Venous Thromboembolism in the Era of Doacs.

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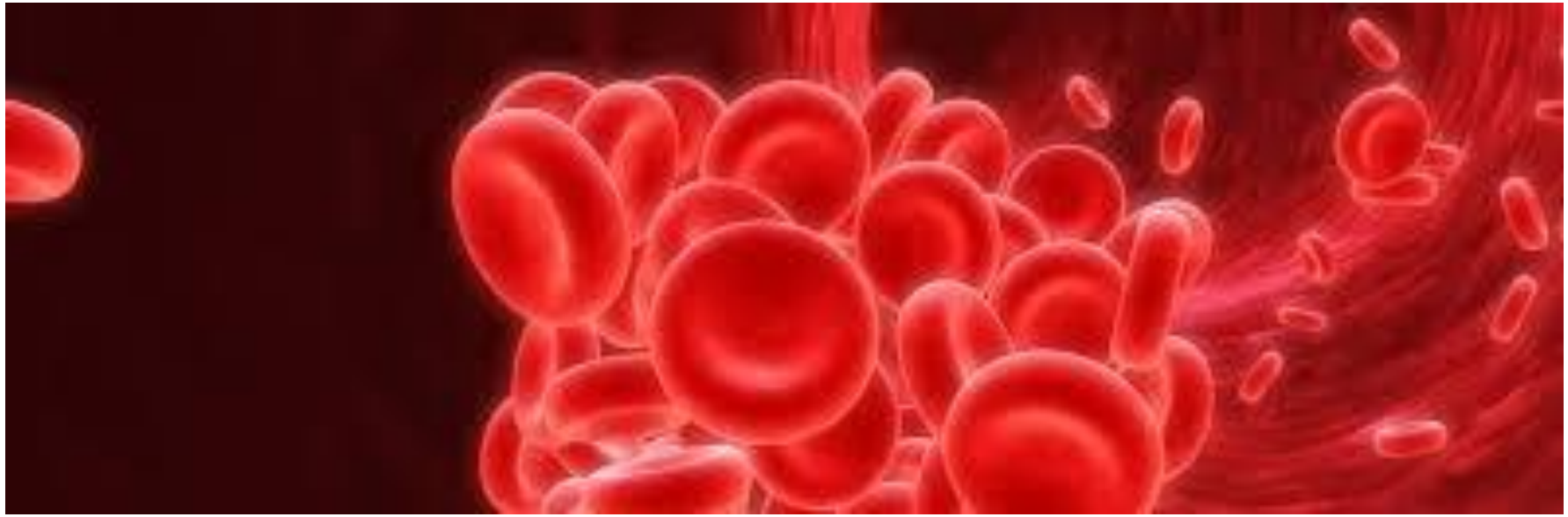
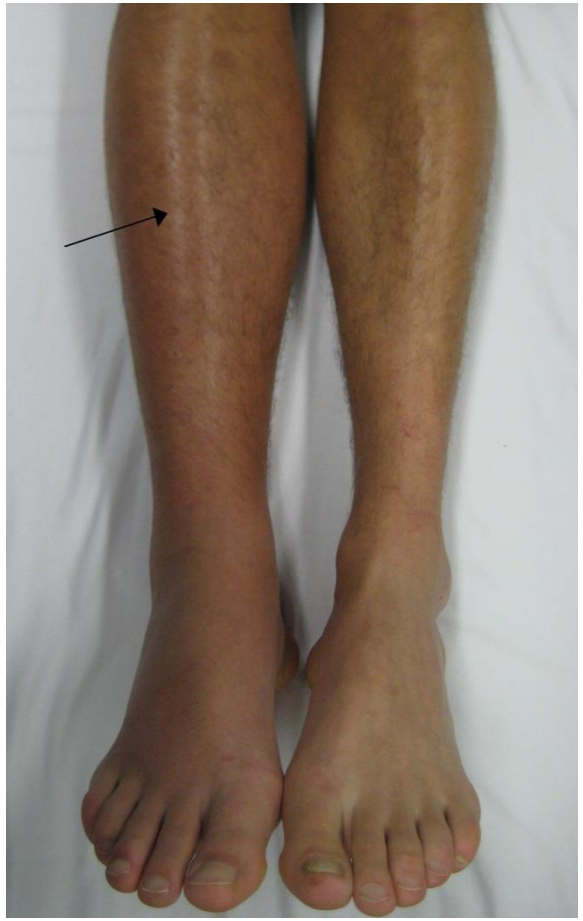


Introduction:

- Venous thromboembolism (VTE)= deep-vein thrombosis (DVT) +/- pulmonary embolism (PE).
- Worldwide the **third most frequently** cardiovascular disorder.
- VTE: about 2/3 DVT, only 1/3 PE (+/- DVT).
- DVT : 90% lower extremities, 5% upper ext, 5% unusual sites (eg visceral or cerebral).

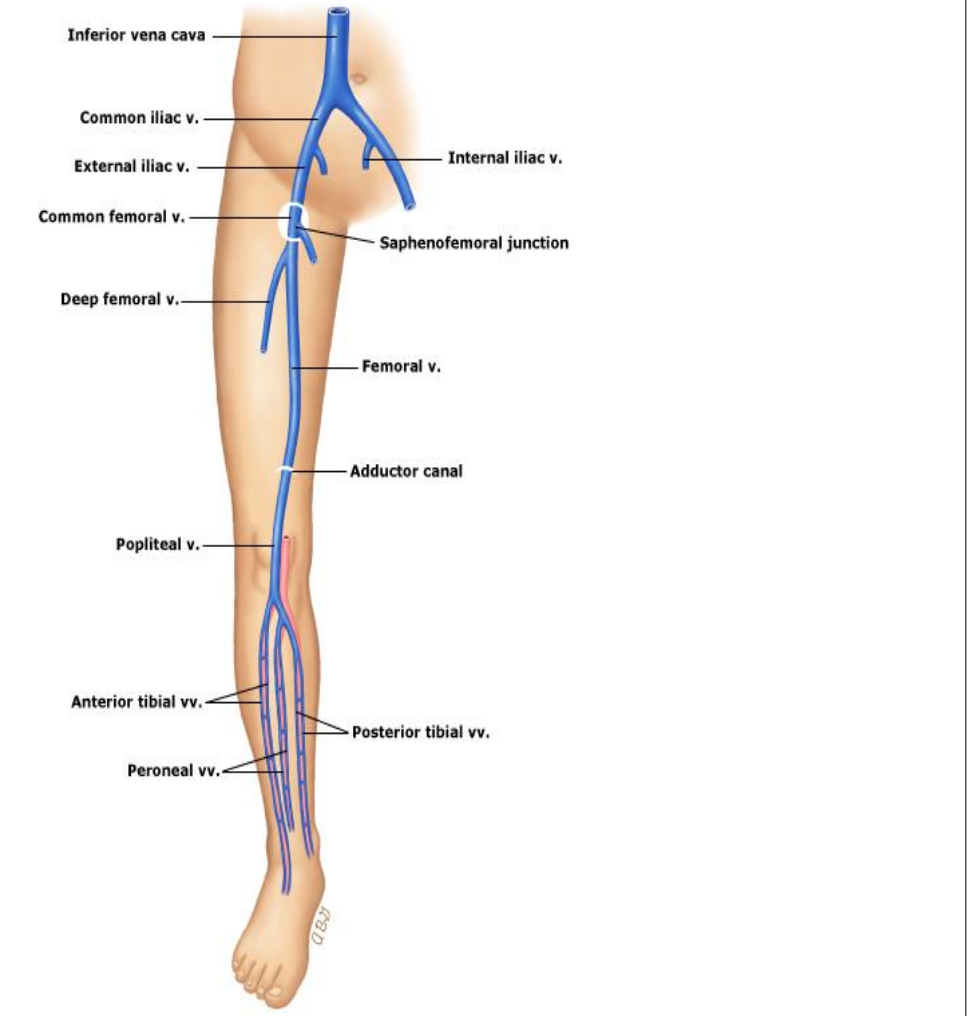


- Deep vein thrombosis of the lower extremity is subdivided:

