VTE, from investigation to treatment

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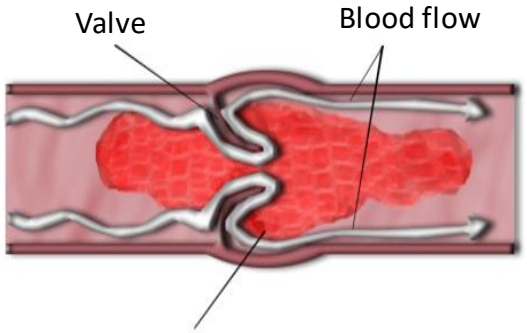
Introduction to VTE and its pathology

- Incidence of VTE is approximately one per 1,000 people annually[1]
- VTE comprises DVT and PE: one-third of cases are PEs; two-thirds are DVTs[1]
- The 30-day mortality risk has been estimated as 3% for DVT and 31% for PE*[2]



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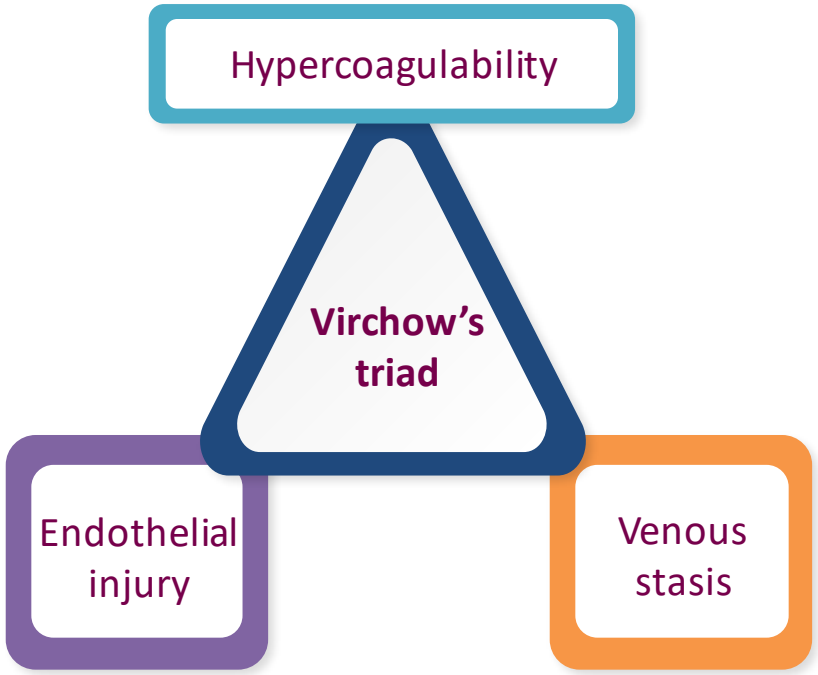


Virchow's triad summarises the factors that contribute to the development of VTE; **venous stasis** is thought to play the biggest role[4]

**Based on a retrospective analysis of 128,223 patients in the Danish National Registry of Patients who had a first-time hospital discharge diagnosis of VTE (74,157 had DVT, 54,066 had PE) (January 1980–December 2011).*[2]
DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism.

1. Stone J, et al. *Cardiovasc Design Ther* 2017;9(Suppl. 3):S276–S284; 2. Søgaard S, et al. *Circulation* 2014;130:829–836;
3. Blood clot diagram. Wikimedia Commons. Available at: https://commons.wikimedia.org/wiki/File:Blood_clot_diagram.png.
Last accessed: August 2020; 4. Behravesh S, et al. *Thrombosis* 2017;2017:3039713.

Examples of risk factors for VTE[1,2]

Physiological factors

- Dehydration
- Obesity (BMI ≥30 kg/m^2)
- Pregnancy

Other factors

- Age over 60 years
- Medical comorbidities*
- Significant reduction in mobility

Cancer

- Cancer type, stage
- Treatment

Medications

- Hormone replacement therapy
- Medications taken to treat active cancer
- Oestrogen-containing contraceptive therapy

Cardiovascular diseases

- Thrombophilia
- Varicose veins with phlebitis
- VTE history or first-degree relative with VTE history

Hospitalisation/surgery

- Surgery with a general anaesthetic and surgical time of >90 minutes (60 minutes if the surgery involves the pelvis or lower limb)
- Critical care admission
- Acute surgical admission with inflammatory or intra-abdominal condition

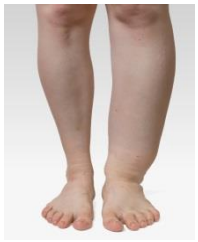
**Heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases and inflammatory conditions.*
BMI: body mass index.

1. NICE clinical guideline (CG92). Venous thromboembolism: reducing the risk for patients in hospital. January 2010. Available at: https://www.nice.org.uk/guidance/cg92/resources; 2. Bahl V, et al. Ann Surg 2009;251:344–350.

Clinical presentation of DVT: Signs and symptoms[1,2]

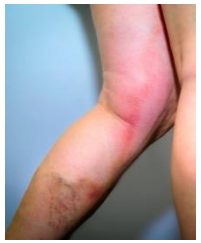
DVT

Leg pain



Swelling

Tenderness



Discolouration

Pitting oedema

If a patient presents with signs or symptoms of DVT, carry out an assessment of their general medical history and a physical examination to exclude other causes[3]

If DVT is suspected, use the two-level DVT Wells score to estimate the clinical probability of DVT[3]

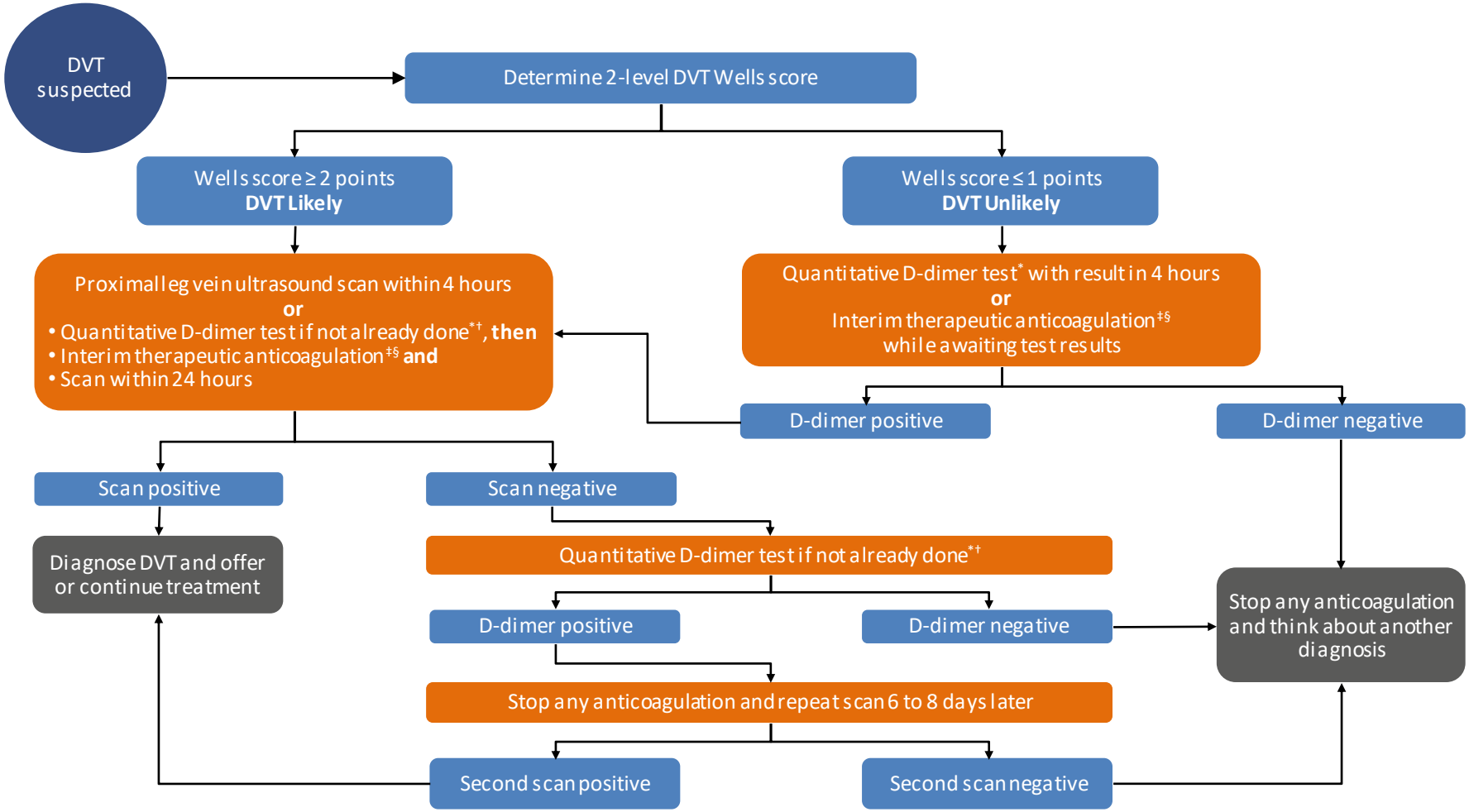
1. Moll S, et al. *Arterioscler Thromb Vasc Biol* 2008;28:373–379; 2. Pai M, et al. Available at: http://www.uptodate.com/contents/deep-vein-thrombosis-dvt-beyond-the-basics. Last accessed: August 2020; 3. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020.

Two-level DVT Wells score to estimate probability of DVT

Two-level Wells DVT risk score[1]	
Clinical feature	**Points**
Active cancer (on treatment/treated in the past 6 months/palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	–2
Clinical probability	
DVT likely	≥2 points
DVT unlikely	≤1 point

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020.

Suspected DVT: diagnosis and initial management



In the AMPLIFY trial, apixaban was given to patients with a confirmed DVT/PE. The use of an appropriate anticoagulant for patients with a suspected DVT/PE whilst awaiting confirmatory diagnostic tests is a clinical decision based on individual patient assessment

**Laboratory or point-of-care test. Consider age-adjusted threshold for people over 50.*
†Note that only one D-dimer test is needed during diagnosis.
‡Measure baseline blood count, renal and hepatic function, PT and APTT but start anticoagulation before results available and review within 24 hours.
§If possible, choose an anticoagulant that can be continued if DVT confirmed.
APTT: activated partial thromboplastin time; LMWH: low-molecular-weight heparin; PT: prothrombin time.

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/resources/visual-summary-pdf-8709091453. Last accessed: August 2020.

Clinical presentation of PE: Signs and symptoms[1,2]

PE

Shortness of breath

Cough

Chest pain

Tachycardia

Hypotension

Low-grade fever

If a patient presents with signs or symptoms of a PE, carry out an assessment of their general medical history and a physical examination to exclude other causes[3]

For suspected PE, refer for a chest X-ray to exclude other causes[3]

If PE is suspected, use the two-level PE Wells score to estimate the clinical probability of PE[3]

1. Taylor Thompson B, et al. Available at: http://www.uptodate.com/contents/pulmonary-embolism-beyond-the-basics. Last accessed: August 2020; 2. Sekhri V, et al. *Arch Med Sci* 2012;8:957–969; 3. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020

Two-level PE Wells score to estimate probability of PE

Two-level Wells PE risk score[1]	
Clinical feature	**Points**
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate >100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical probability simplified scores	
PE likely	>4 points
PE unlikely	≤4 point

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020.

