CLINICAL PRACTICE GUIDELINE DOCUMENT

Editor's Choice – European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis☆

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DEDICATION

These guidelines are dedicated to the memory of Dr Clive Kearon of McMaster University in Hamilton, Ontario, Canada. Dr Kearon extensively reviewed the first and second versions of the manuscript and he was always very punctual. In the first review round he submitted a review of 16 pages with many detailed and helpful comments. Unaware of his illness, we invited him to review the final version of the guidelines on June 2, 2020, but sadly he passed away one day later, on June 3, 2020. We will always remember Dr Kearon for his many contributions to the field of Thrombosis and Antithrombotic Treatment, including these guidelines.



Clive Kearon,
1957—2020

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LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
aHR	adjusted hazard ratio
APC	activated protein C
aPL	antiphospholipid
APS	antiphospholipid syndrome
APTT	activated partial thromboplastin time
AT	antithrombin
ATTRACT	Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis
AVF	arteriovenous fistula
BMI	body mass index
CAVA	CAtheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT
CAVENT	Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis
CAVT	cancer associated venous thrombosis
CDT	catheter directed thrombolysis
CI	confidence interval
CKD	chronic kidney disease

CT	computed tomography
CrCl	creatinine clearance
CRT	catheter related thrombosis
CTV	computed tomography venography
CUS	compression ultrasound scanning
CVC	central venous catheter
CXR	chest X ray
DACUS	Duration of Anticoagulation based on Compression UltraSonography
DASH	Disabilities of the Arm, Shoulder and Hand
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ECG	electrocardiogram
ECS	elastic compression stockings
ESVS	European Society for Vascular Surgery
EU	European Union
GC	Guidelines Committee
GSV	great saphenous vein
GWC	Guideline Writing Committee
HIT	heparin induced thrombocytopenia
HR	hazard ratio
INR	international normalised ratio
IVC	inferior vena cava
IU	international unit
IV	intravenous
LMWH	low molecular weight heparin
MLB	multilayer bandaging
MRI	magnetic resonance imaging
MRV	magnetic resonance venography
NNT	number needed to treat
OR	odds ratio
PCC	prothrombin complex concentrate
PE	pulmonary embolism
PCDT	pharmacomechanical catheter directed thrombolysis
PF4	platelet factor 4
PNH	paroxysmal nocturnal haemoglobinuria
POST	Prospective Observational Superficial Thrombophlebitis
PTS	post-thrombotic syndrome
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
rtPA	recombinant tissue plasminogen activator
RVO	residual venous obstruction
SPC	summary of product characteristics
SSV	small saphenous vein
SVT	superficial vein thrombosis
TORPEDO	Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion
UEDVT	upper extremity deep vein thrombosis
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thromboembolism
WLUS	whole leg ultrasound

1. GENERAL ASPECTS

1.1. Purpose and methods of these guidelines

The European Society for Vascular Surgery (ESVS) has developed a series of clinical practice guidelines for the care of patients with vascular diseases. Their aim is to assist clinicians in selecting the best management strategies to achieve optimal patient outcomes.

These are the first ESVS guidelines on venous thrombosis. In 2017, the ESVS Guidelines Committee (GC), initiated a process to develop these guidelines. The present guideline document addresses acute deep vein thrombosis (DVT) of the lower extremity (unless otherwise stated), upper extremity DVT (UEDVT), superficial vein thrombosis (SVT), and thrombosis in unusual sites. The guideline document also covers topics in addition to treatments, including investigations and health economics, and includes special patient populations. The topic of venous thrombosis is large and therefore the remit of the guideline has been limited to conditions and situations likely to be commonly encountered by clinical teams/end users managing patients with venous thrombosis and others exposed to this condition. Furtheremore, all recent ESVS guidelines have considered the patient's perspective.[1,2]

This guideline document was written and approved by the 16 members of the Guideline Writing Committee (GWC). The GWC consisted mainly of ESVS members, and also eminent thrombosis experts from other societies with relevant clinical experience, strong publication records, and academic profiles. The recommendations in this guideline have been formulated by evaluation of the available scientific evidence, with expert opinion to create pragmatic guidance for patient management.

The recommendations represent the best available knowledge at the time of publication. However, as technology, available evidence, and disease knowledge may evolve rapidly, recommendations can become outdated. It is the aim of the ESVS to update the guidelines when important new insights into the evaluation and management of venous thrombosis become available.

Although guidelines have the purpose of promoting best practice according to specialists in the field, this guideline document should not be seen as the legal standard of care for all patients with venous thrombosis. The document provides guiding principles and pragmatic recommendations to aid clinical decision making. However, the care given to an individual patient may be dependent on many factors, including symptoms, comorbidities, age, level of activity, treatment setting, available techniques, local expertise, and other considerations.

1.2. Methodology

Members of this GWC were selected by the two chairs and approved by the ESVS GC to represent physicians involved in the management of patients with venous thrombosis. The members of the GWC have provided disclosure statements stating all relationships that might be perceived as potential conflicts of interest. These disclosure forms are kept on file at the ESVS headquarters. The ESVS GC was responsible for the overall process of endorsing this guideline. All expert members involved in the GWC have contributed to and approved the final document. The guideline document underwent a formal external expert peer review process, and, additionally, was reviewed and approved by the ESVS GC and by the editors of the *European Journal of Vascular and Endovascular Surgery*. This document was reviewed over three rounds by 18 reviewers, including 11 members of GC (with a review coordinator) and seven external reviewers from Europe and the USA. All reviewers assessed all versions and approved the final version of this document.

1.3. Strategy for creating guidelines

The first GWC meeting was held in May 2018, in Brussels. The table of contents and overall structure of the guideline document was discussed and agreed. Tasks and activities required to create the guideline were evaluated and distributed between GWC members. Contributions from GWC members were compiled into a draft guideline by the co-chairs. At a second meeting, held in Frankfurt in February 2019, the wording/grading of each suggested recommendation was reviewed. If unanimous agreement was not present, reasons for disagreement were discussed and the wording, grade, and level of evidence were amended to try and reach a consensus. If this failed, then the wording, grade, and level of evidence was secured via a majority vote of GWC members. The final version of the guideline was accepted on August 2020. In response to changes in the available evidence and knowledge, it is intended that these guidelines will be updated periodically.

1.4. Literature search and selection

Members of the committee, supported by clinical librarians if necessary, performed a literature search for this guideline in MEDLINE (through PubMed), Embase, and clinical trial databases, and the Cochrane Library up to 31 March 2018. Reference checking and hand searches by individual GWC members added other relevant evidence and literature. Additional relevant references were considered and included as GWC members became aware of them. A second formal literature search for papers published between April 2018 and August 2019 was performed in August 2019. Members of the GWC performed the literature selection based on the information provided in the title and abstract of the retrieved studies.

Criteria for search and selection were (1) English language; (2) level of evidence: when considering which published evidence to include, the literature was considered following the accepted hierarchy of evidence, with priority given to aggregated evidence (meta-analyses), followed by randomised controlled trials (RCTs), then observational studies (the level of available evidence for each section was used to guide the class of each recommendation in the guideline); (3) sample size: larger studies were given more weight than smaller studies; and (4) relevant articles published after the final literature search (August 2019) or in another language were included, but only if they were considered to be of paramount importance to this guideline.

Table 1. Levels of evidence

Level of evidence A	Data derived from multiple randomised clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomised clinical trial or large non-randomised studies
Level of evidence C	Consensus of experts opinion and/or small studies, retrospective studies, and registries

Table 2. Classes of recommendations

Class of recommendation	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy*
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion*
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful

1.5. Weighing the evidence

To define the current guidelines, members of the GWC reviewed and summarised the relevant peer reviewed published literature. Conclusions were drawn based on the available scientific evidence. In keeping with other published ESVS guidelines, the clinical practice recommendations in this document are presented using the European Society of Cardiology grading system. For each recommendation, the letter A, B, or C indicates the level of current evidence guiding the recommendation (Table 1).

Depending on whether the recommendation is strongly supportive of an intervention, weakly supportive, or strongly against an intervention, each recommendation is categorised as either Class I, IIa/IIb, and III, respectively (Table 2). The lower the class number, the greater the evidence and/or general agreement in favour of an intervention.

1.6. The patient's perspective

The importance of patient and public involvement in clinical guideline development is widely recognised and accepted. Patient and public engagement improves validity, increases quality of decisions, and is encouraged by national and international societies.

In order to improve accessibility and interpretability for patients and the public, a plain English summary was produced for this guideline and subjected to a lay review process. Information for patients was drafted for each subchapter which was read and amended by a vascular nurse specialist and one lay person.

Lay summaries were evaluated by eight patients with a history of venous thrombosis in the UK National Health Service and four lay members of the public without venous thrombosis. For all patients and members of the public asked to scrutinise the lay summary, the background and rationale for the ESVS venous thrombosis guidelines was explained. Honest feedback was encouraged on any aspect of the summary. The feedback was collated, and several themes were identified. Firstly, both patients and lay members of the public recognised the importance of venous thrombosis and welcomed the engagement. Several respondents commented that other conditions seemed to get much more public attention than venous thrombosis. All respondents acknowledged the importance of anticoagulant medication and appreciated that significant advances had been made with the widespread use of direct oral anticoagulants (DOACs).

Most feedback related to the use of interventions to reduce long term sequelae of venous thrombosis, particularly compression and early thrombus removal strategies for upper and lower extremity DVT. All respondents offered positive feedback about compression therapy, with the majority of patients with a history of venous thrombosis stating that this was not offered to them at the time of the initial presentation. They appreciated that the recommendations were based on the latest published evidence but expressed that even if the benefit was uncertain or modest, it should be discussed with future patients. Clinical teams managing patients with venous thrombosis should consider this feedback and ensure that potential interventions are discussed with patients and the rationale for offering or not offering early thrombus removal is clearly explained to the patient. Feedback from the focus group was used to amend and improve the clarity of the lay summaries.

2. LOWER EXTREMITY VENOUS THROMBOSIS

2.1. Introduction

2.1.1. Epidemiology and burden of the disease. The annual incidence of first episode of symptomatic DVT in the adult population ranges from 50 to 100 per 100 000 population, with the overall incidence of venous thromboembolism (VTE) around 25% higher with the addition of pulmonary embolism (PE) events.[3,4] Published epidemiology studies are either retrospective, using national or regional patient cohorts studied over several years, or prospective ultrasound based studies performed over 1 — 2 years.[5] The incidence of DVT is slightly greater in women aged 20 — 45 years, but men have a higher incidence between 45 and 60 years of age.[3,6] The incidence is higher for males for all age groups if female specific risk factors (oral contraceptives and pregnancy) are excluded.[7] The incidence increases twofold per 10 year age increase. At least one in 12 middle aged adults will develop either DVT and/or PE in their remaining lifetime and 60% of all VTE events occur in patients aged > 65 years.[3,8] African Americans have a higher incidence of DVT than Caucasians and Native Americans, whereas Asians (China and Korea) have a lower incidence. A seasonal variation occurs, with a higher incidence of VTE in the winter, peaking in February.[9] The rate of recurrent VTE is around 10% the first year and 30% after 5 — 8 years for patients with unprovoked DVT with an unidentified triggering factor (see also Tables 13 and 14).[10] The annual incidence of VTE has not changed in the last two to three decades, although the prevalence of cancer, major surgery, trauma, and obesity has increased, and the widespread availability of improved diagnostic modalities with computed tomography (CT) and magnetic resonance imaging (MRI) leading to increased detection of incidental VTE in patients with cancer.[11]

2.1.2. Risk factors. DVT is considered unprovoked if no clear precipitating risk factor can be identified. Risk factors are either hereditary or more often acquired. For provoked DVT, risk factors include cancer, acute medical illness, surgery, trauma, immobility (often in hospital and lasting at least three days), obesity, inflammatory diseases/infection, hormone therapy (oestrogen containing), pregnancy (particularly the postpartum period), long distance travel, recent hospitalisation, and antiphospholipid syndrome (APS). Primary varicose veins constitute a minor risk factor only. More recently, prolonged computer related "seated immobility syndrome" has also been recognised as a potential risk factor.[12] The most common inherited risk factor is a non-O blood type, which is associated with double the risk of VTE.[13] Another common thrombophilia is heterozygous factor V Leiden gene polymorphism, which may increase the risk of VTE by a factor of 3 — 8 in selected populations. Severe thrombophilia comprising homozygous factor V Leiden, deficiency of antithrombin, protein C or protein S, and APS increases the risk of DVT by a factor of 20 — 80.[14] Important risk factors for arterial thromboembolism such as hypertension and diabetes are also risk factors for VTE, but their significance is far less prominent.[15] For patients with cancer, an externally validated clinical prediction model incorporating D dimer and only one clinical factor (tumour site category) has been shown to predict the risk of VTE.[16]

2.1.3. Pathophysiology of deep vein thrombosis. The precise cause of DVT is likely to vary from patient to patient, but the main pathophysiological factors implicated in thrombosis are considered to be increased procoagulant

activity in the blood, vein wall damage, and impaired venous flow (Virchow's triad). Impaired flow, known also as venous stasis, may result from external compression by aneurysms, tumours, or the right common ilac artery, which compresses and causes fibrosis of the underlying left common iliac vein in May—Thurner syndrome (iliac vein compression syndrome). The thrombotic process leads to increased outflow resistance and decreased outflow volume with increased venous pressure, which, together with perivascular inflammation, is responsible for the characteristic symptoms and signs of DVT. Patients suffer swelling, pain, and tenderness, usually in the calf, but symptoms may also involve the thigh in the case of iliofemoral DVT. The symptoms typically diminish as the inflammatory reaction decreases and usually disappear if the veins can recanalise fully without structural damage to the vein wall or damaged valves. The recanalisation rate is around 80% in calf veins but only 20% in the iliac segments. Prolonged venous obstruction may result in chronic venous outflow obstruction and secondary venous valve damage, causing reflux after recanalisation. Venous obstruction, reflux, or a combination may lead to the development of post-thrombotic syndrome (PTS).[17] The first signs of PTS usually develop within three months of the onset of DVT, and PTS symptoms and signs may progress and deteriorate for years.[18] The most extreme clinical presentation of DVT may occur when there is occlusion of the common femoral and external iliac veins, completely obstructing the outflow of all deep and superficial veins of the limb, as well as collaterals, and is termed phlegmasia cerulea dolens (see Chapter 2.10). Anticoagulation therapy is used to reduce the risk of PE and prevent the progression of DVT. However, resolution of thrombus is dependent on the endogenous fibrinolytic activity in the affected veins.

2.1.4. Clinical manifestations of deep vein thrombosis. Symptoms and signs are generally more severe as the thrombosis extends more proximally, reflecting the greater degree of outflow obstruction and haemodynamic disturbance. Among the three anatomical types of DVT, i.e., iliofemoral, femoropopliteal, and calf DVT (see Chapter 2.2.2.1), iliofemoral DVT tends to be associated with the most severe symptoms. Symptoms from calf DVT may vary, and even be asymptomatic, depending on the collateral drainage. It should be noted that up to 80% of DVT cases may not be clinically apparent, with pain being the only feature. In DVT cases located at iliofemoral level the leg is usually considerably swollen and painful, with decreased mobility and oedema from the groin and distally due to limited venous collateral drainage in the pelvic region. Prominent superficial veins may be seen. For DVT originating in the iliac veins, back pain may be an early feature. Several lower extremity disorders may mimic DVT. These include lymphoedema, SVT, PTS, cellulitis, ruptured Baker cyst, and trauma.[19] Isolated calf DVT is seen in approximately 30% and thrombosis involving the iliofemoral segment accounts for around 30%.[20,21] Iliofemoral DVT is more commonly left sided, probably owing to the frequent compression of the left common iliac vein by the overriding right common iliac artery.[21]

2.1.5. Health economics of deep vein thrombosis. The financial burden of DVT and PE is substantial owing to the treatment costs related to DVT (inpatient or outpatient treatment, re-admission/recurrence) or PE (additional costs for re-admission/recurrence), costs related to complications of treatment, including bleeding and heparin induced thrombocytopenia (HIT), and costs related to long term complications, including PTS and chronic thromboembolic pulmonary hypertension.[22] A health economic modelling study using 2014 values estimated that annual total costs may range from €1.5 to €13.2 billion for the 28 member states of the European Union (EU).[22] The same study estimated that preventable costs may range from €0.5 to €7.3 billion, implying that better prophylaxis, optimisation of outpatient treatment, and earlier hospital discharge of patients with PE and DVT may result in cost savings. Another recent review investigated the economic burden of VTE healthcare costs in the USA.[23] For 375 000 — 425 000 newly diagnosed VTE events per annum in the USA, a conservative cost estimate for medical treatment to the healthcare system was $7 — $10 billion each year, a much higher cost than for the EU.[23]

2.2. Diagnosis and investigation

2.2.1. Diagnosis of deep vein thrombosis and imaging strategies

2.2.1.1. Clinical assessment and pre-test probability score. Several clinical features are known to be suggestive of DVT. These comprise symptoms, signs, and other clinical risk factors. Although useful to raise the clinical suspicion of DVT, these factors cannot be used individually to confirm or exclude the diagnosis. However, when incorporated in decision tools, an individualised pre-test probability of DVT can be assigned to patients, aiding decision making strategies.[24,25]

The most thoroughly studied and validated clinical decision score is the Wells DVT score (Table 3), which categorises the pre-test probability scores of DVT into two (DVT likely if score $\geq$ 2 or unlikely if score $<$ 2) or three groups (high likelihood of DVT if $\geq$ 3; moderate likelihood if 1 — 2; low likelihood if $\leq$ 0).[26] The dichotomised Wells score is simpler and more widely used than the Wells three category version and significant advantages to stratification into three groups have not been demonstrated. Although the Wells DVT score is useful, the probability of DVT in the low risk group has been reported to be as high as 5%.[25] With this risk of a false negative result, the score cannot be used as a standalone test to confirm or exclude DVT. However, when used in conjunction with additional investigations, namely D dimer measurements and/or ultrasound, it is a valuable tool for accurate decision making.[27]

2.2.1.2. D dimer measurement. D dimers are fibrin degradation products and are increased in any condition with increased fibrin formation, such as venous thrombosis. The sensitivity of the most commonly used quantitative assay is

approximately 95%, with a negative predictive value of 99% — 100%.[28] False negatives can still occur, particularly in patients treated with anticoagulants, with calf DVT or with symptoms lasting for longer than two to three weeks.[29] D dimer testing is limited by its low specificity (35% — 55%),[28] and false positives are common as numerous other conditions yield increased D dimer levels, including infection, cancer, and pregnancy. Older age is also associated with higher baseline D dimer concentrations and although age adjusted cutoffs have been introduced, the specificity remains low (51.1%).[30]

2.2.1.3. Ultrasound. Two distinct ultrasound assessment approaches are practised to investigate for DVT in symptomatic patients: two or three point compression ultrasound scanning (CUS) and whole leg ultrasound scanning (WLUS). In CUS, deep vein patency is only assessed in two or three venous territories (usually the common femoral vein, the popliteal vein ± the femoral vein). Although the most proximal segments of the tibial veins can be interrogated during popliteal assessment, isolated calf DVT is not excluded by this technique. However, WLUS provides a more extensive examination, where the entire deep vein network of the leg is scanned from the common femoral vein to the distal veins.[29,31]

Although both CUS and WLUS are safe to exclude suspected symptomatic DVT,[32] each approach has different advantages and limitations, and their applicability varies accordingly. CUS is quicker, simpler, has better reproducibility, and is readily available as comprehensive venous ultrasound skills are not needed. However, as it cannot detect distal (calf) DVT, a negative CUS examination alone cannot exclude calf DVT, and rescanning may be required five to seven days later for confirmation.[33] Conversely, WLUS can be considered conclusive after one assessment, obviating the need for rescanning or additional examinations.[34] Also, detailed investigation of the whole leg may permit prompt identification of other pathological conditions.

