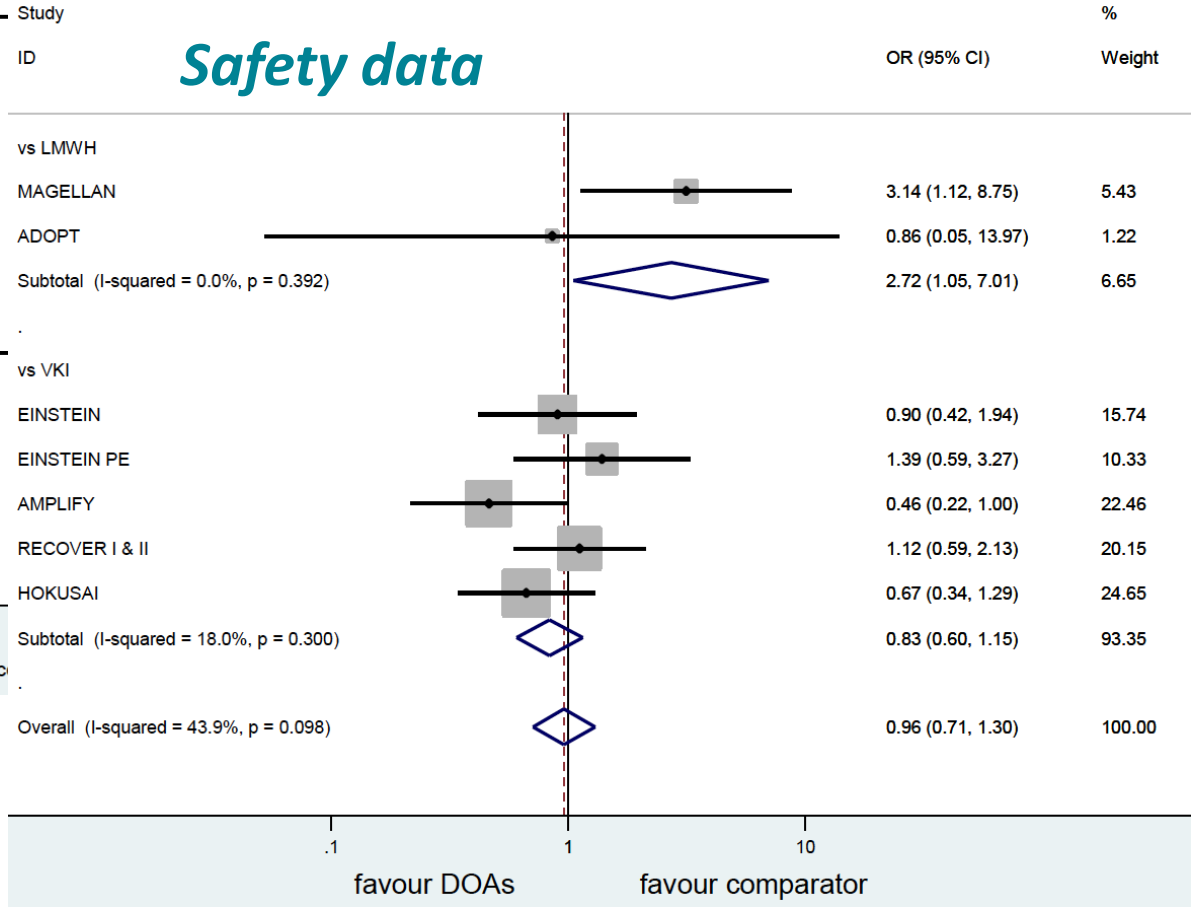
- Paucity of clinical trial data

  (< 10% of the populations in RCTs)
- No comparison with LMWH
- Patients were not representative of cancer patients
- Drug interaction may be clinically relevant
- Liver and renal dysfunction are common in cancer patients