NICE guidance on pulmonary embolism rule-out criteria (PERC)

If clinical suspicion of PE is low,* consider using PERC to help determine whether any further investigations for PE are needed[1]

PERC criteria	Recurrence score
Age ≥50 years	+1
HR ≥100	+1
O2 saturation on room air <95%	+1
Unilateral leg swelling	+1
Haemoptysis	+1
Recent surgery or trauma†	+1
Prior DVT or PE	+1
Hormone use‡	+1

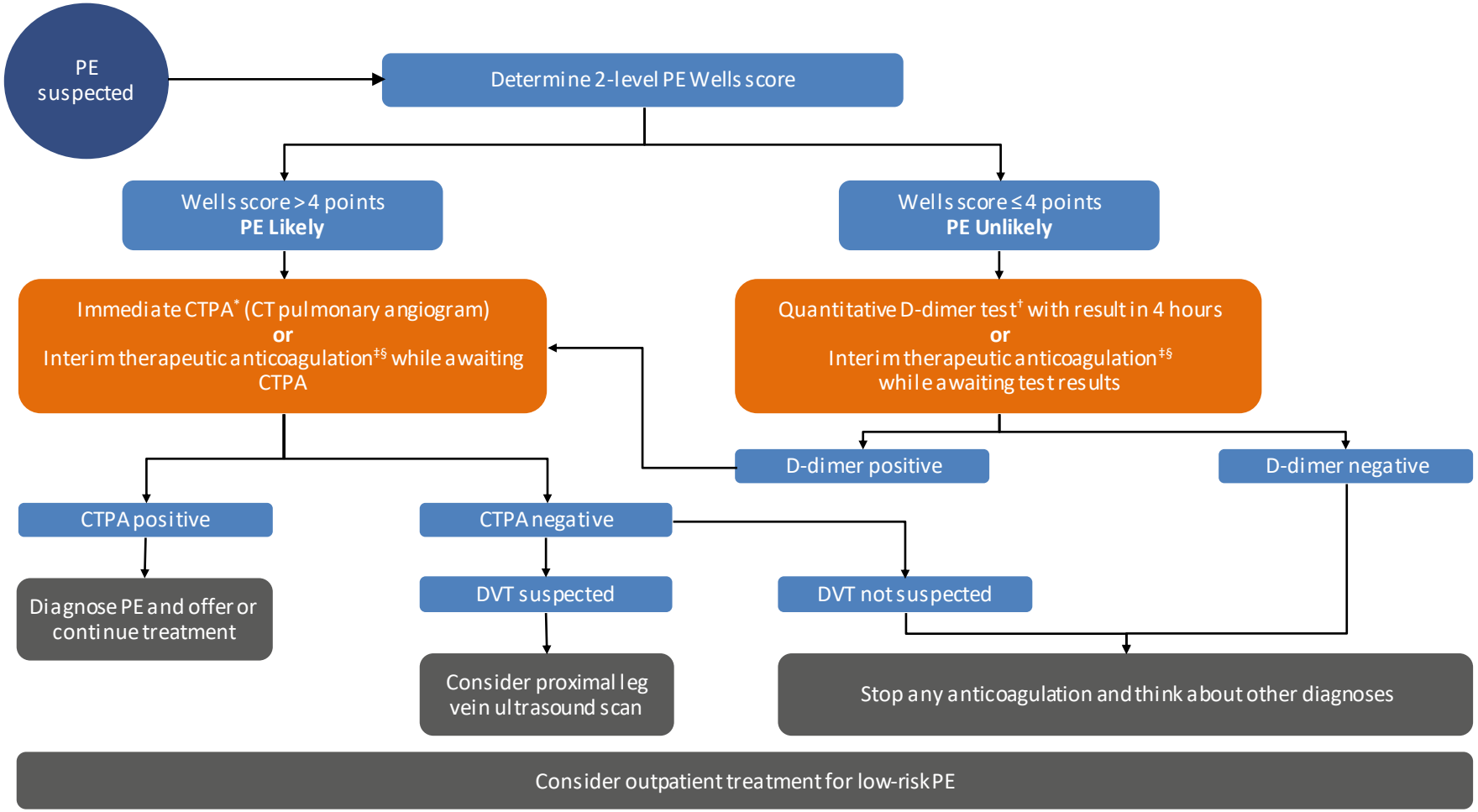
PERC score	Risk of PE
0	No need for further work-up as <2% chance of PE
≥1	PERC cannot be used to rule-out a PE

Adapted from MDCalc.[2]

**The clinician estimates the likelihood of PE to be less than 15% based on the overall clinical impression and other diagnoses are feasible;*[1] *†Surgery or trauma ≤4 weeks ago requiring treatment with general anaesthesia; ‡Oral contraceptives, hormone replacement or oestrogenic hormones use in male or female patients.*

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020; 2. MDCalc. PERC Rule for Pulmonary Embolism. Available at: https://www.mdcalc.com/perc-rule-pulmonary-embolism. Last accessed: August 2020.

Suspected PE: diagnosis and initial management



In the AMPLIFY trial, apixaban was given to patients with a confirmed DVT/PE. The use of an appropriate anticoagulant for patients with a suspected DVT/PE whilst awaiting confirmatory diagnostic tests is a clinical decision based on individual patient assessment

**CT pulmonary angiogram. Assess suitability of V/A SPECT or V/Q planar scan for allergy, severe renal impairment (CrCl <30mL/min estimated using the Cockcroft and Gault formula) or high irradiation risk.*

†Laboratory or point-of-care test. Consider age-adjusted threshold for people over 50.

‡Measure baseline blood count, renal and hepatic function, PT and APTT but start anticoagulation before results are available and review within 24 hours.

§If possible, choose an anticoagulant that can be continued if PE is confirmed.

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/resources/visual-summary-pdf-8709091453. Last accessed: August 2020.

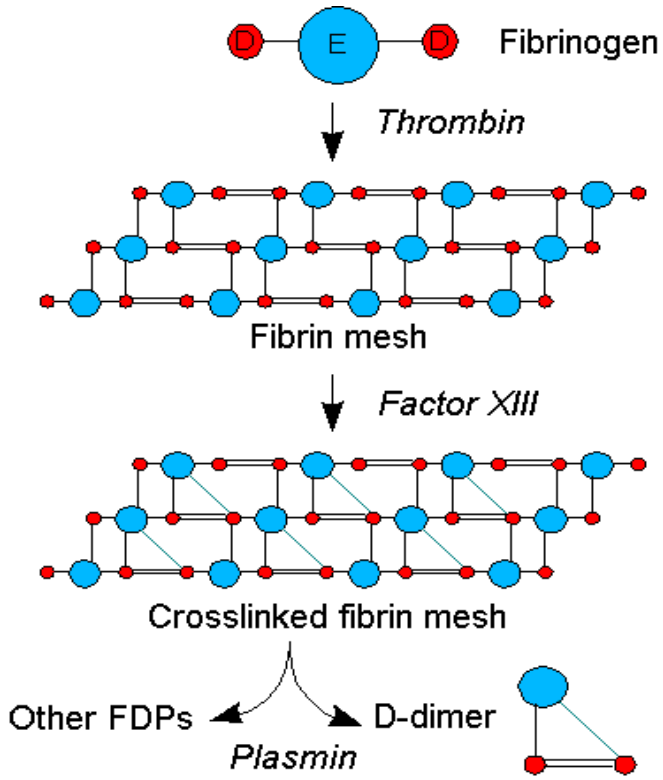
D-dimer and NICE guidance on D-dimer testing

When offering D-dimer testing for suspected DVT or PE, consider a **point-of-care test** if laboratory facilities are not immediately available.

If using a point-of-care D-dimer test, choose a fully **quantitative** test

When using a point-of-care or laboratory D-dimer test, consider **an age-adjusted D-dimer test threshold for people aged over 50**

D-dimer is formed from the breakdown of fibrin[2]

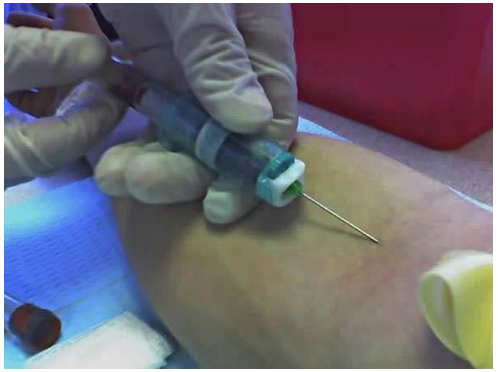


1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020 ; 2. Wikimedia Commons. D-dimer diagram. Available at: https://commons.wikimedia.org/wiki/File:D-dimer.png. Last accessed August 2020.

NICE guidance on initiating anticoagulation for confirmed DVT or PE[1]

For confirmed proximal DVT or PE, offer anticoagulation for at least 3 months[1]

- Carry out baseline blood tests, including:[1]
  - Full blood count
  - Tests of renal and hepatic function
  - PT and APTT
- Do not wait for the results of blood tests before starting anticoagulation[1]
- Review and, if necessary, act on the results of baseline blood tests within 24 hours of starting interim therapeutic anticoagulation



When offering anticoagulation, take into account comorbidities, contraindications and the person's preferences[1]

In the AMPLIFY trial, apixaban was given to patients with a confirmed DVT/PE. The use of an appropriate anticoagulant for patients with a suspected DVT/PE whilst awaiting confirmatory diagnostic tests is a clinical decision based on individual patient assessment

APTT: activated partial thromboplastin time; PT: prothrombin time.

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020;
2. Image source: Wikimedia commons. Available at: https://commons.wikimedia.org/wiki/File:Blooddraw.jpg. Last accessed: August 2020.

NICE guidance on treating a confirmed VTE in patients without renal impairment (CrCl ≥50 mL/min)[1]

Confirmed DVT or PE

PE with haemodynamic instability

Offer continuous UFH infusion and consider thrombolytic therapy

Do not offer elastic graduated compression stockings to prevent PTS or VTE recurrence after a DVT#

Confirmed proximal DVT or PE

When offering anticoagulation, take into account comorbidities, contraindications and the person's preferences

For patients who **do not** have CrCl <15mL/min, active cancer, triple positive APS, extreme body weight <50kg or >120kg, or a PE with haemodynamic instability:*†‡§

Offer either apixaban or rivaroxaban to people with a confirmed proximal DVT or PE

If neither apixaban nor rivaroxaban is suitable offer one of the following:

- LMWH for ≥5 days followed by dabigatran
- LMWH for ≥5 days followed by edoxaban
- LMWH concurrently with a VKA¶

Offer anticoagulation treatment for ≥3 months for people with confirmed proximal DVT or PE

Symptomatic iliofemoral DVT

Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have all of:

- Symptoms of <14 days' duration
- Good functional status
- A life expectancy of ≥1 year
- A low risk of bleeding

All prescribing must be in accordance with the appropriate SmPC

Apixaban, rivaroxaban and edoxaban are not recommended in patients with a CrCl of <15 mL/min, and patients undergoing dialysis. Apixaban and rivaroxaban should also be used with caution in patients with severe renal impairment (CrCl 15–29 mL/min). Dabigatran is contraindicated in patients with a CrCl of <30mL/min.

†The efficacy and safety outcomes of apixaban in the treatment of DVT / PE and prevention of recurrent DVT / PE in patients with active cancer have not been established.