However, WLUS requires a skilled operator, advanced ultrasound machines, and more time, limiting its widespread availability. Also, as WLUS allows for the detection of isolated calf DVT of uncertain clinical significance, overdiagnosis may occur, potentially exposing patients to unnecessary anticoagulation and associated risks,[35] as well as increased healthcare costs. Therefore, appropriate selection of patients for WLUS assessment is necessary.

Considering the differences between these techniques, the Palladio study proposed a comprehensive diagnostic algorithm for DVT, in which WLUS and CUS were used, depending on D dimer measurements and the pre-test probability of DVT.[36] In this study, D dimer measurement and pre-test probability assessment were performed on admission in the study population. On the basis of pre-test probability assessment, patients were stratified into three groups:

- Group 1: pre-test probability unlikely and D dimer negative (DVT excluded)
- Group 2: either pre-test probability for DVT likely or positive for D dimer (CUS only)
- Group 3: pre-test probability for DVT likely and positive D dimer (WLUS)

The results of this study favoured the use of this algorithm, as the incidence of thromboembolic events at three months was negligible in group 1 (< 0.3%), and similar to those reported in other validated algorithms in group 2 (1%). More importantly, by applying such an algorithm, WLUS was performed in only 35% of patients with suspected DVT, of whom half (49%) had DVT. This study demonstrated the potential of this algorithm to safely rule out DVT on the day of referral, while reducing the risk of overdiagnosis of low risk isolated calf DVT.[36] However, this algorithm is not validated, and therefore the GWC is in favour of WLUS whenever there is clinical suspicion of calf DVT and WLUS is available.

2.2.1.4. Computed tomography venography. CT venography (CTV) is an effective technique for the diagnosis of proximal DVT in patients with suspected DVT and PE, with sensitivity and specificity comparable to ultrasound. CTV offers definite advantages over ultrasound when evaluating the pelvic veins or the inferior vena cava (IVC) and can detect concurrent medical conditions that cause pain and swelling. Moreover, owing to its excellent spatial resolution, it may facilitate vessel measurement and case planning, when intervention is deemed necessary. However, CTV is expensive, requires the use of iodine contrast, and involves

Table 3. Wells score for the prediction of lower extremity deep vein thrombosis[26]

Clinical characteristic	Score
Active cancer (patient either receiving treatment for cancer within the previous six months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent cast immobilisation of the lower extremities	1
Recently bedridden for ≥3 days, or major surgery within the previous 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling at least 3 cm larger than on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Unilateral collateral superficial veins (non-varicose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	−2
	Total*

* Wells scoring system: −2 to 1 = deep vein thrombosis is unlikely; 2 to 8 = deep vein thrombosis likely. Or, probability for deep vein thrombosis: −2 to 0 = low; 1 to 2 = moderate; 3 to 8 = high.

radiation exposure, which constitutes a significant concern, particularly in younger patients.[37]

2.2.1.5. Magnetic resonance venography. The role of magnetic resonance venography (MRV) for the diagnosis of lower extremity DVT has been poorly described in the literature. Although a systematic review and meta-analysis found MRV to have equivalent sensitivity and specificity to ultrasound assessment, cautious interpretation of these results is needed, as significant heterogeneity between studies was observed. Like CTV, MRV offers definite advantages over ultrasound when evaluating the pelvic veins or the IVC and can detect concurrent medical conditions that cause pain and swelling, such as extrinsic venous compression syndromes or incidental pelvic malignancies. However, as MRI is relatively expensive and intravenous (IV) contrast is usually required, it has clear disadvantages compared with ultrasound. As such, there may be a role for MRV in patients in whom ultrasound is not appropriate, not feasible, or is inconclusive,[38] although there is no evidence to suggest it can replace venography in such cases.

Recent studies have assessed the role of MRV in follow up after DVT, and differentiation between new and recurrent DVT. In fact, although duplex ultrasound cannot reliably determine the age of a thrombus and therefore distinguish acute recurrent DVT from persisting previous thrombus, magnetic resonance direct thrombus imaging may help distinguish between acute recurrent thrombus and a persisting thrombus in the same location, with further implications for treatment regimens.[39,40] In the Theia study, 119 patients with suspected recurrent DVT had magnetic resonance direct thrombus imaging negative for both DVT and SVT and were not treated with any anticoagulant during follow up. The three month incidence of recurrent symptomatic VTE was 1.7% (95% confidence interval [CI] 0.20% — 5.9%), suggesting that whenever recurrent ipsilateral DVT is suspected and a WLUS is inconclusive, magnetic resonance direct thrombus imaging should be considered for therapeutic management decisions.

2.2.1.6. Venography. Historically, contrast venography was the first line imaging for the diagnosis of DVT and considered the gold standard. Although effective, this procedure is invasive, requires IV contrast, and involves exposure to radiation. Therefore, venography is now seldom performed, except when other investigations yield inconclusive results or concurrent catheter based intervention is being considered.[37]

Given the variety of diagnostic methods available to healthcare professionals involved in the management of DVT, it is imperative that a validated diagnostic pathway is used. Ultrasound is the initial imaging method of choice in modern day practice.

Recommendation 1

When deep vein thrombosis is suspected, a clinical assessment of the pre-test probability is recommended as part of the diagnostic process.

Class	Level	References
I	C	Geersing *et al.* (2014),[27] Kelly & Hunt (2003)[41]

Recommendation 2

All healthcare professionals involved in the diagnosis of deep vein thrombosis should use a validated diagnostic pathway.

Class	Level	Reference
I	C	Ageno *et al.* (2015)[36]

Recommendation 3

For patients with suspected deep vein thrombosis requiring imaging, ultrasound is recommended as the first modality.

Class	Level	References
I	C	Consensus

Recommendation 4

For patients with suspected deep vein thrombosis with a likely pre-test probability and negative compression ultrasound scanning, repeat ultrasound assessment should be considered after 5–7 days.

Class	Level	Reference
IIa	C	Cogo *et al.* (1998)[33]

Recommendation 5

For patients with suspected proximal deep vein thrombosis where ultrasound assessment is inconclusive or not feasible, computed tomography venography, magnetic resonance venography, or venography should be considered.

Class	Level	References
IIa	C	Sampson *et al.* (2007),[38] Karande *et al.* (2016),[37] Dronkers, *et al.* (2016)[42]

Recommendation 6

When performing ultrasound imaging in patients with suspected calf deep vein thrombosis, whole leg ultrasound is recommended.

Class	Level	Reference
I	C	Schellong *et al.* (2003)[34]

2.2.2. Classification of deep vein thrombosis

2.2.2.1. Anatomical level. Depending on the venous territory involved, DVT may be classified as proximal or distal. Thrombosis of the iliac, femoral, and/or popliteal veins is classified as proximal DVT, regardless of the presence of concomitant calf (distal) DVT. Further differentiation into iliofemoral and femoropopliteal DVT can be performed and may be useful. Similarly, thrombosis that is confined to calf (distal) deep veins may be termed as calf or distal DVT.[43] As the risk of PE, risk of developing PTS, and overall prognosis are different depending on the affected venous territory, accurate anatomical classification of DVT is important for diagnostic, therapeutic, and prognostic purposes.

Table 4. Definition of transient or persistent provoked risk factor for deep vein thrombosis. Modified with permission from Kearon *et al.*, 2016[44]

Provoked risk factor	Definition
Transient	
Major*	Half the risk of recurrent VTE after stopping anticoagulant therapy (*vs.* if there was no transient risk factor), when the risk factor occurred up to three months before the VTE
	A >10 fold increase in the risk of having a first VTE
Minor†	Half the risk of recurrent VTE after stopping anticoagulant therapy (*vs.* if there was no transient risk factor), when the risk factor occurred up to two months before the VTE
	A 3–10 fold increase in the risk of having a first VTE
Persistent‡	Cancer, if: • has not received potentially curative treatment • there is evidence that treatment has not been curative (e.g., recurrent or progressive disease) • treatment is ongoing
	Ongoing non-malignant condition associated with at least a twofold risk of recurrent VTE after stopping anticoagulant therapy

VTE = venous thromboembolism.
* Example: major transient risk factors: surgery with general anaesthesia for > 30 min; acute illness confined to bed in hospital for at least three days; caesarean section; oestrogen therapy; pregnancy or puerperium.
† Example: minor transient risk factors: surgery with general anaesthesia for < 30 min; admission to hospital for < 3 days with an acute illness; confined to bed out of hospital for at least three days with an acute illness; leg injury associated with reduced mobility for at least three days.
‡ Example: persistent risk factor: cancer; inflammatory bowel disease.

2.2.2.2. Aetiological classification. DVT may be categorised as either provoked or unprovoked, depending on the presence or absence of associated risk factors. Unprovoked DVT refers to venous thrombosis in the absence of clearly identifiable environmental or acquired risk factors. Similarly, provoked DVT occurs in the presence of such risk factors, which can be further classified as transient or persistent (depending on whether they persist after the event) and into major or minor (Table 4).[44] Understanding the provoked or unprovoked nature of DVT, as well as the chronicity of any provoking risk factors (transient or persistent), has significant prognostic and treatment implications, as recurrence risk and anticoagulation regimens differ accordingly. If a DVT is provoked by a major transient risk factor (such as trauma or surgery, oestrogen therapy, pregnancy, or puerperium), there is a very low risk of recurrence when anticoagulation is stopped, provided the risk factor is no longer present.[45–48] Conversely, when DVT is known to be provoked by a persistent and progressive risk factor (such as malignancy), the risk of recurrence is significantly higher in the same conditions. Finally, patients with unprovoked DVT have an intermediate risk of recurrence.[44] The definition of risk factors associated with provoked DVT are listed in Table 4.

2.2.3. Investigation for pulmonary embolism. Occult PE is known to be prevalent in patients with lower extremity DVT. Several studies have reported that around 30% – 40% of patients with DVT have high probability pulmonary scintigraphy or CT findings suggesting clinically silent PE,[49,50] but prevalences as high as 66% have been reported.[51] For patients diagnosed with DVT, the prevalence of clinically silent PE increases with age,[49] and is higher in patients with proximal DVT,[49,51] compared with those with calf DVT. In a systematic review of patients with calf DVT, the prevalence of silent PE was 13%.[52]

The presence of silent and undetected PE in patients with DVT may be clinically relevant as patients with subsequent pulmonary symptoms may be mistakenly diagnosed as PE, despite anticoagulation, which may lead to unneccessary therapeutic measures such as caval filter insertion.[53] As silent PE can occur even in central pulmonary arteries,[49,51] pulmonary hypertension may ensue. Patients with DVT and silent PE are also more likely to suffer recurrent PE than patients with DVT without silent PE.[49] For patients with silent PE at the time of proximal lower extremity DVT diagnosis, there is increased risk of symptomatic PE occurring during the initial two weeks of treatment,[50,54] whereas no such significant difference remains after three months of treatment.[50]

Routine screening for PE in newly diagnosed DVT patients has therefore been advocated,[49,52] as baseline imaging may be helpful if the patient subsequently develops respiratory symptoms. Moreover, imaging would potentially allow individualisation of anticoagulant treatment to counteract the higher risk of symptomatic PE in those with silent PE, particularly in the first two weeks after diagnosis.[50,54] However, such a strategy would incur added costs,[51] and increase exposure to both radiation and contrast media. In the absence of high quality evidence demonstrating clinical and health economic benefits of routine investigation for PE, such an approach cannot currently be recommended. There may be benefits of screening for PE in subgroups of patients with DVT,[50] such as those with electrocardiogram (ECG) or chest X ray (CXR) abnormalities, free floating thrombus, or cardiac biomarkers, suggesting possible pulmonary involvement, or increased bleeding risk. However, level I evidence for such an approach is lacking.

Recommendation 7		
For patients with deep vein thrombosis, routine investigation for occult pulmonary embolism in the absence of symptoms or signs is not recommended.		
Class	**Level**	**Reference**
III	C	Garcia-Fuster *et al.* (2014)[51]

2.2.4. Investigation for malignancy. The association between DVT and occult malignancy has prompted the question of whether unselected patients with DVT should be routinely investigated for cancer.[55] Between 4% and 12% of patients with unprovoked DVT without a history of malignancy at baseline are diagnosed with cancer during treatment of their VTE,[55–58] usually during the first months after VTE diagnosis.[55,58] In addition to the unprovoked nature of the DVT, several factors have been identified as being independently associated with the diagnosis of malignancy in patients with DVT, including recurrent DVT, advanced patient age, male sex, smoking, low body weight, elevated platelet count, anaemia, chronic lung disease, prior VTE event, and recent surgery.[55,58,59] A risk score based on the presence of these factors, followed by more extensive examination for cancer in those with a high score has therefore been proposed,[59] but external validation is awaited.

Detection of underlying malignancy present at diagnosis of DVT may require extensive investigations, however, and the disease may already be widespread and incurable despite screening and detection.[56] Extensive screening strategies also incur increased costs, are associated with the risks of false positive findings[60] and with hazards from radiation exposure and contrast media. The effects of added physical discomfort and emotional distress to patients should also be considered.

In clinical studies including patients with DVT, limited screening for malignancy has often been defined as a medical history (including asking for red flag cancer symptoms), a full clinical examination and basic blood tests. On occasion, additional investigations such as CXR and sex specific screening tests such as prostate specific antigen in men have also been included.[56,57] Several studies have compared limited screening with more extensive cancer screening protocols including rectal examination, faecal occult blood testing, thoracic CT or positron emission tomography imaging, and mammography and abdominopelvic CT scanning for women.[56,57] Two meta-analyses have amalgamated the published data in patients with unprovoked VTE comparing more extensive investigation strategies with limited screening only.[56,57] Extensive screening diagnosed a higher number of malignancies compared with limited screening (7.5% *vs.* 6.1%; relative risk [RR] 1.22; 95% CI 0.90 — 1.65)[57] but conferred no significant reduction in all cause mortality (RR 0.86; 95% CI 0.58 — 1.27),[56,57] or cancer related mortality (RR 0.86 [95% CI 0.46 — 1.62] in one study,[56] and 0.93 [95% CI 0.54 — 1.58] in another).[57]

Similarly, a recent Cochrane review suggested that there is currently insufficient evidence to draw definitive conclusions concerning the effectiveness of testing for undiagnosed cancer in people with a first episode of unprovoked VTE (DVT or PE) in reducing cancer or VTE related morbidity and mortality.[61]

Based on current evidence, limited rather than extensive screening for occult cancer should be undertaken in patients with provoked or unprovoked DVT. A clinical history and physical examination should be performed, although additional sex specific tests may be warranted, based on findings.

Recommendation 8		
For patients with unprovoked deep vein thrombosis, clinical examination and sex specific cancer screening, as opposed to routine extensive screening, for occult malignancy is recommended.		
Class	**Level**	**References**
I	A	Zhou *et al.* (2017),[56] Klein *et al.* (2017),[57] Kleinjan *et al.* (2012)[60]

2.2.5. Testing for hereditary and acquired thrombophilias

2.2.5.1. Details of thrombophilias and thrombophilia testing. Thrombophilia testing is poorly understood. The intended goal is to detect currently known hereditary or acquired pro-thrombotic states that predispose to VTE. The testing should be used to help assess the risk of recurrent VTE in patients after their first unprovoked event. The term "thrombophilia testing" refers to testing for antithrombin, protein C and protein S deficiencies, activated protein C (APC) resistance and/or factor V Leiden, prothrombin G20210A mutation, and antiphospholipid antibodies (lupus anticoagulant, anti-beta-2 glycoprotein I, and anticardiolipin IgG and IgM antibodies).[62] Previously, homocysteine and C677T methylenetetrahydrofolate reductase mutation were included, but these are now excluded from testing in most centres as the associated risk with VTE is weak.

Thrombophilia testing became popular after the detection of the single gene mutations in the antithrombin, protein C, and protein S genes in the 1980s. It was initially thought that these thrombophilias would explain the majority of VTE. However, thrombophilia testing has fallen out of favour as these investigations usually add little to the clinical management of the patients for the following reasons.

Firstly, the absence of a hereditary thrombophilia in a patient with a strong family history does not exclude a hereditary defect, as only about 50% of families with a strong history of VTE will be diagnosed with a currently recognised thrombophilia. There are probably other inherited defects that remain unrecognised. It is now recognised that clinical factors are more important determinants of the risk of recurrent VTE (National Institute of Health and Care Excellence Clinical Guideline 144).[63–65]

Secondly, being diagnosed and labelled with a thrombophilia may add unnecessary anxiety and medicalisation, particularly as most people with a low risk hereditary thrombophilia such as heterozygous factor V Leiden will never have a VTE event and are not at increased risk of recurrent VTE.

Table 5. Core hereditary and acquired thrombophilias

Thrombophilia
Hereditary
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Factor V Leiden
Activated protein C resistance*
Prothrombin G20210A variants
Dysfibrinogenaemia
Factor XIII 34val
Fibrinogen (G) 10034T
A and/or B alleles of the ABO blood group
Prothrombin Yukuhashi (II R596L)
Acquired
Antiphospholipid antibodies on two occasions more than 12 weeks apart. Three assays are performed: • lupus anticoagulant • anticardiolipin antibodies • anti-beta-2 glycoprotein I antibodies
Paroxysmal nocturnal haemoglobinuria
Myeloproliferative syndromes with JAK2V617F mutation
Other causes
Haemolytic states, e.g., sickle cell crises
Any inflammatory disease such as infections, e.g., pneumonia, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, Adamantiades-Behçet disease.
Nephrotic syndrome (loss of antithrombin in the urine)

* Not everyone has factor V Leiden.

Thirdly, it should be recognised that hereditary thrombophilia has been studied mainly in the white population. For example, factor V Leiden mutation is the most common hereditary thrombophilia, with a prevalence of 5% — 10%, although it is rarely seen in non-white populations.[66,67] Different types of recognised thrombophilia are presented in Table 5. The prevalence and relative risk of development of VTE of the most common hereditary and acquired haematological alterations related to clinical thrombophilia is shown in Table 20 in Chapter 4.4.1.