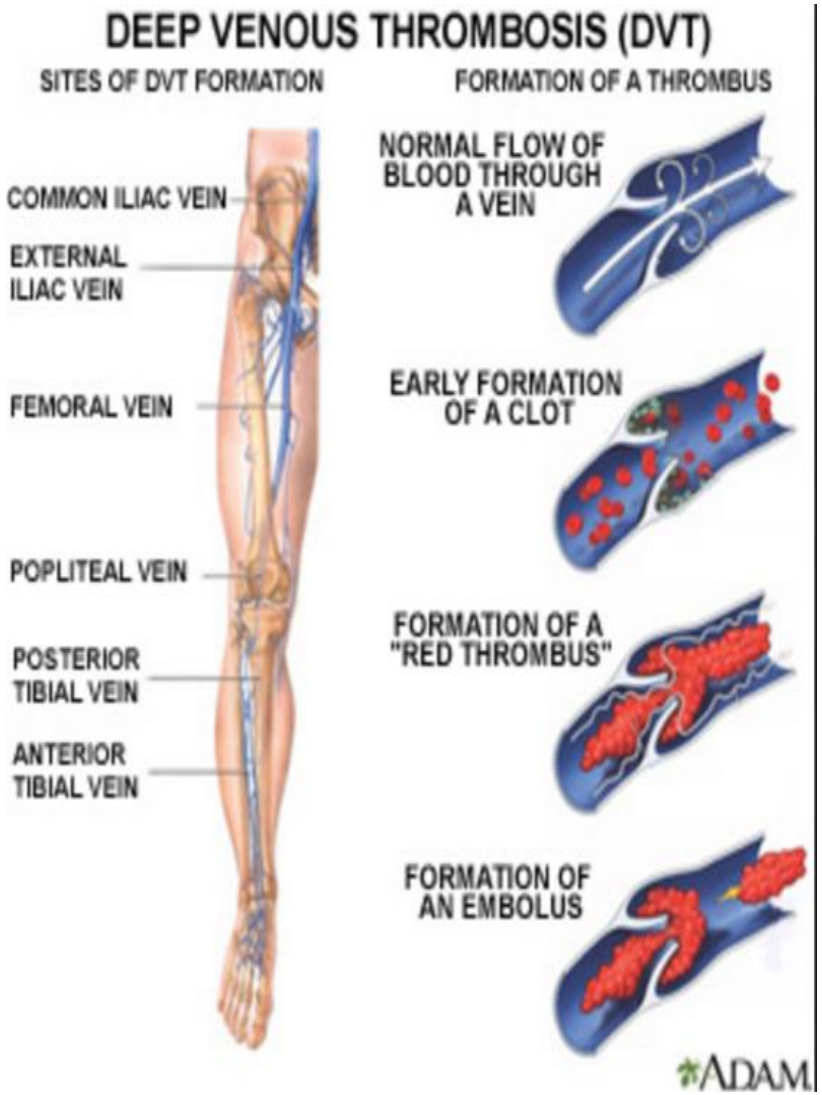
- **Distal (calf) vein thrombosis-**
- thrombi remain confined to the deep calf veins or the muscular

  calf veins,
- **Proximal vein thrombosis-** thrombosis involves the popliteal, femoral,

  or iliac veins.



- Over **90%** of acute PE are due to emboli from the **proximal** DVT of the lower extremities.
- **Proximal DVT** can be identified in **20% to 50%** of patients with **acute PE .**
- In 40-50% of **proximal DVT**, a **silent PE** has already occurred by the time that the patient is seen.



This overview will address:

- Epidemiology and Risk factors for VTE: acquired and inherited.
- Diagnostic approach for DVT and PE
- Recurrence VTE risk assessment.
- Screening for hypercoagulable states.
- Treatment of VTE: old and new. Guidelines and recommendation.
- Summary.

Epidemiology

- Venous thromboembolism (VTE) is a major cause of morbidity and mortality.
- Approximately **1%** of **hospital admissions** in the US.
- Approx **10%** of **hospital death**.

- **Annual incidence** rates of VTE: **100-180 per 100000 person-years**.

- A multifactorial disease; predisposition risk factors, either acquired or inherited (thrombophilias).

- Incident VTE - **idiopathic** ranges from **25% to 40% .**

{Heit, J. A. *Nat. Rev. Cardiol.* 2015}.

- VTE incidence increase markedly with age.
- The overall **age-adjusted annual incidence rate** is higher for **men** (130 per 100,000) than for women (110 per 100,000).
- Incidence rates are higher in women during childbearing years (16–44 years).
- {Heit, J. A. *Nat. Rev. Cardiol.* 2015}.

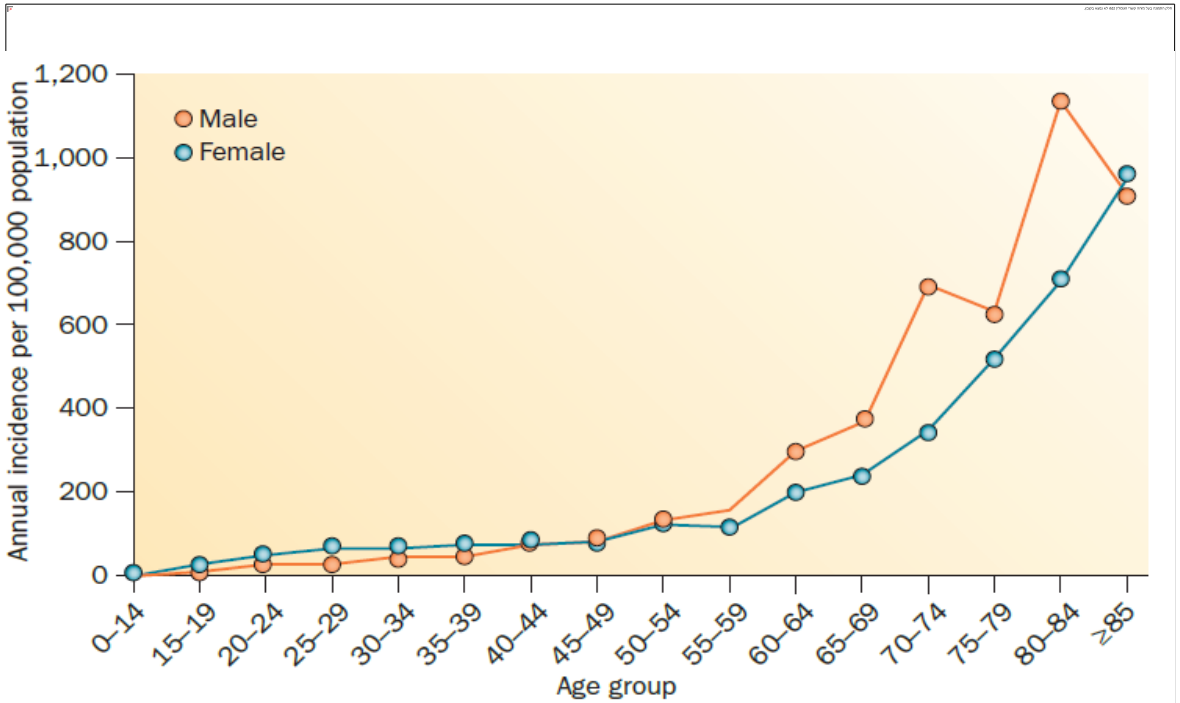


Figure 1 | Annual incidence of venous thromboembolism among residents of Olmsted County, MN, USA, from 1966 to 1990, by age and sex. Permission obtained from the American Medical Association © Silverstein, M. D. *et al.* Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch. Intern. Med.* **158**, 585–593 (1998).

- A susbstantial **increase** in the incidence rate of VTE from **2001 to 2009**, mostly owing to an **increasing** incidence of **PE.**

- {Heit, J. A. *Nat. Rev. Cardiol.* 2015}.