‡The DOACs, including apixaban, should not be used in patients with a history of thrombosis who are diagnosed with antiphosphdipid syndrome.

§See the NICE NG158 guidelines for recommendations in these patient groups.

¶LMWH should be given concurrently with a VKA for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.

#This recommendation does not cover the use of elastic compression stockings for the management of leg symptoms after DVT.

APS: antiphospholipid syndrome; LMWH: low molecular weight heparin; PTS: post-thrombotic syndrome; VKA: vitamin K antagonist.

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020.

NICE guidance on anticoagulation in patients with VTE and renal impairment or established renal failure*

Established renal failure (CrCl <15mL/min)	Severe renal impairment (CrCl 15–29 mL/min)	Moderate renal impairment
Offer one of the following: • LMWH • UFH • LMWH/VKA† • UFH/VKA† †LMWH or UFH should be given concurrently with a VKA for ≥5 days or until the INR is ≥2.0 in 2 consecutive readings, followed by a VKA on its own	Offer one of the following: • Apixaban • Rivaroxaban • LMWH for ≥5 days followed by edoxaban • LMWH/VKA† • UFH/VKA† †LMWH or UFH should be given concurrently with a VKA for ≥5 days or until the INR is ≥2.0 in 2 consecutive readings, followed by a VKA on its own	Offer one of the following: • Apixaban • Rivaroxaban • LMWH for ≥5 days followed by: – Edoxaban – Dabigatran • LMWH/VKA† • UFH/VKA† †LMWH or UFH should be given concurrently with a VKA for ≥5 days or until the INR is ≥2.0 in 2 consecutive readings, followed by a VKA on its own

Apixaban and rivaroxaban should be used with caution in patients with severe renal impairment (CrCl 15–29mL/min) for the treatment of DVT and PE. Apixaban, rivaroxaban and edoxaban are not recommended in patients with a CrCl of <15 mL/min, and patients undergoing dialysis. Dabigatran is contraindicated in patients with a CrCl of <30mL/min.

All prescribing must be in accordance with the appropriate SmPC.

**When giving anticoagulation treatment to people with renal impairment or established renal failure, note the cautions and requirements for dose adjustment and monitoring in the medicine's SmPC and follow locally agreed protocols or advice from a specialist or multidisciplinary team.*

CrCl: creatinine clearance; INR: international normalised ratio; LMWH: low molecular weight heparin; UFH: unfractionated heparin; VKA: vitamin K antagonist.

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020.

NICE guidance on anticoagulation in patients with VTE at extremes of weight*

Consider anticoagulation with regular monitoring of therapeutic levels for people with confirmed proximal DVT or PE who weigh <50 kg or > 120 kg to ensure effective anticoagulation*

**Note the cautions and requirements for dose adjustment and monitoring in the appropriate SmPCs, and follow locally agreed protocols or advice from a specialist or multidisciplinary team.*

See the respective SmPC for specific information on each DOAC.

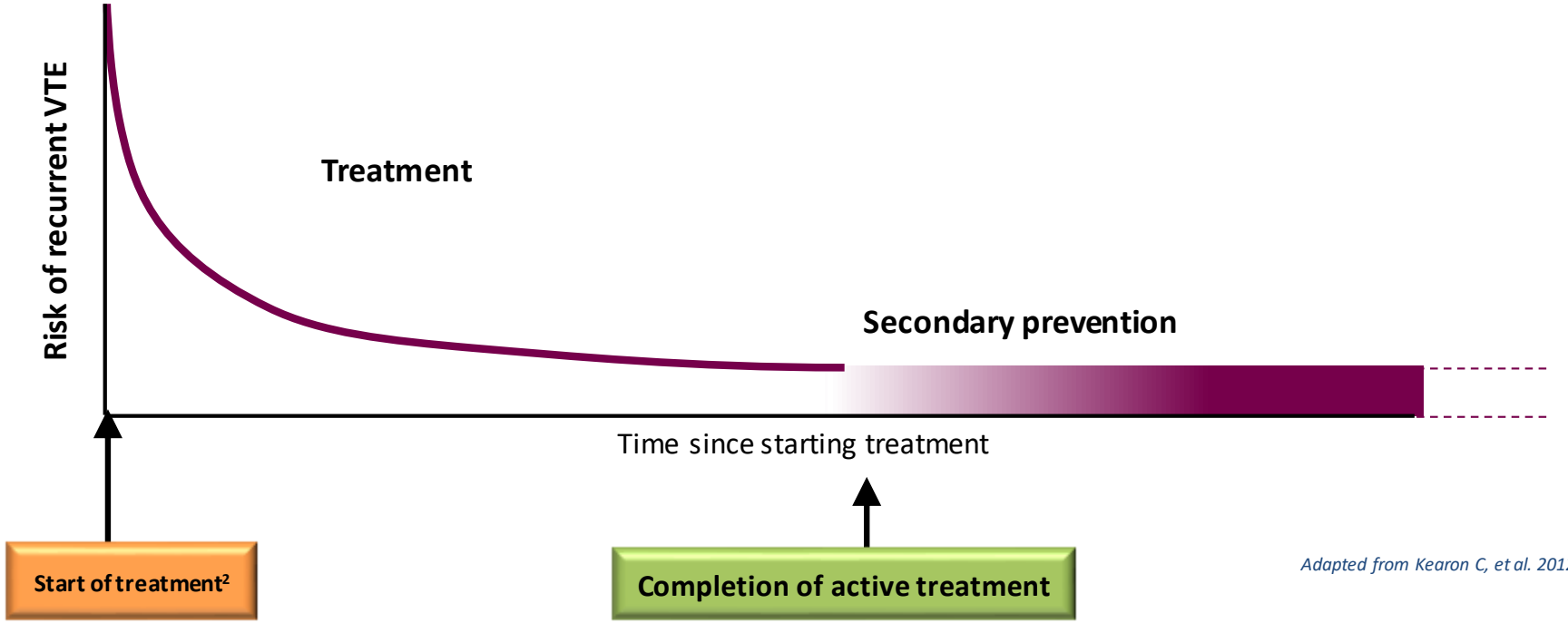
1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020.

Phases of pharmacological treatment in VTE

Initial A/C[1] *(0 to ~7 days)*†‡*

Ongoing treatment for acute VTE *(for ~3–6 months)*§

Long-term treatment for secondary prevention *(from 6 months onwards)*§



Adapted from Kearon C, et al. 2012[1,2]

**Heparin, LMWH or fondaparinux; †As per their SmPCs, apixaban and rivaroxaban do not require initial treatment with parenteral anticoagulation.*[3,4]
‡Parenteral anticoagulant should be taken for ≥5 days before dabigatran or edoxaban.[5,6]
§Includes LMWH and DOACs.
All prescribing must be in accordance with the appropriate SmPC.
A/C: anticoagulation; DOAC: direct oral anticoagulant; LMWH: low-molecular weight heparin; SmPC, summary of product characteristics.

1.Kearon C, et al. *Chest* 2012;141(Suppl.):e419s–e494s; 2. Kearon C. *J Thromb Haemost* 2012;10:507–511;
3. Apixaban SmPC. Available at: http://www.medicines.org.uk ; 4. Rivaroxaban SmPC. Available at: http://www.medicines.org.uk;
5. Dabigatran SmPC. Available at: http://www.medicines.org.uk ; 6. Edoxaban SmPC. Available at: http://www.medicines.org.uk.

Design of DOAC trials in acute VTE treatment

DOAC	Trial	Number of patients	Design	Parenteral required before DOAC?	DOAC dosing	Comparator	Treatment length (months)	Follow-up period	Key inclusion criteria
Dabigatran	RE-COVER[1]	2,564 DVT: 1,749 PE: 786	Double-blind	LMWH/UFH for at least 5 days	Dabigatran 150 mg BD	LMWH or UFH bridge to warfarin	6	30 days after study completion	DVT of the legs/ PE requiring treatment for at least 6 months
	RE-COVER II[2]	2,589 DVT: 1,750 PE: 816							
Edoxaban	Hokusai-VTE[3]	8,240 DVT: 4,921 PE: 3,319	Double-blind	Enoxaparin or UFH for at least 5 days	Edoxaban 60 mg OD†	Enoxaparin or UFH bridge to warfarin	3–12	For duration of treatment	DVT without PE
									PE with or without DVT
Rivaroxaban	EINSTEIN-DVT[4]	DVT: 3,449	Open-label	No	Rivaroxaban 15 mg BD for 21 days, then 20 mg OD	Enoxaparin bridge to VKA	3, 6 or 12*	For duration of treatment	DVT without PE
	EINSTEIN-PE[5]	PE: 4,832							PE with or without DVT
Apixaban	AMPLIFY[6]	5,395 DVT: 3,532 PE: 1,836	Double-blind	No	Apixaban 10 mg BD for 7 days, then 5 mg BD	Enoxaparin bridge to warfarin	6	30 days after study completion	DVT/PE requiring treatment for at least 6 months

Please refer to individual study publications and product SmPCs for further information

**Duration of treatment was determined by the treating physician before randomisation. Most patients received 6 or 12 months of therapy;*
†Patients with body weight ≤60 kg or a CrCl of 30–50 mL/min, and patients receiving concomitant treatment with potent P-gp inhibitors were treated with edoxaban 30 mg OD.
BD: twice daily; CrCl: creatinine clearance; OD: once daily; P-gp: P-glycoprotein; UFH: unfractionated heparin.

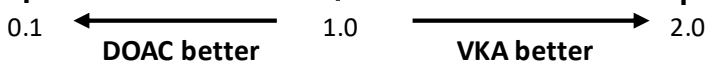
1. Schulman S, et al. *N Engl J Med* 2009;361:2342–2352; 2. Schulman S, et al. *Circulation* 2014;129:764–772;
3. Hokusai-VTE Investigators. *N Engl J Med* 2013;369:1406–1415 4. EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510;
5. EINSTEIN-PE Investigators. *N Engl J Med* 2012;366:1287–1297; 6. Agnelli G, et al. *N Engl J Med* 2013;369:799–808.

Meta-analysis: Pooled data comparison of the efficacy and safety of the DOACs versus VKAs in acute VTE[1]

Recurrent VTE/VTE-related death

	DOACs		Warfarin		Risk ratio (95% CI)
Study	n	Total	n	Total	
AMPLIFY	59	2,609	71	2,635	0.84 (0.60–1.18)
RE-COVER	30	1,274	27	1,265	1.10 (0.66–1.84)
RE-COVER II	30	1,279	28	1,289	1.08 (0.65–1.80)
EINSTEIN-DVT	36	1,731	51	1,718	0.70 (0.46–1.07)
EINSTEIN-PE	50	2,419	44	2,413	1.13 (0.76–1.69)
Hokusai-VTE*	66	4,118	80	4,122	0.83 (0.60–1.14)
Combined (random effects)	271	13,430	301	13,442	0.90 (0.77–1.06)

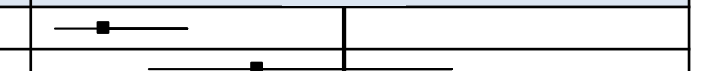
Heterogeneity: I^2=0%; *P*=0.53



Major bleeding

	DOACs		Warfarin		Risk ratio (95% CI)
Study	n	Total	n	Total	
AMPLIFY	15	2,676	49	2,689	0.31 (0.17–0.55)
RE-COVER	22	1,273	29	1,266	0.75 (0.44–1.31)
RE-COVER II	15	1,280	22	1,288	0.69 (0.36–1.32)
EINSTEIN-DVT	14	1,718	20	1,711	0.70 (0.35–1.38)
EINSTEIN-PE	26	2,412	52	2,405	0.50 (0.31–0.80)
Hokusai-VTE	56	4,118	66	4,122	0.85 (0.60–1.21)
Combined (random effects)	148	13,477	238	13,481	0.61 (0.45–0.83)

Heterogeneity: I^2=51%; *P*=0.07



There are no head-to-head randomised clinical trials comparing DOACs
Comparisons cannot be made between individual DOACs based on these data

**For Hokusai-VTE, the event data is for the on-treatment period only.*
CI: confidence interval.

Adapted from van Es et al. 2014.[1]

1. van Es N, et al. *Blood* 2014;124:1968–1975.