2.2.5.1.1. Hereditary antithrombin, protein C, and protein S deficiency. Deficiencies of these natural anticoagulants are inherited as an autosomal dominant trait and account for 10 — 15% of familial thrombophilias. However, such deficiencies are rare in the general population, with an estimated prevalence of about one in 5 000 individuals. Because of their genetic heterogeneity, they are diagnosed by antigenic or functional assays. Deficiencies can be either type 1, where there is a parallel reduction in biochemical activity and antigen concentration, or type 2, a functional defect where biochemical activity is reduced, despite normal antigen concentration.

Antithrombin is the main inhibitor of thrombin. Binding to heparin or heparan sulphate dramatically enhances this inhibitory activity. With the exception of mutations affecting the heparin binding site, homozygous antithrombin deficiency is considered incompatible with life. Heterozygous antithrombin deficiency results in a 5 — 20 fold increased risk of VTE, with affected individuals typically presenting with thrombosis at an early age.

Protein C is a vitamin K dependent protease, synthesised in the liver, which, when activated by thrombin, has an anticoagulant effect by proteolytic degradation of activated factors V and VIII. Homozygotes or compound heterozygotes are just compatible with life (protein C $<$ 0.01 U/mL), presenting with spontaneous skin necrosis in neonatal life (neonatal purpura fulminans), or if less severely affected (protein C 0.4 — 0.6 U/mL) with a 7 — 10 fold increased risk of VTE in later life. Patients with purpura fulminans require protein C replacement with either fresh frozen plasma or protein C concentrates. Individuals with protein C deficiency are at increased risk of skin necrosis during the initiation of vitamin K antagonist (VKA) therapy (known also as warfarin induced skin necrosis) because the half life of protein C is shorter than that of the other vitamin K dependent coagulation factors, resulting in a temporary hypercoagulable state.

Protein S is a vitamin K dependent protease that serves as a co-factor for the anticoagulant function of APC. Protein S circulates in two forms, approximately 40% as free protein S and the remainder reversibly bound to complement 4b binding protein. Only free protein S has cofactor activity for APC. The proportion of free and bound protein S depends on the functional protein integrity and levels of complement 4b binding protein. Reduced concentration of free protein S is associated with an approximately 2 — 10 fold increased risk of VTE and an increased risk of skin necrosis during the initiation of a VKA.

2.2.5.1.2. Factor V Leiden. The factor V Leiden variant is a single point mutation at nucleotide position 1691 in the factor V gene that causes a substitution of arginine by glutamine. This amino acid substitution prevents APC from recognising a cleavage site on factor V, leading to resistance to the anticoagulant action of APC. Factor V Leiden mutation is the most common cause of APC resistance. The variant is more often present in the white population than in other ethnic groups, such as Asians or Africans. Heterozygosity results in a fivefold increase in VTE risk, whereas homozygotes have an 80 fold increase in VTE risk.

2.2.5.1.3. Prothrombin G20210A variant. The prothrombin G20210A variant is a single nucleotide substitution from glutamine to arginine at position 20210 of the prothrombin gene, which results in an approximately 30% increase in prothrombin antigen or activity assays. Carriers have an increased risk of DVT.

2.2.5.1.4. Other hereditary associations. Dysfibrinogenaemias may cause bleeding and thrombotic episodes, sometimes in the same individual. They are extremely rare and best managed by thrombophilia experts. Other hereditary thrombophilias are being described in non-white populations; for example, there is a protein C variant that has a prevalence of 2% in the Chinese population that predisposes to VTE.

2.2.5.1.5. Antiphospholipid syndrome. APS is the association between antiphospholipid (aPL) antibodies and thrombosis and/or certain problems in pregnancy. The key difference between APS and the other thrombophilias is

that the former can cause thrombosis in any vascular bed, not only DVT, and therefore APS is an important cause of stroke at young age, thrombotic myocardial infarction, and placental dysfunction.[68]

Antiphospholipid antibodies are a family of antibodies reactive with proteins that are themselves complexed with negatively charged phospholipids such as beta-2 glycoprotein I. To detect an aPL antibody there are three laboratory tests required (it is important to do all three as many are only positive for one): these are the lupus anticoagulant; anticardiolipin antibodies; and anti-beta-2 glycoprotein I antibodies.[69] Because transient antibodies can occur, the test must be performed again 12 weeks later. The lupus anticoagulant is an *in vitro* phenomenon in which the aPL antibody slows down clot formation, thereby prolonging the clotting time. The lupus anticoagulant assay is a double misnomer: it is neither a test of lupus nor an *in vivo* anticoagulant.

The catastrophic APS is an aggressive variant of APS with multi-organ system involvement that includes small vessel thrombosis and can develop rapidly.[70] It is a life threatening medical condition with a 50% mortality rate. Disseminated intravascular coagulation is present in 25% of cases.

2.2.5.1.6. Paroxysmal nocturnal haemoglobinuria. Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haematological disease caused by somatic mutations in the phosphatidylinositol glycan A gene (*PIGA*) in haematopoietic stem cells.[71] Complement action at the surface of haematopoietic cells, including platelets and leucocytes, induces an increased risk of thromboembolic events.[71] Traditionally, PNH was managed by supportive care (e.g., transfusions and anticoagulation) and allogeneic stem cell transplant. Use of eculizumab, an anti-C5 monoclonal antibody, has significantly changed PNH management and clinical outcomes.[72] However, for patients with PNH with a history of VTE, anticoagulation should be maintained indefinitely.[72]

2.2.5.2. Whether to test for thrombophilias. Rather than focusing on thrombophilias, identifying whether a DVT is provoked or unprovoked, patient sex and age are considered much more useful in determining which patients are at high risk of recurrent DVT and therefore who may need long term anticoagulation. It should be recognised that hospital acquired VTEs (defined as a VTE event during hospital admission and up to 90 days after hospital discharge) account for up to two thirds of all VTE events.[73] For this population, unless there are other risk factors for DVT, the risk of recurrence is low and therefore only three months of anticoagulation is usually required.

The patients and situations that require thrombophilia testing remain controversial. Current opinion is that thrombophilia testing should only be performed when patient management will be affected. The first consideration is whether the DVT is provoked or unprovoked. The risk of recurrent events after a provoked event (the most common provoking factor being hospital admission) is small and therefore there is no merit in routinely testing for thrombophilia.[74,75] In the following circumstances, thrombophilia testing may be potentially useful.

Firstly, in patients with their first unprovoked DVT to identify whether a patient has a high risk of recurrence and therefore long term anticoagulation may be required. Although this is particularly true for younger patients (e.g., age up to 40 — 45 years) where the frequency of thrombophilia is much higher than in the elderly, a negative thrombophilia test should not be an indication to suggest stopping anticoagulation after three to six months of treatment.[76] However, the presence of a severe thrombophilia may encourage extended treatment.[77] Therefore, testing for the most frequent type of acquired thrombophilia that is the APS should be considered if a decision to stop anticoagulation is contemplated.[75]

Secondly, consideration of thrombophilia testing is also important in patients with DVT at an unusual site (e.g., cerebral vein), and particularly in those where the event was unprovoked and who have a strong first degree family history of VTE, particularly those under 45 years of age.

Thirdly, for females with DVT, aPL antibody testing may be especially useful in those with a history of recurrent miscarriages, intra-uterine foetal death, and other late obstetric morbidities due to placental ischaemia, particularly intra-uterine foetal growth restriction and pre-eclampsia. Detection of aPL antibodies is relevant in all of these situations, as these will have an impact on the type and duration of anticoagulation, as well as on thromboprophylaxis to prevent obstetric morbidity.[78]

Fourthly, during future medical or surgical treatment, patients with thrombophilia may be prescribed more intensive thromboprophylaxis measures (in terms of dose and/or duration) in view of their probable higher risk of VTE. In a patient with a proven thrombophilia the risk of recurrent VTE varies depending on the type of thrombophilia, and risk is greater with combined defects.

2.2.5.3. Timing and details of thrombophilia tests. Thrombophilia testing should not be performed in the acute period after a recent VTE, and especially if the patient is receiving heparin, warfarin, or DOAC. Plasma level assays should better be performed at least two weeks after stopping VKAs or at least three days after stopping a DOAC, although some thrombophilia testing (i.e., antithrombin activity) can be performed while taking DOACs or VKAs. Genetic testing can be performed at any time. Abnormal (phenotypic) plasma thrombophilia tests should always be repeated on a second set of blood samples on a different day for confirmation. Patients studied while receiving anticoagulants should be retested at a later date, as levels of proteins C and S, and routine lupus anticoagulant testing are affected by VKAs and DOACs.

The laboratory performing the testing should follow international laboratory standards, such as the International Society on Thrombosis and Haemostasis guidelines for lupus anticoagulant.[79]

As the detection of combined hereditary thrombophilic defects may significantly influence decisions on type and duration of anticoagulation, patients with high risk thrombophilias (see Chapter 4.4.2. on specific considerations) should be referred to an expert in thrombophilia, who can provide appropriate patient counselling and long term follow up. This is particularly important as there have been rapid advances in the modern management of these conditions. For example, those with antithrombin deficiency may need plasma or recombinant antithrombin concentrates at times of haemostatic stress when they cannot receive anticoagulation. See Fig. 1 for a flowchart for diagnosis and investigations for DVT.

Recommendation 9

For patients with provoked deep vein thrombosis, thrombophilia testing is not recommended.

Class	Level	Reference
III	C	Stevens *et al.* (2016)[74]

Recommendation 10

For patients with unprovoked deep vein thrombosis, routine testing for inherited thrombophilias is not recommended.

Class	Level	References
III	C	Stevens *et al.* (2016),[74] Connors (2017),[75] Garcia-Horton *et al.* (2017)[76]

Recommendation 11

For patients with unprovoked deep vein thrombosis and a family history of venous thromboembolism in a first degree relative, testing for hereditary thrombophilia should be considered.

Class	Level	Reference
IIa	C	Moll (2015)[77]

Recommendation 12

For patients with unprovoked deep vein thrombosis, testing for antiphospholipid antibodies should be considered if a decision to stop anticoagulation is contemplated.

Class	Level	Reference
IIa	C	Moll (2015)[77]

2.3. Treatment of deep vein thrombosis: anticoagulation

2.3.1. Phases of anticoagulation for deep vein thrombosis. Anticoagulation treatment for DVT may be divided into three distinct phases:[80,81] (1) an initial treatment phase (up to 10 days) with the aim of rapidly instigating anticoagulation therapy to prevent propagation of DVT and PE; (2) a principal treatment phase (first three months) to maintain therapeutic levels of anticoagulation to prevent propagation of DVT and PE, and reduce the risk of early recurrent VTE; and (3) an extended treatment phase (beyond three months, with no scheduled stop date) with the specific aim of reducing the long term risk of recurrent VTE.

After the principal treatment period (three months), the recurrence risk varies depending on the underlying risk factors. Extended anticoagulation treatment may be required for specific patient groups at high risk of recurrent VTE.

2.3.2. Anticoagulation mechanisms of action. Indirect anticoagulants, including the heparins, fondaparinux, or danaparoid, require the presence of antithrombin for inhibiting factor IIa (thrombin) and factor Xa, while direct anticoagulants act without the requirement of any co-factor (Fig. 2). Unfractionated heparin (UFH) inhibits both factor IIa and factor Xa with a Xa/IIa inhibition ratio of 1:1, while in low molecular weight heparins (LMWH) the Xa/IIa inhibition ratio varies between 2:1 and 4:1 and depends on the molecular weight of the LMWH.[82] LMWHs with a smaller mean molecular weight are excreted predominantly via the kidney and may therefore accumulate in patients with renal insufficiency.

VKAs, such as warfarin, acenocoumarol, and phenprocoumon, are administered orally and inhibit the gamma carboxylation of coagulation factors II, VII, IX, and X, a modification that is necessary for their functional activity. Of note, functional activity of the coagulation inibitors protein C and protein S also requires such gamma carboxylation and are therefore also decreased by VKA. As the half life of protein C is relatively short compared with the clotting factors, there is a transient hypercoagulable shift during the initiation of VKA. Consequently, it is essential that effective overlapping anticoagulation is ensured with heparins or fondaparinux during the initiation of VKA therapy. Parenteral anticoagulation should only be discontinued when it has been given for a minimum of five days and a therapeutic international normalised ratio (INR) $>$ 2.0 is achieved with VKA and maintained over two consecutive days.[80] Direct anticoagulants do not require the presence of antithrombin and include the thrombin (IIa) inhibitors hirudin and argatroban, and the DOAC dabigatran, which inhibits factor IIa. DOACs that inhibit factor Xa are also called oral factor Xa inhibitors, and include apixaban, edoxaban, and rivaroxaban.

2.3.3. Anticoagulant properties and dosing for the treatment of venous thrombosis. Details are provided in Tables 6—8.

2.3.3.1. Unfractionated heparin. Unfractionated heparin is currently only used in special clinical situations, such as severe renal insufficiency, haemodialysis, pending interventions, or for critically ill patients. Body weight should be assessed and activated partial thromboplastin time (APTT) evaluation is necessary for accurate and safe administration. Dosing information is summarised in Tables 6 and 7.[82,84] An APTT ratio of 1.5 — 2.5 should be reached within 24 hours of starting treatment. A lower APTT in the first 24 hours is associated with a higher incidence of recurrent DVT.[85] As numerous variables can affect APTT results, including sample collection, processing,

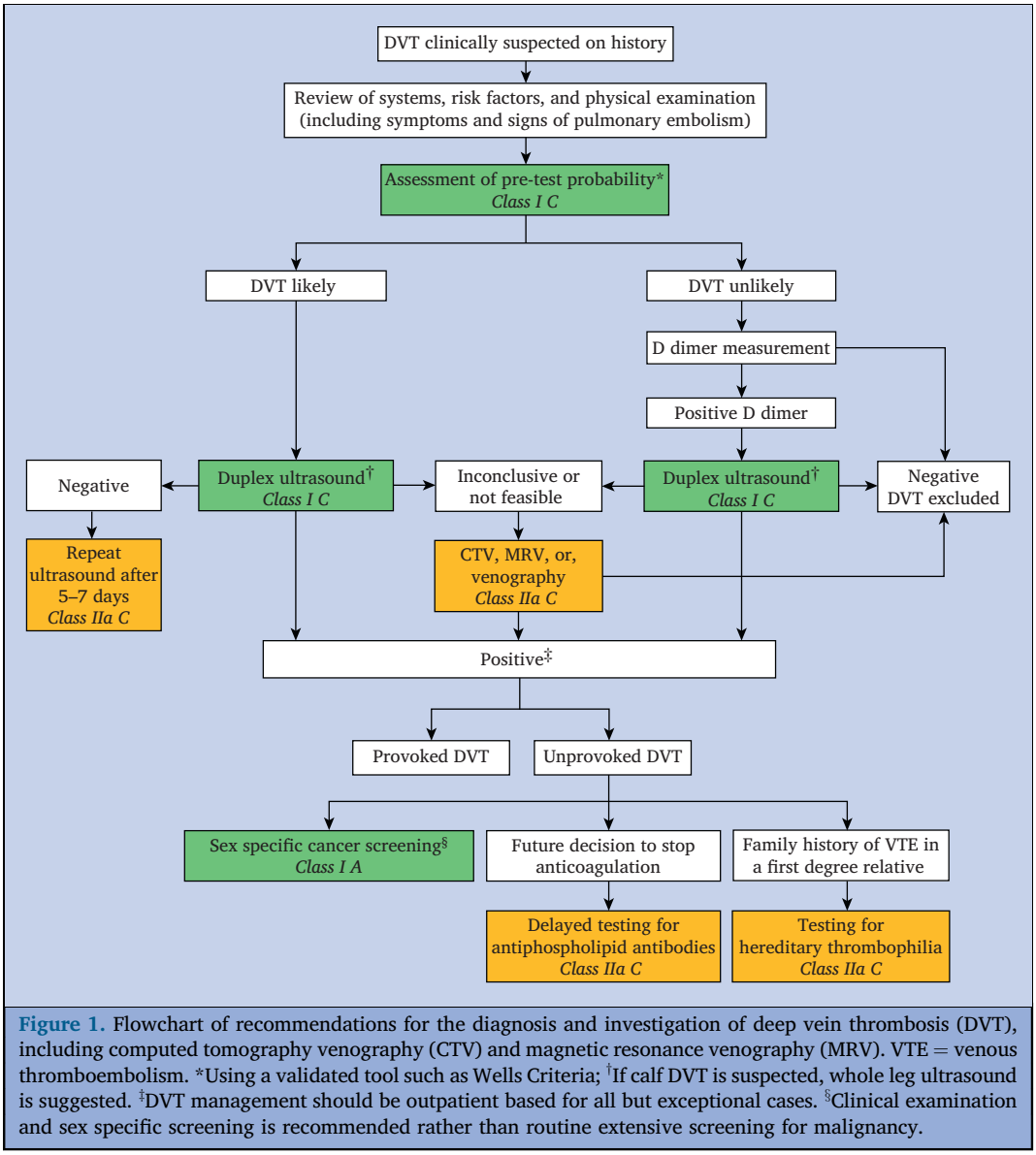


Figure 1. Flowchart of recommendations for the diagnosis and investigation of deep vein thrombosis (DVT), including computed tomography venography (CTV) and magnetic resonance venography (MRV). VTE = venous thromboembolism. *Using a validated tool such as Wells Criteria; †If calf DVT is suspected, whole leg ultrasound is suggested. ‡DVT management should be outpatient based for all but exceptional cases. §Clinical examination and sex specific screening is recommended rather than routine extensive screening for malignancy.

reagents, laboratory instrument, and, importantly, biological factors such as acute phase reaction, monitoring of antifactor Xa activity (target 0.3 — 0.7 IU/mL) can produce more reliable results than APTT monitoring.[84]

2.3.3.2. Low molecular weight heparins. LMWHs are given subcutaneously, with the dose adjusted for patient body weight. LMWHs may be administered once or twice daily according to the specific summary of product characteristics (SPC), which also recommend specific dose adjustments according to renal function. Monitoring is only recommended in special situations; target peak values of antifactor Xa activity four hours after the last injection of 0.6 — 1.0 international units (IU)/mL for twice daily administration (b.d.), and 1.0 — 2.0 IU/mL for once daily (o.d.) administration have been suggested without firm evidence.[86] To assess potential accumulation, measurement of trough levels is more informative.

2.3.3.3. Fondaparinux. Fondaparinux is given subcutaneously at a standard treatment dose of 7.5 mg o.d., while patients weighing $<$ 50 kg receive 5 mg and those weighing $>$ 100 kg receive 10 mg. Because of its low molecular weight, fondaparinux may accumulate in renal insufficiency and should thus not be used in patients with a creatinine clearance (CrCl) $<$ 30 mL/minute.