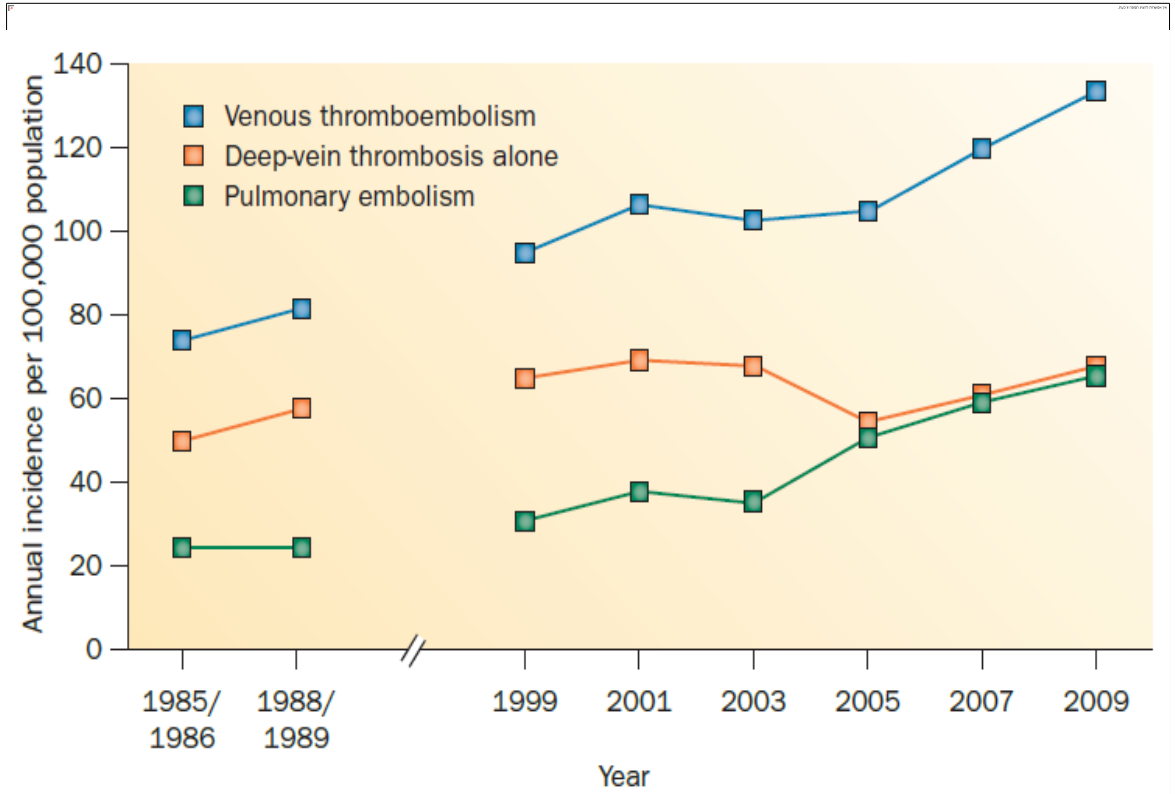
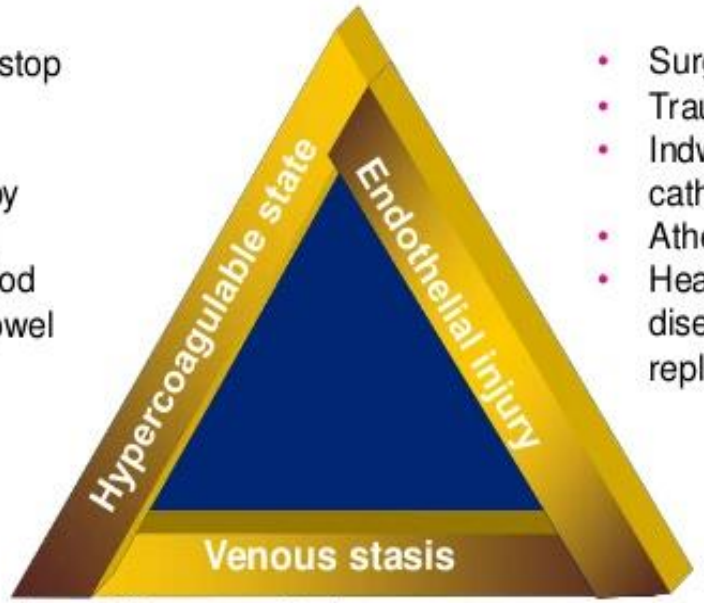


Figure 3 | Trends over time in the incidence of venous thromboembolism, deep-vein thrombosis alone, and pulmonary embolism (with or without deep-vein thrombosis) among residents of Worcester, MA, USA. Permission obtained from Elsevier © Huang, W. *et al.* Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009). *Am. J. Med.* **127**, 829–839 (2014).

Etiology

Virchow's triad

- Acute phase postop
- Cancer
- Thrombophilia
- Estrogen therapy
- Pregnancy and postpartum period
- Inflammatory bowel disease



- Surgery
- Trauma
- Indwelling catheter
- Atherosclerosis
- Heart valve disease or replacement

- Immobility or paralysis
- Heart failure
- Venous insufficiency or varicose veins
- Venous obstruction from tumour, obesity or pregnancy

Virchow R, ed. *Gesammelte Abhandlungun zur Wissenschaftichen Medicin*. Von Meidinger Sohn, Frankfurt, 1856.

CAUSES OF VENOUS THROMBOSIS

- **INHERITED THROMBOPHILIA**
  - **Factor V Leiden mutation**
  - **Prothrombin gene mutation**
  - **Protein S deficiency**
  - **Protein C deficiency**
  - **Antithrombin (AT) deficiency**
  - **Homocysteinemia**
  - Rare disorders

    Dysfibrinogenemia

- **ACQUIRED DISORDERS**
  - **Malignancy**
  - Presence of a central venous catheter
  - Surgery, especially orthopedic
  - Trauma
  - **Pregnancy**
  - **Oral contraceptives**
  - Hormone replacement therapy
  - Tamoxifen, Bevacizumab, Thalidomide, Lenalidomide
  - **Immobilization**
  - Congestive failure
  - Antiphospholipid antibody syndrome
  - **Myeloproliferative disorders**
  - Polycythemia vera
  - Essential thrombocythemia
  - Paroxysmal nocturnal hemoglobinuria
  - Inflammatory bowel disease
  - Nephrotic syndrome
  - **Hyperviscosity**
  - Waldenstrom's macroglobulinemia
  - Multiple myeloma
  - Marked leukocytosis in acute leukemia
  - **Sickle cell anemia**
  - **HIV/AIDS**

Diagnostic Approach: Clinical Pretest Probability (CPTP)

- VTE is diagnosed in approx. 1.5 per 1000 persons each year.
- For each patient who is diagnosed with VTE, the diagnosis is excluded in approx. 9 others.

- Therefore it is important to evaluate the CPTP:
- CPTP is higher if:

1. symptoms and signs are typical for DVT/PE.
2. symptoms and signs are more severe.
3. there are risk factors for VTE
4. VTE is thought to be the most likely diagnosis

- The **Wells DVT score** and **Wells PE score** are most widely used and best validated.

Pretest probability of deep vein thrombosis (Wells score)

Clinical feature	Score
Active cancer (treatment ongoing or within the previous six months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than three days or major surgery, within four weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared to the asymptomatic leg (measured below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or more likely than that of deep venous thrombosis	-2
Score	
High probability	3 or greater
Moderate probability	1 or 2
Low probability	0 or less
Modification:	
This clinical model has been modified to take one other clinical feature into account: a previously documented deep vein thrombosis (DVT) is given the score of 1. Using this modified scoring system, DVT is either likely or unlikely, as follows:	
DVT likely	2 or greater
DVT unlikely	1 or less

Adapted from:

1. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 1997; 350:1795

2. Wells PS, Anderson,DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003; 349:1227.

Wells criteria and 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 (Wells criteria)	
High	>6.0
Moderate	2.0 to 6.0
Low	<2.0
Simplified clinical probability assessment (Modified Wells criteria)	
PE likely	>4.0
PE unlikely	≤4.0

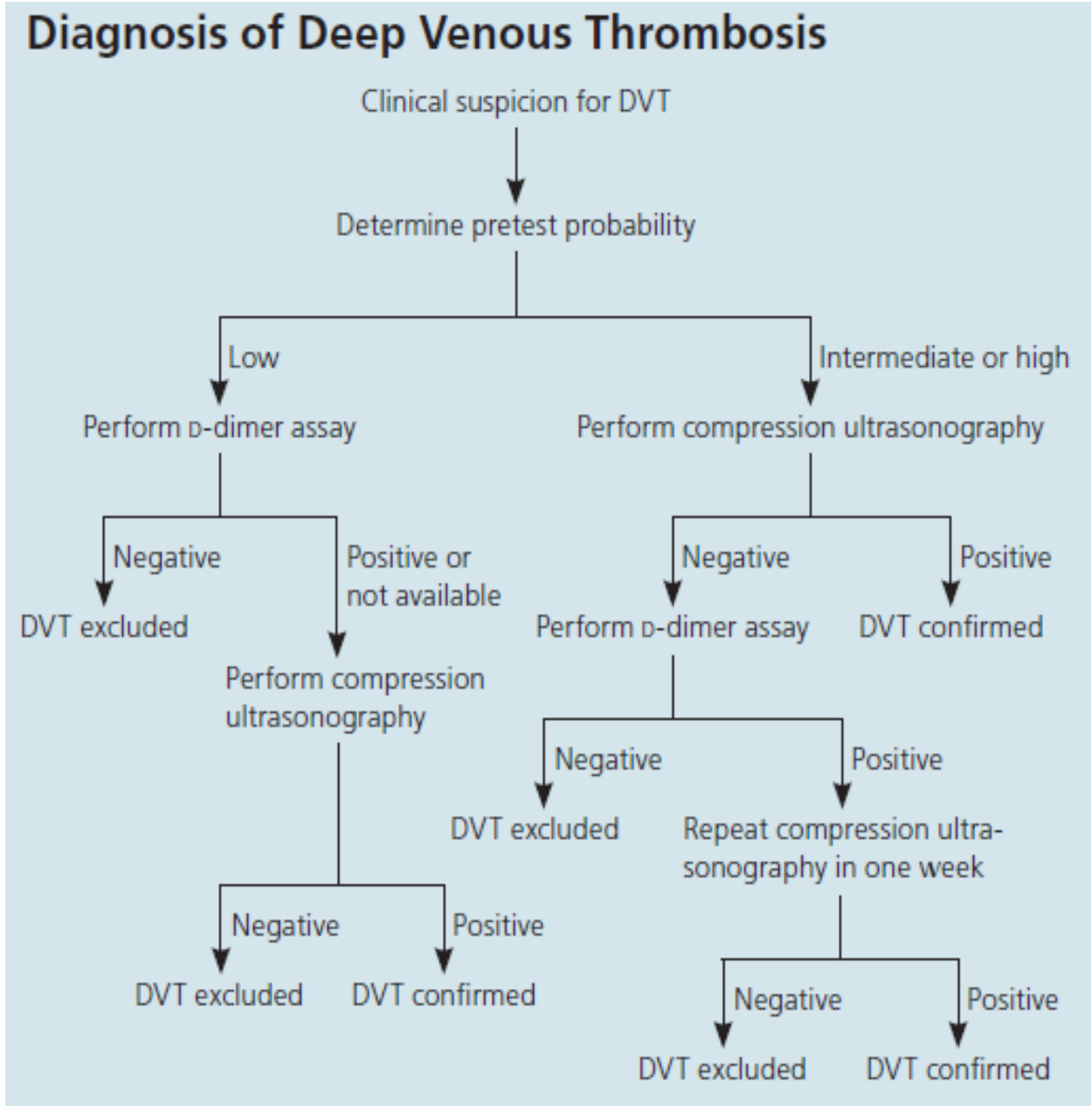
DVT: deep vein thrombosis; PE: pulmonary embolism.