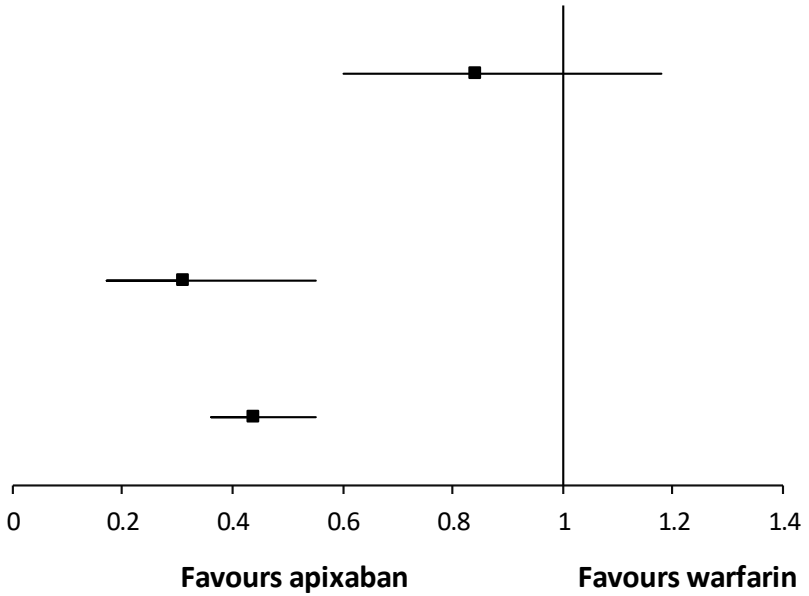
AMPLIFY: Apixaban was non-inferior to warfarin in the treatment of acute VTE and had a significantly lower incidence of major bleeding

Apixaban vs enoxaparin/warfarin

Apixaban was non-inferior to warfarin for first VTE recurrence/VTE-related death and had a lower risk of major bleeding for the treatment of acute VTE[1]

	HR (95% CI)	*P* value
Primary efficacy outcome* (mean study duration: ~6 months)		
First recurrent VTE or VTE-related death	0.84 (0.60–1.18)	<0.001 Non-inferiority
Safety outcomes[†]		
Major bleeding (primary safety endpoint)	0.31 (0.17–0.55)	<0.001 Superiority
Major or CRNM bleeding	0.44 (0.36–0.55)	<0.001

Overall TTR in patients randomised to warfarin = 61%



**All efficacy analyses included data for patients in the ITT population for whom the outcome status at 6 months was documented; †All safety analyses included data obtained from patients during study treatment, defined as the time from administration of the first dose until 48 hours after the last dose was administered.*

1. Agnelli G, et al. *N Engl J Med* 2013;369:799–808.

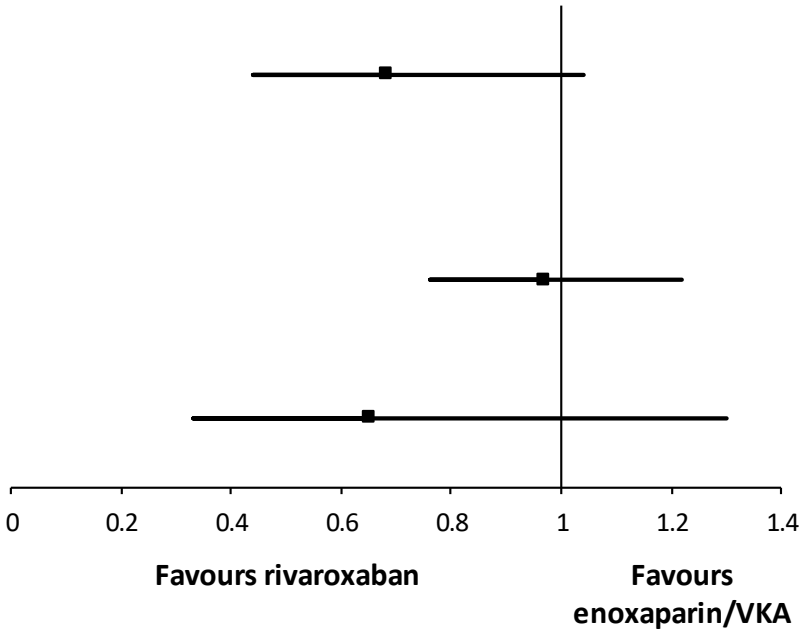
EINSTEIN-DVT: Rivaroxaban was non-inferior to enoxaparin/VKA in the treatment of acute DVT, with no significant difference in major or CRNM bleeding

Rivaroxaban vs enoxaparin/VKA

Rivaroxaban was non-inferior to enoxaparin/VKA in the treatment of acute DVT with no significant difference in rates of major or CRNM bleeding[1]

	HR (95% CI)	*P* value
Primary efficacy outcome* (mean study duration: ~9 months)		
Recurrent VTE†	0.68 (0.44–1.04)	<0.001 Non-inferiority‡
Safety outcomes¶		
Major or CRNM bleeding (primary safety endpoint)	0.97 (0.76–1.22)	0.77
Major bleeding	0.65 (0.33–1.30)	0.21

Overall TTR in patients randomised to warfarin = 57.7%



**The primary efficacy analysis was performed on an ITT basis; †Recurrent VTE was defined as the composite of DVT or non-fatal or fatal PE; ‡The non-inferiority margin was 2.0; ¶The safety analyses included all patients who received the assigned study drug.*

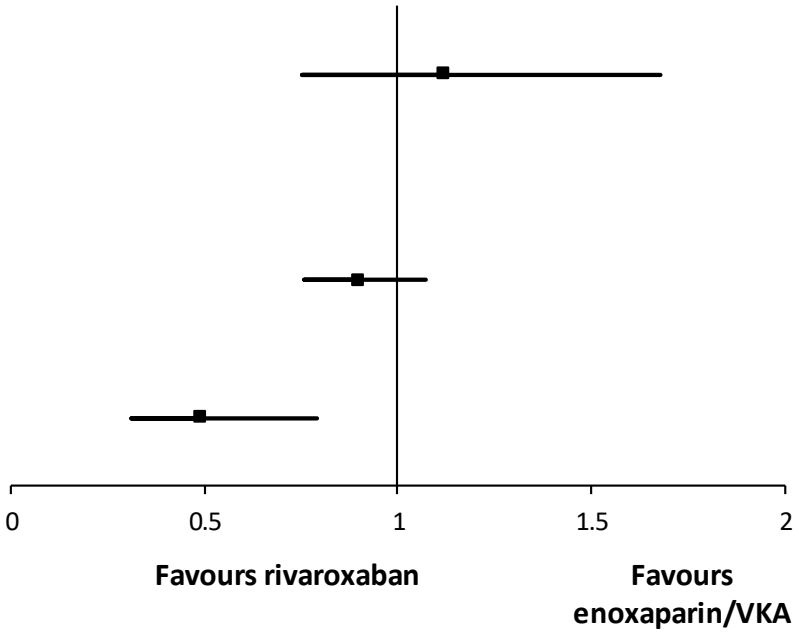
1. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510.

EINSTEIN-PE: Rivaroxaban was non-inferior to enoxaparin/VKA in the treatment of acute PE, with no significant difference in major or CRNM bleeding

Rivaroxaban was non-inferior to enoxaparin/VKA in the treatment of acute PE with no significant difference in rates of major or CRNM bleeding[1]

	HR (95% CI)	*P* value
Primary efficacy outcome* (mean study duration: ~9 months)		
Recurrent VTE[†]	1.12 (0.75–1.68)	0.003 Non-inferiority[‡]
Safety outcomes[¶]		
Major or CRNM bleeding (primary safety endpoint)	0.90 (0.76–1.07)	0.23
Major bleeding	0.49 (0.31–0.79)	0.003

Overall TTR in patients randomised to warfarin = 62.7%



**The primary analysis was performed on an ITT basis; [†]Recurrent VTE was defined as the composite of DVT or non-fatal or fatal PE; [‡]The non-inferiority margin was 2.0; [¶]The population for the safety analysis included all patients who received at least one dose of a study drug.*

1. The EINSTEIN Investigators. *N Engl J Med* 2012;366:1287–1297.

The features of DOACs compared with VKAs that may benefit appropriate patients with a VTE[1–5]

- Reach peak concentration quickly
- No significant food interactions
- Less drug/drug interactions
- No requirement for routine coagulation monitoring
- Practical concerns:
  - Dosing is dependent on the specific DOAC[1-4]
  - Suboptimal adherence can impair treatment outcomes (due to the short half-life of the DOACs[1-5])

VKA: vitamin K antagonist.

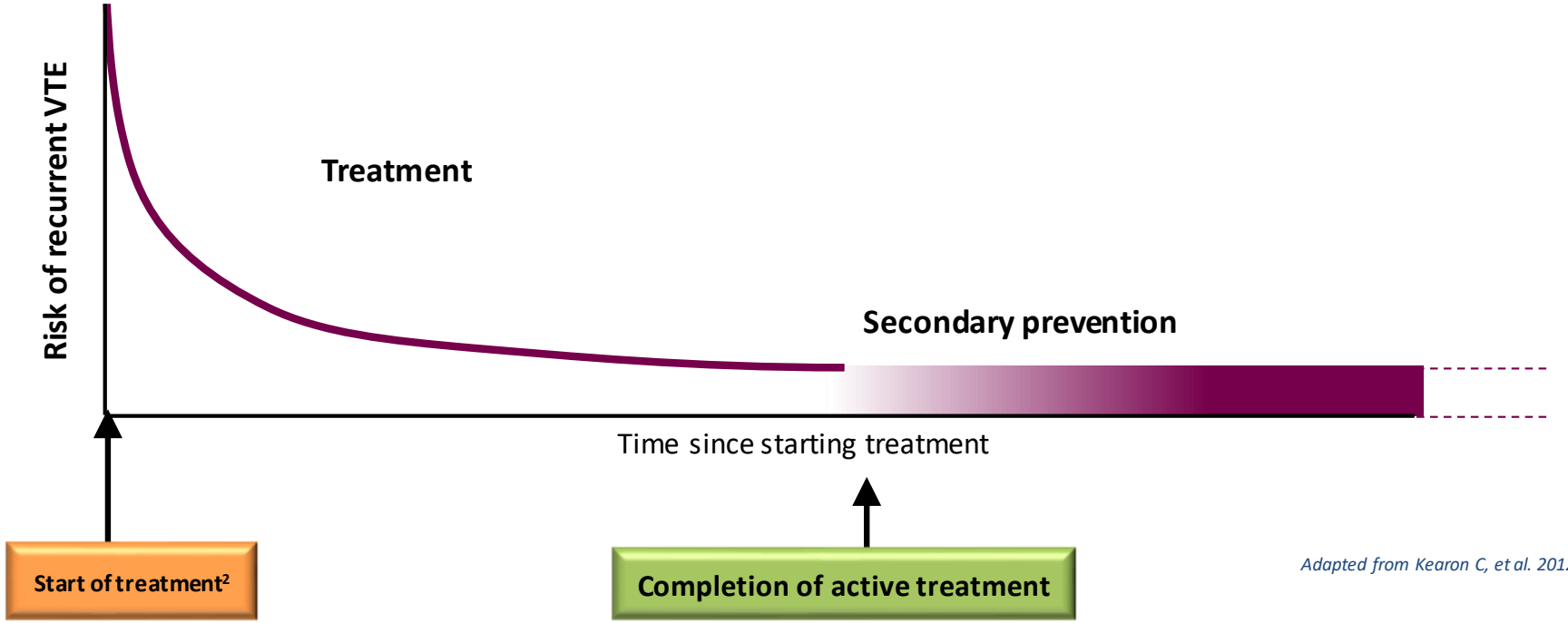
1. Apixaban SmPC. Available at: www.medicines.org.uk; 2. Dabigatran SmPC. Available at: www.medicines.org.uk; 3. Rivaroxaban SmPC. Available at: www.medicines.org.uk; 4. Edoxaban SmPC. Available at: www.medicines.org.uk; 5. Mekaj YH, et al. *Ther Clin Res Manag* 2015;11:967–977.

