The latest on the diagnosis and treatment of venous thromboembolism

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Disclosures

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- Pfizer
- Bayer
- Sanofi
- Leo Pharma
- Servier

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- Pfizer
- Sanofi

Objectives

1. Describe the approach to the diagnosis of deep vein thrombosis (DVT) and pulmonary embolism (PE)
2. Be familiar with the latest treatment modalities for venous thromboembolism (VTE)
3. Learn how to determine duration of anticoagulation

VTE=venous thromboembolism
DVT=deep vein thrombosis
PE= pulmonary embolism

DIAGNOSIS of DVT and PE

Diagnosing deep vein thrombosis and pulmonary embolism

- DVT and PE cannot be diagnosed based on symptoms and signs alone
- Prompt and accurate diagnosis is important
  - Appropriate treatment
  - Avoid thrombus extension or embolization
- But, VTE is frequently suspected but diagnosed in 20% of suspected cases
- Not ideal to perform testing in all suspected cases

1. Dronkers et al J Thromb Haemost 15; 2017 1040-1043
2. Dronkers et al J Thromb Haemost 15, 2017 2270-2273

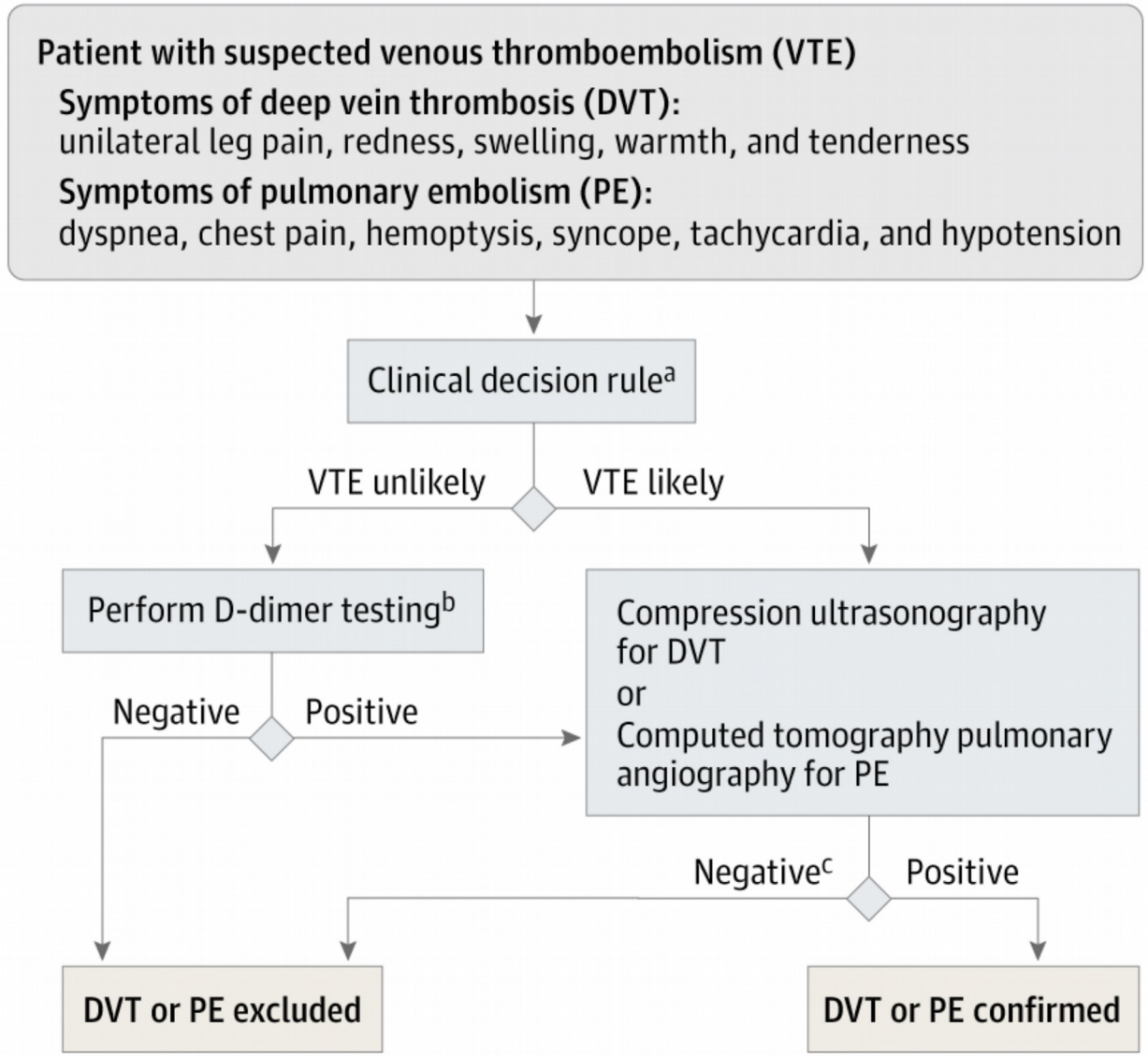
Diagnosing deep vein thrombosis and pulmonary embolism

- Overall, VTE can be excluded in **29% (95% CI 20-40%)** of patients with suspected DVT and in **28% (95% CI 20-37%)** of patients with suspected PE[1,2] with the use of diagnostic algorithm including pretest probability and d-dimer testing

- Almost 30% of suspected VTE cases can be ruled out safely without imaging

1. Geersing GJ *BMJ* 2014
2. van ES N *Ann Intern Med* 2016

Diagnostic management of patients with suspected DVT or PE



JAMA. 2018;320(15):1583-1594. doi:10.1001/jama.2018.14346

Clinical prediction rule for DVT

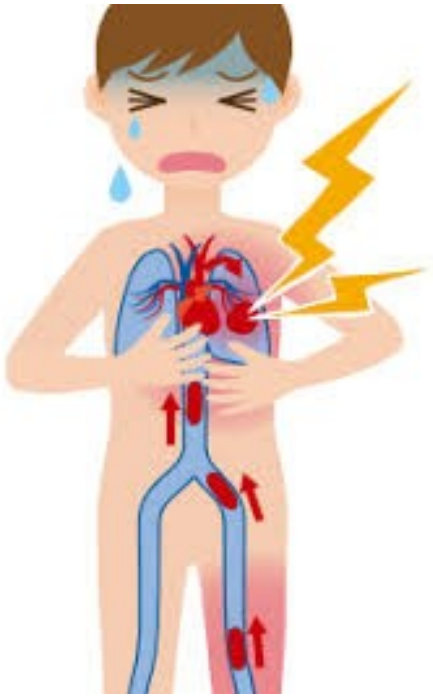
Pretest Probability – Wells Score

Clinical variable		Points
Active cancer		+1
Bed rest or major surgery within 4 weeks		+1
Calf swelling > 3 cm compared to other leg		+1
Collateral non varicose superficial veins		+1
Entire leg swollen		+1
Tenderness along deep vein traject		+1
Pitting edema in symptomatic leg		+1
Paralysis, paresis or recent plaster immobilization		+1
Previously documented DVT		+1
Alternative diagnosis as or more likely than DVT		-2
Number of points	**Clinical probability**	**Prevalence of DVT**
≤ 1	Unlikely	4 – 8%
> 1	Likely	24 – 32%

Wells, Lancet 1997; 350: 1795-8.

Slide provided by G LeGal

Clinical prediction rule for PE



Modified Wells criteria: clinical assessment for pulmonary embolism

Clinical symptoms of DVT (leg swelling, pain with palpation)	3.0
Other diagnosis less likely than pulmonary embolism	3.0
Heart rate >100	1.5
Immobilization (≥3 days) or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Probability	**Score**
Traditional clinical probability assessment	
High	>6.0
Moderate	2.0 to 6.0
Low	<2.0
Simplified clinical probability assessment*	
PE likely	>4.0
PE unlikely	≤4.0

Data from van Belle, A, et al. JAMA 2006; 295:172.

D-dimer

- Fibrin degradation products
  - Simple, cheap, fast blood test
  - Highly sensitive to the presence of a blood clot
  - Positive in almost all patients with PE and DVT
  - Low likelihood of DVT or PE if negative
- Various assays with variable performance
  - Latex qualitative (SimpliRED)
  - ELISA high sensitivity assays