2.3.3.4. Dabigatran. Dabigatran is administered at a dose of 150 mg b.d., which is started after at least five days of initial parenteral anticoagulation. However, patients aged $\geq$ 80 years, or with concomitant verapamil, should receive 110 mg b.d., while patients aged between 75 and 80 years, those at increased risk of bleeding, or those with a CrCl of 30 — 50 mL/minute may use either dosing regimens, depending on the thromboembolic risk. As dabigatran is primarily excreted by the kidney it is contraindicated in patients with a CrCl $<$ 30 mL/minute and renal function should be monitored.

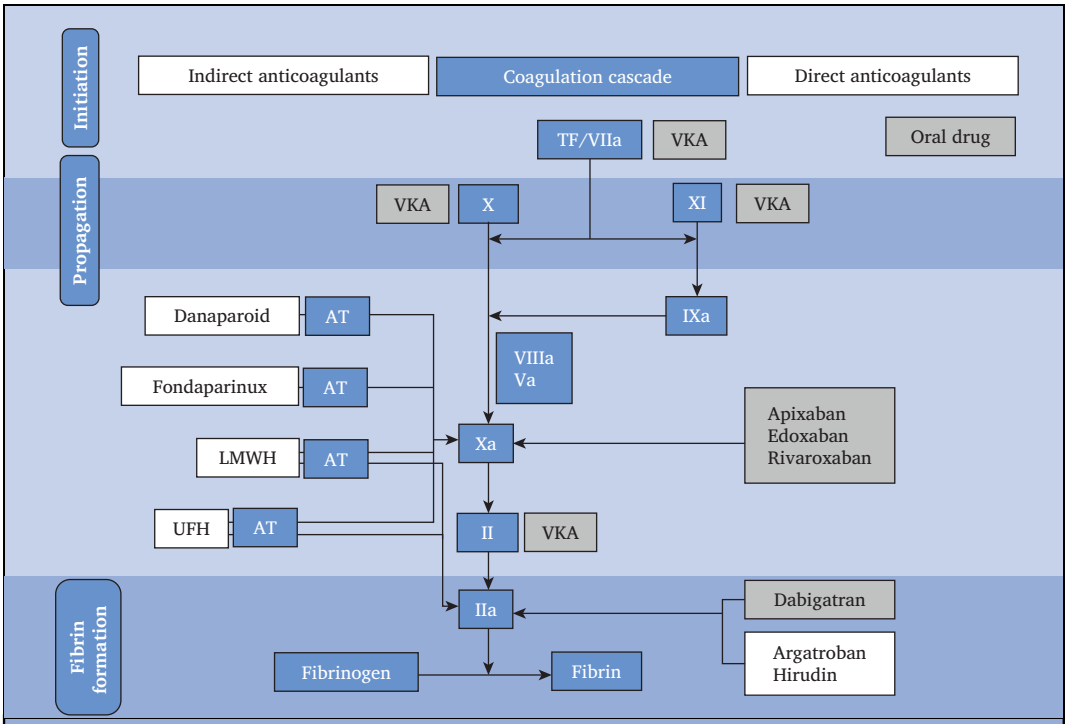


Figure 2. The three phases of the coagulation cascade (initiation, propagation, and fibrin formation) and targets for anticoagulants. Indirect anticoagulants, which require the presence of antithrombin (AT), are shown on the left. Direct anticoagulants, which do not require the presence of antithrombin, are shown on the right. These agents directly inhibit factor Xa or factor IIa (thrombin) and include hirudin, argatroban, and the direct oral anticoagulant dabigatran. Apixaban, edoxaban, and rivaroxaban are direct oral anticoagulants that directly inhibit factor Xa. VKA = vitamin K antagonist; TF = tissue factor; LMWH = low molecular weight heparin; UFH = unfractionated heparin. Modified with permission from Bauersachs, 2008.[83]

Table 6. Recommended initial unfractionated heparin dosing for the treatment of deep vein thrombosis. Reproduced from Smythe, 2016[84]

Administration	Bolus	Maintenance dose
Infusion		
Non-body weight adjusted	5 000 IU	1 250–1 280 IU/h
Body weight adjusted	80 IU/kg	18 IU/kg/h
Subcutaneous		
Fixed dose	333 IU/kg	250 IU/kg every 12 h
Adjusted dose	5 000 IU	17 500 IU every 12 h; APTT adjusted

IU = international units; APTT = activated prothrombin time.

Table 7. Nomogram for dose adjustment of the infusion of unfractionated heparin, in relation to the measured activated partial thromboplastin time (APTT), as an alternative to the ratio of measured APTT/normal value. Target APTT is 46–70 s, corresponding to an APTT/normal value ratio of 1.5–2.5. Modified with permission from Hirsh *et al.*, 2008[82]

APTT	Ratio APTT/ normal value	Dose adjustment
<35 s	<1.2	80 IU/kg bolus, then increase 4 IU/kg/h
35–45 s	1.2–1.5	40 IU/kg bolus, then increase 2 IU/kg/h
46–70 s	1.5–2.5	No change
71–90 s	2.5–3.0	Decrease 2 IU/kg/h
>90 s	>3.0	2 h pause infusion, then decrease 3 IU/kg/h

IU = international units.

2.3.3.5. Edoxaban. Edoxaban, like dabigatran, requires at least five days of parenteral anticoagulation before starting oral dosing at 60 mg o.d., reduced to 30 mg o.d. if CrCl is < 30 – 50 mL/minute or with concomitant potent P-glycoprotein inhibitors, e.g., ciclosporin, dronedarone, erythromycin, or ketoconazole.

2.3.3.6. Apixaban. Apixaban is started without initial parenteral therapy but requires a higher dose (10 mg b.d.) for seven days, followed by the standard treatment dose of 5 mg b.d. In contrast to treatment for atrial fibrillation, no dose adjustment is performed in DVT treatment in the presence of renal insufficiency. However, in patients with a CrCl of 15 – 29 mL/minute, apixaban should be used with caution, and is not recommended with a CrCl < 15 mL/minute. A lower dose of 2.5 mg b.d. is used for extended therapy.

2.3.3.7. Rivaroxaban. Rivaroxaban is started without initial parenteral therapy but requires a higher dose (15 mg b.d.) for three weeks, followed by the standard treatment dose of 20 mg o.d. In contrast to atrial fibrillation, no fixed dose

Table 8. Pharmacological properties of oral anticoagulants. Modified with permission from Bauersachs, 2014.[87] For reversal agents see Table 10

	VKA	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Target	Vitamin K dependent clotting factors (II, VII, IX, X)	Thrombin (IIa)	Factor Xa	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No	No
Dosing	o.d. (INR adjusted)	b.d.	10 mg b.d. for first 7 d followed by 5 mg b.d.	60 mg o.d.	15 mg b.d. for inital three w, followed by 20 mg o.d.
Reduced dosing for extended therapy	NA	NA	2.5 mg b.d. after six mo	NA	10 mg o.d. after six mo
Bioavailability − %	100	≈6	50	60	80–100*
Time to peak − h	1.5	1.5–3.0	1.5–3.5	1–2	2–4
Half life − h	36–42	12–17	12–15	10–14	5–13
Renal elimination − %	Negligible	80	≈ 27	≈50	≈ 35
Plasma protein binding − %	99	35	87	55	95
Drug–drug interactions	Multiple	P-gp inhibitors	CYP3A4 and P-gp inhibitors	P-gp inhibitors	CYP3A4 and P-gp inhibitors
Routine coagulation monitoring	Yes	No	No	No	No

VKA = vitamin K antagonist; INR = international normalised ratio; NA = not applicable; P-gp = P-glycoprotein; CYP = cytochrome P450; o.d. = once daily; b.d. = twice daily

* Bioavailability of rivaroxaban calculated for 10 mg dose.

adjustment is required for patients with a CrCl of 15 − 49 mL/minute and a dose of either 20 or 15 mg o.d. can be selected, respectively, depending on the risk of bleeding or thromboembolism. A rivaroxaban dose of 20 or 15 mg should be taken with food, which improves its bioavailability. A lower dose of 10 mg o.d. is used for extended therapy.

2.3.4. Bleeding and other adverse events

2.3.4.1. Risk assessment. At present, any anticoagulation therapy is associated with an increased risk of bleeding. Therefore, it is important to assess both the general and individualised bleeding risk. Several risk scores have been proposed. For DVT treatment, the American College of Chest Physicians (ACCP) consensus categorisation of bleeding risk is frequently advocated but has not been validated. It considers risk factors such as age, previous bleeding, cancer, renal or liver failure, thrombocytopenia, diabetes, antiplatelet treatment, poor INR control, comorbidities, recent surgery, frequent falls, and alcohol abuse.[80] The problem with this categorisation and other bleeding risk scores is their poor positive predictive value.[88] Nevertheless, clinical consideration of the risk factors should influence the decision on the duration of anticoagulant treatment. The risk of bleeding is frontloaded, with a higher risk during the first three months and gradual reduction in bleeding risk over time.

For patients with acute VTE treated with UFH, the bleeding risk is < 3% in the initial phase.[89] Risk factors for bleeding include a higher heparin dose and age > 70 years. LMWH use is associated with a lower risk of major bleeding than UFH in patients treated for DVT.[89] Impaired renal function and increased age are risk factors for bleeding with LMWH. DOACs have a statistically significantly lower risk of major bleeding compared with LMWH/VKA (RR 0.61, 95% CI 0.45 − 0.83) and a lower risk of intracranial haemorrhage (RR 0.37, 95% CI 0.21 − 0.68), or fatal bleeding (RR 0.36, 95% CI 0.15 − 0.84).[90] Gastrointestinal bleeding may be higher with dabigatran, rivaroxaban, and edoxaban than with VKA therapy.[80,90–92]

2.3.4.2. Management of bleeding in patients on anticoagulation. Warfarin is the drug most strongly associated with drug induced emergency hospitalisations,[93] primarily resulting from gastrointestinal bleeding complications, which require inpatient treatment in > 80% of cases. Around 6% of hospital admissions due to warfarin are because of intracranial haemorrhage. Even though vitamin K is a specific and direct antidote to VKA, it may take up to 24 hours or longer for the INR to normalise.[94–96] Therefore, in cases of severe bleeding that require immediate reversal of VKA, clotting factors should be administered. Three factor prothrombin complex concentrate (PCC) contains factors II, IX, and X; the four factor PCC also contains factor VII. Fresh frozen plasma was found to be inferior to PCC.[97]

The British Committee for Standards in Haematology issued some guideline recommendations concerning the reversal of VKA for clinical scenarios with major bleeding or

a high INR without bleeding.[96] Their recommendations are summarised in Table 9.

2.3.4.2.1. Unfractionated heparin reversal. Protamine sulphate completely reverses the action of UFH, with 1 000 IU (10 mg) of protamine sulphate able to neutralise around 1 000 units of heparin. Dosage varies depending on the duration since the last dose and route of administration of heparin. However, high doses of protamine sulphate may increase the risk of bleeding.[98]

2.3.4.2.2. Low molecular weight heparin reversal. Depending on the specific LMWH, the ratio of anti-Xa to anti-IIa activity varies. Protamine can only neutralise anti-IIa activity, and therefore LMWH is only partially (30% − 40%) neutralised by protamine.[99] Around 0.5 − 1 mg of protamine is given per 1 mg of enoxaparin (depending on whether the last dose was more or less than eight hours previously, respectively).[100] Therefore, 1 mg or 100 IU protamine neutralises the anti-IIa activity of 0.01 mL or 1 mg enoxaparin. For the residual smaller molecules in LMWH with anti-FXa activity and for the very small molecule fondaparinux, no antidote is currently licensed.[101]

2.3.4.2.3. Dabigatran reversal with idarucizumab. Idarucizumab has been developed as a direct antidote to dabigatran. This is a humanised monoclonal antibody fragment, which binds dabigatran with high affinity and specificity, and rapidly reverses its anticoagulant activity. Idarucizumab has been tested in $>$ 500 patients taking dabigatran who had uncontrolled bleeding or patients who were about to undergo an urgent procedure.[102] Median maximum percentage reversal of dabigatran was 100%. Median time to the cessation of bleeding was 2.5 hours and peri-procedural haemostasis was assessed as normal in 93%, mildly abnormal in 5%, and moderately abnormal in 1.5%. There were no serious adverse safety signals.[102]

Idarucizumab has been licensed and is available in many countries as a specific antidote for dabigatran in an IV dose of 2 $\times$ 2.5 g/50 mL, for emergency operations, urgent interventions, and for life threatening or uncontrolled bleeding.

2.3.4.2.4. Factor Xa inhibitor reversal with andexanet alpha. Andexanet alpha is a modified rFXa peptide that has no intrinsic procoagulatory activity but still allows the molecule to bind FXa inhibitors, heparin−antithrombin (AT), and fondaparinux−AT, and thus reduce their anticoagulant activity. Andexanet alpha is given as an IV bolus, followed by a two hour IV infusion. In the ANNEXA-4 study (Prospective Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Have Acute Major Bleeding), 352 patients who had acute major bleeding within 18 hours after the administration of a factor Xa inhibitor were included. Bleeding was predominantly intracranial in 64% or gastrointestinal in 26%. The bolus dose of andexanet alpha was 400 mg, and the infusion dose was 480 mg, for apixaban or rivaroxaban taken $>$ 7 hours before. For patients who had taken enoxaparin, edoxaban, or rivaroxaban $\leq$ 7 hours earlier or at an unknown time, the bolus dose was 800 mg and the infusion dose was 960 mg.[103] After bolus administration, the median antifactor Xa activity decreased by 92% from baseline in patients receiving rivaroxaban or apixaban. These levels remained similar during the two hour infusion. Four hours after the infusion, there was a median decrease from baseline Xa activity of 42% in the patients on rivaroxaban and of 32% in those receiving apixaban. Twelve hours after the andexanet alpha infusion, clinical haemostasis was adjudicated as excellent or good in 82% (95% CI 77 − 87). Within 30 days, death occurred in 14% and a thrombotic event in 10%.

Andexanet alpha is currently available only in the USA and Europe. It is indicated for patients taking rivaroxaban and apixaban, when reversal of anticoagulation is needed owing to life threatening or uncontrolled bleeding. In the low dose regimen (after eight hours or with $\leq$ 5 mg of apixaban or $\leq$ 10 mg rivaroxaban) the initial IV bolus is 400 mg at a target rate of 30 mg/minute followed by IV infusion 4 mg/minute for up to 120 minutes; for the high dose regimen (therapeutic doses and $<$ 8 hours or unknow time interval) 800 mg at a target rate of 30 mg/minute followed 8 mg/min for up to 120 minutes. A PCC would represent a general reversal agent for the factor Xa inhibitors, if andexanet alpha is not available.[104] It should not be administered prophylactically in the case of emergency or urgent procedures, but it is recommended to have PCC available in case of uncontrolled bleeding.

2.3.4.2.5. Practical considerations for reversal of direct oral anticoagulants. As DOACs have a short half life (see

Table 9. Recommendations for the reversal of warfarin, adapted from the Guidelines of the British Committee for Standards in Haematology[96]

All hospitals managing patients on warfarin should stock a licensed four factor PCC
Emergency anticoagulation reversal in patients with major bleeding should be with 25−50 IU/kg four factor PCC and 5 mg IV vitamin K
Recombinant factor VIIa is not recommended for emergency anticoagulation reversal
FFP produces suboptimal anticoagulation reversal and should only be used if PCC is not available
Non-major bleeding anticoagulation reversal should be with 1−3 mg IV vitamin K
Patients with an INR >5.0 but who are not bleeding should have 1−2 doses of warfarin withheld, and their maintenance dose should be reduced. The cause of the elevated INR should be investigated
Patients with an INR >8.0 should receive 1−5 mg of oral vitamin K

PCC = prothrombin complex concentrate; IV = intravenous; FFP = fresh frozen plasma; INR = international normalised ratio.

Table 8), unless the patient has renal impairment, DOACs usually merely need to be discontinued to facilitate elective surgical procedures (see Table 16).

For bleeding, including life threatening bleeding in patients treated with a DOAC, the therapeutic management is summarised in Table 10.[105]

2.3.4.3. Heparin induced thrombocytopenia. HIT is a significant cause of morbidity and death due to life and limb threatening thrombosis. This extremely prothrombotic disorder is caused by an immune reaction against platelet factor 4 (PF4) complexes with heparin or other polyanions, ultimately initiating a vicious cycle with further platelet activation, aggregation, potential arterial and/or venous thrombosis, and thrombocytopenia, which may also lead to bleeding.[106]

Risk factors for HIT include duration and type of heparin exposure, patient population, trauma, and other clinical factors. The incidence of HIT varies from $< 0.1\%$ in obstetric patients, around 0.6% in medical patients receiving LMWH in prophylactic or therapeutic doses (including VTE treatment), 1% — 3% in cardiac surgery patients, and 1% — 5% in post-operative patients receiving UFH.[107] There is a 10 fold higher likelihood of HIT in patients receiving UFH *vs.* LMWH. Fondaparinux does not appear to cause HIT.[108]

The initial suspicion of HIT is based on clinical features, most practically summarised in the 4T test (Table 11),[108] a clinical scoring system for evaluating the clinical probability of HIT.[109] A low score has a negative predictive value of 99.8% (95% CI 97 — 100), and intermediate and high probability scores have positive predictive values of 14% (95% CI 9 — 22) and 64% (95% CI 40 — 82), respectively.[110]

The scores from the 4T test help determine subsequent management, which has been summarised in published algorithms.[111] With an intermediate or high probability of HIT, heparin should be immediately replaced by an alternative anticoagulant (see Chapter 2.3.4.3.1), and a PF4/heparin immunoassay should be obtained. As the sensitivity is high, a negative test result generally rules out HIT. If positive, this should be confirmed with a functional test, e.g., heparin induced platelet activation assay test or serotonin release assay. With a high probability and/or positive tests, diagnostic screening for asymptomatic thrombosis should be conducted. With a low probability 4T test, HIT is reliably excluded.