Phases of pharmacological treatment in VTE

Initial A/C[1] *(0 to ~7 days)*†‡*

Ongoing treatment for acute VTE *(for ~3–6 months)*§

Long-term treatment for secondary prevention *(from 6 months onwards)*§

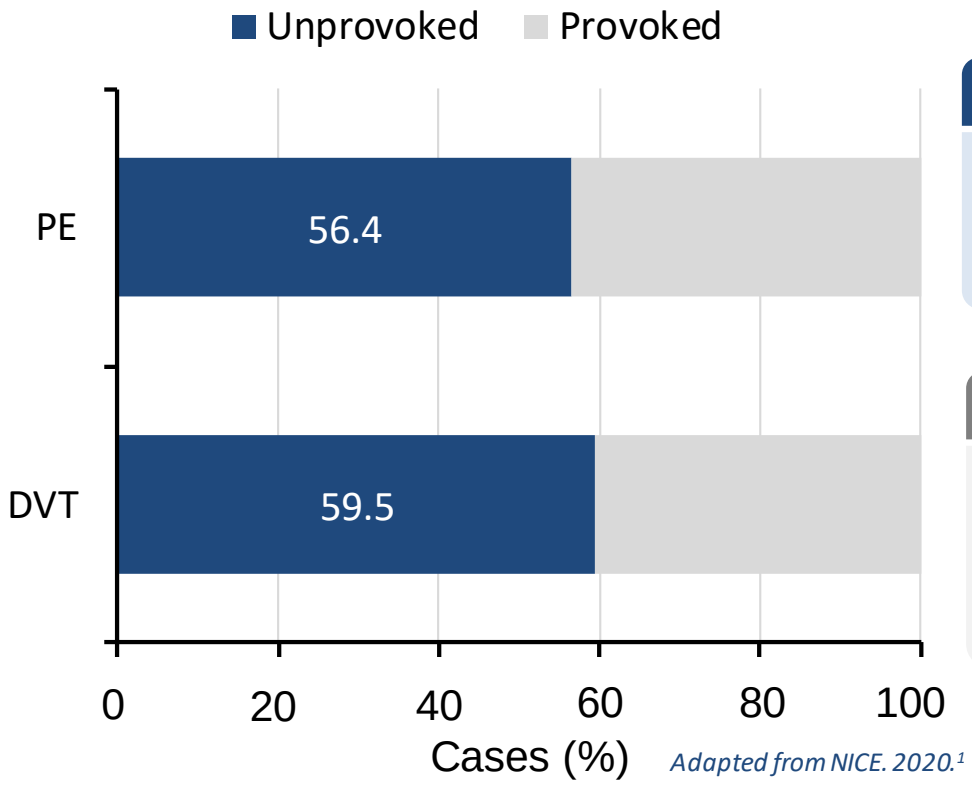


Adapted from Kearon C, et al. 2012[1,2]

**Heparin, LMWH or fondaparinux; †As per their SmPCs, apixaban and rivaroxaban do not require initial treatment with parenteral anticoagulation.*[3,4]
‡Parenteral anticoagulant should be taken for ≥5 days before dabigatran or edoxaban.[5,6]
§Includes LMWH and DOACs.
All prescribing must be in accordance with the appropriate SmPC.
A/C: anticoagulation; DOAC: direct oral anticoagulant; LMWH: low-molecular weight heparin; SmPC, summary of product characteristics.

1.Kearon C, et al. *Chest* 2012;141(Suppl.):e419s–e494s; 2. Kearon C. *J Thromb Haemost* 2012;10:507–511;
3. Apixaban SmPC. Available at: http://www.medicines.org.uk ; 4. Rivaroxaban SmPC. Available at: http://www.medicines.org.uk;
5. Dabigatran SmPC. Available at: http://www.medicines.org.uk ; 6. Edoxaban SmPC. Available at: http://www.medicines.org.uk.

Over half of VTEs are unprovoked and long-term anticoagulation should be considered in these patients



Adapted from NICE. 2020.[1]

Unprovoked VTE[2]

DVT or PE in a patient with **no recent major clinical risk factor for VTE,*** who is **not having hormonal therapy†**

Provoked VTE[2]

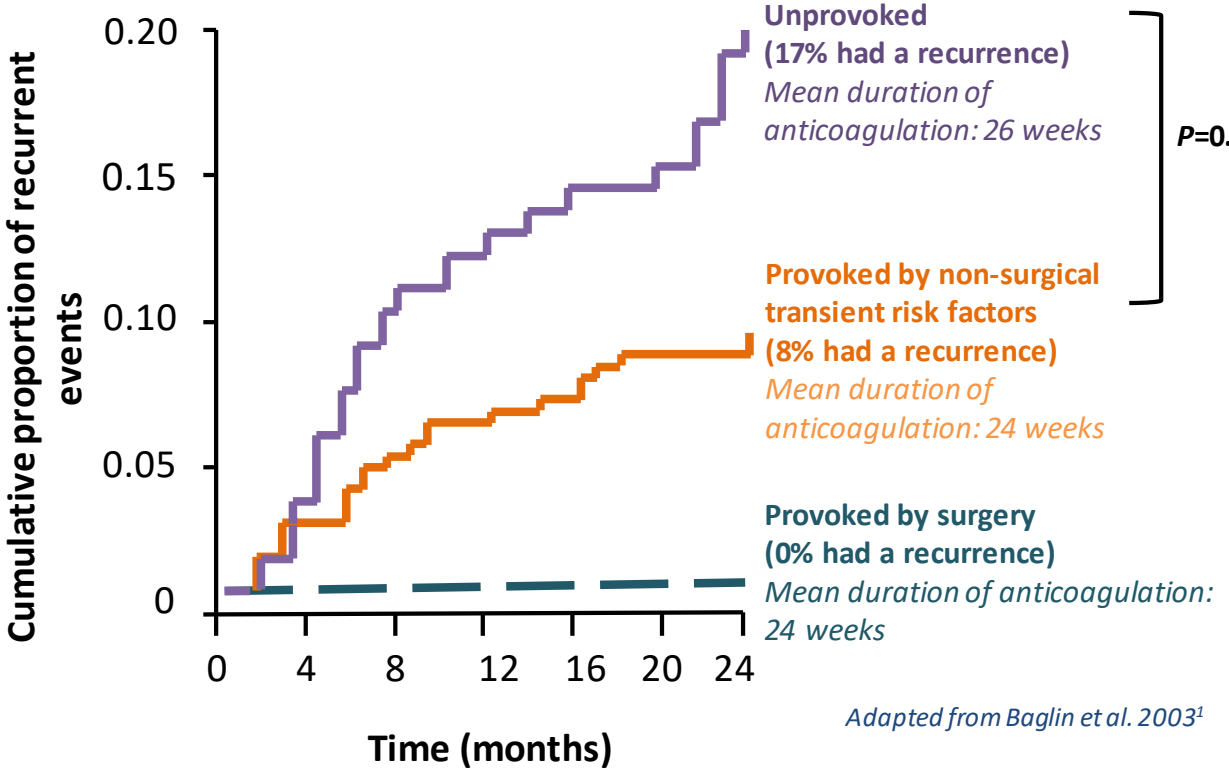
DVT or PE in a patient with a **recent (within 3 months) and transient major clinical risk factor for VTE*** – or who is having **hormonal therapy†**

**E.g. surgery, trauma, significant immobility (bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair), pregnancy or puerperium; †Oral contraceptive or hormone replacement therapy.*

1. National Institute for Health and Care Excellence. Economic modelling report for pharmacological treatment in people with confirmed deep vein thrombosis and/or pulmonary embolism. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/evidence/g-economic-modelling-report-on-pharmacological-treatment-pdf-8710588340. Last accessed: August 2020; 2. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020.

Stopping anticoagulation increases recurrence risk in unprovoked VTE and VTE with non-surgical transient risk factors

Cumulative proportions of recurrent thrombosis after cessation of anticoagulant therapy following first-episode VTE (n=558)[1]



Adapted from Baglin et al. 2003[1]

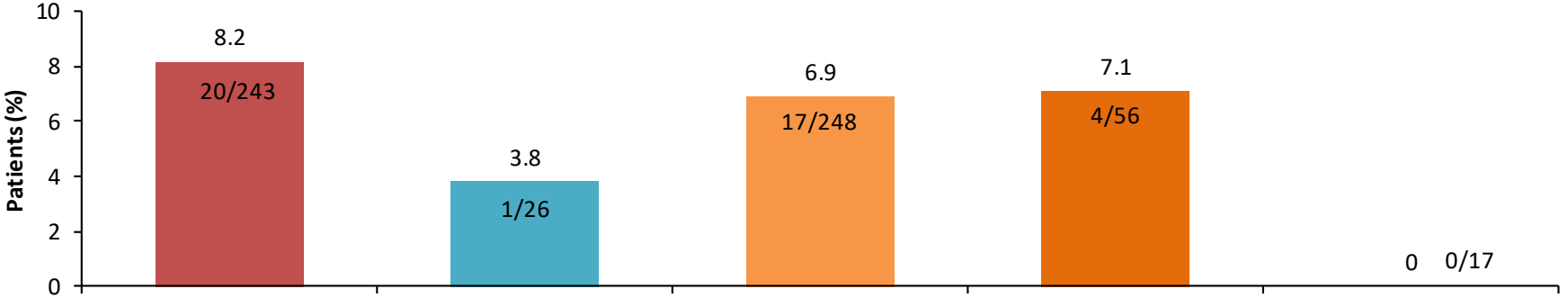
Unprovoked VTE has an estimated 30% risk of recurrence within 5 years[2]

Patients with non-surgical transient risk factors are also at risk of recurrence[1]

1. Baglin T, et al. *Lancet* 2003;362:523–526; 2. Kearon C, et al. *Blood* 2014;123(12):1794–1801.

Crude incidences of recurrent VTE according to baseline risk factor profiles in the placebo arm of EINSTEIN-Extension