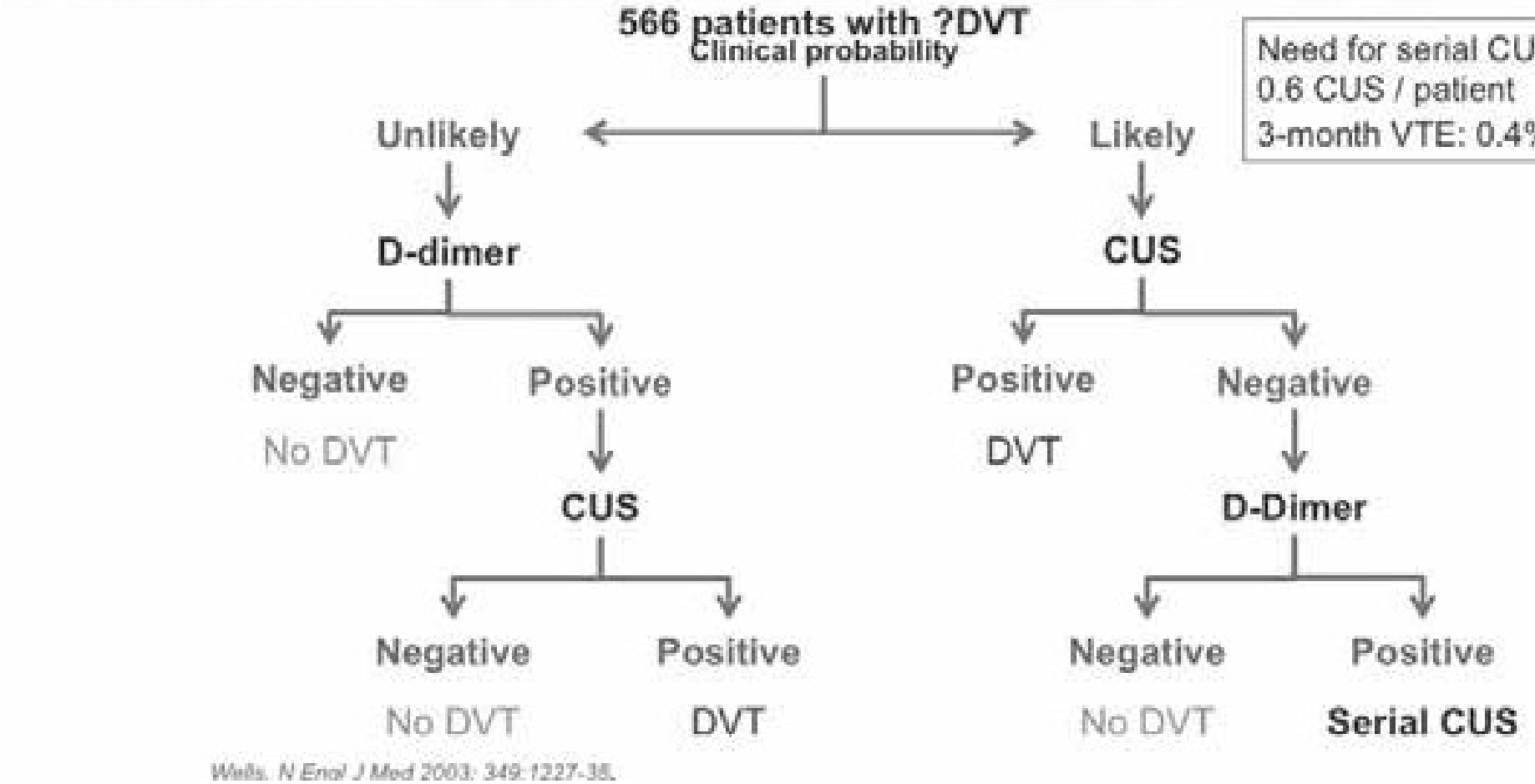
Characteristics of the different classes of D-dimer assays

Technique	Examples†	Sensitivity	Specificity	Comments
Microplate ELISA	Asserachrom Ddi, Enzygnost (Dade Behring Inc, Deerfield, Ill), and Fibrinostika FbDP	High	Low	Considered the gold standard; suitable for batch analysis and not useful in real time
VIDAS ELISA (bioMérieux SA, Marcy-Étoile, France)		High	Low	Similar sensitivity as classic microplate ELISAs; quantitative; suitable for real-time use
Membrane ELISA (immunofiltration)	Instant IA and NycoCard	High	Low-intermediate	Rapid, suitable for real-time use; comparable sensitivity to microplate ELISA; qualitative or semiquantitative
First-generation latex agglutination	Dimertest latex and D-Dimertest	Intermediate	Intermediate	Rapid, but insufficiently sensitive to be clinically useful
Whole blood agglutination	SimpliRED	Generally high, intermediate in some studies	Intermediate	Rapid, can be performed on whole blood; qualitative or semiquantitative
Second-generation latex agglutination (immunoturbidimetric)	TinaQuant and Liatest	High	Intermediate	Rapid and semiquantitative; comparable sensitivity to microplate ELISA

*ELISA indicates enzyme-linked immunosorbent assay.

Arch Intern Med. 2002;162(7):747-756. doi:10.1001/archinte.162.7.747

DVT – Diagnostic Strategy



Slide provided by G LeGal

Whole-Leg CUS

623 patients with ? DVT

↓

Proximal and distal CUS

↓

No DVT → **No treatment**

222 DVT
Treatment

No need for serial CUS
1 CUS / patient
3-month risk of VTE: 0.5% (0.1-1.8)

Elias, Thromb Haemost 2003; 89 : 221-7.

Slide provided by G LeGal

Whole-Leg or Serial Proximal?

- Two RCTs available

	Bernardi et al.		Gibson et al.	
	Proximal	Whole-leg	Proximal	Whole-leg
N	1045	1053	257	264
DVT, n (%)	231 (22.1)	278 (26.4)	59 (23.0)	99 (37.5)
Prox DVT	231	213	59	61
Distal DVT	0	65	0	38
3-month VTE	0.9% (0.3-1.8)	1.2% (0.5-2.2)	2.0 (0.6-5.1)	1.2 (0.2-4.3)

Slide provided by G LeGal

Natural history based on serial proximal CUS studies
Proximal extension and risk of VTE in non-treated patients at 3 months

Table 1 Performances and safety of proximal compression ultrasonography for diagnosing DVT in outcome management studies. Distal DVTs were not searched for in these studies

Source, year	Patients (*n*)	Incidence of DVT (%)	Proportion of proximal DVTs detected by the second CUS % (95% CI)	3-month thromboembolic risk, % (95% CI)*
Birdwell *et al.*[15], 1998	405	16	2 (0.8–4.2)	0.6 (0.1–2.1)
Cogo *et al.*[11], 1998	1702	24	0.9 (0.3–1.2)	0.7 (0.3–1.2)
Bernardi *et al.*[12], 1998	946	28	5.7 (1.9–12.8)	0.4 (0–0.9)
Wells *et al.*[13], 1997	593	16	1.8 (0.3–5.2)	0.6 (0.1–1.8)
Perrier *et al.*[16], 1999	474	24	NA*	2.6 (0.2–4.9)
Kraaijenhagen *et al.*[14], 2002	1756	22	3 (1.9–5.2)	0.7 (0.3–1.6)
Pooled estimate	5876	23	NA	0.6 (0.4–0.9)

*During 3-month follow-up in patients left untreated after normal proximal compression ultrasonography.
DVT, deep vein thrombosis; CUS, compression ultrasonography; NA, not applicable.
NA*: In the study by Perrier *et al.*, only one CUS limited to proximal veins was realized in patients with a positive ELISA D-dimer measurement.

J Thromb Haemost 2007;5:55-59

Natural history based on whole leg CUS
Risk of VTE in non-treated patients at 3 months

Table 2 Performances and safety of a single proximal and distal compression ultrasonography for diagnosing DVT in outcome management studies

		Incidence of DVT %, (*n*)			3-month thromboembolic risk, % (95% CI) *
Source, year	Patients (*n*)	All *n* (%)	Proximal *n* (%)	Distal *n* (%)	Single proximal and distal CUS
Elias *et al.*[18], 2003	623	204 (33)	112 (55)	92 (45)	0.5 (0.1–1.8)
Schellong *et al.*[19], 2003	1646	275 (17)	121 (44)	154 (56)	0.3 (0.1–0.8)
Stevens *et al.*[20], 2004	445	61 (14)	42 (69)	19 (31)	0.8 (0.2–2.3)
Subramaniam *et al.*[21], 2005	526	113 (22)	49 (43)	64 (57)	0.2 (0.01–1.3)
Pooled estimate	3240	653 (20)	324 (50)	329 (50)	0.3 (0.1–0.6)

*During 3-month follow-up in patients left untreated after a normal complete (proximal and distal) compression ultrasonography.
NA, not applicable; DVT, deep vein thrombosis.

J Thromb Haemost 2007;5:55-59

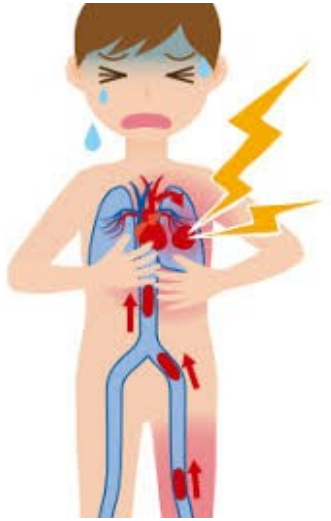
Whole-Leg or Serial Proximal?

	Advantages	Disadvantages
Serial proximal	Safety No risk of overtreatment Easy to perform Short (3-4 min) Few inconclusive tests	Repeated testing
Whole-leg	Safety Stand-alone test Alternative diagnosis	Risk of overtreatment Difficult to perform Longer (12-14 min) More inconclusive tests

Slide from M Righini

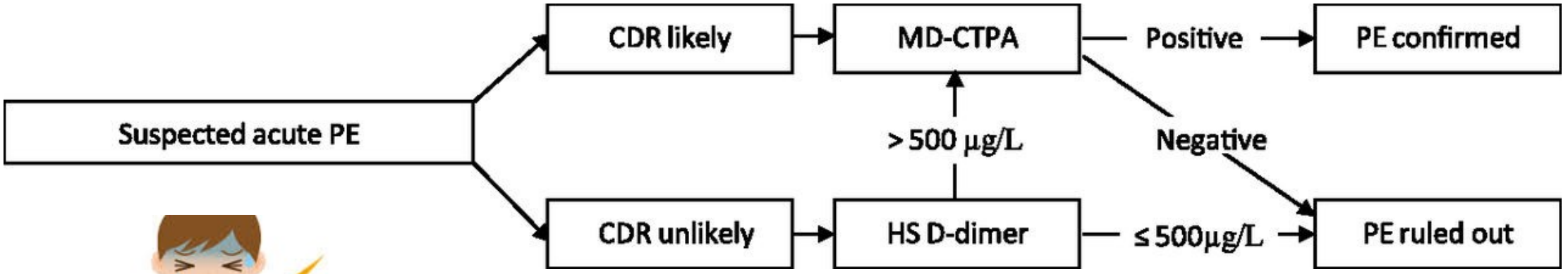
Age-adjusted d-Dimer

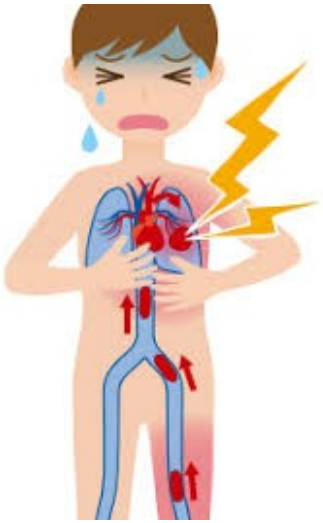
- D-dimer levels increase with age
- Elderly patients are less likely to have a negative d-dimer
- Using an age-adjusted cut-off may increase the yield of the d-Dimer test
  - Age adjusted cut off = age x 10 (ug/L) in patients aged >50 yo
  - Derived and validated among patients with suspected PE
  - Integrated into clinical practice (ESC, ACP) for PE