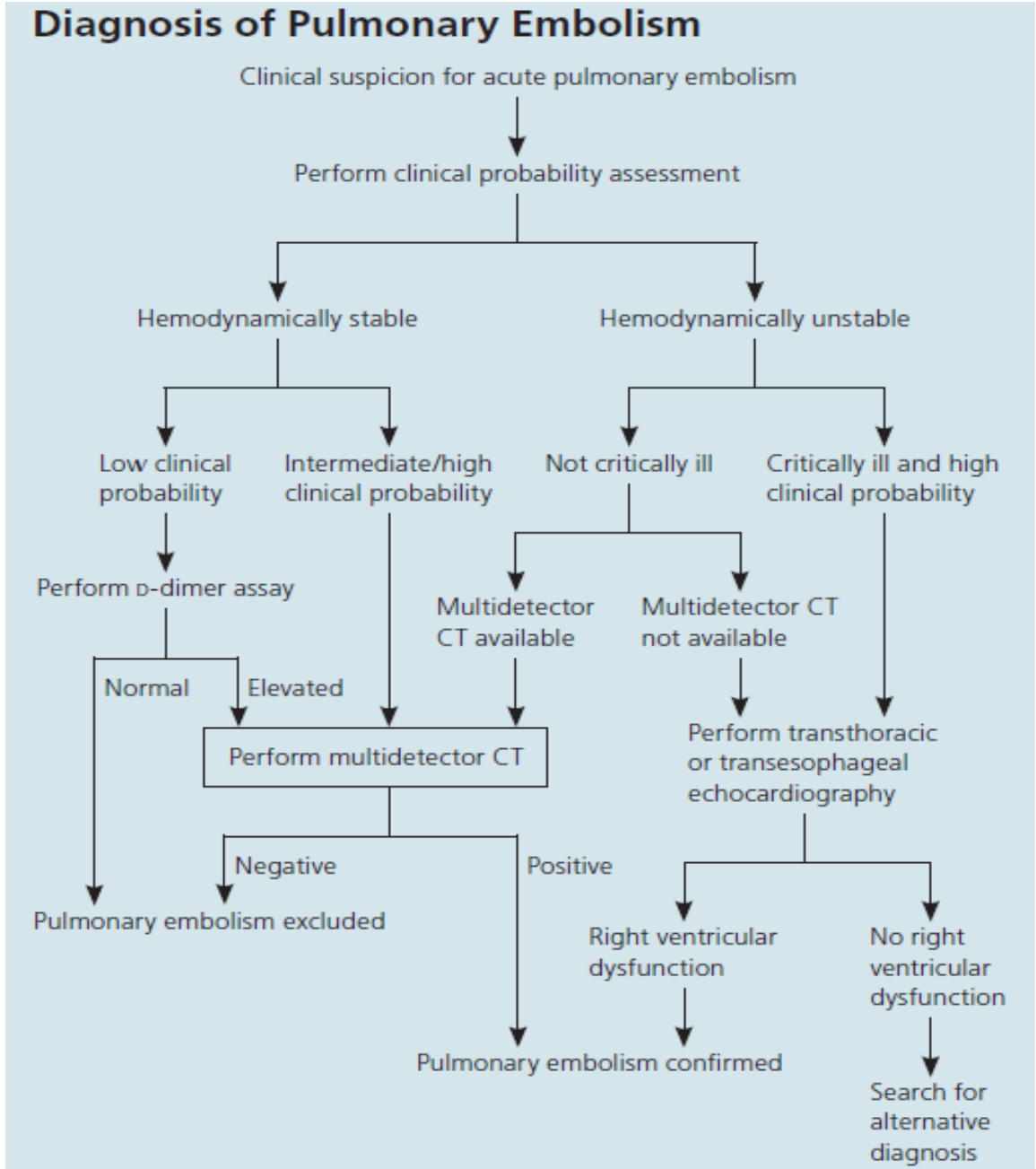
Data from van Belle A, Buller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 2006; 295:172.

Graphic 54767 Version 3.0

D-Dimer

- D-dimer is a degradation product of cross-linked fibrin, broken down by plasmin.
- D-dimers are increased and greater than 500 ng/mL in nearly all patients with VTE.
- When D-dimers are less than 500 ng/mL, the likelihood of venous thromboembolism was <10%.
- It is a sensitive test but lacks specificity for the diagnosis of DVT. (Cutoff value <500 ng/mL).
- **Age-adjusted cut-off values** of D-Dime (= **age [years] x 10 ng/mL)** for patients aged over 50 years have h**igher specificity.**


Diagnosis of Deep Venous Thrombosis
Clinical suspicion for DVT
Determine pretest probability
Low
Intermediate or high
Perform D-dimer assay
Perform compression ultrasonography
Negative
Positive or not available
Negative
Positive
DVT excluded
Perform compression ultrasonography
Perform D-dimer assay
DVT confirmed
Negative
Positive
Negative
Positive
DVT excluded
DVT confirmed
DVT excluded
Repeat compression ultrasonography in one week
Negative
Positive
Negative
Positive
DVT excluded
DVT confirmed


Diagnosis of Pulmonary Embolism
Clinical suspicion for acute pulmonary embolism
Perform clinical probability assessment
Hemodynamically stable
Hemodynamically unstable
Low clinical probability
Intermediate/high clinical probability
Not critically ill
Critically ill and high clinical probability
Perform D-dimer assay
Multidetector CT available
Multidetector CT not available
Normal
Elevated
Perform multidetector CT
Perform transthoracic or transesophageal echocardiography
Negative
Positive
Pulmonary embolism excluded
Right ventricular dysfunction
No right ventricular dysfunction
Pulmonary embolism confirmed
Search for alternative diagnosis

Recurrence of VTE

- VTE recurs frequently: **30%** of patients with VTE experience recurrence **within 5 years.**
- The risk of first recurrence is highest within the first 6–12 months .
- Randomized controlled trials have shown that patients with VTE benefit from a minimum of 3 months of anticoagulant therapy.
- Although secondary prophylaxis is effective in preventing recurrence, the duration of acute treatment does not affect the rate of recurrence beyond an initial 3 months of prophylactic anticoagulation medication.

- {Prandoni, P. Haematologica 2007: 92, 199–205}**.**

- The International Society on Thrombosis and Haemostasis considered a recurrence rate of **5%** at **one year** and of **15%** at **five years** after stopping anticoagulant therapy acceptable to justify discontinuation of anticoagulant therapy.

- Whereas a risk of **10%** at **one year** and **30%** at **5 years** is unacceptably high.

- {Kearon C. J Thromb Haemost 2010; 8: 2313–5}.

- On the other hand, the reported **annual incidence** of **major bleeding** in patients on **warfarin** with an INR range of 2.0–3.0 was estimated to be between **1.1% and 2.3%** in selected patients

- Patients with an expected annual recurrence rate of < 5% could safely discontinue treatment.