This study looked at the EINSTEIN Extension and EINSTEIN CHOICE randomized, double-blind studies of the efficacy and safety of rivaroxaban (20 mg OD) with placebo and rivaroxaban (20mg OD or 10 mg OD) with aspirin (100 mg), respectively, for extended treatment of VTE. Results shown are of recurrent VTE rates for the placebo arm of EINSTEIN Extension. This was not a pre-specified endpoint. No clinical conclusions can be made from these results



Examples of major persistent risk factors

- Active cancer (excluding basal cell or squamous cell skin cancer)*

Examples of minor persistent risk factors

- IBD
- Lower extremity paralysis or paresis
- CHF
- BMI >30kg/m^2
- Calculated CrCl <50 mL/min†
- APS‡
- Family history of VTE or known thrombophilia‡

Examples of minor transient risk factors

- Immobilisation
- Travel > 8 hours
- Pregnancy§
- Puerperium
- Use of oestrogen
- Lower limb trauma with transient impairment of mobility

Examples of major transient risk factors

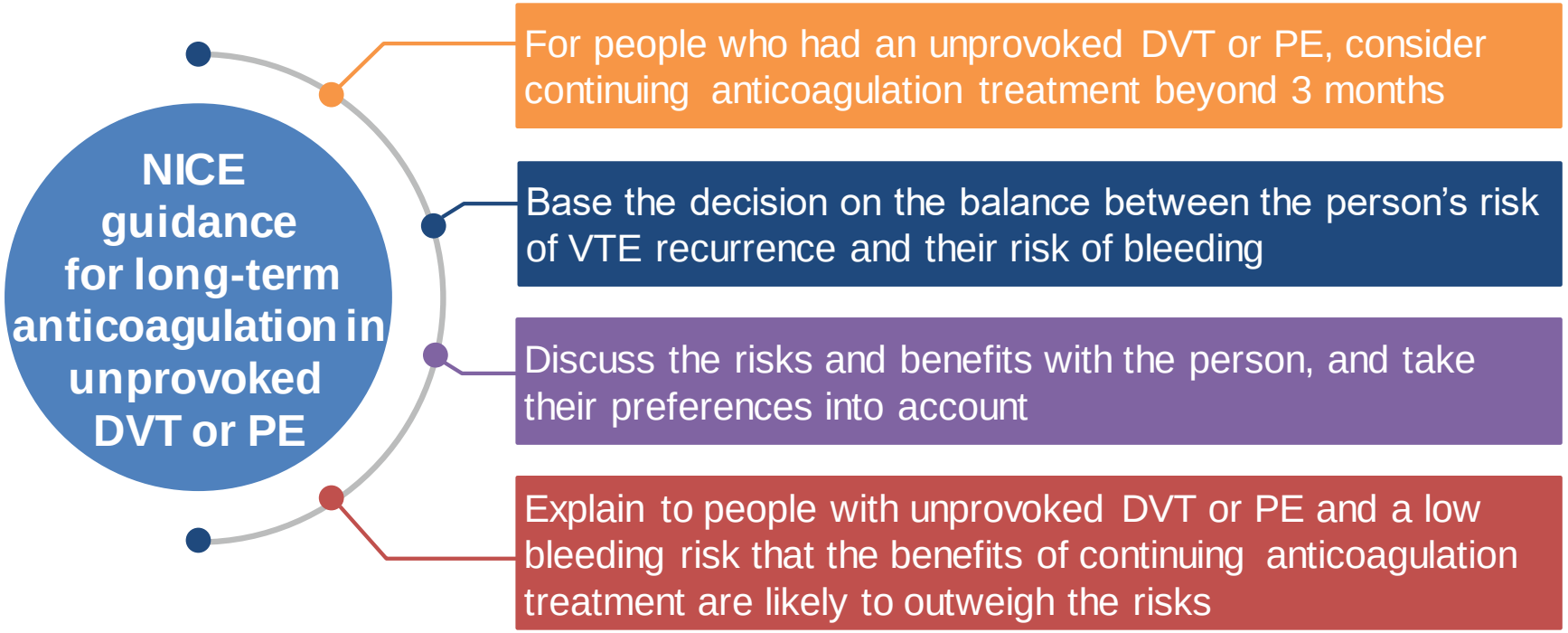
- Major surgery or trauma
- Caesarean section

**The efficacy and safety outcomes of apixaban in the treatment of DVT / PE and prevention of recurrent DVT / PE in patients with active cancer have not been established.*
†Apixaban, rivaroxaban and edoxaban are not recommended in patients with a CrCl of <15 mL/min, and patients undergoing dialysis. Apixaban and rivaroxaban should also be used with caution in patients with severe renal impairment (CrCl 15 –29 mL/min). Dabigatran is contraindicated in patients with a CrCl of <30mL/min.
‡The DOACs, including apixaban, should not be used in patients with a history of thrombosis who are diagnosed with antiphosphdipid syndrome.
§Avoid use of apixaban during pregnancy and breast feeding. Rivaroxaban is contraindicated during pregnancy and breast feeding

‡Known thrombophilia includes deficiency of antithrombin, protein C, or protein S, factor V Leiden or prothrombin gene mutation.
APS: antiphospholipid syndrome; BMI: body mass index; CHF: congestive heart failure.

1. Prins MH, et al. *Blood Adv* 2018;2:788–796; 2. Apixaban SmPC. Available at: http://www.medicines.org.uk.

Long-term anticoagulation should be considered in unprovoked VTE because of the high risk of recurrence[1]



1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020.

The HAS-BLED score can be used to assess the risk of major bleeding in people on anticoagulation for unprovoked VTE[1]

Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal* and liver† function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding‡	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
HAS-BLED Score	**Cumulative incidence for major bleeding**	
3	5.3% (4.9–5.6)	High risk for major bleeding
≥4	8.0 (7.3–8.7)	

Adapted from CammAJ et al, 2010, and Brown JD, et al, 2018 [2,3]

Discuss stopping anticoagulation if the HAS-BLED score is ≥4 and cannot be modified[1]

**Abnormal renal function is the defined as the presence of chronic dialysis, renal transplantation, or a serum creatinine level of ≥200 µmol/L; †Abnormal liver function is defined as chronic hepatic disease (e.g. cirrhosis), or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit of normal; ‡Bleeding refers to previous bleeding history and/or predisposition to bleeding.*

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020; 2 Camm AJ, et al. *Eur Heart J* 2010;31(19):2369–2429. 3. Brown JD, et al. *J Am Heart Assoc* 2018;7:e007901.

NICE recommendations for long-term anticoagulation for the prevention of recurrent VTE[1]

Patients in whom long-term anticoagulation is considered appropriate

Does the patient have any of the following comorbidities?

- Renal impairment (CrCl <15mL/min)*†
- Active cancer‡
- APS§
- Body weight <50kg or >120kg
- PE with haemodynamic instability

Patients without comorbidities

- Offer continued treatment with the current anticoagulant if it is well tolerated
- If the current treatment is not well tolerated, or the clinical situation or person's preferences have changed, consider switching to apixaban if the current treatment is a DOAC other than apixaban

Patients with comorbidities

- Consider carrying on with the current treatment if it is well tolerated

Take into account the persons preferences, and their clinical situation when selecting an anticoagulant for long-term treatment. All prescribing must be in accordance with the appropriate SmPC

**Apixaban, rivaroxaban and edoxaban are not recommended in patients with a CrCl of <15 mL/min, and patients undergoing dialysis. Apixaban and rivaroxaban should also be used with caution in patients with severe renal impairment (CrCl 15–29 mL/min).[2–4] †Dabigatran is contraindicated in patients with a CrCl of <30mL/min.[5]*
‡The efficacy and safety outcomes of apixaban in the treatment of DVT / PE and prevention of recurrent DVT / PE in patients with active cancer have not been established.[2]
§The DOACs, including apixaban, should not be used in patients with a history of thrombosis who are diagnosed with antiphosphdipid syndrome.[2–5]

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020;
2. Apixaban SmPC. Available at: http://www.medicines.org.uk; 3. Rivaroxaban SmPC. Available at: http://www.medicines.org.uk;
4. Edoxaban SmPC. Available at: http://www.medicines.org.uk; 5. Dabigatran SmPC. Available at: http://www.medicines.org.uk.

Design of DOAC trials for the prevention of recurrent VTE

Study drug	Trial	Patients (n)	Treatment before randomisation	Study drug dosing	Comparator	Treatment length (months)
Dabigatran	RE-MEDY[1]	2,866	3–12 months of approved anticoagulant or dabigatran	Dabigatran 150 mg BD	Warfarin INR 2.0–3.0	6–36
Rivaroxaban	EINSTEIN-CHOICE[2]	3,365	6–12 months of anticoagulation, such as VKA or DOAC	Rivaroxaban 10 mg or 20 mg OD	Aspirin 100 mg	6–12
Dabigatran	RE-SONATE[1]	1,343	6–18 months of oral anticoagulant or dabigatran	Dabigatran 150 mg BD	Placebo	6 or 12
Rivaroxaban	EINSTEIN-EXT[3]	1,197	6 or 12 months of VKA or rivaroxaban	Rivaroxaban 20 mg OD	Placebo	30
Apixaban	AMPLIFY-EXT[4]	2,482	6–12 months of standard therapy or apixaban	Apixaban 2.5 mg or 5 mg BD*	Placebo	12

There are no head-to-head studies between these agents. There are limitations such as differing patient populations, designs and outcomes, and caution should therefore be exercised when interpreting the results. No conclusions about the relative efficacy of any of these agents should be drawn from the trial data. Please refer to the individual SmPCs for further information.

**Apixaban 5 mg BD is not a licensed dose for the prevention of VTE recurrence.[5] Results shown for the apixaban arm will be for the licensed dose of apixaban 2.5 mg BD only.*

BD: twice daily; INR: International Normalised Ratio; OD: once daily; VKA: vitamin K antagonist.

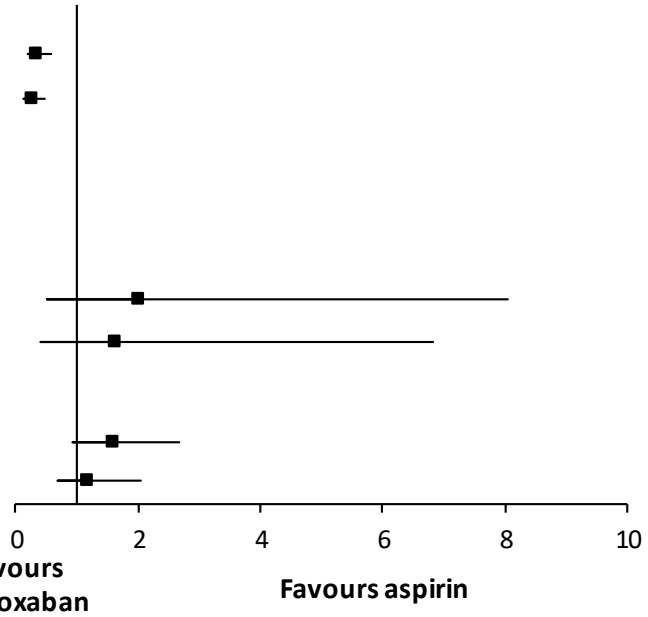
1. Schulman S, et al. *N Engl J Med* 2013;368:709–718; 2. Weitz JI, et al. *N Engl J Med* 2017;376:1211–1222;
3. EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510; 4. Agnelli G, et al. *N Engl J Med* 2013;368:699–708;
5. Apixaban SmPC. Available at: http://www.medicines.org.uk .