2.3.4.3.1. Alternative anticoagulants in suspected or confirmed heparin induced thrombocytopenia. Non-heparin anticoagulants that have been used in HIT include argatroban, bivalirudin, desirudin, danaparoid, and fondaparinux. However, only argatroban and danaparoid are currently available and licensed for acute HIT. Argatroban has a short half life (40 — 50 minutes) and can be used in patients with renal insufficiency. It is administered as an IV continuous infusion with monitoring and dose adjustment targeted to an APTT of 1.5 — 3.0 times baseline.[110] Danaparoid has a renal mode of excretion and is initiated with an IV bolus followed by a dose adjusted to an anti-Xa activity of 0.5 — 0.8 units/mL (danaparoid specific).[110]

After discontinuation of heparin and initiation of alternative anticoagulation, the platelet count should recover if the patient truly had HIT. Early overlapping with VKA during this phase could cause hypercoagulabilty owing to the rapid reduction in protein C levels, and INR monitoring may be complex as argatroban also affects the INR. Therefore, after the acute phase of HIT, bridging with fondaparinux to VKA has been suggested.[112,113]

2.3.5. Pathways of care for deep vein thrombosis. The introduction of LMWH led to increasing outpatient

Table 10. Management of bleeding in patients taking direct oral anticoagulants (DOACs). Modified with permission from Steffel *et al.*, 2018[105]

Major bleeding	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non-life threatening	Assess type and dose of DOAC and last intake	
	Local haemostatic measures	
	Fluid replacement	
	Red blood cell substitution, if necessary	
	Platelet substitution (in case of thrombocytopenia or thrombopathy)	
	FFP as plasma expander, if necessary (not as reversal agent)	
	Tranexamic acid can be considered as adjuvant (1 g IV, repeat every 6 h, if necessary)	
	Desmopressin can be considered in special cases	
	Estimate normalisation of plasma levels: Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl < 30 mL/min: > 48 h	Estimate normalisation of plasma levels: 12–24 h
	Maintain diuresis	Maintain diuresis
	Consider idarucizumab (see below)	
Life threatening	All of the above measures	All of the above measures
	Idarucizumab	Andexanet alpha
	Alternatively, PCC 50 U/kg (with additional 25 U/kg if clinically needed)	

FFP = fresh frozen plasma; IV = intravenous; CrCl = creatinine clearance; PCC = prothrombin complex concentrate.

Table 11. The "4Ts" scoring system for heparin induced thrombocytopenia. Modified from Cuker *et al.*, 2012.[109] The 4Ts score is the sum of the values for each of the four categories. Scores of 1–3, 4–5, and 6–8 are considered to correspond to a low, intermediate, and high probability of heparin induced thrombocytopenia, respectively

4Ts	2 points	1 point	0 points
Thrombocytopenia	Platelet drop >50% and platelet nadir >20 000/μL	Platelet drop 30%–50% or platelet nadir 10–19 000/μL	Platelet count drop <30% or platelet nadir <10 000/μL
Timing of platelet count fall	Clear onset days 5–10 or platelet drop <1 day with prior heparin exposure within 30 d	Consistent with days 5–10 fall but not clear (e.g., missing platelet counts) onset after day 10; or drop <1 d (prior heparin exposure 30–100 days ago	<4 d without recent heparin exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction after IV UFH bolus	Progressive or recurrent thrombosis; non-necrotising (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

IV = intravenous; UFH = unfractionated heparin.

treatment of DVT. The safety and efficacy of such an approach was established in randomised studies in the 1990s,[114,115] and confirmed by a Cochrane Review published in 2018.[116] The introduction of DOACs as recommended first line treatment for DVT,[80,117] has further facilitated outpatient treatment, which is now well established as the standard of care for most patients with uncomplicated DVT. Conditions excluded in the original RCTs on home treatment included "massive" or recurrent DVT, PE or a high probability of developing PE, pregnancy, the presence of a contraindication for anticoagulation, comorbidity requiring hospitalisation, living far from a healthcare facility, and the presence of social circumstances not supporting home treatment, such as the possibility of non-compliance, lack of family support, living alone, and difficulty returning if complications develop. Although these conditions only affect a minority of patients in daily practice, they may be potential obstacles for outpatient management.

Recommendation 13

For most patients with deep vein thrombosis, outpatient management is recommended.

Class	Level	References
I	A	Levine *et al.* (1996),[114] Koopman *et al.* (1996),[115] Othieno *et al.* (2018)[116]

2.3.6. Anticoagulation therapy for the treatment of provoked deep vein thrombosis. Provoking factors for DVT can be transient (such as surgery or hospital admission with bed rest [strict or with bathroom privileges] lasting at least three days) or persistent (such as thrombophilia) and may be associated with varying risks of DVT recurrence (see Table 4).[44] Treatment options for cancer associated venous thrombosis (CAVT) are presented in Chapter 4.3. The duration of treatment for lower extremity DVT depends on the balance of bleeding risk due to anticoagulation and the risk of recurrence with and without anticoagulation. One published expert consensus suggested that a risk of VTE recurrence > 5% per year or >15% at five years would justify extended anticoagulant therapy as the benefits outweigh the risks.[118] In view of the reduced bleeding risks of DOACs, these recurrence rates should be lowered to < 3% per year, or even further when prophylactic doses of rivaroxaban or apixaban are to be used. The presence or absence of a recognisable risk factor when diagnosing VTE allows more accurate estimation of the potential risk of recurrence. Risk stratification for extended treatment is discussed in Chapter 2.3.7.4.

2.3.6.1. Risk of recurrence after provoked deep vein thrombosis. The risk of recurrent venous thrombosis after unprovoked and provoked VTE was evaluated in a meta-analysis.[119] The risk of recurrent VTE after provoked DVT (due to a transient risk factor) after stopping anticoagulation was 3.3% per patient year up to 24 months. Specifically, the risk of recurrent VTE was much lower when the provoking factor was surgery (0.7% per patient year) compared with patients with a non-surgical transient provoking factor (such as immobilisation, hormone therapy, long distance travel, fractures, major trauma, pregnancy, or non-surgical illness; 4.2% per patient year). In a more recent study that was a pooled analysis of the EINSTEIN-Extension[120] and EINSTEIN CHOICE[121] RCTs comparing rivaroxaban with aspirin or placebo in patients with VTE, one year VTE recurrence rates were provided in relation to baseline risk factor profiles.[122] In this analysis, index VTE events were classified as unprovoked or provoked by major transient or persistent, or minor transient or persistent risk factors, and rates of recurrence at one year were calculated. After unprovoked VTE, or VTE provoked by minor persistent or transient risk factor, rates of recurrence with placebo were 10.0%, 10.7%, and 7.1%, respectively. Recurrence rates in patients with VTE provoked by minor persistent or minor transient risk factors were not significantly lower than that with unprovoked VTE (hazard ratio [HR] 0.81, 95% CI 0.56 – 1.16). For patients with unprovoked VTE, provoked VTE by a minor persistent risk factor and provoked VTE by a minor transient provoking risk factor, anticoagulation with

rivaroxaban reduced recurrence rates to 2%, 2.4%, and 0.4%, respectively, at 12 months. Therefore, these findings suggest that patients with provoked DVT and minor risk factors may benefit from extended anticoagulation therapy, similarly to patients with unprovoked DVT (see Chapter 2.3.7).

2.3.6.2. Duration of anticoagulation therapy after provoked deep vein thrombosis. The risk of recurrent events after discontinuation of anticoagulation for DVT has been studied extensively. In one patient level analysis including seven trials,[123] nearly 3 000 patients were included with > 4 000 patient years of follow up, with 40% of patients with provoked DVT. Groups were stratified on the basis of initial anticoagulation duration: 1 — 1.5 months, three months, and six months. The study included comparative studies comparing anticoagulation treatment durations between 1 — 1.5 months and 3 months,[124—126] 1 — 1.5 months and six months,[127] and three months *vs.* six months.[126] The risk of recurrence over a period of 24 months after stopping anticoagulation therapy for provoked DVT depends on the different anticoagulation durations. Recurrent thrombosis was more likely in the first six months after stopping anticoagulation in the group treated with 1 — 1.5 months of therapy than in patients treated for ≥ 3 months (HR 2.89, 95% CI 1.25 — 6.69; $p = .013$).[123,124] In addition, risk of recurrence was similar in the first six months after stopping anticoagulation in the group treated with three months of therapy, compared with patients treated for longer, with no differences in all haemorrhages (RR 0.96; 95% CI 0.66 — 1.40) or in major bleeding (RR 0.73, 95% CI 0.24 — 2.27).[123,126] While this strategy may be beneficial for patients with proximal DVT as a result of a major transient risk factor (e.g., surgery), patients with proximal DVT provoked by a persistent risk factor (see Chapter 2.1.2 on risk factors and also Table 4) may benefit from extended anticoagulation. Periodic assessment of the presence and intensity of the provoking risk factor, and bleeding risk is suggested to help inform the decision whether or not to continue anticoagulation. Advice from other specialties may be needed where the provoking factor is a chronic illness (e.g., autoimmune disease).

2.3.6.3. Choice of anticoagulation for the treatment of provoked deep vein thrombosis. Most of the RCTs that have evaluated the efficacy and safety of different anticoagulant medications for DVT have included patients with unprovoked DVT, with a variable proportion of patients with provoked DVT. Therefore, the analysis of this subgroup is challenging.

Traditionally, the treatment of DVT has been dominated by the use of IV UFH or subcutaneous LMWH for the initial acute phase (up to 10 days), followed by a VKA such as acenocoumarol, phenprocoumon, or warfarin, or LMWH for the principal phase of treatment (three months). The role of LMWH in the principal treatment of provoked DVT not related to cancer has not been well defined. One recent Cochrane Review concluded that there are no differences between LMWH and VKA in terms of bleeding complications, recurrent VTE, or death after symptomatic DVT.[128] Included studies evaluated patients with provoked and unprovoked VTE, but differences between them were not studied owing to a lack of explicit data in the original papers.[128] The efficacy and safety of LMWH and VKA may therefore be considered equivalent when treating provoked and unprovoked DVT and, as suggested in the Cochrane Review, for a relatively short period of treatment, LMWH may be a good alternative to VKA in patients with provoked DVT due to the challenges of dose adjustment with VKAs. In this scenario, the preferences of the patient will be very important in order to decide between VKA and LMWH. Cost issues may also influence further decision making.

Table 12. Relative recurrence rates in patients with provoked and unprovoked venous thromboembolism (VTE)

Drug	Trial	Provoked VTE			Unprovoked VTE		
		Provoked VTE	Recurrence in treatment group	Recurrence in control group	Unprovoked VTE	Recurrence in treatment group	Recurrence in control group
Apixaban	AMPLIFY	544 (10.1)	Unknown	Unknown	4 851 (89.9)	Unknown	Unknown
Rivaroxaban*	EINSTEIN	1 311 (38)	18/676 (2.7)	21/635 (3.3); VKA arm	2 148 (62)	18/1 065 (1.7)	30/1 083 (2.8); VKA arm
Edoxaban†	HOKUSAI	2 272 (27.6)	32/1 132 (2.8)	38/1 140 (3.3); warfarin	5 968 (72.4)	98/2 986 (3.3)	108/2 982 (3.6); warfarin
Dabigatran‡	RE-COVER and RE-COVER II	3 290 (64.4)	39/1 660 (2.3)	38/1 630 (2.3); warfarin	1 817 (35.6)	21/893 (2.4)	17/924 (1.8); warfarin

Data are presented as *n* (%). AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep vein Thrombosis as First Line Therapy; VKA = vitamin K antagonist; DVT = deep vein thrombosis; PE = pulmonary embolism.

* Groups defined as "spontaneous DVT/PE" or "secondary DVT/PE" (in the rivaroxaban arm, 19.5% of patients presented a recent surgery or trauma, 15.3% immobilisation, 8.1% oestrogen therapy, 6.8% active cancer, 0.3% puerperium, and 6.2% a known thrombophilic condition; in the standard therapy arm, 19.5% of patients presented a recent surgery or trauma, 15.1% immobilisation, 6.7% oestrogen therapy, 5.2% active cancer, 0.6% puerperium, and 6.8% a known thrombophilic condition).

† Groups defined as "patients with a temporary risk factor" or "patients without a temporary risk factor", including patients with unprovoked VTE, cancer or previous VTE.

‡ Groups defined as "non-idiopathic VTE" or "idiopathic VTE".

The use of DOACs was a major advance in the treatment of DVT as these medications have a similar efficacy to and a better safety profile than VKAs.[129] All these drugs have a similar efficacy in the treatment of acute symptomatic VTE, with a significant reduction in the risk of major bleeding in both provoked and unprovoked DVT. One meta-analysis showed an equivalent effect of DOACs in preventing recurrent symptomatic VTE compared with VKA (RR 0.89, 95% CI 0.75 — 1.05) and a reduction in major bleeding (RR 0.63, 95% CI 0.51 — 0.77). The net clinical benefit favoured DOACs with a RR of 0.79 (95% CI 0.70 — 0.90).[129]

When analysing all pivotal trials, the risk of bleeding has been reported to be consistently lower with DOACs in patients treated for provoked and unprovoked DVT. Even during the principal treatment period of three months, which is the recommended duration of treatment for most patients with provoked DVT, bleeding complications favour DOACs.[120,130–133] In a large RCT evaluating rivaroxaban, in the first three months of treatment, the efficacy outcome (recurrent VTE) was non-inferior compared with treatment with LMWH (initial phase) followed by VKA (principal treatment phase) and the safety outcomes were also similar in terms of first major or clinically relevant non-major bleeding.[120] Apixaban and edoxaban showed a benefit with significantly fewer major or clinically relevant bleeding events in this three month period.[130,131] Dabigatran showed a better risk profile than VKA in terms of any bleeding and a slightly better outcome in terms of major haemorrhages in the first three months.[133] Analysing the risk profiles of these drugs in provoked and unprovoked VTE, apixaban, edoxaban, and dabigatran appear to be the safest options during the first three months of treatment. However, it should be noted that there are no direct drug comparisons between the DOACs.

Regarding the efficacy of DOACs, data comparing results on provoked and unprovoked DVT are shown in Table 12.

A meta-analysis of published data indirectly compared the efficacy and safety of DOAC treatment for three to six months in patients with provoked and unprovoked DVT.[134] This study was based on an indirect network meta-analysis comparison because there are no RCTs that directly compare DOACs. In this study, all DOACs demonstrated comparable results in terms of efficacy, but some differences were detected in terms of risk profile. Apixaban had a lower risk of major or clinically relevant non-major bleeding than other DOACs, and dabigatran was also better than rivaroxaban and edoxaban. These results should be interpreted with caution owing to the suboptimal methodology and the treatment period, as participants in included studies were treated for up to 12 months.

In summary, the natural history of provoked VTE is relatively benign compared with unprovoked VTE, so medications to reduce this already low risk must be as safe as possible while achieving a high level of efficacy to maintain as favourable a risk benefit balance as possible. DOACs seem to be the recommended treatment to achieve this goal owing to an efficacy similar to VKA but a significantly better risk profile. The major trials have significant variations in the proportions of patients with provoked VTE (ranging from 10% to 64%) and direct comparisons between subgroups with provoked VTE are not presented, However, apixaban, edoxaban, and dabigatran seem to be the safest options for the first three months of treatment in pivotal trials.

Recommendation 14

For patients with a provoked proximal deep vein thrombosis with a major transient risk factor, three months of anticoagulation treatment is recommended over a shorter duration.

Class	Level	References
I	A	Boutitie *et al.* (2011),[123] Kearon *et al.* (2004)[124]

Recommendation 15

For patients with a provoked proximal deep vein thrombosis with a major transient risk factor, three months of anticoagulation treatment over six months or longer duration should be considered.

Class	Level	References
IIa	A	Boutitie *et al.* (2011),[123] Pinede *et al.* (2001)[126]

Recommendation 16

For patients with provoked proximal deep vein thrombosis, treatment with a direct oral anticoagulant is recommended over a vitamin K antagonist for the principal treatment phase.

Class	Level	Reference
I	A	Kakkos *et al.* (2014)[129]

Recommendation 17

In selected patients with provoked proximal deep vein thrombosis with a persistent risk factor other than malignancy, anticoagulation beyond three months should be considered after evaluation of thrombotic and bleeding risks, with periodic reassessment.

Class	Level	Reference
IIa	C	Consensus

Recommendation 18

In selected patients with provoked proximal deep vein thrombosis with a minor transient risk factor, anticoagulation beyond three months may be considered, after evaluation of thrombotic and bleeding risks with periodic reassessment.

Class	Level	Reference
IIb	C	Prins *et al.* (2018)[122]

Table 13. Cumulative incidence for recurrent venous thromboembolism (VTE) after stopping anticoagulation in men and women with unprovoked VTE[10]

Follow up after stopping anticoagulation	Cumulative incidence of recurrent venous thromboembolism (95% confidence interval) − %	
	Men	Women
In the first year	11.9 (9.6–14.4)	8.6 (6.8–11.3)
2 y	18.3 (14.4–22.5)	13.6 (10.1–17.5)
5 y	28.6 (22.3–35.0)	21.2 (14.4–28.6)
10 y	41.2 (28.4–55.6)	28.8 (19.8–38.4)

Table 14. Pooled rates of recurrent venous thromboembolism after stopping anticoagulant treatment in patients with unprovoked proximal deep vein thrombosis[123]

Length of treatment − mo	Recurrent episodes of venous thromboembolism within 2 y		
	per 100 patient y	95% CI	Events/ patient y
1 or 1.5	14.2	10.3–19.6	37/261
3	10.2	7.9 –13.3	57/558
6	10.2	7.2–14.4	32/314
12 or 27	8.9	6.0–13.3	24/269

CI = confidence interval.

2.3.7. Anticoagulation therapy for the treatment of unprovoked deep vein thrombosis. DVT is defined as *unprovoked* if the patient does not have an important transient or persistent provoking risk factor for thrombosis. The term *unprovoked* is preferred to *idiopathic*, which implies that there is no reason for the DVT.[44] Details of provoking risk factors are provided in Chapter 2.2.2.2, but a careful clinical history is required as the distinction between provoked and unprovoked DVT is important, as patients with a major transient provoking risk factors have a lower risk of recurrence after discontinuation of oral anticoagulation. Patients with unprovoked DVT may still have underlying comorbidities and conditions that modulate their risk of recurrence, e.g., severe thrombophilia.

2.3.7.1. Risk of recurrence after unprovoked deep vein thrombosis. A recent systematic review and meta-analysis of RCTs and prospective observational studies, which included 7 515 patients with a first unprovoked VTE who completed at least three months of anticoagulation, showed a high long term risk of VTE recurrence at 10 years (Table 13).[10] Recurrent thrombosis was higher in men (41.2%; 95% CI 28.4 — 55.6) than in women (28.8%; 95% CI 19.8 — 38.4). The recurrent VTE mortality rate was 4% (95% CI 2 — 6).

The case fatality rate of recurrent VTE was found to be 2.6% (95% CI 0.86 — 5.0) in another systematic review based on 6 758 patients from 18 studies, and the pooled rate of fatal recurrent VTE was 0.17 (95% CI 0.047 — 0.33) per 100 patient years.[135]

In a meta-analysis, the risk of recurrent VTE after unprovoked VTE two years after stopping the anticoagulation was 7.4% per patient year.[119] One study reported individual patient level data from seven trials and also demonstrated that the risk of recurrent DVT when the initial event was provoked was around half the risk compared with an unprovoked VTE (HR 0.55, 95% CI 0.41 — 0.74; $p < .001$), regardless of duration of the anticoagulation treatment or the location of VTE.[123] The published data clearly indicate that there is a high and continuing risk of recurrence after unprovoked DVT (Table 13). As discussed in Chapter 2.3.6.3 and demonstrated in Table 12, in patients with unprovoked DVT, DOACs are the preferred anticoagulants during the principal treatment phase.