- These patients are those with **major transient risk factors**. (**provoked VTE**):
- The overall rate of recurrence was **3.3%** per patient-year,
- **0.7%** per patient-year for patients with a **surgical risk factor**
- **4.2%** per patient-year for patients with **non-surgical risk factors (ie** pregnancy/ puerperium, HRT, trauma….).

- For all other patients, including those with **previous** episodes of **VTE**, **cancer**, or **unprovoked events**, this treatment duration may not be sufficient.

- {Ageno W, J Thromb Haemos, 11 (Suppl. 1): 151–160}.
- {Iorio A. Arch Intern Med 2010; 170: 1710–6}.

- The **cumulative risk of recurrence** after proximal DVT and PE treatment discontinuation:

- **11%** after **1 year**,
- **29.1%** after **5 years**,
- And **39.9%** after **10 Years**.

- It was **higher** if the index event was **unprovoked**:
- 15% at 1 year,
- 40.5% at 5 years,
- And 52.5% at 10 years.

- {Prandoni P et al.Haematologica 2007; 92: 199–205}.

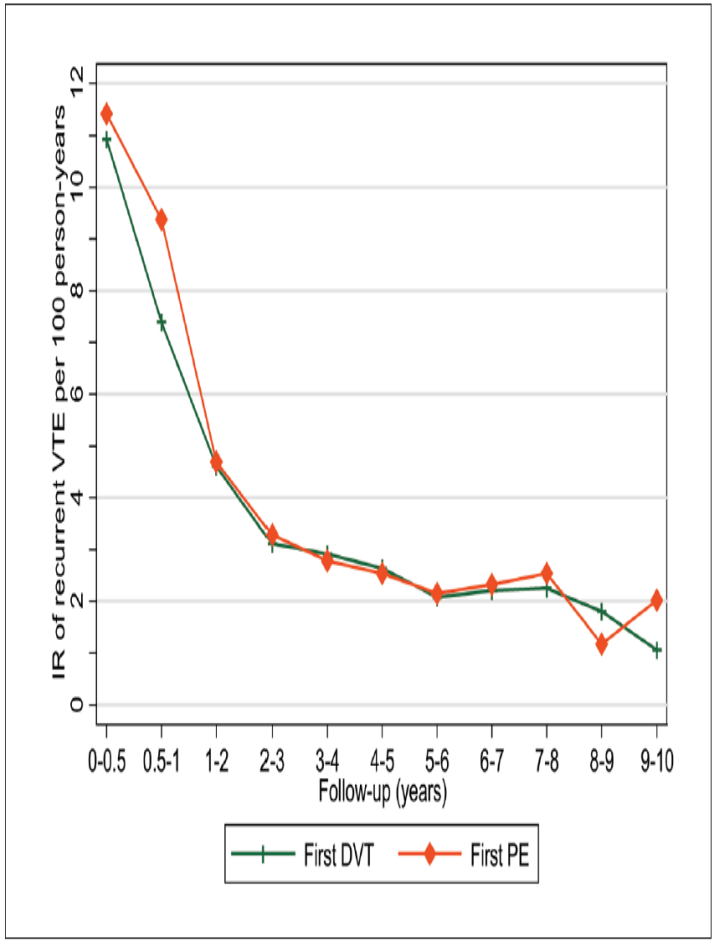


Figure 4: Incidence rates of recurrent VTE per 100 person-years and time since first VTE following first DVT and first PE.

Table 3. Inherited or Secondary Thrombophilia: Estimated Prevalence by Population, and Incidence and Relative Risk of Incident or Recurrent Venous Thromboembolism by Thrombophilia[1]

	Prevalence (Whites, %)			Incident VTE		Recurrent VTE	
Thrombophilia	Normal	Incident VTE	Recurrent VTE	Incidence* (95% CI)	Relative Risk (95% CI)	Incidence* (95% CI)	Relative Risk (95% CI)
Antithrombin deficiency	0.02–0.04	1–2	2–5	500 (320–730)	17.5 (9.1–33.8)	10 500 (3800–23 000)	2.5
Protein C deficiency	0.02–0.05	2–5	5–10	310 (200–470)	11.3 (5.7–22.3)	5100 (2500–9400)	2.5
Protein S deficiency	0.01–1	1–3	5–10	710 (530–930)	32.4 (16.7–62.9)	6500 (2800–11 800)	2.5
Factor V Leiden†	3–7	12–20	50–50	150 (80–260)	4.3‡ (1.9–9.7)	3500 (1900–6100)	1.3 (1.0–3.3)
Prothrombin G20210A†	1–3	3–8	15–20	350	1.9 (0.9–4.1)		1.4 (0.9–2.0)
Combined	-	-	-	840 (560–1220)	32.4 (16.7–62.9)	5000 (2000–10 300)	-
Hyperhomocysteinemia	-	-	-	-	-	-	2.5
Antiphospholipid Ab	-	-	-	-	-	-	2.5
Factor VIII (>200 IU/dL)	-	-	-	-	-	-	1.8 (1.0–3.3)

CI indicates confidence interval; VTE, and venous thromboembolism.

*Per 100 000 person-years.

†Heterozygous carriers.

‡Homozygous carriers relative risk ≈80.

VTE recurrence prediction algorithms

- Several **VTE recurrence prediction algorithms** have been proposed:

- In the **'Men continue and HERDOO2' rule:**
- Men are at high risk of recurrence after idiopathic VTE.

- Women with idiopathic VTE with ≥ 2 risk factors had high risk of VTE recurrence:
- **H**yperpigmentaion/ **E**dema/**R**edness
- increased **D**-Dimer level prior to stopping warfarin therapy,
- **o**lder age (≥65 years),
- **o**besity (BMI ≥30 kg/m2),
- {Rodger MA. CMAJ 2008; 179: 417–26}.

- In the **DASH prediction model**
- increased **D**-dimer level after termination of anticoagulat therapy,
- **A**ge <50 years,
- male **s**ex,
- women—VTE unrelated to **h**ormonal therapy
- predicted an increased risk of recurrence after an idiopathic VTE.

- {Tosetto A. J Thromb Haemost 2012; 10: 1019–25}.

DASH Prediction Score Derived From Cox Regression Analysis

DASH Predictors (*N = 1,818 VTE cases*)	ß coefficient*	P-value	Recurrence score
1. **D**-dimer abnormal, after stopping AC	0.96	<0.0001	+ 2
2. **A**ge < 50 yr	0.43	0.002	+ 1
3. **S**ex - male	0.58	<0.0001	+ 1
4. **H**ormone use at VTE onset	-1.05	0.002	- 2
DASH Prediction Rule			
DASH Score	≤ 1.0	2.0	≥ 3.0
Annualized VTE Recurrence Rate	3.1%	6.4%	12.3%

*Cox regression coefficients after backward elimination and optimism correction

Table adapted from Tosetto A, Iorio A, Marcucci M, et al. J Thromb Haemost. 2012;366:1019-1025.

TABLE 11] Risk Factors for Bleeding with Anticoagulant Therapy and Estimated Risk of Major Bleeding in Low-, Moderate-, and High-Risk categories[a]

Risk Factors[b]	Categorization of Risk of Bleeding[d]		
	Estimated Absolute Risk of Major Bleeding		
	Low Risk[e] (0 Risk Factors)	Moderate Risk[e] (1 Risk Factor)	High Risk[e] (≥2 Risk Factors)
Age >65 y[184-193]			
Age >75 y[184-188,190,192,194-202]			
Previous bleeding[185,191-193,198,201-204]			
Cancer[187,191,195,198,205]			
Metastatic cancer[181,204]			
Renal failure[185,191-193,196,199,201,206]			
Liver failure[186,189,195,196]			
Thrombocytopenia[195,204]			
Previous stroke[185,192,195,207]			
Diabetes[185,186,196,200,202]			
Anaemia[185,189,195,198,202]			
Antiplatelet therapy[186,195,196,202,208]			
Poor anticoagulant control[189,196,203]			
Comorbidity and reduced functional capacity[191,196,204]			
Recent surgery[189,209,c]			
Frequent falls[195]			
Alcohol abuse[191,192,195,202]			
Nonsteroidal anti-inflammatory drug[210]			
Anticoagulation 0-3 mo[f]			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6[g]	3.2	12.8[h]
Anticoagulation after first 3 mo[f]			
Baseline risk (%/y)	0.3[i]	0.6	≥2.5
Increased risk (%/y)	0.5	1.0	≥4.0
Total risk (%/y)	0.8[j]	1.6[j]	≥6.5

HAS-BLED score

Condition	Points
H - Hypertension	1
A - Abnormal renal or liver function (1 point each)	1 or 2
S - Stroke	1
B - Bleeding	1
L - Labile INRs	1
E - Elderly (> 65 years)	1
D - Drugs or alcohol (1 point each)	1 or 2

HAS-BLED score	Bleeds per 100 patient-years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.5

Note: HAS-BLED has been validated for warfarin, but not for the new anticoagulants.