EINSTEIN-CHOICE: Rivaroxaban 20 mg OD and 10 mg OD reduced the risk of recurrent VTE compared with aspirin with no significant difference in the incidence of major bleeding

Rivaroxaban vs aspirin

The EINSTEIN-CHOICE trial was a double-blind, randomised trial comparing two doses of rivaroxaban (20 mg OD or 10 mg OD) with aspirin 100 mg OD for 6–12 months in patients with DVT or PE who had completed 6–12 months of anticoagulation therapy[1]

	HR (95% CI)	*P* value
Primary efficacy outcome*		
Recurrent VTE		
Rivaroxaban 20 mg (n=1,107)	0.34 (0.20–0.59)	<0.001
Rivaroxaban 10 mg (n=1,127)	0.26 (0.14–0.47)	<0.001
Safety outcomes†		
Major bleeding (primary safety outcome)		
Rivaroxaban 20 mg (n=1,107)	2.01 (0.50–8.04)	0.32
Rivaroxaban 10 mg (n=1,127)	1.64 (0.39–6.84)	0.50
Major or CRNM bleeding		
Rivaroxaban 20 mg (n=1,107)	1.59 (0.94–2.69)	0.08
Rivaroxaban 10 mg (n=1,127)	1.16 (0.67–2.03)	0.60



**The primary efficacy outcome of recurrent VTE was a composite of symptomatic recurrent fatal or non-fatal VTE. Efficacy outcomes were assessed in all the patients who had undergone randomisation and received at least one dose of a study drug (ITT population). Efficacy and safety outcomes were analysed with the use of a Cox proportional hazards model, stratified according to the index diagnosis (DVT or PE); †Safety outcomes were considered during the time from administration of the first dose of a study drug to 48 hours after the administration of the last dose. Bleeding episodes were defined according to the criteria of the International Society on Thrombosis and Haemostasis.*

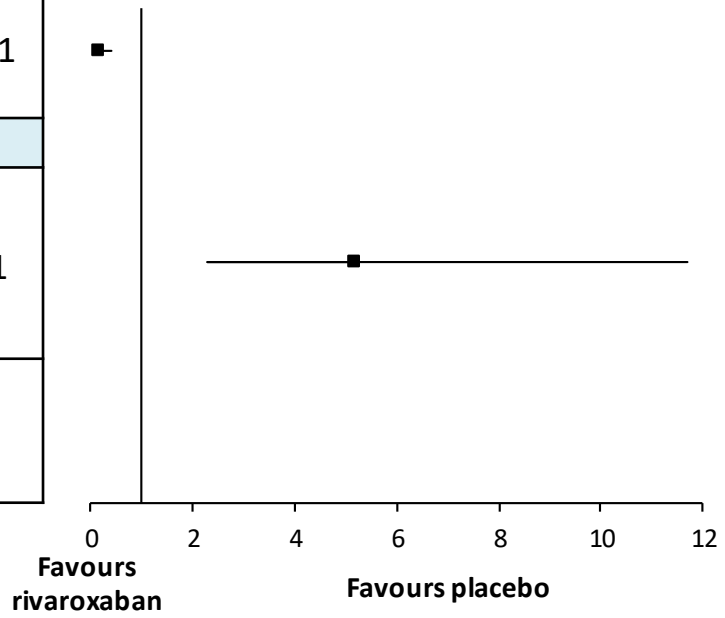
1. Weitz JI, et al. *N Engl J Med* 2017;376:1211–1222.

EINSTEIN-Extension: Rivaroxaban reduced the risk of VTE recurrence but had a significantly higher incidence of major or CRNM bleeding compared with placebo[1]

Rivaroxaban vs placebo

The EINSTEIN-Extension trial was a placebo-controlled, double-blind, randomised trial comparing 6–12 months of rivaroxaban treatment (20 mg OD) with placebo in patients who had completed 6–12 months of anticoagulation therapy for VTE[1]

	HR (95% CI)	*P* value
Primary efficacy outcome*		
Recurrent VTE	0.18 (0.09–0.39)	<0.0001
Safety outcomes†		
Major or CRNM bleeding (primary safety endpoint)†	5.19 (2.30–11.70)	<0.001
Major bleeding	HR not reported	0.11



**The primary efficacy analysis was performed on an ITT basis; †The safety analysis included all patients who received the assigned study drug.*

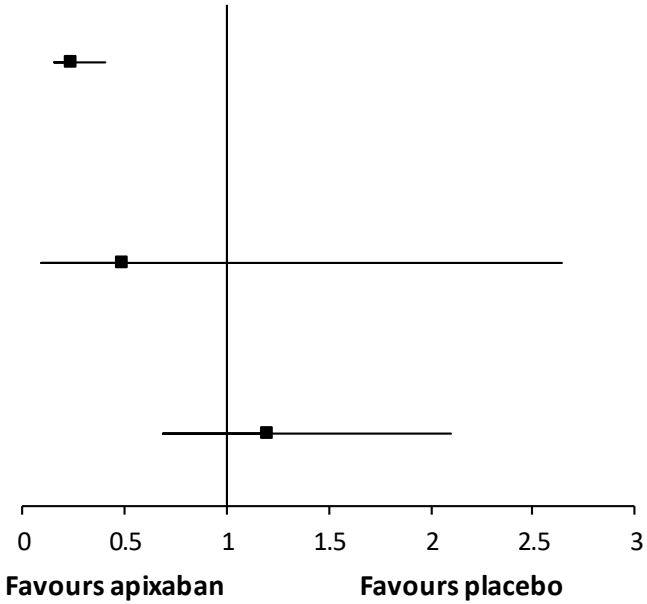
1. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510.

AMPLIFY-EXT: Apixaban reduced the risk of recurrent VTE and all-cause death with no significant difference in the rate of major bleeding compared with placebo

Apixaban vs placebo

The AMPLIFY-EXT trial was a randomised, double-blind study comparing apixaban (2.5 mg and 5 mg BD*) with placebo in patients who had completed 6–12 months of anticoagulation therapy for VTE[1]

	RR (95% CI)	*P* value
Primary efficacy outcome (data for 2.5 mg dose only)†		
Recurrent VTE or all-cause death	0.24 (0.15–0.40)	<0.0001
Safety outcomes (data for 2.5 mg dose only)‡		
Major bleeding (primary safety endpoint)	0.49 (0.09–2.64)	NS
Major or CRNM bleeding	1.20 (0.69–2.10)	NS



**The recommended dose of apixaban for recurrent DVT and PE is 2.5 mg BD.[2]*

†Efficacy data are based on the ITT analysis, which included 2,482 patients of the 2,486 patients randomised; ‡Safety analyses included data from patients during the time that they were receiving treatment (the time between administration of the first dose of a study drug and 48 hours after administration of the last dose).

NS: not significant; RR: relative risk.

1. Agnelli G, et al. *N Engl J Med* 2013;368:699–708;
2. Apixaban SmPC. Available at: http://www.medicines.org.uk .

Selecting patients for long-term treatment

- Consider the following factors when selecting patients for long-term treatment:
  - Provoked/unprovoked VTE
  - If provoked VTE, is the provoking factor major or minor and transient or persistent?
  - First event or recurrence?
  - Thrombus site/burden
  - Bleeding risk during anticoagulation
  - Comorbidities
  - Patient preference

The decision of whether to **extend anticoagulation** beyond 3 months should be based on the **risk of recurrent VTE**, and should be balanced against the **risk of bleeding**, taking into account the **preferences of the patient**[1,2]

1. Kearon C, et al. *Blood* 2014;123:1794–1801;
2. Mazzolai L, et al. *Eur Heart J* 2017;38:1028–1033.

DOAC dosing regimens across each stage of VTE treatment

Please refer to the individual DOAC SmPCs for full dosing recommendations

	Initial VTE treatment	Ongoing VTE Treatment	Prevention of Recurrent VTE
Apixaban[1]	**10 mg BD** Day 1–7	**5 mg BD** Day 8 onwards for at least 3 months*	**2.5 mg BD** Following at least 6 months of oral anticoagulant therapy
Apixaban, renal criteria[1]	Use with caution in severe renal impairment (CrCl 15–29 mL/min). Not recommended in CrCl <15 mL/min or in patients undergoing dialysis		
Dabigatran[2]	**Parenteral anticoagulant** For at least 5 days (not to be taken concomitantly with dabigatran)	**150 mg BD** for at least 3 months* A dose reduction to 110mg BD is recommended in patients receiving concomitant verapamil or aged ≥80 years. A dose reduction to 110 mg BD† should be considered in patients: age 75-80 years, or with gastritis, oesophagitis or gastroesophageal reflux, or at increased risk of bleeding	
Dabigatran, renal criteria[2]	Consider a dose reduction to 110 mg BD based on individual assessment of bleeding and thromboembolic risk if CrCl 30 -50 mL/min. Contraindicated in CrCl <30 mL/min.		
Rivaroxaban[3]	**15 mg BD with food** Day 1–21	**20 mg OD with food** Day 22 onwards for at least 3 months*	**10 mg OD** Following at least 6 months of oral anticoagulant therapy Consider 20 mg OD with food in patients in whom risk of recurrent VTE is considered high or who have developed recurrent VTE on 10 mg OD
Rivaroxaban, renal criteria[3]	Consider a dose reduction from 20 mg OD to 15 mg OD (after the initial 15 mg BD for 3 weeks) in moderate (CrCl 30 –49 mL/min) or severe (CrCl 15–29 mL/min) renal impairment if the patient's assessed bleeding risk outweighs the risk for recurrent DVT and PE. When the recommended dose is 10 mg OD, no dose adjustment is necessary. Use with caution in severe renal impairment. Not recommended in CrCl <15 mL/min.		
Edoxaban[4]	**Parenteral anticoagulant** For at least 5 days (not to be taken concomitantly with edoxaban)	**60 mg OD** For at least 3 months* A dose adjustment to 30 mg OD is required in patients with CrCl 15–50 mL/min, or body weight ≤60 kg, or concomitant use with ciclosporin, dronedarone, erythromycin or ketoconazole	
Edoxaban, renal criteria[4]	The recommended dose is 30 mg OD in moderate or severe renal impairment (CrCl 15 –50 ml/min). Not recommended in CrCl <15 ml/min or in patients undergoing dialysis.		

The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.

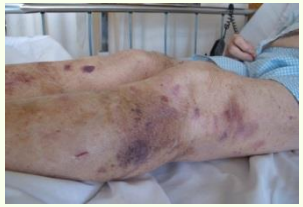
**Short duration of treatment (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation).*

†Daily dose of dabigatran of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding.

1. Apixaban SmPC. Available at: http://www.medicines.org.uk; 2. Dabigatran SmPC. Available at: http://www.medicines.org.uk;
3. Rivaroxaban SmPC. Available at: http://www.medicines.org.uk; 4. Edoxaban SmPC. Available at: http://www.medicines.org.uk.