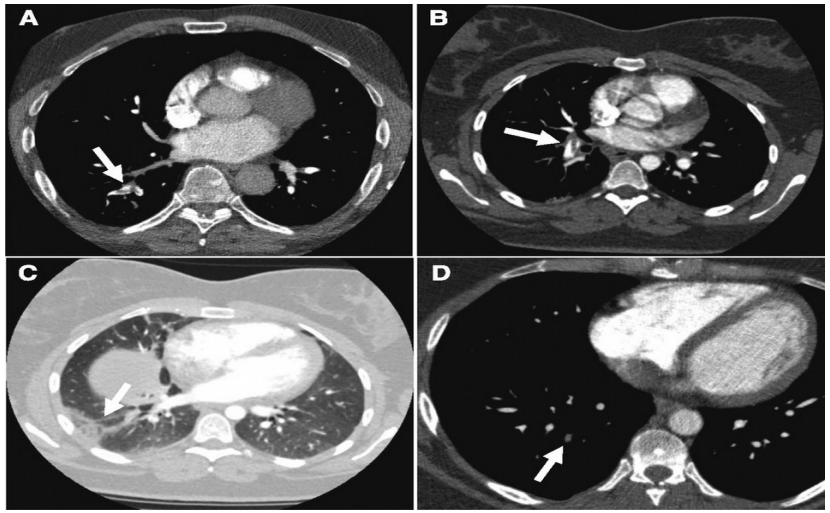


- Could we use in patients with suspected DVT?
  - Promising data from retrospective studies
  - Ongoing management outcome study: ADJUSTt-DVT

CTPA-based diagnostic algorithm for PE







Menno V. Huisman, and Frederikus A. Klok Blood 2013;121:4443-4448

Emerging diagnostic approaches/assays

- Clinical Decision Rule
  - PERC rule for suspected PE
  - YEARS rule for suspected PE
  - ADJUST-DVT
- Diagnostic imaging
  - ED performed US
  - Magnetic Resonance Venography for DVT
  - MRI for PE
  - V/Q Single-Photon Emission Computed Tomography

TREATMENT of ACUTE DVT and PE

Outpatient vs. inpatient VTE management

Home versus in-patient treatment for deep vein thrombosis (Review)

Othieno R, Abu Affan M, Okpo E

THE COCHRANE COLLABORATION®

Home treatment
VTE recurrence: 0.61 (0.42-0.90)
Mortality: 0.72 (0.45-1.15)
Major bleeding: 0.67 (0.33-1.36)

2.7. In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B).

Kearon et al, Chest 2012

Outpatient vs. inpatient VTE management

Pulmonary embolism

- Safe in about 20-30% of PE cases
- Several scores exist to assess PE patients' risk for poor outcomes in the weeks after PE
- None were designed to evaluate who to treat in- vs. outpatient

Kearon et al, Chest 2012

OUTPATIENT PE

Table 1 Hestia criteria

Hestia criteria
1. Hemodynamically unstable?*
2. Thrombolysis or embolectomy necessary?
3. Active bleeding or high risk of bleeding?†
4. Oxygen supply to maintain oxygen saturation > 90% > 24 h?
5. Pulmonary embolism diagnosed during anticoagulant treatment?
6. Intravenous pain medication > 24 h?
7. Medical or social reason for treatment in the hospital > 24 h?
8. Creatinine clearance of less than 30 mL/min?‡
9. Severe liver impairment?§
10. Pregnant?
11. Documented history of heparin-induced thrombocytopenia?
If one of the questions is answered with **YES**,
The patient can NOT be treated at home

*Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure < 100 mmHg with heart rate > 100 beats per minute; condition requiring admission to an intensive care unit. †Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 × 109/L), uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg). ‡Calculated creatinine clearance according to the Cockroft-Gault formula. §Left to the discretion of the physician.

Journal of Thrombosis and Haemostasis, **11**: 686–692

Many PE patients can be safely discharged

- Hemodynamically stable
- No need for supplemental O2
- No significant comorbidity (eg. CHF NY3-4, COPD on home O2)
- No contraindication to anticoagulation
- Able to obtain daily anticoagulation
- Adequate pain control
- Adequate social support

***Adverse events: 22/221 (4.5%) in inpatients vs. 0/275 in outpatients.**
***Of note, of patients treated at home, 35% were normotensive but had RV dysfunction.**

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journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Temporal trends in outpatient management of incident pulmonary embolism and associated mortality

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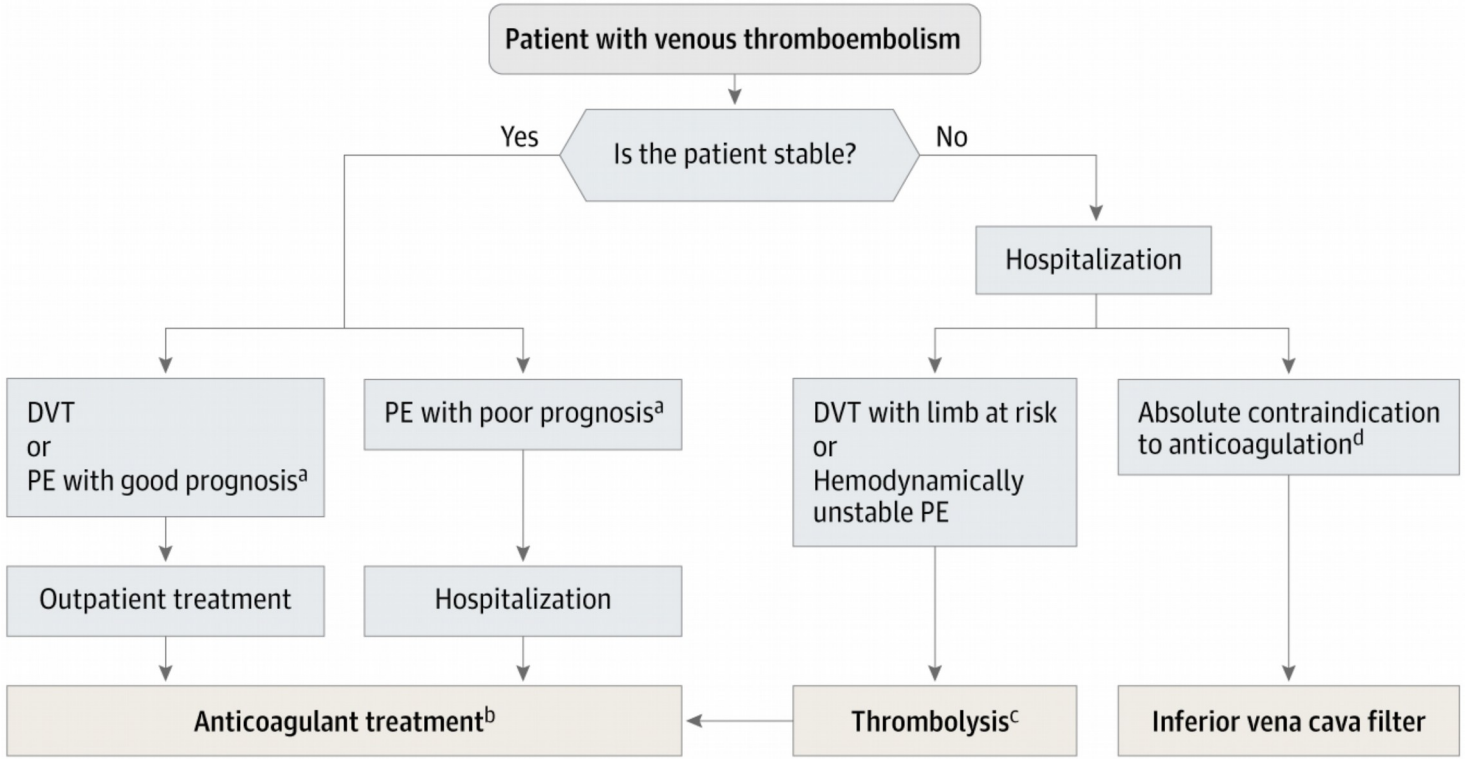
[e] Division of Pulmonary Medicine, Jewish General Hospital, Montreal, QC, Canada

- 11% of Quebec patients with PE were treated as outpatients between 2000-2010
- 30% increase in outpatient PE management from 2000-2004 to 2005-2010
- No change in mortality, no change in recurrence rates

JAMA. 2018;320(15):1583-1594. doi:10.1001/jama.2018.14346



Approach to Initial Treatment of Venous Thromboembolism (Onset Through Days 5-10)Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