Pisters R et al. Chest 2010;138(5):1093-1100.

CHEST

Official publication of the American College of Chest Physicians

Executive Summary : Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Gordon H. Guyatt, Elie A. Akl, Mark Crowther, David D. Gutterman, Holger J. Schuünemann and for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel

Chest 2012;141;7S-47S
DOI 10.1378/chest.1412S3

[Evidence-Based Medicine]

CHEST

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

PODCAST

European Heart Journal (2014) **35**, 3033–3080
doi:10.1093/eurheartj/ehu283

ESC GUIDELINES

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

Acute DVT Treatment

ACCP 2012

2.1 Initial Anticoagulation for Patients With Acute DVT of the Leg

2.1. In patients with acute DVT of the leg treated with VKA therapy, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B).

2.5 Choice of Initial Anticoagulant Regimen in Patients With Proximal DVT

2.5.1. In patients with acute DVT of the leg, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) **and over SC UFH** (Grade 2B for LMWH; Grade 2C for fondaparinux).

2.5.2. In patients with acute DVT of the leg treated with LMWH, we suggest once- over twice-daily administration (Grade 2C).

ACCP 2016

Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date) Anticoagulant

1. In patients with proximal DVT or pulmonary embolism (PE), we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B).

***2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy** (all Grade 2B).

Cancer associated Thrombosis

ACCP 2012

3.3.2. In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy (Grade 2B). In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2B).

3.1.5. In patients with DVT of the leg and active cancer, if the risk of bleeding is not high, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B), and if there is a high bleeding risk, we suggest extended anticoagulant therapy (Grade 2B).

ACCP 2016

*3. In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).

11. In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), or (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B).

Distal DVT

ACCP 2012

2.3 Anticoagulation in Patients With Isolated Distal DVT

2.3.1. In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C).

2.3.2. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension (see text), we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C).

2.3.4. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B); **we suggest anticoagulation if the thrombus extends but remains confined to the distal veins** (Grade 2C); **we recommend anticoagulation if the thrombus extends into the proximal veins** (Grade 1B).

ACCP 2016

13. In patients with acute isolated distal DVT of the leg and (i) without severe symptoms or risk factors for extension (see text), we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (Grade 2C) **or (ii) with severe symptoms or risk factors for extension (see text), we suggest anticoagulation over serial imaging of the deep veins** (Grade 2C).

15. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we (i) recommend no anticoagulation if the thrombus does not extend (Grade 1B), **(ii) suggest anticoagulation if the thrombus extends but remains confined to the distal veins** (Grade 2C), **and (iii) recommend anticoagulation if the thrombus extends into the proximal veins** (Grade 1B).

Distal DVT

ACCP 2012

3.1.3. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor (see remark), we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C)

ACCP2016

7. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C), we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B), and we recommend treatment with anticoagulation for 3 months over extended therapy (no scheduled stop date) (Grade 1B).

Remarks: Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants.

Provoked DVT/PE

ACCP 2012

3.1 Duration of Long-term Anticoagulant Therapy

3.1.1. In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), **(ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B), **or (iii) extended therapy** (Grade 1B regardless of bleeding risk).

3.1.2. In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), **(ii) treatment of a longer time-limited period (eg, 6 or 12 months)** (Grade 1B), **and (iii) extended therapy if there is a high bleeding risk** (Grade 1B). **We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B).

ACCP 2016

Duration of Anticoagulant Therapy

5. In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), **(ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months)** (Grade 1B), **or (iii) extended therapy (no scheduled stop date)** (Grade 1B).

6. In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) **and (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months)** (Grade 1B). **We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk** (Grade 2B), **and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding** (Grade 1B).

Unprovoked DVT

ACCP 2012

3.1.4. In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B). After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy.

3.1.4.1. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).

3.1.4.2. In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B).

ACCP 2016

8. In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B), and we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B).

9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

ACCP 2012

3.1.4.3. In patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see remark), we suggest 3 months of anticoagulant therapy over extended therapy in those with a low or moderate bleeding risk (Grade 2B) and recommend 3 months of anticoagulant treatment in those with a high bleeding risk (Grade 1B).

Second Unprovoked DVT/PE

ACCP 2012

3.1.4.4. In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B), and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Grade 2B).

3.1.4.5. In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of anticoagulant therapy over extended therapy (Grade 2B).

ACCP 2016

10. In patients with a second unprovoked VTE and who have a (i) low bleeding risk (see text), we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months (Grade 1B); (ii) moderate bleeding risk (see text), we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B); or (iii) high bleeding risk (see text), we suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 2B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

ACCP 2016

Aspirin for Extended Treatment of VTE

***12. In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE** (Grade 2B).

Catheter directed Thrombolysis

ACCP 2012

2.9 Catheter-Directed Thrombolysis for Patients With Acute DVT

2.9. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).

Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

ACCP 2016

Catheter-Directed Thrombolysis for Acute DVT of the Leg

16. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C).

Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

patients who are most likely to benefit from

CDT have iliofemoral DVT, symptoms for <14 days, good functional status, life expectancy of ≥1 year, and a low risk of bleeding (Tables 14 and 15, e-Table 15).

IVC Filter Insertion

ACCP 2012

2.13 Vena Cava Filters for the Initial Treatment of Patients With DVT

2.13.1. In patients with acute DVT of the leg, we recommend against the use of an IVC filter in addition to anticoagulants (Grade 1B).

2.13.2. In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B).

2.13.3. In patients with acute proximal DVT of the leg and an IVC filter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B).

ACCP 2016

Role of Inferior Vena Cava Filter in Addition to Anticoagulation for Acute DVT or PE

17. In patients with acute DVT or PE who are treated with anticoagulants, we recommend against the use of an inferior vena cava (IVC) filter (Grade 1B).

ESC 2014

Recommendations	Class[a]	Level[b]	Ref[c]
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C	
IVC filters should be considered in case of recurrence of PE, despite therapeutic levels of anticoagulation.	IIa	C	
Routine use of IVC filters in patients with PE is not recommended.	III	A	341, 355

Pulmonary Embolism Severity Index (PESI)

Table 7 Original and simplified PESI

Parameter	Original version[214]	Simplified version[218]
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
	Risk strata[a]	
	Class I:≤65 points very low 30-day mortality risk (0–1.6%) **Class II: 66–85 points** low mortality risk (1.7–3.5%) **Class III: 86–105 points** moderate mortality risk (3.2–7.1%) **Class IV: 106–125 points** high mortality risk (4.0–11.4%) **Class V: >125 points** very high mortality risk (10.0–24.5%)	**0 points**= 30-day mortality risk 1.0% (95% CI 0.0%–2.1%) **≥1 point(s)**= 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

b.p.m. = beats per minute; PESI = Pulmonary embolism severity index.
[a]based on the sum of points.

Table 9 Classification of patients with acute PE based on early mortality risk

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III–V or sPESI ≥1[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	–	+	Both positive	
	Intermediate–low	–	+	Either one (or none) positive[e]	
Low		–	–	Assessment optional; if assessed, both negative[e]	

PE = pulmonary embolism; PESI = Pulmonary embolism severity index; RV = right ventricular; sPESI = simplified Pulmonary embolism severity index.

[a]PESI Class III to V indicates moderate to very high 30-day mortality risk; sPESI ≥1 point(s) indicate high 30-day mortality risk.

[b]Echocardiographic criteria of RV dysfunction include RV dilation and/or an increased end-diastolic RV–LV diameter ratio (in most studies, the reported threshold value was 0.9 or 1.0); hypokinesia of the free RV wall; increased velocity of the tricuspid regurgitation jet; or combinations of the above. On computed tomographic (CT) angiography (four-chamber views of the heart), RV dysfunction is defined as an increased end-diastolic RV/LV (left ventricular) diameter ratio (with a threshold of 0.9 or 1.0).

[c]Markers of myocardial injury (e.g. elevated cardiac troponin I or -T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma).

[d]Neither calculation of the PESI (or sPESI) nor laboratory testing are considered necessary in patients with hypotension or shock.

[e]Patients in the PESI Class I–II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also to be classified into the intermediate-low-risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index.