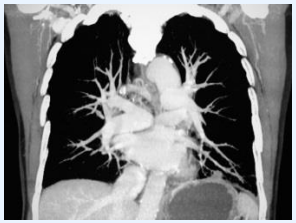
Consider the implications of secondary complications

PTS: A complication of DVT



- Caused by damage to venous valves by thrombus in acute DVT[1]
- Annual incidence is 1/1,000 PY, and 20–50% of patients develop PTS as a long-term sequela[1]
- Anticoagulation is required to prevent thrombus formation[1]
- Risk factors include old age and impaired venous circulation[2]

CTEPH: A complication of PE



- Caused by obstruction of major pulmonary arteries[3]
- Affects 0.1–9.1% of patients who have had symptomatic PE[3]
- Lifelong anticoagulation at an INR of 2–3 is recommended[3]
- The 5-year survival rate in patients with inoperable CTEPH is approximately 68%[4]

CTEPH: chronic thromboembolic pulmonary hypertension; PTS: post-thrombotic syndrome; PY: person years.

1. Farrell JJ, et al. *Cardiovasc Diagn Ther* 2016;6:623–631; 2. Schulman S, et al. *J Thromb Haemost* 2006;4:734–742;
3. Lang IM, et al. *Circulation* 2014;130:508–518; 4. Saouti N, et al. *Respir Med* 2009;103:1013–1019.

Summary of NICE recommendations for oral anticoagulation for confirmed VTE[1]

Acute treatment[1]

When offering anticoagulation, take into account comorbidities, contraindications and the person's preferences

For patients **who do not have** CrCl <15mL/min, active cancer, triple positive APS, extreme body weight <50kg or >120kg, or a PE without haemodynamic instability :[*†‡§]

Offer either apixaban or rivaroxaban to people with a confirmed proximal DVT or PE

If neither apixaban nor rivaroxaban is suitable offer one of the following:

- LMWH for ≥5 days followed by dabigatran
- LMWH for ≥5 days followed by edoxaban
- LMWH concurrently with a VKA for ≥5 days or until the INR is ≥2.0 in 2 consecutive readings, followed by a VKA on its own

Offer anticoagulation treatment for ≥3 months for people with confirmed proximal DVT or PE

Long-term treatment (beyond 3 months) in appropriate patients[1]

For people **who do not have** CrCl <15mL/min, active cancer, established triple positive APS, extreme body weight <50kg or >120kg, or a PE with haemodynamic instability:[*†‡]

- Offer continued treatment with current anticoagulant if it is well tolerated
- If the current treatment is not well tolerated or clinical situation or person's preferences have changed, consider switching to apixaban if current treatment is a DOAC other than apixaban

When prevention of recurrent DVT and PE is indicated, the 2.5 mg BD dose of apixaban should be initiated following completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant

See the guidelines for further details. All prescribing must be in accordance with the appropriate SmPC.

**The efficacy and safety outcomes of apixaban in the treatment of DVT / PE and prevention of recurrent DVT / PE in patients with active cancer have not been established.[2]*

†The DOACs, including apixaban, should not be used in patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome.[2–5]

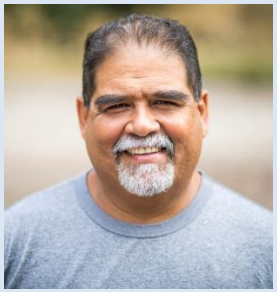
‡Apixaban, rivaroxaban and edoxaban are not recommended in patients with a CrCl of <15 mL/min and patients undergoing dialysis, and should also be used with caution in patients with severe renal impairment (CrCl 15–29 mL/min). Dabigatran is contraindicated in patients with a CrCl of <30mL/min.[2–5]

§See the NICE NG158 guidelines for recommendations in these patient groups.

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020;
2. Apixaban SmPC. Available at: http://www.medicines.org.uk; 3. Rivaroxaban SmPC. Available at: http://www.medicines.org.uk;
4. Dabigatran SmPC. Available at: http://www.medicines.org.uk; 5. Edoxaban SmPC. Available at: http://www.medicines.org.uk.

Patient case study

Patient: Antonio*



Patient information	
Age	61
Weight/BMI	96.2 kg/ 32.4 kg/m^2
Blood pressure	149/97 mmHg
CrCl (Cockcroft–Gault)	62 mL/min

Patient history

- Provoked DVT 5 years ago following a hip replacement
- Gastrointestinal bleeding from gastric ulcers (17 months previously) – successfully treated
- Works as a computer programmer and has a sedentary lifestyle
- Mild symptomatic heart failure (LVEF = 42%)

Medications

- Enalapril 10 mg BD

Presentation

- Visited his GP with pain and swelling in his left leg and calf; back of calf was red with pitting oedema
- Had experienced worsening pain in his left leg for almost 2 weeks following a long-haul flight (8 hours) and a 2-hour wait for his luggage

**Patient is fictitious.*
GP: general practitioner; LVEF: left ventricular ejection fraction.

Questions for discussion (1)

Q	What risk factors does Antonio have for a VTE?

Q What risk factors does Antonio have for a VTE?

A Antonio has the following risk VTE factors:

Physiological factors

- Dehydration
- Obesity (BMI ≥30 kg/m^2)
- Pregnancy

Other factors

- Age over 60 years
- Medical comorbidities*
- Significant reduction in mobility

Cancer

- Cancer type, stage
- Treatment

Medications

- Hormone replacement therapy
- Medications taken to treat active cancer
- Oestrogen-containing contraceptive therapy

Cardiovascular diseases

- Thrombophilia
- Varicose veins with phlebitis
- VTE history or first-degree relative with VTE history

Hospitalisation/surgery

- Surgery with a general anaesthetic and surgical time of >90 minutes (60 minutes if the surgery involves the pelvis or lower limb)
- Critical care admission
- Acute surgical admission with inflammatory or intra-abdominal condition

**Heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases and inflammatory conditions.*

1. NICE clinical guideline (CG92). Venous thromboembolism: reducing the risk for patients in hospital. January 2010. Available at: https://www.nice.org.uk/guidance/cg92/resources. Last accessed: August 2020;
2. Bahl V, et al. *Ann Surg* 2009;251:344–350.

Questions for discussion (2)

After conducting a physical exam, Antonio scored 3 on the two-level Wells DVT risk score

Q	Should he be referred for a ultrasound scan?

Questions for discussion (2)

After conducting a physical exam, Antonio scored 3 on the two-level Wells DVT risk score

Q	Should he be referred for a ultrasound scan?
A	Yes, Antonio should be referred for an ultrasound scan if DVT is likely after conducting a physical examination and the two-level Wells score test

1. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020.

Questions for discussion (3)

Antonio was prescribed 3 months treatment with apixaban and has his follow-up review in general practice

Q When deciding the length of treatment, what risk factors need to be considered?

Questions for discussion (3)

Antonio was prescribed 3 months treatment with apixaban and has his follow up review in general practice

Q When deciding the length of treatment, what risk factors need to be considered?

A The following risk factors should be considered for long term treatment:[1]

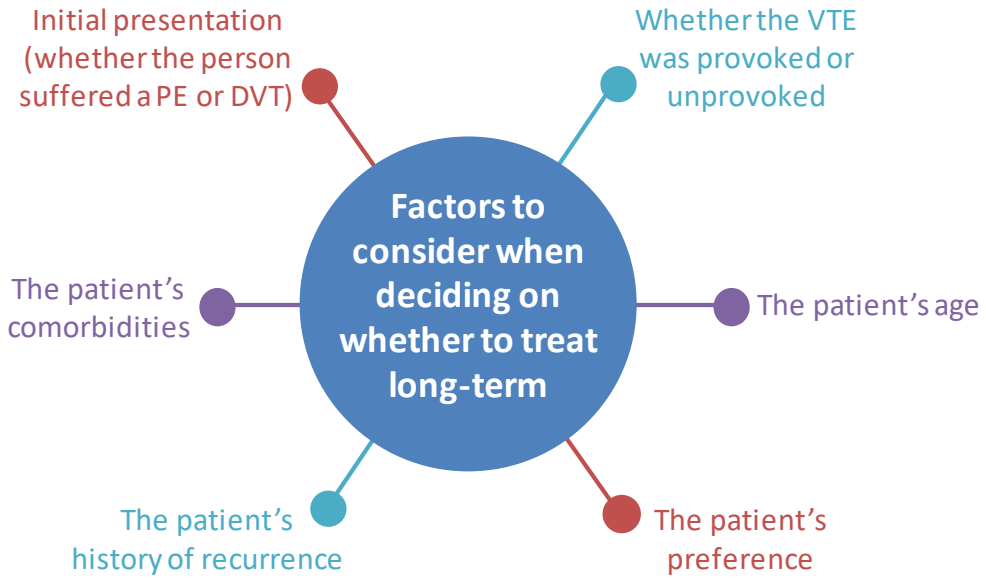
- Unprovoked VTE
- **Provoked VTE with minor transient or persistent provoking factor**
- **Recurrent VTE**
- Thrombus site/burden
- **No additional risk of major bleeding**
- **Medical comorbidities**

The decision of whether to **extend anticoagulation** beyond 3 months should be based on the **risk of recurrent VTE**, and should be balanced against the **risk of bleeding**, taking into account the **preferences of the patient**[1,2]

1. Kearon C, et al. *Blood* 2014;123:1794–1801;
2. Mazzolai L, et al. *Eur Heart J* 2017;38:1028–1033.

Selecting patients for long-term treatment – it is important to have decision pathways in place

A review should take place between **3 and 6 months post-diagnosis** to decide on the need for long-term anticoagulation for the prevention of recurrent VTE. This review should be **scheduled at the time of discharge**[1]



Adapted from BMS-Pfizer Expert and Anticoagulation UK Working Group Meeting. 2018[1]

In most cases, the decisions should be made by secondary care specialists or those in settings such as a dedicated VTE centre[1]

1. BMS-Pfizer Expert and Anticoagulation UK Working Group Meeting. Developing Optimal Standards of Care for the Prevention of Recurrent Venous Thromboembolism (VTE): Consensus Statement. Available at: http://www.anticoagulationuk.org/news/2019-01-11-developing-optimal-standards-of-care-for-the-prevention-of-recurrent-venous-thromboembolism-vte-consensus-statement. Last accessed August 2020.

Summary

- The incidence of VTE is approximately one per 1,000 people annually[1] with an estimated 30-day mortality risk of 3% for DVT and 31% for PE[2]
  - Effective treatment is therefore important
- The two-level Wells risk score aids in VTE diagnosis, which may also require USS, chest X-ray or D-dimer testing[3]
- Primary care health professionals have an important role in identifying potential cases of VTE, ensuring that prompt anticoagulation treatment is given when indicated, and supporting patients during anticoagulation treatment[4]
- Long-term treatment should be considered in appropriate patients, and may reduce the risk of recurrence and secondary complications[5–9]

1. Stone J, et al. *Cardiovasc Design Ther* 2017;9(Suppl. 3):S276–S284; 2. Søgaard S, et al. *Circulation* 2014;130:829–836; 3. National Institute for Health and Care Excellence. NICE Guidance NG158. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. March 2020. Available at: https://www.nice.org.uk/guidance/ng158/. Last accessed: August 2020; 4. Patel R. *Int J Gen Med* 2016;9:107-115; 5. Agnelli G, et al. *N Engl J Med* 2013;368:699–708; 6. Schulman S, et al. *N Engl J Med* 2013;368:709–718; 7. EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510; 8. Weitz JI, et al. *N Engl J Med* 2017;376:1211–1222; 9. Apixaban SmPC. Available at: http://www.medicines.org.uk.