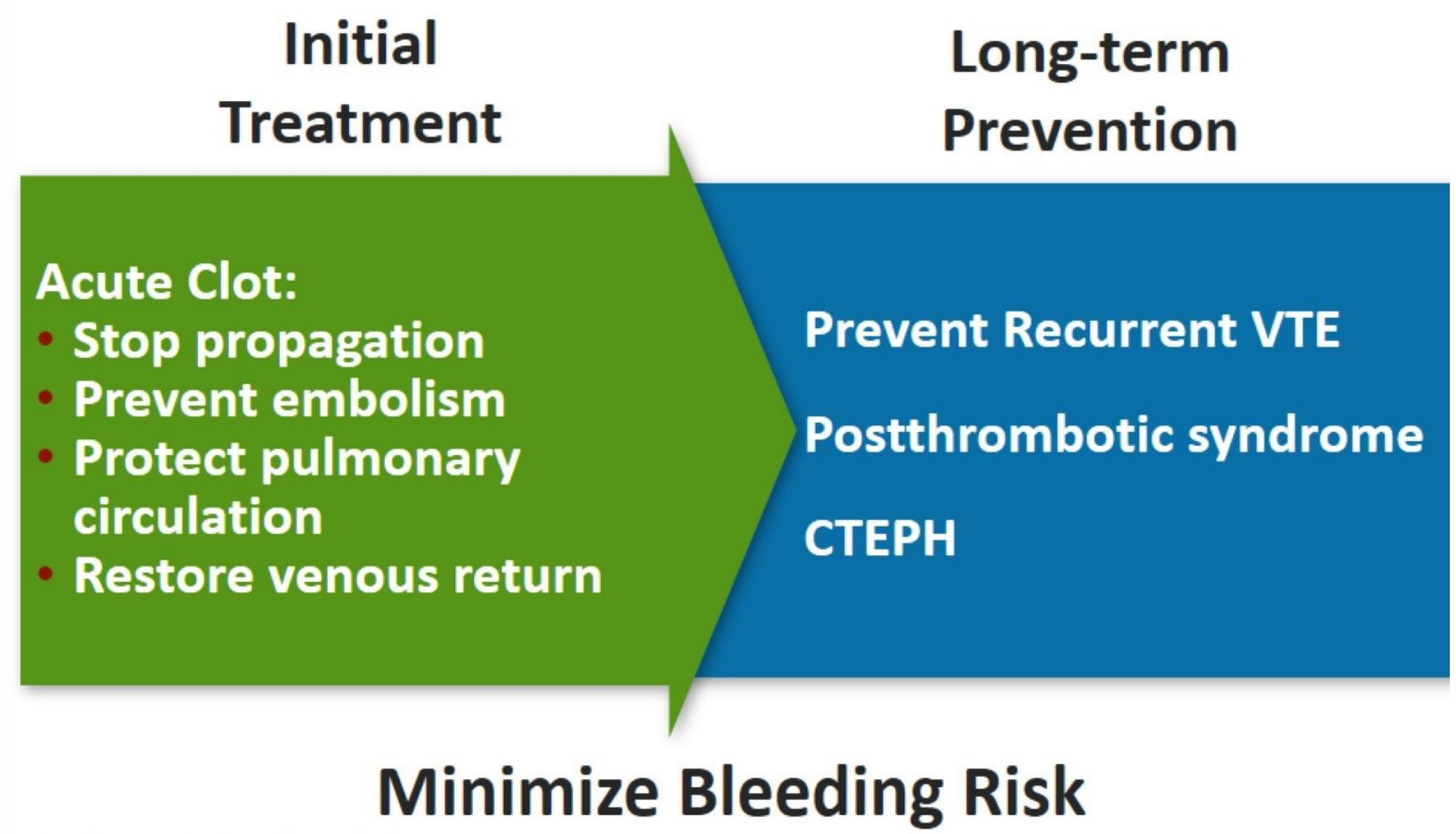
[a]Assessment of 30-day mortality risk with the Pulmonary Embolism Severity Index score or its simplified version or the Hestia criteria.

[b]Initiate treatment with direct oral anticoagulants (rivaroxaban or apixaban, or initial low-molecular-weight heparin followed by dabigatran or edoxaban). Vitamin K antagonists, following a low-molecular-weight heparin lead-in, are indicated for patients with a creatinine clearance of less than 30 mL/min and those with concomitant use of potent P-glycoprotein inhibitors or cytochrome P450 3A4 inhibitors or inducers.

[c]Catheter-directed thrombolysis for DVT and systemic thrombolysis for PE.

[d]Active bleeding, high risk of bleeding, or other contraindication to anticoagulant therapy.

Goals of Treatment



CTEPH = chronic thromboembolic pulmonary hypertension

Conventional and new VTE treatment paradigm

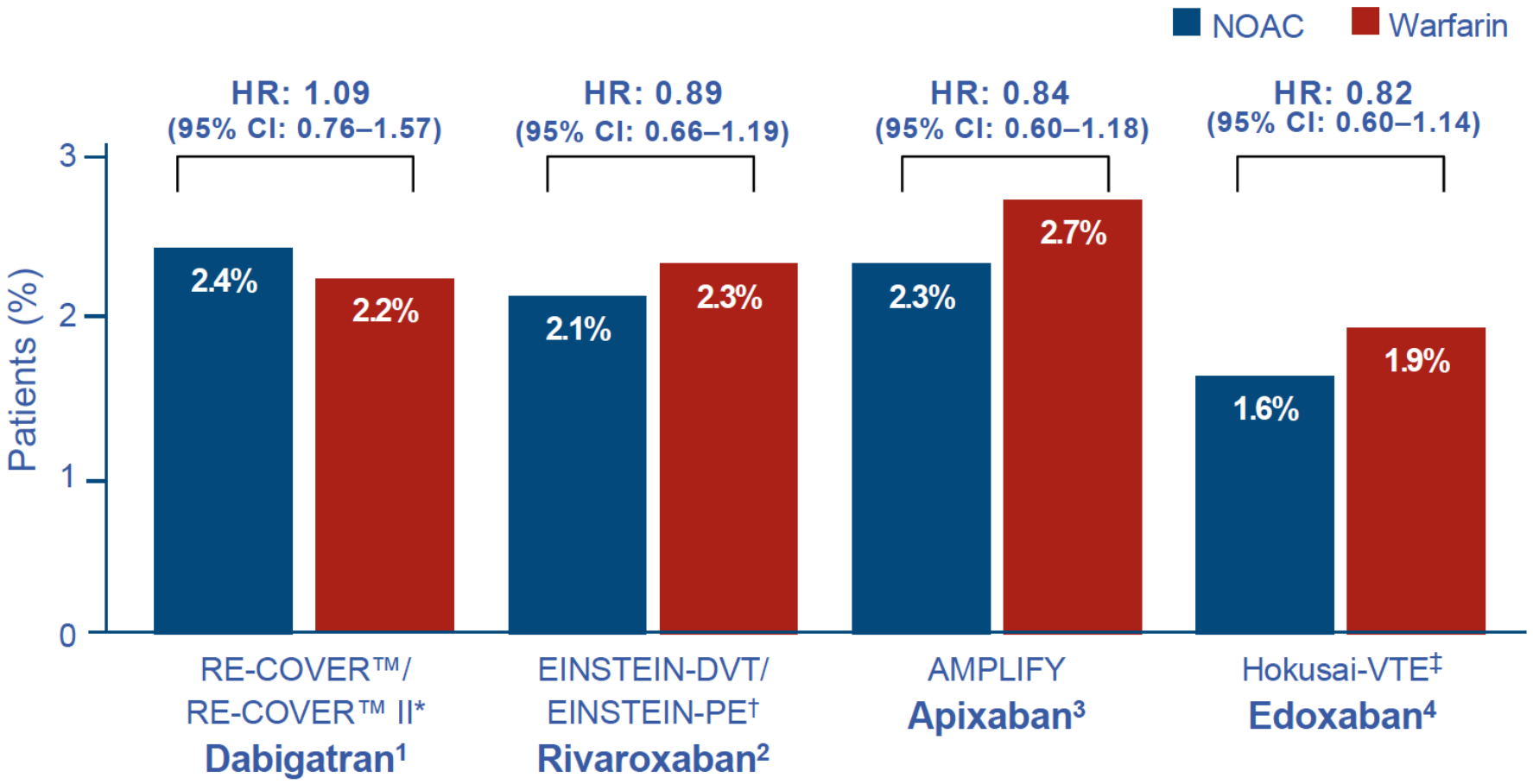
Conventional therapy

- Low molecular weight heparin (LMWH) plus vitamin K antagonist (VKA)

New therapy

- Direct oral anticoagulant (DOAC)
  - Single oral drug approach
  - Higher initial dose