PE- Acute Phase

ACCP 2012

5.1. In patients with acute PE, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B).

5.3. In patients with acute PE, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h (Grade 1B).

ECS 2014

Recommendations	Class[a]	Level[b]	Ref[c]
PE without shock or hypotension (intermediate–or low-risk)[d]			
Anticoagulation: combination of parenteral treatment with VKA			
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress.	I	C	352
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A	273, 274, 281, 353
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0).	I	B	352, 354
Anticoagulation: new oral anticoagulants			
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B	296
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B	297
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) is recommended following acute-phase parenteral anticoagulation.	I	B[e]	293, 294
As an alternative to VKA treatment, administration of edoxaban* is recommended following acute-phase parenteral anticoagulation.	I	B	298
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.[f]	III	A	293, 295–298

ACCP 2016

Systemic Thrombolytic Therapy for PE

21. In patients with acute PE associated with hypotension (eg, systolic BP <90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2B).

***22. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy** (Grade 1B).

***23. In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy** (Grade 2C).

ESC 2014

Recommendations	Class[a]	Level[b]	Ref[c]
PE with shock or hypotension (high-risk)			
It is recommended that intravenous anticoagulation with UFH be initiated without delay in patients with high-risk PE.	I	C	
Thrombolytic therapy is recommended.	I	B	168
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.[d]	I	C	313
Percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed.[d]	IIa	C	

ACCP 2016

***24. In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over CDT** (Grade 2C).

***25. In patients with acute PE associated with hypotension and who have (i) a high bleeding risk, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention** (Grade 2C).

Subsegmental PE

ACCP 2016

Whether to Anticoagulate Subsegmental PE

***19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation** (Grade 2C) **or (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C).

Remarks: Ultrasound (US) imaging of the deep veins of both legs should be done to exclude proximal DVT. Clinical surveillance can be supplemented by serial US imaging of the proximal deep veins of both legs to detect evolving DVT (see text). Patients and physicians are more likely to opt for clinical surveillance over anticoagulation if there is good cardiopulmonary reserve or a high risk of bleeding.

Recurrent VTE

ACCP 2016

*29. In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C).

*30. In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).

Acute VTE Treatment NOAC Trials:

Drug	Trial	Age (y)	Male (%)	Unprovoked (%)	Prior VTE (%)	Immobility (%)	Known Thrombophilia (%)	Active Cancer (%)
Apixaban	AMPLIFY[1]	57	58.7	89.8	16.2	NR	2.5	2.7
Rivaroxaban	EINSTEIN-DVT[2]	~56	56.8	62	19.3	15.2	6.5	6.0
	EINSTEIN-PE[3]	~58	52.9	64.5	19.5	15.8	5.4	4.6
Dabigatran	RE-COVER[4]	~55	58.4	NR	25.6	NR	NR	4.8
	RE-COVER II[5,6]	~55	60.6	NR	NR	NR	NR	NR
Edoxaban	HOKUSAI-VTE[7]	56	57.2	65.7	18.4	NR	NR	2.5

Head-to-head studies do not exist, and direct comparisons between agents may not be made.

NR=not reported

1. Agnelli G et al. *N Engl J Med.* 2013;369:799–808.
2. The EINSTEIN Investigators. *N Engl J Med.* 2010;363:2499–2510.
3. The EINSTEIN-PE Investigators. *N Engl J Med*. 2012;366:1287–1297.
4. Schulman S et al. *N Engl J Med.* 2009;361:2342–2352.
5. Schulman S et al. *Blood* (ASH Annual Meeting Abstracts) 2011;118: Abstract 205.
6. ClinicalTrials.gov Identifier: NCT00680186. Study results. Available at: http://clinicaltrials.gov/ct2/show/results/NCT00680186 Accessed 26/09/13.
7. The HOKUSAI-VTE Investigators. *N Engl J Med*. 2013. DOI: 10.1056/NEJMoa1306638.

Summary of NOAC Trial Results in Acute VTE Treatment

	Trial	Design	Study Drug	Comparator	Recurrent VTE + VTE death	Major Bleeding	Major + CRNM Bleeding
					NOAC vs Comparator (%), *P*-value		
Apixa	AMPLIFY[1]	D-B 6 m N=5395	Apixa 10 mg BD for 7d, then 5 mg BD	Enoxa/Warfarin	**Non-inferiority** 2.3 vs 2.7 *P*<0.001 (NI)	**Superiority** **RRR 69%** 0.6 vs 1.8 *P*<0.001	**Superiority** **RRR 56%** 4.3 vs 9.7 *P*<0.001
Riva	EINSTEIN-DVT[2]	O-L 3, 6, or 12 m N=3449	Riva 15 mg BD for 21d, then 20 mg OD	Enoxa/VKA	**Non-inferiority** 2.1 vs 3.0 *P*<0.001 (NI)	**Not signif.** 0.8 vs 1.2 *P*=0.21	**Not signif.** 8.1 vs 8.1 *P*=0.77
	EINSTEIN-PE[3]	O-L 3, 6, or 12 m N=4832	Riva 15 mg BD for 21d, then 20 mg OD	Enoxa/VKA	**Non-inferiority** 2.1 vs 1.8 *P*=0.003 (NI)	**Superiority** **RRR 51%** 1.1 vs 2.2 *P*=0.003	**Not signif.** 10.3 vs 11.4 *P*=0.23
Dabi	RE-COVER[4]	D-B 6 m N=2564	LMWH or UFH/ Dabi 150 mg BD	LMWH or UFH/ Warfarin	**Non-inferiority** 2.4 vs 2.1 *P*<0.001 (NI)	**Not signif.** 1.6 vs 1.9 *P*=0.38	**Superiority** **RRR 37%** 5.6 vs 8.8 *P*=0.002
	RE-COVER II[5,6]	D-B 6 m N=2568	LMWH or UFH/ Dabi 150 mg BD	LMWH or UFH/ Warfarin	**Non-inferiority** 2.4 vs 2.2 *P*<0.0001 (NI)	**Not signif.** 1.2 vs 1.7 NR*	Not reported

Head-to-head studies do not exist, and direct comparisons between agents may not be made.

The duration of follow-up differed between trials therefore event rates should not be compared or interpreted as an indicator of the risk of the population.

*Not significant based on 95% CI for hazard ratio. ***P*-value for overall study period and on-Tx period. NR=not reported.

1. Agnelli G et al. *N Engl J Med*. 2013;369:799–808. 2. The EINSTEIN Investigators. *N Engl J Med*. 2010;363:2499–2510. 3. The EINSTEIN-PE Investigators. *N Engl J Med*. 2012; 366:1287–1297. 4. Schulman S et al. *N Engl J Med*. 2009;361:2342–2352. 5. Schulman S et al. *Blood* (ASH Annual Meeting Abstracts) 2011;118: Abstract 205. 6. ClinicalTrials.gov Identifier: NCT00680186. Study results. Available at: http://clinicaltrials.gov/ct2/show/results/NCT00680186 . Accessed 26/09/13. 7. The HOKUSAI-VTE Investigators. *N Engl J Med*. 2013. DOI: 10.1056/NEJMoa1306638.

Overview: NOAC Trials for Acute VTE Treatment

	Apixaban[1]	Rivaroxaban [2,3]		Dabigatran[4,5]	Edoxaban[6]
Trial design: double-blind	+	–		+	+
No LMWH and/or UFH lead-in (ie. single agent)	+	+		–	–
Duration of treatment	6 months	3, 6 or 12 months		6 months	3-12 months
Non-inferior efficacy vs comparator* (recurrent or fatal VTE)	+	DVT +	PE +	+	+
Major bleeding vs comparator*	↓	NS	↓	NS	NS
Major or CRNM bleeding vs comparator*	↓	NS	NS	↓[4]	↓
Dosing	BD	BD then OD		BD	OD

Head-to-head studies do not exist, and direct comparisons between agents may not be made.

* Comparator was LMWH or UFH followed by either a VKA (warfarin or acenocoumarol) in the rivaroxaban trials or warfarin in the other NOAC trials. NS=no significant difference.

1. Agnelli G et al. N Engl J Med 2013; 369: 799-808.
2. The EINSTEIN Investigators. *New Engl J Med* 2010; 363: 2499-510
3. The EINSTEIN-PE Investigators. *New Engl J Med* 2012; 366: 1287-97
4. Schulman S et al. *N Engl J Med*. 2009;361:2342–2352.
5. Schulman S et al. *Blood* (ASH Annual Meeting Abstracts) 2011;118: Abstract 205.
6. The HOKUSAI-VTE investigators. *N Engl J Med* 2013.DOI:10.1056/NEJMoa1306638

+ indicates "Yes" **– indicates "No"**

↓ significant reduction

Extended VTE Treatment NOAC Trial Designs

Drug	Trial	Patients	Design	Tx Before Randomisation	Study Drug	Comparator	Length of Tx (mo.)
Apixaban	**AMPLIFY-EXT**[1]	2486	Double-blind	6–12 mo. of AC	Apixa 2.5 mg or 5 mg BD	Placebo	12
Rivaroxaban	**EINSTEIN-Extension**[2]	1197	Double-blind	6–12 mo. of VKA or riva	Riva 20 mg OD	Placebo	6 or 12
Dabigatran	**RE-SONATE**[3]	1353	Double-blind	6–18 mo. of VKA	Dabi 150 mg BD	Placebo	6
	RE-MEDY[3]	2866	Double-blind	3–12 mo. of VKA	Dabi 150 mg BD	**Warfarin**	6-36

Head-to-head studies do not exist, and direct comparisons between agents should not be made.