NOACs in cancer patients

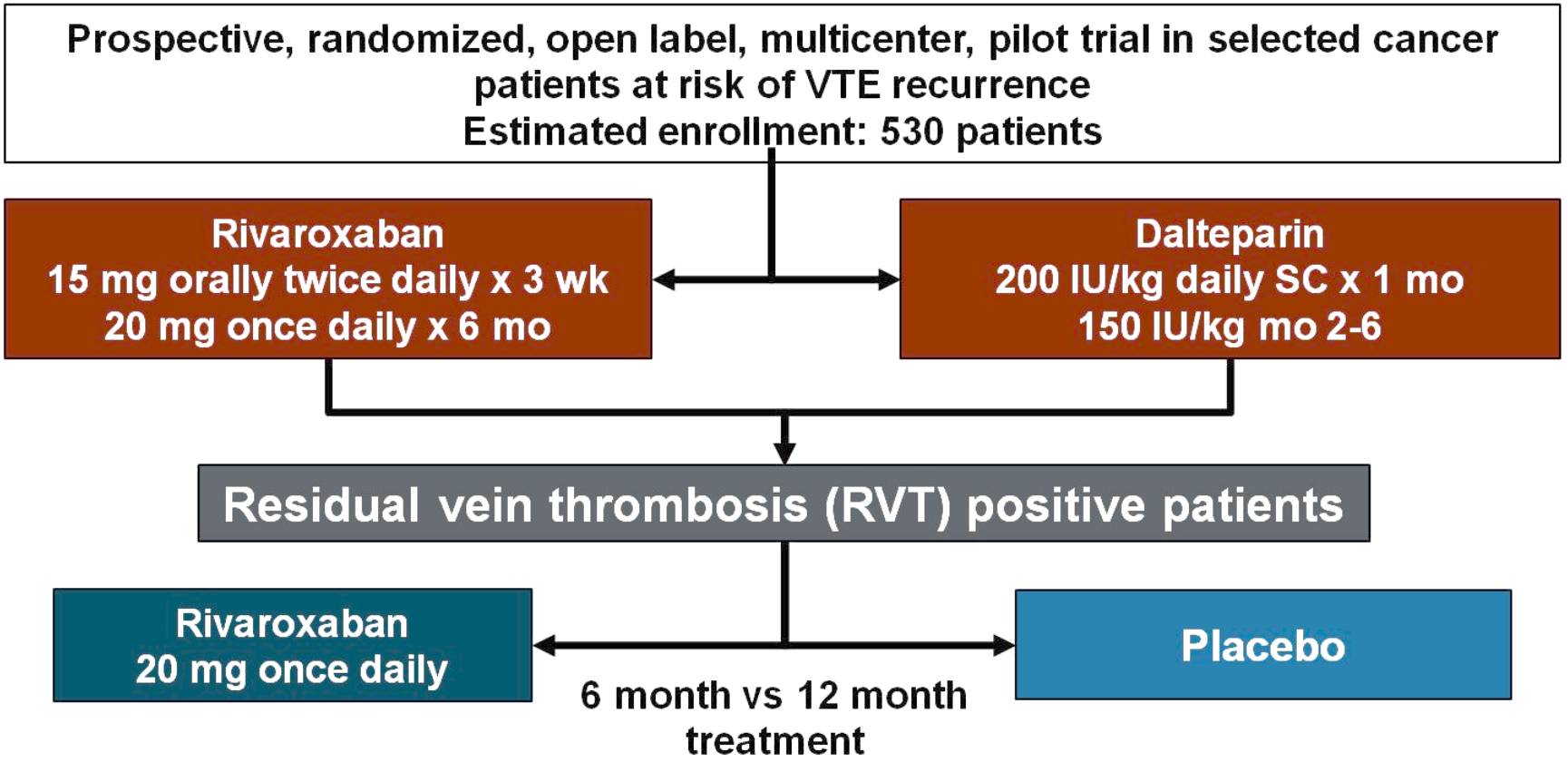
Int J Cardiol doi:10.1016/j.ijcard.2016.12.168





Meta-analysis
N = 1952

SELECT-D
Study Design



Primary efficacy: incidence of recurrent VTE

Secondary outcomes: safety, acceptability, biomarker identification, and health economics

Young A, et al. *J Clin Oncol*. 2014;32. Abstract TPS9661.[20]

NOACs in fragile patients

EINSTEIN pooled analysis

- Elderly (>75 years)
- Body weight < 50 kg
- Renal failure (CrCl < 50 mL/min)
- n = 790

Outcome	Rivaroxaban, %	Enoxaparin/ VKA, %	HR (95% CI)	*P* Value
Recurrence of thromboembolism	2.7	3.8	0.68 (0.39 - 1.18)	-
Overall	2.1	2.3	0.89 (0.66 - 1.19)	< .0001
Major bleeding	1.3	4.5	0.27 (0.13 - 0.54)	-
Overall	1.0	1.7	0.54 (0.37 - 0.79)	.002

Büller HR, et al. 54th Annual ASH Annual Meeting and Exposition; 2012.[6]

Key messages

- **The paradigm of DVT treatment is rapidly changing. The evidence for NOACs is strong enough to spread the use of these drugs instead of VKAs**
- **A single drug approach is very attractive and very useful for an outpatient management of patients with DVT**
- **More data is needed in patients with massive pulmonary embolism (after lytics ?)**
- **Extended treatment is the rule for unprovoked DVT/PE but no firm recommendations about when to stop**

Many thanks

NOACs in VTE drug selection according to patient's risk profile and duration of therapy

João Morais

Head of Cardiology Division and Research Centre

Leiria Hospital Centre

Portugal

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