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

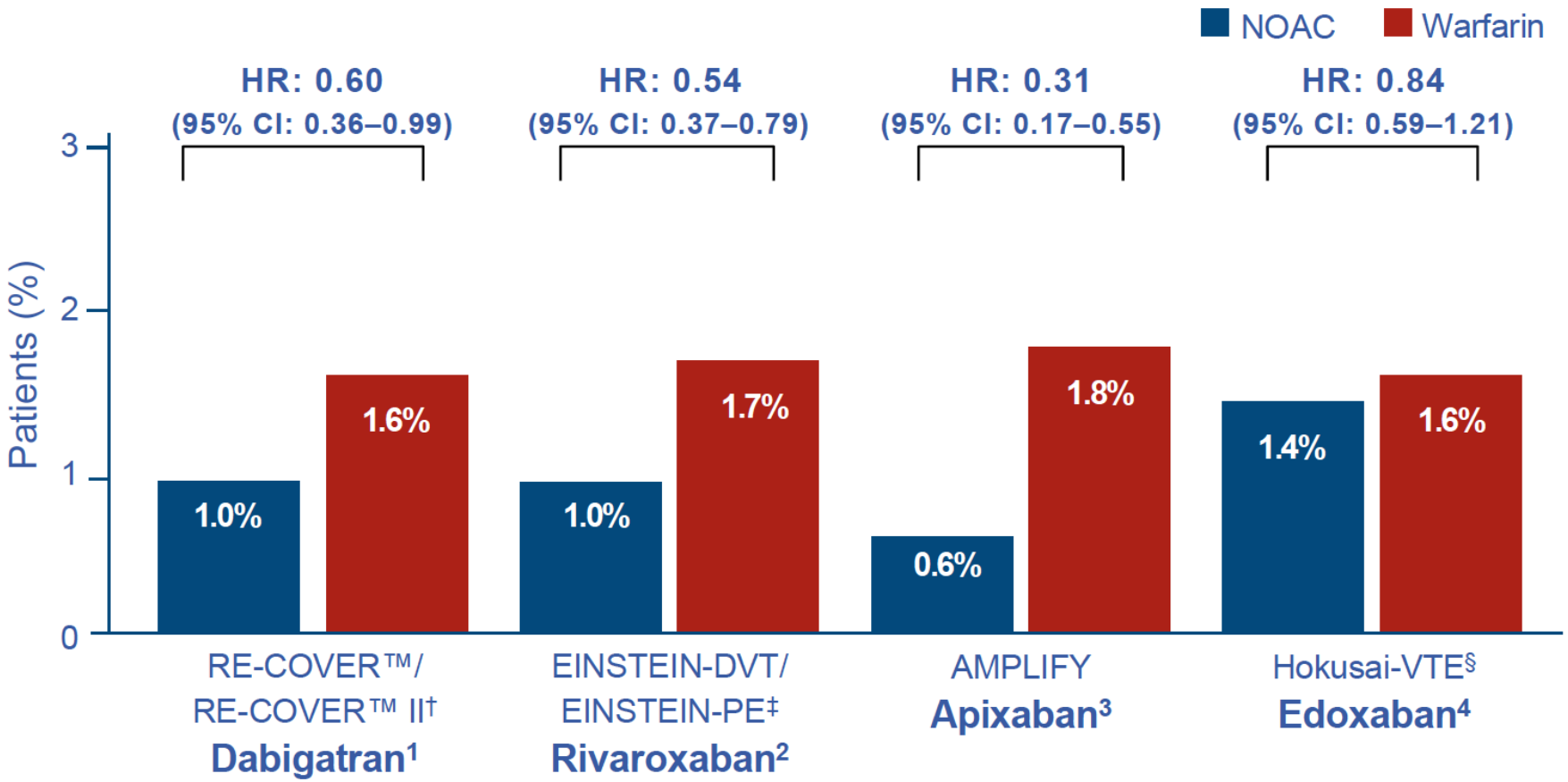


Direct comparisons cannot be made as no head-to-head data are available

*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

Treatment of acute VTE: DOACs safer than LMWH/VKA

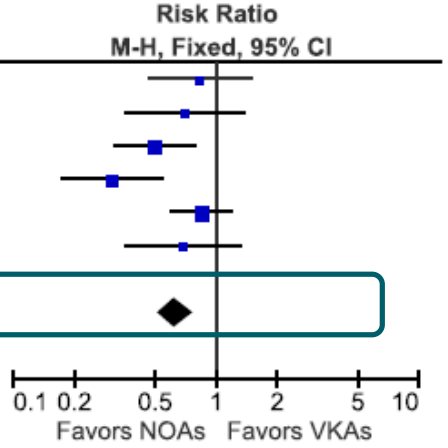
Major bleeding

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)



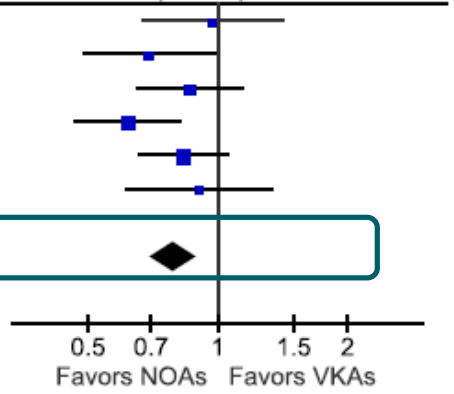
Net clinical benefit

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)



Which patients are candidates for direct oral anticoagulants?

- Any patient with acute DVT/PE and without severe renal (< 30 ml/min) or liver insufficiency (?)

- Keep in mind, no or insufficient evidence for
  - Severe renal failure (<30 ml/min)
  - Antiphospholipid syndrome (triple positive)
  - Heparin induced thrombocytopenia
  - Unusual site thrombosis

DOACs for acute VTE

- Recommended for the acute treatment of DVT and PE (2016 ACCP and 2014 and 2017 ESC)
- Health Canada approved: all 4 DOACs
- RAMQ formulary with VTE indication: Rivaroxaban and Apixiban
- Dabigatran and Edoxaban require 5 days of LMWH lead in
- No direct comparison study (ongoing COBRA study: riv vs. apix)
- DOACs generally avoided in patients with concomitant use of potent P-glycoprotein inhibitors or cytochrome P4503A4 inhibitors or inducers
  - Azole antimycotics (eg ketoconazol), several PIs for HIV, antiepileptic drugs (ex. Phenytoin, CBZ)

DOACs dosing, renal dosing and therapeutic considerations in Canada

Rivaroxaban	VTE treatment and secondary prevention 15 mg twice daily x 3 weeks, then 20 mg once daily, with food to improve absorption.	Avoid if CrCl <30 mL/min Caution if CrCl 15-30 ml/min; no dose adjustment	Contraindicated in liver disease with bleeding risk Caution in elderly. Underweight patients have slightly increased levels/response Contraindicated with drugs that are BOTH P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, posaconazole, ritonavir) Caution with clarithromycin and fluconazole Antiplatelets increase bleeding risk; co-administer with caution
Apixiban	VTE treatment and secondary prevention DVT/PE treatment (10 mg BID for seven days, then 5 mg BID) DVT/PE prevention of recurrence (2.5 mg BID after at least six months of treatment)	Caution if CrCl 15 to 29 mL/min, but no dosage adjustment recommended. Not recommended if CrCl <15 mL/min or on dialysis	Contraindicated with strong inhibitors of BOTH CYP3A4 and P-gp (e.g., itraconazole, ketoconazole, ritonavir, clarithromycin, osaconazole, voriconazole, and HIV protease inhibitors) Avoid strong inducers of BOTH CYP3A4 and P-gp (e.g., carbamazepine, phenytoin, phenobarbital, St. John's wort, rifampin). Caution with antiplatelets. Prasugrel and ticagrelor not recommended. Contraindicated in hepatic disease with coagulopathy and clinically significant bleeding risk.

DOACs dosing, renal dosing and therapeutic considerations in Canada

Not on RAMQ formulary

Not on RAMQ formulary for DVT/PE indication; hence no CV code

Edoxaban	VTE treatment and secondary prevention Following 5 to 10 days' treatment with a parenteral anticoagulant) (60 mg once daily; 30 mg once daily if body weight <60 kg)	30 mg once daily for CrCl 30 to 50 mL/min. Not recommended if CrCl <30 mL/min.	Not recommended in severe hepatic impairment Contraindicated in hepatic disease with coagulopathy and clinically significant bleeding risk Avoid rifampin (P-gp inducer). Avoid use of other strong CYP3A4 and P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbital) Reduce dose to 30 mg once daily with certain P-gp inhibitors (e.g., cyclosporine, dronedarone, erythromycin, ketoconazole, quinidine, but NOT amiodarone or verapamil)
Dabigatran	Following 5 to 10 days' treatment with a parenteral anticoagulant)/prevention of recurrence (150 mg BID; 110 mg BID for patients >80 years, and for patients at higher risk of bleeding, including patients >75 years of age with at least one other bleeding risk factor)	Contraindicated if CrCl <30 mL/min CrCl 30 to 50 mL/min., a dose reduction to 110 mg BID can be considered based on risk/benefit, but is not recommended	Causes gastrointestinal symptoms in over 10% of patients. Caution if 75 years or older, poor renal function, or underweight Drugs that increase gastric pH could reduce efficacy. Take dabigatran at least 2 hrs before antacids. Caution with antiplatelets.Ticagrelor or prasugrel not recommended Ketoconazole and other strong P-gp inhibitors contraindicated