1. Agnelli G *et al*. *N Engl J Med* 2013;368:699–708.
2. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510.
3. Schulman S *et al*. *N Engl J Med* 2013;368:709–18.

Extended VTE Treatment NOAC Trials: Patient Characteristics

Percentage of patients with certain risk factors was different among extended VTE trials:

Drug	Trial	Age (y)	Male (%)	Index Event PE (%)	Unprovoked (%)	Active Cancer (%)	Immobility (%)	Prior VTE (%)	Known Thrombophilia (%)
Apixaban	**AMPLIFY-EXT[1]**	~57	57.4	34.6	91.7	1.7	2.8	12.7	3.8 (Inherited)
Rivaroxaban	**EINSTEIN-Extension[2]**	~58	57.9	38.0	73.7	4.5	13.9	16.1	8.1
Dabigatran	**RE-SONATE[3]**	~56	55.5	33	NR	Excluded	6.6	0.1	11.5
	RE-MEDY[3]	~55	61	35	NR	4.2	7.0	53.4	18.4

Head-to-head studies do not exist, and direct comparisons between agents should not be made.

1. Agnelli G *et al*. *N Engl J Med* 2013;368:699–708.
2. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510.
3. Schulman S *et al*. *N Engl J Med* 2013;368:709–18.

Results of NOAC Trials for Extended VTE Treatment

Drug	Trial	Dose	Recurrent VTE + VTE death	Major Bleeding	Major + CRNM Bleeding
			NOAC vs Comparator (%), *P*-value		
Apixa	**AMPLIFY-EXT**[1] **(placebo** comparator)	2.5 mg BD	**Superiority 81% RRR** 1.7 vs 8.8 *P*<0.001	**Not signif.** 0.2 vs 0.5 NR*	**Not signif.** 3.2 vs 2.7 NR*
		5 mg BD	**Superiority 80% RRR** 1.7 vs 8.8 *P*<0.001	**Not signif.** 0.1 vs 0.5 NR*	**Not signif.** 4.3 vs 2.7 NR*
Riva	**EINSTEIN-Extension**[2] **(placebo** comparator)	20 mg OD	**Superiority 82% RRR** 1.3 vs 7.1 *P*<0.001	**Not signif.** 0.7 vs 0 *P*=0.11	**Significant increase** 6.0 vs 1.2 *P<0.001*
Dabi	**RE-SONATE**[3] **(placebo** comparator)	150 mg BD	**Superiority 92% RRR** 0.4 vs 5.6 *P*<0.001	**Not signif.** 0.3 vs 0 *P*=1.0	**Significant increase** 5.3 vs 1.8 *P=0.001*
	RE-MEDY[3] **(warfarin** comparator)	150 mg BD	**Non-inferiority** 1.8 vs 1.3 *P*=0.01 (NI)	**Not signif.** 0.9 vs 1.8 *P*=0.06	**Significant reduction 46% RRR** 5.6 vs 10.2 *P*<0.001

Head-to-head studies do not exist, and direct comparisons between agents may not be made.

The duration of follow-up differed between trials therefore event rates should not be compared or interpreted as an indicator of the risk of the population.

*Not significant based on 95% CI for relative risk. NR=not reported.

1. Agnelli G *et al*. *N Engl J Med* 2013;368:699–708. 2. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510. 3. Schulman S *et al*. *N Engl J Med* 2013;368:709–18.

Overview: NOAC Trials for Extended VTE Treatment

	Apixaban[1]		Rivaroxaban[2]	Dabigatran[3]		Edoxaban
Trial design: double-blind	+		+	+		N/A
Comparator	Placebo		Placebo	Warfarin	Placebo	N/A
Duration of treatment	12 months		6 or 12 months	6-36 months	6 months	N/A
Superior efficacy (recurrent or fatal VTE) vs comparator	2.5 mg +	5 mg +	+	vs warfarin –	vs placebo +	N/A
Major bleeding vs comparator	2.5 mg NS	5 mg NS	NS	vs warfarin NS	vs placebo NS	N/A
Major or clinically-relevant non-major bleeding vs comparator	2.5 mg NS	5 mg NS	↑	vs warfarin* ↓	vs placebo* ↑	N/A
Low dose option	+		–	–		N/A
Dosing	BD		OD	BD		N/A

Head-to-head studies do not exist, and direct comparisons between agents may not be made.

NS=no significant difference

+ indicates "Yes" **– indicates "No"**

↓ significant reduction

↑ significant increase

1. Agnelli G et al. *N Engl J Med* 2013; 368: 699-708
2. The EINSTEIN Investigators. *N Engl J Med*. 2010;363:2499-2510
3. Schulman S et al. *N Engl J Med.* 2013; 368:709-718

Investigations for thrombophilia

- No thrombophilia testing for “provoked” DVT/PE

- Consider testing for APL in unprovoked DVT/PE if stopping anticoagulation treatment is planned.

- Consider testing for hereditary thrombophilia in unprovoked DVT/PE and a **first degree** relative with VTE, if stopping anticoagulation treatment is planned.

- Do not routinely offer thrombophilia testing to first degree relatives of patients with a history of VTE and thrombophilia.

- Do not perform thrombophilia testing at the time of VTE diagnosis or during the initial 3-month of anticoagulant therapy.

- When testing for thrombophilias following VTE, a 2-stage testing approach is advised.

- Genotype-based tests (FVL and PTM) and antibody titers (anticardiolipin and beta-2 glycoprotein I) can be performed at any point. Lupus anticoagulants if treated with heparins.
- All others after completion of 3 mo anticoagulant therapy.

Choosing Wisely®

An initiative of the ABIM Foundation

American Society of Hematology

Ten Things Physicians and Patients Should Question

2

Don't test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility).

Thrombophilia testing is costly and can result in harm to patients if the duration of anticoagulation is inappropriately prolonged or if patients are incorrectly labeled as thrombophilic. Thrombophilia testing does not change the management of VTEs occurring in the setting of major transient VTE risk factors. When VTE occurs in the setting of pregnancy or hormonal therapy, or when there is a strong family history plus a major transient risk factor, the role of thrombophilia testing is complex and patients and clinicians are advised to seek guidance from an expert in VTE.

3

Don't use inferior vena cava (IVC) filters routinely in patients with acute VTE.

IVC filters are costly, can cause harm and do not have a strong evidentiary basis. The main indication for IVC filters is patients with acute VTE and a contraindication to anticoagulation such as active bleeding or a high risk of anticoagulant-associated bleeding. Lesser indications that may be reasonable in some cases include patients experiencing pulmonary embolism (PE) despite appropriate, therapeutic anticoagulation, or patients with massive PE and poor cardiopulmonary reserve. Retrievable filters are recommended over permanent filters with removal of the filter when the risk for PE has resolved and/or when anticoagulation can be safely resumed.

6

Don't treat with an anticoagulant for more than three months in a patient with a first venous thromboembolism (VTE) occurring in the setting of a major transient risk factor.

Anticoagulation is potentially harmful and costly. Patients with a first VTE triggered by a major, transient risk factor such as surgery, trauma or an intravascular catheter are at low risk for recurrence once the risk factor has resolved and an adequate treatment regimen with anticoagulation has been completed. Evidence-based and consensus guidelines recommend three months of anticoagulation over shorter or longer periods of anticoagulation in patients with VTE in the setting of a reversible provoking factor. By ensuring a patient receives an appropriate regimen of anticoagulation, clinicians may avoid unnecessary harm, reduce health care expenses and improve quality of life. This *Choosing Wisely*® recommendation is not intended to apply to VTE associated with non-major risk factors (e.g., hormonal therapy, pregnancy, travel-associated immobility, etc.), as the risk of recurrent VTE in these groups is either intermediate or poorly defined.

Summary

- VTE is a multifactorial disorder, with a significant morbidity and mortality.
- Optimizing diagnosis is advised using pretest probability assessment.
- Treat an acute VTE for a 3 month period, if provoked or high risk of bleeding unprovoked.
- Treat acute VTE for extended period if unprovoked without high bleeding risk.
- Treat with Doacs instead of VKA.
- Reassess extended anticoagulant therapy annually.


Thank
You!