2.3.7.2. Duration of anticoagulation therapy after unprovoked deep vein thrombosis. Patients with unprovoked DVT require the same anticoagulation up to three months as patients with provoked DVT (see Chapter 2.3.6.2), but in view of the higher risk of recurrence, many studies have evaluated the potential role of extended anticoagulation beyond three months.

A study comparing three months of VKA to 12 months of VKA in patients with unprovoked DVT demonstrated that there was a similar rate of recurrent events whenever anticoagulation was discontinued, named the “catch up phenomenon”.[136] The results of an individual patient meta-analysis comparing rates of recurrent VTE after discontinuation of anticoagulation in patients after unprovoked DVT are summarised in Table 14.[123] Results were stratified into groups, depending on the duration of initial anticoagulation, and the conclusion was that the risk of recurrence after unprovoked proximal DVT remains high after stopping anticoagulation, irrespective of the duration of initial anticoagulation therapy (Tables 13 and 14), supporting extended anticoagulation with no scheduled stop date.

Recommendation 19

For patients with unprovoked proximal deep vein thrombosis, treatment with a direct oral anticoagulant is recommended over treatment with low molecular weight heparin followed by a vitamin K antagonist for the principal treatment phase.

Class	Level	Reference
I	A	Kakkos *et al.* (2014)[129]

2.3.7.3. Extended anticoagulation after unprovoked deep vein thrombosis. 2.3.7.3.1. Vitamin K antagonists and aspirin for extended anticoagulation. Several trials have

compared placebo with different antithrombotic regimens, including VKA, DOACs, or aspirin for extended treatment after unprovoked DVT. One study compared three with 27 months of VKA treatment.[137] Two studies examined aspirin 100 mg for extended treatment of 37 and 24 months after unprovoked VTE.[138,139] Three studies have evaluated extended therapy (beyond three months) on recurrent VTE using rivaroxaban,[120] apixaban,[140] or dabigatran.[141]

These studies were analysed in a systematic review and meta-analysis, which included a total of 6 778 patients.[142] The duration of extended anticoagulation ranged from six to 37 months (average 19.4 ± 11.7 months). In the placebo group recurrent VTE events were observed in 9.7% *vs.* 2.8% in the active treatment group (odds ratio [OR] 0.21, 95% CI 0.11 — 0.42; $p < .001$), with the annual event rate being 6.0% *vs.* 1.7%.[142]

The smallest RR reduction (38%) in recurrent events was observed with aspirin (OR 0.62, 95% CI 0.44 — 0.87), while the reduction was 91% (OR 0.09, 95% CI 0.03 — 0.25) for the VKA studies, and 84% (OR 0.16, 95% CI 0.11 — 0.24) for the three DOAC studies.

Another meta-analysis on the use of DOACs for extended anticoagulation showed similar results and, additionally, demonstrated reduced all cause mortality with DOACs *vs.* placebo.[129]

2.3.7.3.2. Reduced dose of direct oral anticoagulants for extended anticoagulation. Within a DOAC study one treatment arm also included a reduced, prophylactic dose of a DOAC.[140] In this randomised, double blind study, two doses of apixaban (2.5 mg and 5 mg, twice daily) were compared with placebo administered for 12 months. Recurrent symptomatic VTE or death from VTE occurred in 8.8% of the patients receiving placebo, compared with 1.7% with 2.5 mg of apixaban (7.2% difference, 95% CI 5.0 — 9.3) and 1.7% with 5 mg of apixaban (7.0% difference, 95% CI 4.9 — 9.1). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5 mg apixaban group, and 0.1% in the 5 mg apixaban group. The rates of clinically relevant non-major bleeding were 2.3% in the placebo group, 3.0% in the 2.5 mg apixaban group, and 4.2% in the 5 mg apixaban group.[140] This study showed that in patients with equipoise for continuation of anticoagulation, a reduced dose of apixaban was effective and safe for extended treatment.

These findings were mirrored in a similar study (EINSTEIN CHOICE) examining both a therapeutic and prophylactic dose of rivaroxaban (20 mg once daily and 10 mg once daily, respectively) for extended treatment.[121] Again, patients with equipoise concerning further anticoagulation were included after 6 — 12 months of initial anticoagulation and aspirin 100 mg once daily was the comparator rather than placebo. The study drugs were administered for up to 12 months. Symptomatic recurrent fatal or non-fatal VTE occurred in 1.5% of the patients receiving 20 mg of rivaroxaban and in 1.2% receiving 10 mg of rivaroxaban, compared with 4.4% receiving aspirin (HR for 20 mg rivaroxaban *vs.* aspirin 0.34; 95% CI 0.20 — 0.59; HR for 10 mg rivaroxaban *vs.* aspirin 0.26, 95% CI 0.14 — 0.47 [$p < .001$ for both comparisons]). Rates of major bleeding were 0.5% in the group receiving 20 mg rivaroxaban, 0.4% in the group receiving 10 mg rivaroxaban, and 0.3% in the aspirin group; the rates of clinically relevant non-major bleeding were 2.7%, 2.0%, and 1.8%, respectively. The study concluded that in patients with equipoise for continued anticoagulation after VTE, the risk of a recurrent VTE event was significantly lowered by a treatment dose (20 mg) or a prophylactic dose (10 mg) of rivaroxaban compared with aspirin, without a significant increase in bleeding rates.

A meta-analysis based on 5 847 patients for efficacy and 5 842 patients for safety outcomes confirmed that reduced dose DOACs were as effective as full dose treatment in preventing recurrent VTE at one year (RR 1.12, 95% CI 0.67 — 1.87), and more effective than aspirin or placebo (RR 0.26, 95% CI 0.14 — 0.46).[143] Rates of major or clinically relevant non-major bleeding events were similar between patients receiving reduced dose DOACs and those receiving aspirin or placebo (RR 1.19, 95% CI 0.81 — 1.77). There was a trend towards fewer bleeding events when reduced dose and full dose DOACs were compared (RR 0.74, 95% CI 0.52 — 1.05). For patients in whom there is clinical equipoise for continued anticoagulation these findings indicate that using a reduced dose of a DOAC offers a new option for extended anticoagulation with protection against recurrent VTE, yet a reduced bleeding risk. However, it is likely that patients at high risk of recurrence or bleeding were not included in most of these studies and therefore the GWC is suggesting that patients at very high risk of recurrence, such as those with active cancer or severe thrombophilia (Table 15), should not be offered a reduced DOAC dose. Treatment options for CAVT and DVT in patients with thrombophilia are presented, in detail, in Chapters 4.3 and 4.4, respectively.

2.3.7.3.3. Direct oral anticoagulants *vs.* vitamin K antagonists for extended anticoagulation. In one study, patients deemed to be at high risk of recurrent VTE received extended therapy with VKA or with the DOAC dabigatran.[141] Recurrent VTE events occurred in 26 of 1 430 (1.8%) patients in the dabigatran group and in 18 of 1 426 (1.3%) patients in the warfarin group (HR 1.44, 95% CI 0.78 — 2.64 [$p = .01$ for non-inferiority with a HR of 2.85 as the non-inferiority margin]). Major bleeding occurred in 13 patients in the dabigatran group (0.9%) and 25 patients in the warfarin group (1.8%) (HR 0.52, 95% CI 0.27 — 1.02). Major or clinically relevant bleeding was less frequent with dabigatran (HR 0.54, 95% CI 0.41 — 0.71). Therefore, in patients considered at high risk of recurrence, dabigatran was effective for extended treatment after VTE and carried a lower risk of bleeding than warfarin.

2.3.7.4. Risk stratification for extended treatment after unprovoked deep vein thrombosis. The risk of recurrence after unprovoked VTE may vary from < 20% to > 40% after 10 years (Table 13), implying that a policy of indefinite anticoagulation for all patients, would expose all patients to the bleeding risk of anticoagulation for 10 years, when up to 80% would not have suffered from recurrence within 10 years without anticoagulation. This dilemma should drive treating clinicians to select anticoagulation medications with

Table 15. Suggested duration of anticoagulation in relation to stratification of the risk of venous thromboembolism recurrence. High risk: anticoagulation should not be stopped unless there is a strong contraindication. Intermediate risk: further factors should be considered, including specific risk factors for thrombosis, bleeding risk and patient preference. Low risk: anticoagulation can be stopped after three or a maximum of six months

Risk of recurrence	Duration of anticoagulation	Underlying risk factors
High	Indefinite anticoagulation, unless there is a high risk of bleeding	Active cancer, persistent major risk factor, e.g., chronic rheumatic disorder, severe thrombophilia*
Medium	Equipoise: consider extended anticoagulation, preferably with lowest bleeding risk	Recurrent venous thromboembolism
		Unprovoked event
		Minor, soft, and transient risk factor, e.g., travel
		Male sex, obesity, heart failure, chronic obstructive pulmonary disease/significant comorbidities
		Pulmonary embolism (more likely to continue) *vs.* deep vein thrombosis
Low	Stop anticoagulation (3 mo)	Clear and major transient risk factor (e.g., surgery, leg injury with a reduced mobility, confined to bed in hospital)
		Combined oral contraceptives or hormonal therapy – now discontinued; pregnancy†, puerperium
		Calf vein thrombosis

* Severe thrombophilia = antithrombin deficiency, antiphospholipid syndrome, homozygous FV Leiden or prothrombin 20210 mutation, combination thrombophilia. Definitions modified from Kearon *et al.*, 2016,[44] and Prins *et al.*, 2018.[122]
† Treatment should continue for three months and at least until the end of puerperium (6 weeks post partum).

the lowest bleeding risk and to try to predict the individual risk of recurrence. A recent review summarises details of the current prediction models in a tabular format.[144]

2.3.7.4.1. Prediction models for recurrent venous thromboembolism. Several models to predict the risk of recurrent VTE after a first unprovoked VTE have been developed, and a systematic review was performed to assess their accuracy.[145]

- The HERDOO2 model,[146] a prognostic model to guide duration of anticoagulation, recommended that all men receive indefinite anticoagulation, and female patients with fewer than two predictors of recurrence (post-thrombotic signs, D dimer level $\geq$ 250 pg/L while on anticoagulation, body mass index (BMI) $\geq$ 30 kg/m^2, or age $>$ 65 years) could, potentially, safely discontinue anticoagulant therapy five to seven months after unprovoked VTE. Of note, the HERDOO2 model includes oestrogen associated VTE as a component of unprovoked VTE.
- The Vienna prediction model[147] used a Cox proportional hazards model, including sex, site of index event, and D dimer as predictors. An individualised cumulative recurrence rate after one and five years can be estimated using an internet calculator (http://www.meduniwien.ac.at/user/georg.heinze/zipfile/ViennaPredictionModel.html) or a nomogram. The Vienna prediction model does not include oestrogen associated VTE as a component of unprovoked VTE.
- The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire score[148] also used a Cox proportional hazards model and included abnormal D dimer levels, age $<$ 50 years, male sex, and hormone use, and can be used to calculate an individualised cumulative recurrence risk at one, two, and five years.

The definition of unprovoked VTE was not uniform for the three prediction models, in particular with respect to pregnancy, immobility, and hormone intake. A systematic review assessed study quality based on the PROBAST assessment tool for prognostic model studies.[145] According to predefined criteria of quality assessment the Vienna and DASH models were developed with generally strong methodology, but the HERD002 model had many methodological concerns. All models were considered at least at moderate risk of bias, primarily due to the need for further external validation, which had only been performed for the Vienna score[149] and the HERDOO2 model.[150]

2.3.7.5. Bleeding risk of extended anticoagulation. The risk of extending anticoagulation to prevent VTE recurrence has to be balanced against the bleeding risk. A systematic review and meta-analysis evaluated seven studies with 6 778 patients receiving coumadin (warfarin), DOACs and aspirin for extended anticoagulation, mostly for unprovoked VTE.[142] The duration of follow up varied from six to 37 months. Major bleeding occurred in 12 patients in the control group (0.4%) and 25 of 3 815 (0.7%) patients in the active treatment group (OR 1.64, 95% CI 0.69 – 3.90; p = .30).

A meta-analysis of two trials examining a reduced DOAC dose for extended anticoagulation in 5 847 patients[143] showed that rates of major or clinically relevant non-major bleeding events were similar between patients receiving reduced dose DOACs and those receiving aspirin or placebo (RR 1.19, 95% CI 0.81 – 1.77). There was a trend towards fewer bleeding events with reduced dose DOAC *vs.* full dose DOAC (RR 0.74, 95% CI 0.52 – 1.05),

Table 16. Timing of last direct oral anticoagulant (DOAC) intake before start of an elective intervention. Modified with permission from Steffel *et al.*, 2018[105]

Creatinine clearance (mL/min)	Timing for last DOAC intake* − no bridging with LMWH/UFH†			
	Dabigatran		Apixaban/edoxaban/rivaroxaban	
	Low bleeding risk‡	High bleeding risk‡	Low bleeding risk‡	High bleeding risk‡
≥80	≥24 h	≥48 h	≥24 h	≥48 h
50–79	≥36 h	≥72 h	≥24 h	≥48 h
30–49	≥48 h	≥96 h	≥24 h	≥48 h
15–29	Not indicated	Not indicated	≥36 h	≥48 h
<15	No official indication for use			

LMWH = low molecular weight heparin; UFH = unfractionated heparin.
* If no important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e., 12 h or 24 h after last intake).
† Resume full dose of DOAC ≥ 24 h after low bleeding risk intervention and 48 (~72) h after high bleeding risk interventions. Patients undergoing a planned intervention should receive a written note indicating the anticipated date and time of their intervention, and the date and time of the last intake of their DOAC (and any other medication).
‡ Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk: with a high frequency of bleeding and/or important clinical impact.

while the reduced dose was as effective as the full dose treatment in preventing recurrent VTE at one year (RR 1.12, 95% CI 0.67 − 1.87), and more effective than aspirin or placebo (RR 0.26, 95% CI 0.14 − 0.46). The safety of the reduced dose of apixaban and rivaroxaban in conjunction with the lack of validated risk stratification tools for bleeding has downplayed the notion that patients with more than two risk factors should not receive anticoagulation for extended treatment. Further refinement of the decision making process using clinical assessment of the severity/bleeding potential of risk factors and specific relative contraindications for DOACs (e.g., higher risk of gastrointestinal bleeding for edoxaban, rivaroxaban, and dabigatran, and higher risk of dyspepsia with dabigatran) is recommended.

2.3.7.6. Risk stratification for duration of anticoagulation. It should be noted that these prediction models focused on unprovoked VTE. However, there is increasing evidence that patients with provoked VTE may also have a substantial risk of recurrence, particularly those with weak transient and/or persistent risk factors.[44] This was assessed in a pooled analysis[122] of the EINSTEIN-Extension[120] and EINSTEIN CHOICE studies,[121] as described in detail in Chapter 2.3.6.1. Recurrence rates in patients with VTE provoked by minor persistent or minor transient risk factors were not significantly lower than those with unprovoked VTE, while anticoagulation with rivaroxaban in patients with unprovoked VTE, or provoked by a minor persistent or transient provoking risk factor, reduced recurrence rates to 2%, 2.4%, and 0.4%, respectively, at 12 months. Therefore, these findings suggest that, in addition to patients with unprovoked DVT, patients with provoked DVT and minor risk factors may also benefit from extended anticoagulation therapy.

The risk of recurrence after provoked and unprovoked DVT ranges from a very low risk of recurrence (e.g., provoked by a major transient risk factor) to a very high risk of recurrence (e.g., patients with cancer or severe thrombophilia such as APS) (Table 15). Decisions regarding extended anticoagulation are mostly straightforward at the extremes of this spectrum. As these two patient groups (low risk of recurrence with major transient provoking factor or high risk of recurrence with major persisting risk factors) represent more than two thirds of patients with DVT, the duration of anticoagulation can easily be determined for the majority of patients with DVT.

For the intermediate group, careful evaluation and balancing of the individual risks of recurrence and bleeding and patient preference is necessary. If there is a decision to extend anticoagulation, low dose DOACs should be considered (Table 15).

In summary, there is strong evidence that the majority of patients with unprovoked DVT may benefit from extended anticoagulation, which is much safer in modern practice with the use of DOACs than in the past. The reduced dose of rivaroxaban and apixaban is also an option for most patients requiring extended treatment, with further reductions of bleeding without a compromise in their efficacy. The biological behaviour of provoked DVT with persistent or transient minor risk factors is close to unprovoked DVT, so a strategy for extended anticoagulation similar to unprovoked DVT should be discussed with the patient.

2.3.8. Bridging therapy before and after invasive procedures. Inevitably, patients treated by anticoagulation for DVT will require invasive interventions and when considering whether or when to stop anticoagulation, careful consideration should be given to the balance between bleeding and thrombotic risks, taking into account the time since the most recent DVT event. For some interventions where the bleeding risk is low, it may be feasible to proceed with the procedure without stopping anticoagulation. The timing of the last dose before the invasive procedure will depend on the medication. The most unpredictable agents are VKAs, where several days of omission may be required for the INR to drop to normal (non-anticoagulated) levels owing to the long half life. Omission of LMWHs can be 24 hours prior to the invasive procedure, whereas DOACs should be stopped between 24 and 72 hours before the intervention,

depending on the specific medication, renal function, and bleeding risk of the procedure.[105] Suggested time intervals for stopping DOACs before an elective procedure are summarised in Table 16. In the event of major bleeding or if an emergency invasive procedure is needed, advice on reversal of anticoagulation is presented in Chapter 2.3.4.2.

Traditionally, patients stopping anticoagulation (particularly VKAs) prior to an invasive procedure would require hospital admission for IV infusion of UFH. This has the specific advantage of having a short half life, allowing maximum anticoagulation right up to the time of the invasive procedure. However, this would require frequent blood tests to evaluate the APTT. As DOACs can often be stopped as little as 24 hours prior to the invasive procedure, usually no bridging anticoagulation is needed.[151] For patients on VKAs, bridging therapy with weight adjusted doses of LMWH may offer a practical solution to maintaining therapeutic anticoagulation, while avoiding hospital admission. This may be suggested for the initial three month period of DVT treatment, or for patients with cancer, owing to the high risk of VTE recurrence.[152] Bridging is not recommended after three months because of the higher risk of bleeding.[153] However, in the presence of co-existing specific high risk indications (such as the presence of some prosthetic heart valves), an IV UFH infusion may still be considered the optimal bridging option.

Recommendation 20

For patients with unprovoked deep vein thrombosis, re-assessment of bleeding risk is recommended before continuing anticoagulation beyond three months.

Class	Level	References
I	C	Consensus

Recommendation 21

For patients with unprovoked proximal deep vein thrombosis who are at low or moderate bleeding risk, extended anticoagulation beyond three months, with periodic re-evaluation of bleeding risk, is recommended.