EXTENDED TREATMENT

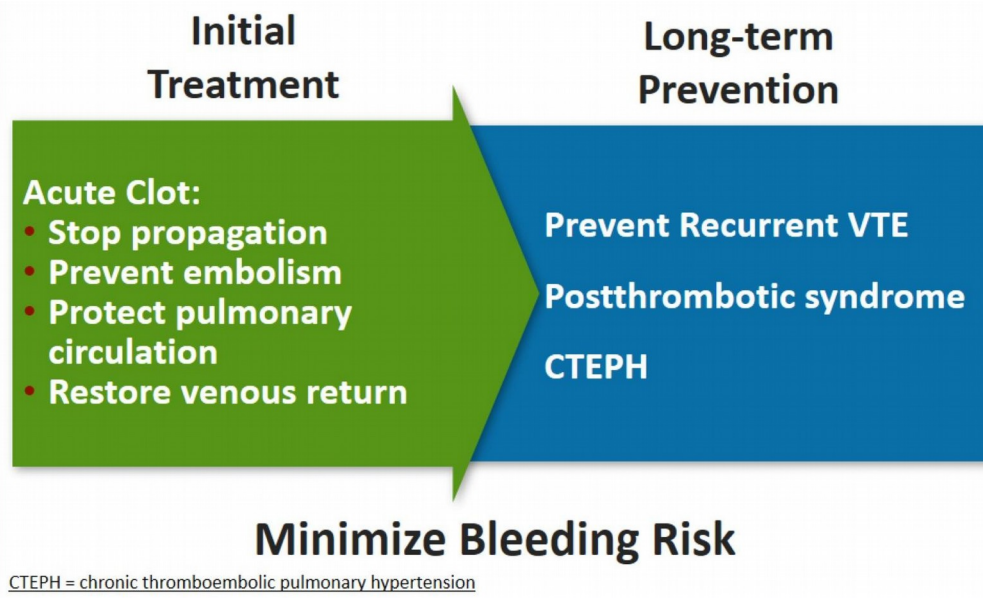
Treatment of acute VTE episode

Initial phase:
(5-7 days following VTE diagnosis)
DOAC alone
LMWH ⊔ VKA or DOAC

3 months

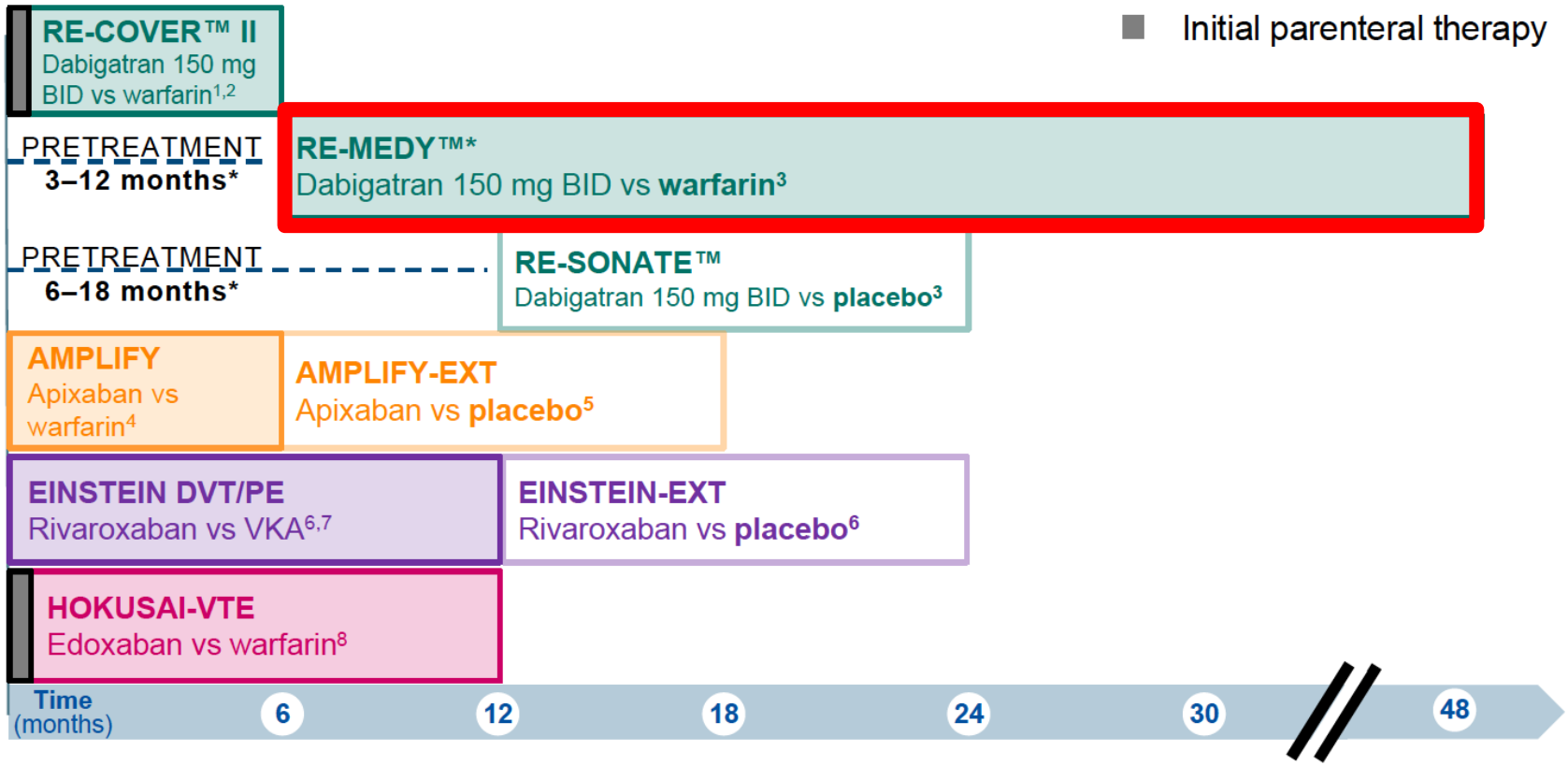
Long-term phase
DOAC
VKA

Extended phase ? (duration ?)



CTEPH = chronic thromboembolic pulmonary hypertension

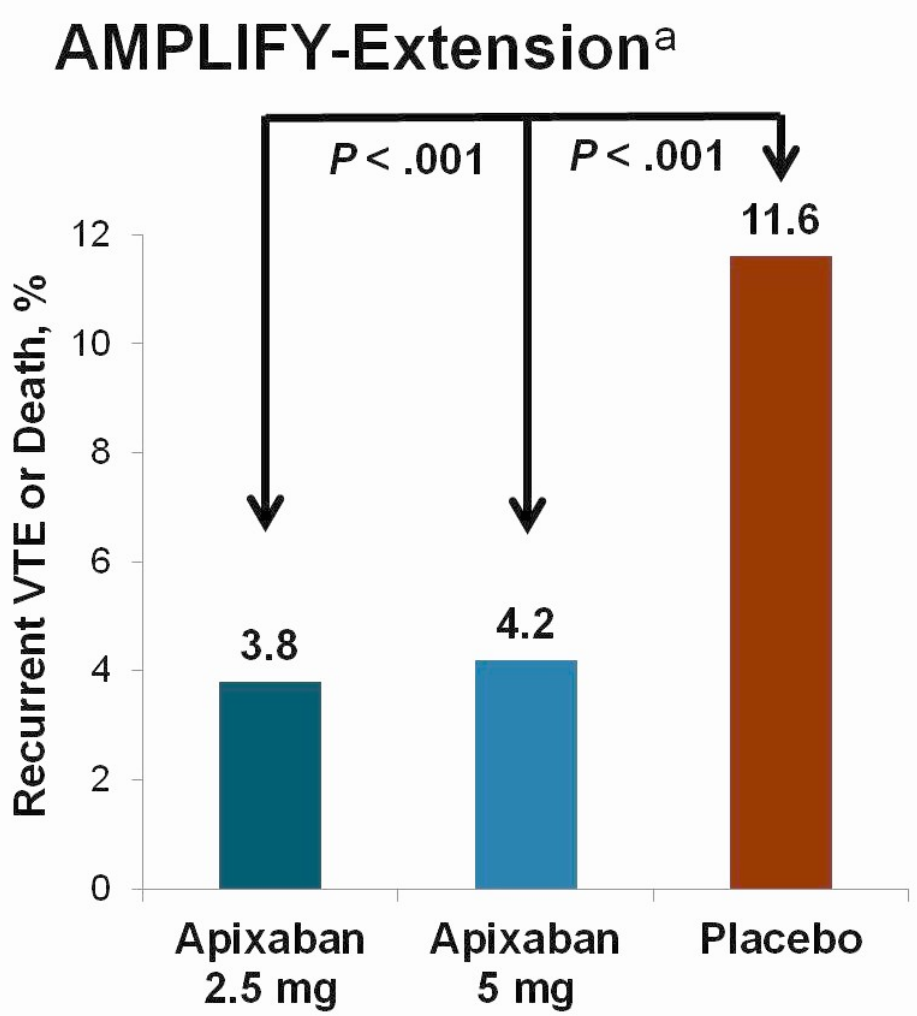
What long-term data exist for NOACs compared with warfarin in secondary prevention of VTE?

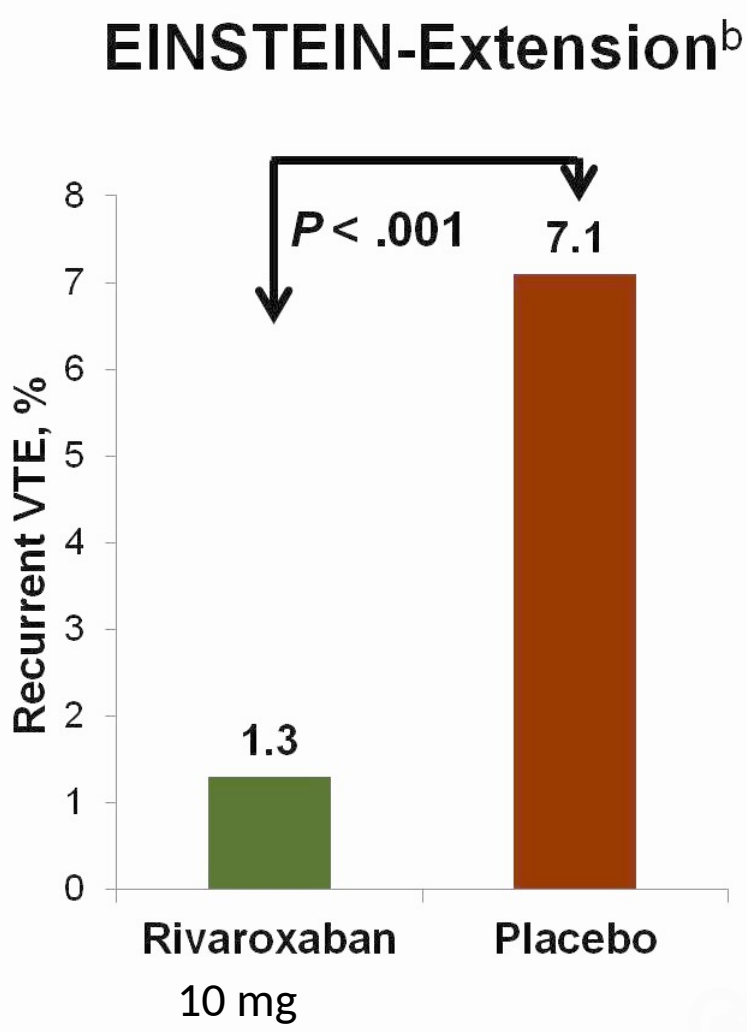


*Original protocol, 3–6 months pretreatment, 18 months on study drug; amendment allowed 3–12 months pretreatment, then up to 36 months on study drug

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 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]

Summary of efficacy data of DOACs in the treatment of venous thromboembolism:

** As effective as VKA**

Agent	Trial Name	Dose (mg), frequency	Comparator (INR indicated if VKA)	Recurrent VTE (%) (vs. VKA %)	Relative risk for recurrent VTE (95% CI)	Number of patients randomized
Rivaroxaban	EINSTEIN-DVT	15 BID → 20 OD	INR 2.0-3.0	2.1 (vs. 3.0)	0.68 (0.44-1.04)	3,449
	EINSTEIN-PE	15 BID → 20 OD	INR 2.0-3.0	2.1 (vs. 1.8)	1.12 (0.75-1.68)	4,832
	EINSTEIN-extension	10 OD	Placebo	1.3 (vs. 7.1)	0.18 (0.09-0.39)	1,197
Dabigatran	RE-COVER	150 BID	INR 2.0-3.0	2.4 (vs. 2.1)	1.10 (0.65-1.84)	2,564
	RE-COVER II	150 BID	INR 2.0-3.0	2.4 (vs. 2.2)	1.08 (0.64-1.80)	2,568
	RE-MEDY	150 BID	INR 2.0-3.0	1.8 (vs. 1.3)	1.44 (0.78-2.64)	2,856
	RE-SONATE	150 BID	Placebo	0.4 (vs. 5.6)	0.08 (0.02-0.25)	1,343
Apixaban	AMPLIFY	10 BID → 5 BID	INR 2.0-3.0	2.3 (vs. 2.7)	0.84 (0.60-1.18)	5,395
	AMPLIFY-EXT	2.5 BID 5.0 BID	Placebo Placebo	3.8 (vs. 11.6) 4.2 (vs. 11.6)	0.33 (0.22-0.48) 0.36 (0.25-0.53)	2,486
Edoxaban	Hokusai-VTE	60 OD	INR 2.0-3.0	3.2 (vs. 3.5)	0.89 (0.70-1.13)	8,292

Summary of safety data of DOACs in the treatment of acute venous thromboembolism:

** Similar, or less bleeding than VKA**

Agent	Trial Name	Dose (mg), frequency	Comparator (INR indicated if VKA)	Major bleeding (%) (vs. comparator %)	Relative risk for major bleeding (95% CI)	Number of patients randomized
Rivaroxaban	EINSTEIN-DVT	15 BID→ 20 OD	INR 2.0-3.0	0.8 (1.2)	0.65 (0.33-1.30)	3,449
	EINSTEIN-PE	15 BID→ 20 OD	INR 2.0-3.0	1.1 (2.2)	0.49 (0.31-0.79)	4,832
	EINSTEIN-extension	10 OD	Placebo	0.7 (0)	Not estimable	1,197
Dabigatran	RE-COVER	150 BID	INR 2.0-3.0	1.6 (vs. 1.9)	0.82 (0.45-1.48)	2,564
	RE-COVER II	150 BID	INR 2.0-3.0	1.2 (vs. 1.7)	0.69 (0.36-1.32)	2,568
	RE-MEDY	150 BID	INR 2.0-3.0	0.9 (vs. 1.8)	0.52 (0.27-1.02)	2,856
	RE-SONATE	150 BID	Placebo	0.3 (vs. 0)	Not estimable	1,343
Apixaban	AMPLIFY	10 BID → 5 BID	INR 2.0-3.0	0.6 (vs. 1.8)	0.31 (0.17-0.55)	5,395
	AMPLIFY-EXT	2.5 BID 5.0 BID	Placebo	0.2 (vs. 0.5) 0.1 (vs. 0.5)	0.49 (0.09-2.64) 0.25 (0.03-2.24)	2,486
Edoxaban	Hokusai-VTE	60 OD	INR 2.0-3.0	1 (vs.2)	0.84 (0.59-1.21)	8,292

Extended treatment: Who?

Unprovoked VTE=

- **VTE** in the *absence* of a major or mino **provoking risk factor (s)** …
  - **Major** (in the 3 months prior to in E)
    - e.g. surgery with general anesthetic
    bedridden with immobilization for > 3
  - **Minor** (in the 2 months prior to in
    - e.g. surgery with general anesthetic for <30 min or injury/illness with immobilization <3 days
  - **Persistent**
    - Active cancer (ongoing or non-curative therapy)

Weakly Provoked

Cancer

Slide provided by M Rodger

Kearon on behalf of ISTH SSC, JTH, 2016

Guidelines: Anticoagulants after short term (3-6 months) therapy for VTE?

ACCP:

Provoked by major transient/strong temporary:

- **Recommend** stop anticoagulation at 3 months

Unprovoked or weakly provoked by transient factor:

- **Suggest** anticoagulants should be continued ***indefinitely*** in patients with non-high bleeding risk (Grade 2B- Weak recommendation)
- **Recommend** stop anticoagulation in patients with high bleeding risk at 3 months (Grade 1B)

Kearon, Chest, 2016

VTE risk stratification

- Single predictors not good enough
  - Normal D-Dimer off of anticoagulants
    - 3.6% per year with ~2 years follow-up (Verhovsek, Ann Intern Med 2008)
    - >5% per year in men and women (non-hormone associated) (Kearon, Ann Intern Med 2015)
  - Normal Compression Ultrasound at completion of DVT therapy
    - ~6% per year with ~1 year follow-up
- Clinical Decision Rules
  - DASH and Vienna-not prospectively validated
  - HERDOO2

Slide provided by M Rodger

"Men Continue and HERDOO2"

- **Men should continue** anticoagulants
  - -13.9% annual risk of recurrent VTE over 1.5 years f/u off of anticoagulants in derivation study

- **Women with ≥ 2 HERDOO points should continue** anticoagulants
  - -14.1% annual risk of recurrent VTE over 1.5 years f/u off of anticoagulants in derivation study

- **Women with ≤ 1 HERDOO point can discontinue** anticoagulants
  - -**1.6%** annual risk of recurrent VTE over 1.5 years f/u off of anticoagulants in derivation study

Slide provided by M Rodger

HERDOO Points in ♀

+1 **H**yperpigmentation **E**dema or **R**edness (**HER**) in either leg

+1 **D**-Dimer (Vidas) ≥ *250 ug/L (not 500)*

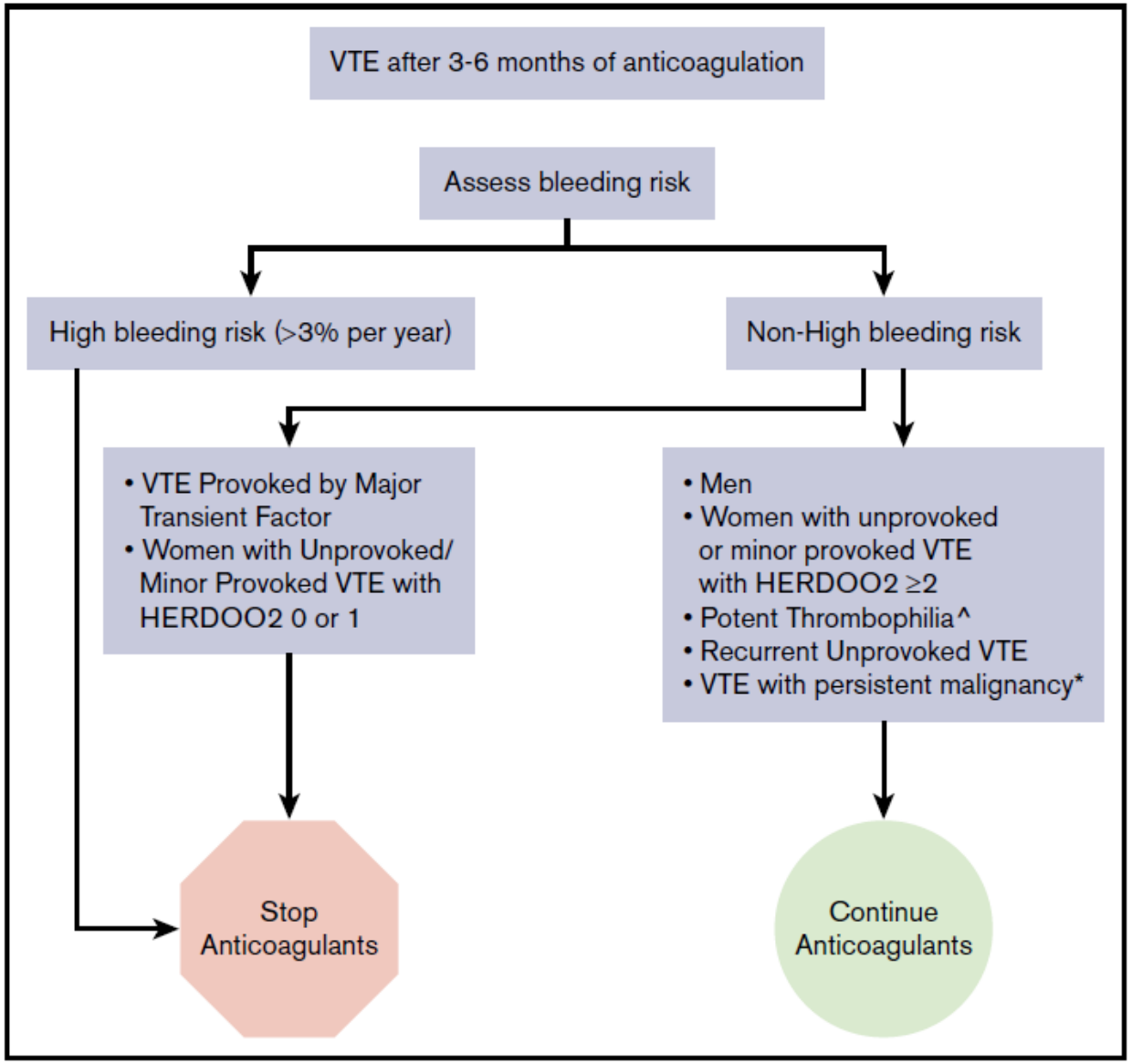
+1 **O**besity, BMI ≥ 30

+1 **O**lder age ≥ 65

=___ **HERDOO points**

Rodger, CMAJ, 2008

Approach to extended treatment of VTE



Slide provided by M Rodger

Bleeding risk determination in patients with unprovoked VTE: **KNOWLEDGE GAP**

- Major bleeding risk prediction rules for VTE patients on and off anticoagulants are lacking and/or non-validated
  - HAS-BLED score (low 0-2; high >=3)

- Bleeding in the era of DOACs vs VKAs?