Class	Level	References
I	A	Kakkos *et al.* (2014),[129] Agnelli *et al.* (2013),[140] Weitz *et al.* (2017)[154]

Recommendation 22

For patients with unprovoked proximal deep vein thrombosis requiring extended anticoagulation beyond three months, treatment with direct oral anticoagulants should be considered over vitamin K antagonists.

Class	Level	References
IIa	B	Kakkos *et al.* (2014),[129] Schulman *et al.* (2013)[141]

Recommendation 23

For patients with unprovoked proximal deep vein thrombosis requiring extended anticoagulation beyond six months but not deemed to be at very high risk of recurrence, use of a reduced dose of the direct oral anticoagulants apixaban (2.5 mg twice a day) or rivaroxaban (10 mg once a day) should be considered.

Class	Level	References
IIa	B	Agnelli *et al.* (2013),[140] Weitz *et al.* (2017)[154]

Recommendation 24

For patients with unprovoked deep vein thrombosis, aspirin is not recommended for extended antithrombotic therapy.

Class	Level	References
III	A	Becattini *et al.* (2012),[138] Brighton *et al.* (2012)[139]

2.4. Recurrent deep vein thrombosis

Accurate documentation of the full extent of the primary DVT is imperative, including at the end of anticoagulation therapy if possible, to establish a new baseline. This is likely to be useful in the diagnosis of recurrent (second or subsequent) DVT in the future should recurrent symptoms arise.[155,156] However, as recent WLUS and imaging for PE may not be readily available, diagnosis of a new event may be difficult.[31]

2.4.1. Strategies to reduce the risk of recurrence. As described in Chapters 2.3.6.1 and 2.3.7.1, the likelihoood of recurrent DVT after discontinuation of anticoagulation is high, particularly in patients with unprovoked DVT (Tables 13 and 14). For patients with provoked DVT, the overall recurrence rate after stopping anticoagulation is approximately half the rate for unprovoked DVT,[157] but may be as high as the population with unprovoked DVT for patients with minor risk factors, and much lower in patients with major, transient provoking factors.[122] Consequently, several strategies and clinical trials have been tested in an attempt to reduce the risk.

2.4.1.1. Unfractionated heparin, low molecular weight heparins, vitamin K antagonists, and direct oral anticoagulants. Detailed descriptions of the evidence for anticoagulation to reduce the risk of recurrent VTE is presented in Chapters 2.3.6 and 2.3.7. The wide range of anticoagulants now available allows individualised management of patients with DVT.

2.4.1.2. Aspirin. Prior to the DOACs, aspirin was widely investigated for the prevention of recurrent VTE. In a pooled analysis of two large RCTs, the DVT recurrence rate was 13.8% in the aspirin groups and 19.1% in the placebo group (HR 0.68, 95% CI 0.51 — 0.90; $p = .007$).[138,139]

Despite the benefit for aspirin over placebo, the superior risk reduction associated with DOACs means that aspirin is not recommended for extended therapy.

2.4.1.3. Sulodexide. Sulodexide is a purified mixture of two glycosaminoglycans (LMWH 80% and dermatan sulphate 20%) that has been used for the prevention of DVT. In a multicentre, double blind study including 615 patients with first ever unprovoked VTE who had completed 3 — 12 months of oral anticoagulant treatment, recurrent VTE rate was reduced at two years in patients randomised to sulodexide and elastic stockings, compared with placebo and stockings (15/307 *vs.* 30/308; HR 0.49, 95% CI 0.27 — 0.92, $p = .02$).[158] No major bleeding episodes were seen in this study. The investigators concluded that in patients with unprovoked VTE, sulodexide reduces the risk of VTE recurrence after anticoagulation is stopped, without causing any bleeding.

2.4.2. Management of anticoagulation treatment failures. Although VKA, LMWH, and DOACS are all highly effective, no medication is associated with 100% efficacy while on treatment. In the event of suspected treatment failure, treating clinical teams should first verify whether a new VTE event has occurred, or whether symptoms are attributable to the index event, or another cause. If there is convincing evidence of recurrence despite anticoagulation, compliance with medication should be carefully verified, using relevant laboratory assays, if necessary. Anticoagulation dosing should be re-assessed, taking into account renal function and patient body weight.

For true treatment failures, i.e., recurrence despite verified anticoagulation therapy, changing the type of anticoagulation (e.g., switching to LMWH if an oral anticoagulant is used), escalating the dose of LMWH or DOAC (if a prophylactic dose is used), switching to VKAs with a higher INR target (e.g., 2.5 — 3.5 instead of 2.0 — 3.0) or adding an antiplatelet agent are recognised strategies, albeit supported by a low level of evidence.[159—161] The possibility of underlying thrombophilia and cancer should also be reconsidered. Bleeding risk stratification (see Chapter 2.3.4.1) should be re-evaluated prior to amending the anticoagulation strategy.

2.4.3. Management of recurrent deep vein thrombosis. Literature is scarce on the natural history and optimal management of recurrent DVT, a condition traditionally thought to be associated with increased recurrent VTE rates requiring indefinite anticoagulation and increased PTS rates. Patients with a provoked recurrent DVT may well be managed with a three month course of anticoagulation. However, patients with unprovoked recurrent DVT may require a much longer or indefinite course of anticoagulation, as shown by the Duration of Anticoagulation (DURAC) trial,[162] where 227 patients with a second (recurrent) episode of VTE were randomly assigned to six months or indefinite anticoagulation. After four years of follow up, a third episode of VTE (second recurrence) was observed in 20.7% in the group assigned to six months of therapy and 2.6% in the group assigned to continuing therapy. The RR of a second recurrence in the group assigned to six months therapy, compared with the group assigned to indefinite duration therapy, was 8.0 (95% CI 2.5 — 25.9). There was no difference in mortality between the two groups, although there was a trend toward a higher risk of major haemorrhage in the group in whom anticoagulation was continued indefinitely.

Recommendation 25

For patients with deep vein thrombosis, repeat whole leg ultrasound may be considered at the end of anticoagulant treatment to determine the new baseline anatomic status.

Class	Level	References
IIb	C	Meissner (2001),[155] Ascher et al. (2004)[156]

Recommendation 26

For patients with a second or subsequent unprovoked deep venous thrombosis, extended anticoagulation therapy beyond three months is recommended.

Class	Level	References
I	B	Schulman *et al.* (1997)[162]

Recommendation 27

For patients with recurrent deep vein thrombosis occurring while compliant with treatment, switching the type of anticoagulation, increasing the dose of low molecular weight heparin or direct oral anticoagulant to therapeutic dose, or switching to vitamin K antagonists with a higher international normalised ratio target should be considered.

Class	Level	References
IIa	C	Kyrle (2016),[159] Schulman, (2017),[160] Piran & Schulman (2018)[161]

2.5. Monitoring and surveillance after deep vein thrombosis

2.5.1. Residual vein obstruction and deep vein thrombosis recurrence. In the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study, ultrasound was used to determine the presence of residual obstruction. The term residual vein thrombosis is used in the original publication, but residual venous obstruction (RVO) is the preferred terminology in this document. Residual obstruction was considered present if there was non-compressibility of 40% of the vein diameter.[163] Patients with a first episode of DVT, treated by anticoagulation for three months, were managed according to the presence of RVO. Those with RVO were randomised to either stop or continue anticoagulation for nine additional months, whereas for those without RVO, anticoagulation therapy was stopped. Outcomes were recurrent VTE and/or major bleeding. Dicontinuation of oral anticoagulation therapy was associated with a non-significant trend for a higher risk of RVO than its continuation (15.2 per 100 person years *vs.* 10.1 per 100 person years; HR 1.58, 95% CI 0.85 2.93, $p = .15$). Of the 78 (30.2%) patients without RVO, only one (1.3%; 0.63 per 100 person years) had

a recurrence. The adjusted HR for patients with RVO *vs.* those without was 24.9 (95% CI 3.4 — 183.6; $p = .002$). One major bleeding event (1.1%; 0.53 per 100 person years) occurred in patients who stopped and two occurred (2.3%; 1.1% person years) in those who continued oral anticoagulation. It was concluded that absence of RVO identified a group of patients at very low risk of recurrent thrombosis who could safely stop anticoagulation.

The extended DACUS study was a prospective study to assess the optimal duration of VKA therapy in patients with a first unprovoked DVT evaluated for the presence of an RVO three months after VKA administration;[164] those without RVO suspended VKA, while those with RVO continued oral anticoagulation for up to two years. After VKA therapy was stopped, the rates of recurrent proximal DVT were 1.4% and 10.4% in the non-RVO and RVO groups, respectively (RR 7.4, 95% CI 4.9 — 9.9). These results indicate that in patients with persistent RVO, treatment extended to two years substantially reduces, but does not eliminate, the risk of recurrent thrombosis.

A systematic review evaluated the predictive value of RVO on recurrent VTE in 14 studies (including five RCTs). The authors concluded that RVO was associated with a modest increase in recurrent VTE risk, and there did not seem to be any predictive value for patients with unprovoked DVT, after discontinuation of anticoagulation.[165]

2.5.2. D dimer surveillance. D dimer testing one month after the discontinuation of anticoagulation in patients with a first unprovoked proximal DVT or PE who had received a VKA for at least three months was performed in one study.[166] Patients with a normal D dimer level did not resume anticoagulation, whereas those with an abnormal D dimer level were randomly assigned either to resume or to discontinue treatment. The study outcome was the composite of recurrent VTE and major bleeding during an average follow up of 1.4 years. The D dimer assay was abnormal in 223 of 608 patients (36.7%). A total of 18 events (all VTEs) occurred among the 120 patients who stopped anticoagulation (15.0%), compared with three events (two VTEs and one major bleeding) among the 103 patients who resumed anticoagulation (2.9%), for an adjusted HR of 4.26 (95% CI 1.23 — 14.6; $p = .02$). VTE recurred in 24 of 385 (6.2%) patients with a normal D dimer level. Among patients who stopped anticoagulation, the adjusted HR for recurrent VTE among those with an abnormal D dimer level, compared with those with a normal D dimer level, was 2.27 (95% CI 1.15 — 4.46; $p = .02$). The authors concluded that patients with an abnormal D dimer level one month after the discontinuation of anticoagulation have a significantly higher incidence of recurrent VTE, which is reduced by extending anticoagulation.

2.5.3. Surveillance combining D dimer and ultrasound. In a study of 620 consecutive outpatients with a first proximal DVT, who had completed at least three months of anticoagulation (unprovoked in 483 and associated with minor risk factors in 137), the investigators performed serial D dimer testing, and assessed the presence of RVO on ultrasound defined as incompressibility of at least 4 mm.[167] For patients without RVO and with negative D dimer ($n = 517$), anticoagulation was stopped and D dimer was repeated after one and three months. Anticoagulation was resumed in 63 of the 72 patients in whom D dimer reverted to positivity. During a mean follow up of three years, recurrent VTE developed in 40 of the 517 patients (7.7%) without RVO and with negative D dimer, leading to an annual rate of 3.6% (95% CI 2.6 — 4.9), which was 4.1% (95% CI 2.9 — 5.7) in individuals with unprovoked DVT, and 2.2% (95% CI 1.1 — 4.5) in those with DVT associated with minor risk factors. Males with unprovoked DVT had an even higher recurrence rate during follow up. Major bleeding complications occurred in eight patients while on anticoagulation, leading to an annual rate of 1.2% (95% CI 0.6 — 2.4). It was concluded that discontinuing anticoagulation in patients with a first episode of proximal DVT based on the assessment of RVO and serial D dimer led to an overall annual rate of recurrent VTE lower than 5.0%, which is the rate deemed acceptable by the Subcommittee on Control of Anticoagulation of the International Society on Thrombosis and Haemostasis.

Recommendation 28

For patients with deep vein thrombosis who are potential candidates for extended anticoagulation, residual vein obstruction on ultrasound, and/or D dimer level may be considered in the decision making process.

Class	Level	References
IIb	B	Siragusa *et al.* (2011),[164] Palareti *et al.* (2014),[168] Prandoni *et al.* (2015)[169]

2.6. Treatment of deep vein thrombosis: use of inferior vena cava filters

2.6.1. Use of inferior vena cava filters. The earliest version of the modern IVC filter (Greenfield filter) was first used in 1972. The conical design, which is the hallmark of the majority of IVC filters, requires a large volume of thrombus in the filter before the luminal area is significantly reduced. Modern IVC filters are delivered (and retrieved) percutaneously via common femoral or jugular venous access and delivery systems are as small as 6 Fr. The use of IVC filters has been associated with considerable controversy in recent years, largely owing to concerns about the overuse of filters for questionable indications and failure to retrieve filters that were designed to be temporary, with subsequent thrombotic complications. It should be noted that the sole purpose of IVC filters is to prevent PE and therefore to reduce PE associated morbidity and mortality. Nevertheless, IVC filters are the only viable treatment option for patients with DVT where anticoagulation is contraindicated, although randomised trials are urgently needed.[170] Although an IVC filter is a possible means of minimising major PE, it has no positive effect on the DVT itself.

2.6.2. Summary of randomised trials on inferior vena cava filters. To date, high quality randomised clinical trials evaluating the use of IVC filters for the prevention of PE are scarce.

2.6.2.1. PREPIC trial. In the PREPIC trial (*Prevention du Risque d'Embolie Pulmonaire par Interruption Cave*), 400 patients with proximal DVT, with or without concomitant symptomatic PE, were randomised to a permanent IVC filter or no filter.[171] The study employed a two by two factorial design and patients were also randomised to the LMWH enoxaparin or IV UFH (aiming for an APTT ratio of 1.5 — 2.5). All patients underwent baseline and follow up ventilation perfusion scans either when symptoms of potential PE occurred or between 8 and 12 days to assess for asymptomatic PE. The primary outcome measure was the occurrence of PE (either symptomatic or asymptomatic), within 12 days of randomisation. A range of symptom based secondary outcomes were also evaluated. By day 12, symptomatic or asymptomatic PE occurred in only two patients (1.1%) in the filter group *vs.* nine patients (4.8%) in the no filter group. Up to two years, there were six PE events in the filter group (one death) and 12 in the no filter group (five deaths; OR 0.5, 95% CI 0.19 — 1.33, $p = .16$), but recurrent DVT occurred in 37 patients (20.8%) in the filter group *vs.* 21 patients (11.6%) assigned to no filter (OR 1.87, 95% CI 1.1 — 3.2; $p = .02$). Mortality rates were similar in the two groups at two years (43 *vs.* 40 patients in the filter and no filter groups, respectively). The eight year outcomes were published in 2005 and showed that symptomatic PE occurred in nine patients (6%) in the filter group *vs.* 24 (15%) in the no filter group ($p = .008$). However, recurrent DVT was more common in the filter group (57 *vs.* 41 patients, $p = .042$). The authors concluded that despite the reduction in PE risk, the increased risk of recurrent DVT and lack of survival benefit meant that the systematic use of IVC filters cannot be recommended for this population.

2.6.2.2. FILTER-PEVI study. In the FILTER-PEVI study (Filter Implantation to Lower Thromboembolic Risk in Percutaneous Endovenous Intervention),[172] 141 patients undergoing early thrombus removal were randomised to IVC filter or no filter. Patients with and without PE at presentation were included. Only symptomatic patients were investigated and pulmonary emboli were identified in one patient in the filter group compared with eight in the no filter group. However, there was no difference in mortality and the study was weakened by a lack of pre-operative imaging of the pulmonary arteries.

Recommendation 29

For patients with proximal deep vein thrombosis who have contraindications to anticoagulation during the initial or principal treatment phase, temporary inferior vena cava filter insertion is recommended.

Class	Level	Reference
I	C	Turner *et al.* (2018)[170]

Recommendation 30

For patients who are anticoagulated for deep vein thrombosis, the routine use of inferior vena cava filters is not recommended.

Class	Level	Reference
III	B	Prepic Study Group (2005)[171]

2.7. Treatment of deep vein thrombosis: compression therapy

Compression therapy is used for both upper and lower extremity DVT. This chapter will focus on compression therapy in the management of lower extremity DVT. Compression therapy is a non-invasive treatment option, which is readily available and is associated with few complications. Adverse events in compression trials for DVT are usually mild and mainly involve itching and minor skin changes, reported in 2% — 6% with knee length compression.[173–175] More adverse effects are reported with thigh length compression (25% — 40.7%).[176,177] Contraindications to compression are limited to two categories of patients: patients with severe lower extremity arterial disease (ankle brachial index < 0.50 or absolute ankle pressure < 60 mmHg),[178] and patients with severe congestive heart failure as there might be a risk of systemic fluid overload.

2.7.1. Compression therapy for the treatment of acute deep vein thrombosis. In the acute phase of DVT, patients often experience pain and swelling of the leg due to the obstruction of the deep venous system by the thrombosis and the associated inflammatory response. Elastic compression stockings (ECS) are intended to counteract the increased venous pressure, to improve venous flow and thereby to reduce oedema and optimise calf muscle function.[179,180] Four trials and one substudy to a trial have assessed the value of ECS in the subacute and acute phase.[173,181–184] Two of them have assessed symptomatology in the first 7 — 9 days,[181,182] and both studies showed a significant reduction in pain and swelling, with one also showing an improvement in clinical severity scores.[181] However, no significant benefits in terms of oedema reduction or pain relief were found beyond the early period.[173,181,182,185] One study found significant reductions in the incidence of irreversible skin signs with compression in the acute phase (multilayer bandaging [MLB] or compression hosiery), as well as improved quality of life (QoL) in patients initially treated with compression hosiery.[185] The effects were independent of the severity of symptoms and similar for MLB and compression hosiery. Based on these data it may be concluded that QoL can be enhanced and costs can be greatly reduced when compression hosiery is used in the acute phase.[185]

For the treatment of DVT, reduction of RVO may be beneficial, as RVO has been associated with (a moderate) increased risk of recurrent thrombosis.[186] Two studies have specifically studied the effect of compression in the acute phase on thrombus resolution,[183,184] and both found that the use of ECS did reduce the amount of RVO but did not affect the risk of recurrent DVT.

Table 17. The Villalta scale for diagnosis and defenition of severity of post-thrombotic syndrome (PTS), adopted from Villalta *et al.*, 1994[191]

Items	Symptoms or signs			
	Absent	Mild	Moderate	Severe
Subjective symptoms				
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paraesthesia	0	1	2	3
Pruritis	0	1	2	3
Objective clinical signs				
Oedema	0	1	2	3
Hyperpigmentation	0	1	2	3
Venous ectasia	0	1	2	3
Redness	0	1	2	3
Skin induration	0	1	2	3
Pain during calf compression	0	1	2	3
Ulcer	Absent		Present	
Total score*				

* Score < 5 no PTS, 5–9 mild PTS, 10–14 moderate PTS, >15 or venous ulceration severe PTS.