- Lack of readily available reversal agent for DOACs despite HC approval of idarucizumab and andexanet alfa?

Low dose DOACs the ideal anticoagulant for extended VTE therapy?

- Effective?
  - Caution-AMPLIFY extension and EINSTEIN Choice head to head comparisons of low dose DOAC vs placebo
  - COVET (NCT03196349): RCT VKA (2-3) vs Riv 10mg OD vs Apix 2.5mg BID
  - RENOVE (NCT03285438): RCT low dose DOACs vs usual dose DOACs
- No bleeding?
  - Caution-AMPLIFY extension and EINSTEIN Choice: point estimates don't suggest a major bleeding risk benefit with lower dose DOACs
  - VKA cautionary tale- Trials of INR 1.5-2 vs INR 2-3 showed 1.5-2 was inferior and without major bleeding risk benefit (Kearon, NEJM, 2003)

Courtesy of M Rodger

Aspirin the ideal drug?

- Effective?
  - Only 32% RRR with residual risk of recurrent VTE ~5% per year (Weitz, NEJM, 2017) (compared to >80% RRR with DOACs)
- No bleeding?
  - 0.5% per year risk of major bleeding

Courtesy of M Rodger

What to offer patients regarding anticoagulant options for long-term secondary prevention

Don't offer

- Aspirin (unless won't take anticoagulant)
- Dabigatran (other options without acute coronary syndrome signal)
- Low dose DOACs –not yet! (waiting for head to head trials to prove they work /cause less bleeding)

Help patients choose from these 3 options:

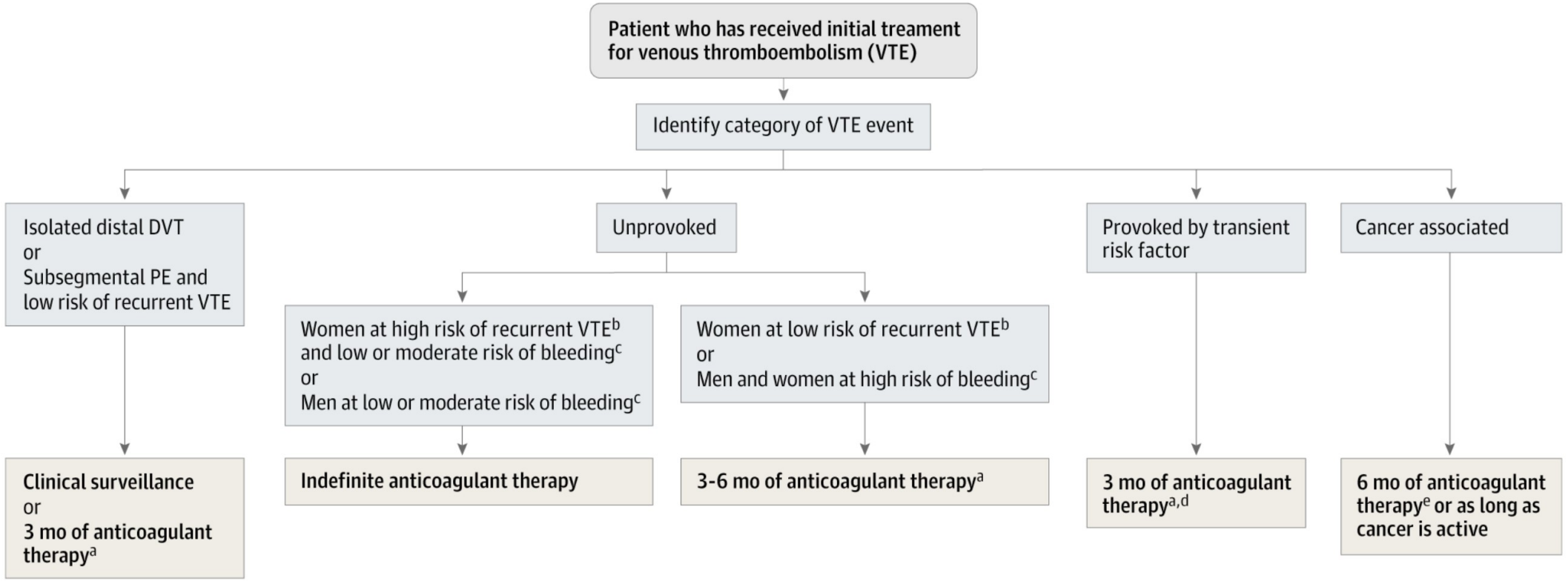
- Vitamin K antagonists
  - Effective, inexpensive, easily reversible but definitely causes more bleeding and require monitoring
- Apixaban (5mg BID dose)
  - Twice a day pill that does not require monitoring and <u>might</u> have lowest bleeding risk but more expensive than VKA and is not easily reversible
- Rivaroxaban (20mg OD dose)
  - Once a day pill that does not require monitoring but <u>might</u> cause slightly more bleeding than apixaban, is more expensive than VKA and is not easily reversible

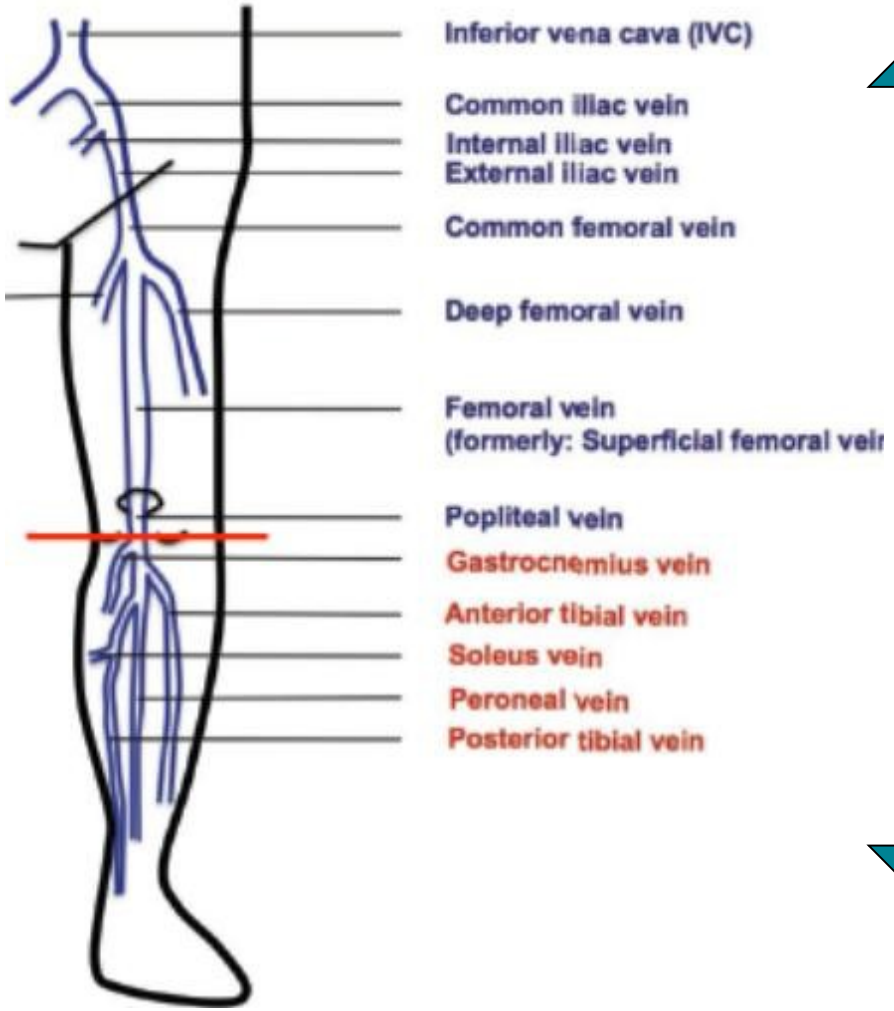
Courtesy of M Rodger

JAMA Network™

From: **Venous ThromboembolismAdvances in Diagnosis and Treatment**

JAMA. 2018;320(15):1583-1594. doi:10.1001/jama.2018.14346





Proximal DVT

EARLY TREATMENT
AGGRESSIVE
FULL DOSE ANTICOAGULANT

Distal DVT

CONTROVERSIAL
TREAT IF HIGH RISK FOR PROPOGATION
OR SYMTPOMATIC

Superficial vein

IF TREAT, TREAT WITH PROPHYACTIC-INTERMEDIATE DOSE LMWH,
FONDAPARINUX 2.5 sc die, or
RIVAROXABAN 10 die

Conclusion

- Past 10 years has seen substantial progress in the management of VTE allowing for diagnostic and therapeutic strategies tailored to individual patient characteristics
- Further studies will help
    1. Improve diagnostic algorithms for special populations (e.g. pregnant women, recurrent VTE)
    2. Stratify bleeding risk in VTE patients
    3. Define DOAC use in special populations (e.g. cancer, renal impairment, splanchnic vein thrombosis. HIT)
    4. DOAC dosing for extended treatment (low vs. therapeutic dose)