2.7.2. General remarks on the post-thrombotic syndrome. PTS is the most frequent complication of DVT, affecting 20% – 50% of patients one to two years after DVT.[187–190] This chronic condition is characterised by variable symptoms and signs of venous insufficiency such as pain, leg heaviness and discomfort, pretibial oedema, skin induration, hyperpigmentation, and venous ulceration in the most severe cases. The Villalta scale is a tool to diagnose and define the severity of PTS using these signs and symptoms (Table 17).[191] Owing to its frequency, potential severity, and chronicity, PTS is not only costly, but is also associated with a significant decrease in QoL.[192–194] Currently, there is no cure for PTS. Therefore, acute treatment of DVT should include prompt actions to encourage prevention of the PTS.

PTS is thought to be a result of chronic venous hypertension, caused by a combination of vein wall remodelling, venous outflow obstruction, and valvular reflux.[169,195] Known risk factors for PTS include older age,[189,196] obesity,[189,196–198] history of ipsilateral DVT,[188,189,199] proximal DVT,[199,200] pre-existing primary venous incompetence,[199] and inadequate anticoagulation during first three months of treatment.[201]

2.7.3. Initiation of compression in the acute phase for the prevention of post-thrombotic syndrome. Usually ECS are prescribed and fitted once the acute oedema has resolved. Until recently, there were limited data on the effect of immediate compression in the very early stage of the thrombosis on the long term prevention of PTS. Only three small RCTs had been published.[176,182,183] The first of these trials,[181] randomised 45 patients between inelastic bandages plus walking exercises ($n = 15$), thigh high compression hosiery (23 – 32 mmHg) plus walking exercises ($n = 15$), and no compression with bed rest ($n = 15$). The trial had lower compliance in the mobile group (50%) than the bedrest group (70%). After two years, a reduced incidence of PTS was seen in patients randomised to compression therapy and ambulation, (31% *vs.* 82% in the control group; $p < .01$),[176] however it is uncertain whether the reduction in PTS was the effect of early compression or walking exercises. The second trial randomised 69 patients to either immediate MLB or no compression before application of ECS.[182] This study found no difference in PTS between the groups after one year. The third trial, with 73 patients,[183] compared acute initiation of compression hosiery (25.5 – 32.5mmHg) with hosiery starting after 14 days. Better recanalisation based on the size of the residual thrombus measured by colour ultrasound was detected at 14 and 90 days in patients in the group where hosiery was applied early, but long term effects on PTS were not assessed. More recently, additional data have become available. In a pre-specified substudy within the IDEAL DVT trial,[184] 592 patients received no compression or acute compression within 24 hours of DVT diagnosis with either MLB or compression hosiery (ankle pressure 35 mmHg). The mean time from diagnosis until the assessment of RVO was 5.3 ± 1.9 months. A significantly lower proportion of patients who received compression therapy immediately after DVT had RVO (46.3% *vs.* 66.7%; OR 0.46, 95% CI 0.27 – 0.80). In addition, PTS was less prevalent in patients without RVO (46.0% *vs.* 54.0%; OR 0.65, 95% CI 0.46 – 0.92). Both MLB and compression hosiery provided similar outcomes. It was also observed that in patients with thrombosis of the common femoral vein, RVO is not reduced.[184]

2.7.4. Compression for prevention of post-thrombotic syndrome. The role of ECS in the prevention of PTS has been the subject of debate based on conflicting outcomes in prospective studies.[174,181,202–204] Five clinical trials assessed the value of (sub)acute ECS for the prevention of PTS. The medium sized trials recruited 194 patients[202] and 180 patients,[174] respectively, and showed a strong beneficial effect with the use of ECS initiated in the acute or subacute phase of DVT and continued for two years, with reductions of total PTS incidence from 70% to 31% ($p < .001$) and from 61% to 28% ($p = .011$), respectively. These two trials had high compliance rates (> 80%). The SOX trial (Compression Stockings to Prevent the Post-Thrombotic Syndrome; 803 patients) showed no benefit for ECS *vs.* sham stockings (52.6% *vs.* 52.3%; HR 1.00, 95% CI 0.81 – 1.24) with a low compliance with therapy in the trial (55.6%).[203] A smaller trial of 69 patients also reported no differences between groups but did not present specific numbers,[204] and compliance with therapy was 60%. Several meta-analyses have been performed in an attempt to combine the available evidence. Varying methodologies have been applied in the selection of studies and the presentation of data, with outcomes varying from significant reductions in PTS incidence to no effect of ECS. A recent Cochrane meta-analysis reviewing ECS initiated in the acute and subacute phase concluded that although there is significant heterogeneity between studies the overall effect of ECS for the prevention of PTS is more likely to favour compression.[205] This would probably be more so when only trials with good compliance were to be assessed. The latest meta-analysis showed a 38% RR reduction for the occurrence of PTS, a RR

of 0.62 (95% CI 0.38 — 1.01; $p = .05$) with the application of ECS in patients with DVT.[205] Knee length ECS seem to be equally effective as thigh length ECS. One trial with 267 participants reported that there is no clear difference in effectiveness of knee length ECS *vs.* thigh length ECS (RR 0.92, 95% CI 0.66 — 1.28; $p = .60$). More patients experienced adverse effects with thigh length ECS (40.7%) *vs.* knee length ECS (27.3%; $p = .017$).[177] However, a meta-analysis of 674 reports suggested that the current body of evidence was limited, and, at present, there is equipoise and further studies of compression stockings to prevent PTS are needed.[206] Of note, ECS do not prevent recurrent DVT.[207]

2.7.5. Duration of compression stocking use for the prevention of post-thrombotic syndrome. Three trials evaluated different durations of ECS therapy. One study with 169 patients[208] showed no significant benefit for prolonged treatment of 24 months *vs.* treatment for six months in terms of PTS incidence (assessed by CEAP classification) of 20% and 13%, respectively ($p = .20$). The OCTAVIA trial (518 patients)[209] highlighted the importance of adherence as it showed that prolonged ECS treatment for another year did not demonstrate non-inferiority in patients without complaints and excellent adherence after one year. The incidence of PTS was 19% and 13%, respectively, for an absolute difference of 6.9% (95% CI upper limit 12.3). The IDEAL DVT trial (864 patients)[175] was another non-inferiority trial that was designed to assess whether individualised duration of ECS treatment beyond the first six months was non-inferior to a standard duration of ECS treatment. It was found that it is possible to select patients who can stop treatment as early as six months based on the Villalta score, without increasing the incidence of PTS at 24 months. PTS incidence was 28.9% for individualised duration *vs.* 27.8% for standard duration, for an absolute difference of 1.1% (OR 1.06, 95% CI 0.78 — 1.44). This strategy proved to be highly efficient as treatment could be stopped at six months in 54.6% of patients and in an additional 10% of patients at 12 months, and this strategy was also demonstrated to be highly cost effective.[210] A practical algorithm to guide contemporary practice regarding use of ECS in DVT is shown in Fig. 3

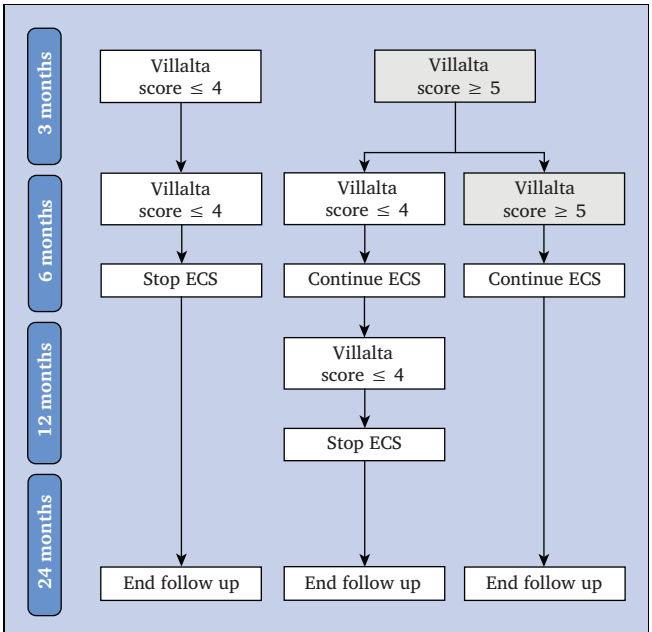


Figure 3. Suggested algorithm for individualisation of treatment with elastic compression stockings. Patients with two consecutive low (≤ 4) Villalta scores six months after the deep vein thrombosis are instructed to stop elastic compression stocking (ECS) treatment. Those with one low and one high (≥ 5) score are instructed to continue treatment. There is an additional assessment at 12 months, and those with two consecutive low scores can stop treatment at that point. Those with scores of five or higher continue treatment for 24 months or longer if necessary. Reproduced from ten Cate-Hoek *et al.*, 2014.[211]

Recommendation 31

For patients with proximal deep vein thrombosis, early compression at 30 — 40 mmHg with either multilayer bandaging or compression hosiery, applied within 24 hours, is recommended to reduce pain, oedema, and residual venous obstruction.

Class	Level	References
I	A	Partsch & Blattler (2000),[181] Roumen-Klappe *et al.* (2009),[182] Arpaia *et al.* (2007),[183] Amin *et al.* (2018)[184]

Recommendation 32

For patients with proximal deep vein thrombosis, use of below knee compression stockings should be considered in order to reduce the risk of post-thrombotic syndrome.

Class	Level	References
IIa	A	Kahn *et al.* (2014),[173] Prandoni *et al.* (2004),[174] Partsch *et al.* (2004),[176] Brandjes *et al.* (1997),[202] Aschwanden *et al.* (2008),[208] Ginsberg *et al.* (2001)[212]

Recommendation 33

For patients with proximal deep vein thrombosis and with limited symptoms and signs, as described in the Villalta score, it is recommended to limit the use of below knee stockings to six or 12 months.

Class	Level	References
I	A	Ten Cate-Hoek *et al.* (2018)[175] Aschwanden *et al.* (2008),[208] Mol *et al.* (2016)[209]

2.8. Treatment of deep vein thrombosis: early thrombus removal and stenting

The concept of "best medical therapy" involving formal anticoagulation using either injectable or oral anticoagulants combined with ECS has been shown to be suboptimal for the prevention and treatment of PTS.[203] The increasing

recognition that after best executed anticoagulant management PTS develops in 25% — 75% of patients with extensive lower extremity DVT has inspired ongoing attempts at early thrombus removal.[174,187,189,202,213] Research has clearly linked the development and progression of PTS to the persistence of venous thrombus and venous valvular injury that stems from the inflammatory reaction to this thrombus.[214]

2.8.1. Thrombus removal strategies

2.8.1.1. Surgical thrombectomy. Thrombectomy may be performed for acute iliofemoral DVT under general anaesthesia with common femoral venotomy and thrombus extraction using a Fogarty embolectomy catheter from the level of IVC. Distally, the thrombus can be extruded through the venotomy by manual massage of the entire leg, starting at the foot, or with gentle catheterisation and thrombectomy. The method has evolved over the years, with adjuvant venous stenting potentially used to restore iliac vein outflow instead of the previously used creation of an arteriovenous fistula (AVF) in the groin. Temporary IVC filters as an adjunct to surgical thrombectomy have been used, despite the lack of evidence for this practice.

A Swedish RCT compared venous thrombectomy in 13 patients with oral anticoagulants in 17 patients with iliofemoral DVT and 10 year follow up.[215] Patency at 10 years was significantly better in the surgical group compared with the oral anticoagulation group (83% *vs.* 41%, respectively). In addition, a reduction in leg swelling (71% *vs.* 46%) and leg ulcers (18% *vs.* 8%) was observed in favour of the surgical group. The surgical procedure was without stenting but with AVF. A recent comparative study demonstrated non-inferiority after surgical thrombectomy in 40 patients compared with 31 patients receiving thrombolysis, including stenting in both groups. After two years, 85% in the surgical thrombectomy group and 87% in the thrombolysis group did not develop PTS.[216] There were no deaths observed in either of the trials.

2.8.1.2. Catheter directed thrombolysis. Catheter directed thrombolysis (CDT) involves the delivery of a thrombolytic drug through a multiple side hole catheter positioned directly into the thrombosed vein. The intrathrombus instillation can be done either as continuous infusion or as pulsatile injections (pulse spray technique); the latter has been shown to achieve better primary patency, including normal valve function in the long term.[217] Ultrasound assisted (or accelerated) thrombolysis refers to drug infusion via a catheter, including a core wire, which simultaneously emits ultrasound energy into the thrombus material to improve the effectiveness of thrombolysis. However, a small RCT (45 patients) failed to demonstrate an advantage for ultrasound assisted thrombolysis compared with CDT.[218] The most commonly used lytic drugs are the plasminogen activators urokinase or recombinant tissue plasminogen activator (rtPA).[219] The lytic drug is infused together with either UFH or LMWH, both weight adjusted, given in a solution of saline. The amount of plasminogen activator and infusion volume varies in the literature from 20 to 120 mL, but rtPA should not exceed 1 mg/hour.[220]

A thrombus free popliteal vein is usually the most used accessible vein and thus punctured under ultrasound guidance in prone position. Even if a thrombosed popliteal vein is accessed, patency can be restored, as was demonstrated in one study, where 90% patency rates were reported after eight months in 39 limbs.[221] Puncturing the posterior tibial vein is also feasible. An important advantage of the fluoroscopy assisted techniques is the possibility of stenting persistent iliac obstructive lesions. The rate of stenting after CDT ranges from 17% to 80%.[217,218,222]

Major bleeding is more likely with CDT compared with anticoagulation alone and defined as intracranial bleeding, or bleeding requiring surgical intervention, cessation of therapy, or blood transfusion. A suggested international threshold for major bleeding is 7%, which has not been exceeded in the majority of publications reporting outcomes after CDT, generally respecting a broad range of recommended exclusion criteria.[222,223] Major bleeding rates with CDT are reported to range from 2.2% to 3.3%.[222,224] The occurrence of peri-procedural PE does not seem to be a major concern.[222,223,225,226] In two studies including 108 patients treated with CDT and 69 patients treated with CDT and other thrombus removal procedures, respectively, no PEs were identified when using a symptom based investigation protocol.[227,228]

2.8.1.3. Pharmacomechanical catheter directed thrombolysis. The term refers to procedures combining the use of lytic infusion for thrombolysis with adjunctive catheter based devices to promote mechanical removal of thrombus. A range of pharmacomechanical catheter directed thrombolysis (PCDT) devices are available and the main rationale for their use is to accelerate thrombus removal compared with CDT, which may take several days. The PEARL study (Peripheral Use of AngioJet Rheolytic Thrombectomy with a Variety of Catheter Lengths; an industry sponsored device registry) including 329 patients from 32 centres in the USA showed that 73% had completed treatment within 24 hours, clearly shorter than the two to three days with CDT.[217,218,229] Major bleeding was 1.7% in the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) study.[223] Several novel mechanical thrombectomy devices (with or without lysis) have become available recently, but high quality prospective evidence is currently lacking to evaluate whether they confer any benefit over PCDT or CDT.

2.8.2. Summary of randomised trials evaluating early thrombus removal. There have been four RCTs (TORPEDO [Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion], CaVenT [Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thromosis], ATTRACT, and CAVA [CAtheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT]) examining the effectiveness of early thrombus removal strategies,[213,222,223,226,230] all of which suffered from a combination of methodological and technological flaws. Published studies have therefore not served to fully settle the controversy over the question of the role of early thrombus removal

augmented by stenting. The most significant studies are the CaVenT, ATTRACT, and CAVA studies.[222,223,226] The CaVenT study compared adjunct CDT with rtPA in addition to anticoagulant treatment with anticoagulant treatment alone followed by continued oral anticoagulants in both groups for at least six months. The primary efficacy outcome was the presence of PTS, defined as a score of ≥ 5 on the Villalta scale in the leg with the index DVT, or an ulcer in that leg, at the 24 month visit. The study demonstrated a significant reduction in PTS in the interventional group with an absolute risk reduction of 14.4% at 24 months.[222] The long term follow up results of the CaVenT trial demonstrated that the absolute risk reduction increased to 28% after five years follow up. The number needed to treat (NNT) decreased from seven to four.[213] No difference in QoL was detected, but the study was not powered for this endpoint. A significant worsening in QoL was detected for patients who developed PTS in the whole study population.[231] Moreover, a cost effectiveness analysis demonstrated a net benefit of treatment with an incremental cost effectiveness ratio of US$20 000 per quality adjusted life year.[232]

The ATTRACT study was a multicentre RCT to evaluate PCDT and CDT for the prevention of PTS in patients with femoral or more proximal DVT compared with standard therapy with oral anticoagulants alone.[223] The protocol used three different modalities (CDT alone or combined with PCDT using Angiojet/Trellis-8) in the patients randomised to the treatment group at the discretion of the treating physician. The primary efficacy outcome was similar to that of the CaVenT study, i.e., the presence of PTS, defined as a score of ≥ 5 on the Villalta scale in the leg with the index DVT, or an ulcer in that leg, occurring at any time from the six month post-randomisation follow up visit to the 24 month visit (inclusive). Over 24 months, there was no difference in the proportion of patients who developed PTS between the two treatment groups (47% with CDT/PCDT *vs.* 48% with standard therapy; RR 0.96, 95% CI 0.82 — 1.11, $p = .56$). PCDT led to more major bleeding within 10 days (1.7% PCDT *vs.* 0.3% standard therapy; $p = .049$), and no difference in recurrent VTE over 24 months (12.5% PCDT *vs.* 8.5% standard therapy; $p = .087$). Intervention reduced leg pain and swelling up to 30 days but did not significantly improve QoL from baseline to 24 months. Intervention significantly reduced PTS severity scores and significantly reduced the development of moderate to severe PTS (18% with PCDT *vs.* 24% with standard therapy; RR 0.73, 95% CI 0.54 — 0.98, $p = .035$) over 24 months of follow up.

The CAVA study was a multicentre RCT comparing the use of ultrasound accelerated thrombolysis *vs.* standard anticoagulation therapy alone.[226] In contrast to ATTRACT, this study only enrolled iliofemoral DVT thereby addressing one of the criticisms raised about the inclusion criteria of the ATTRACT study. However, as with ATTRACT, the study took a long time (seven years) to complete recruitment, with almost 12% of patients withdrawing consent after randomisation. ATTRACT suffered from similar issues, although the exact numbers were not reported in the same way. Overall, CAVA randomised 184 patients: 91 to intervention and 93 to standard therapy, with 77 receiving therapy and 75 remaining in the standard therapy group after screening failure/withdrawal of consent. The primary outcome of the study after 12 months follow up showed no difference between the two treatment groups, with 22 of 77 (29%) of those undergoing intervention *vs.* 26 of 75 (35%) of those on standard therapy going on to develop PTS ($p = .42$). Unlike ATTRACT, it was not possible to assess for a difference in severity of symptoms between the groups.

These data led to the conclusion that for patients with acute proximal DVT, PCDT did not prevent PTS but did increase major bleeding. A pre-specified iliofemoral subgroup analysis of ATTRACT did demonstrate that in patients undergoing PCDT for iliofemoral DVT, PTS severity scores were reduced with early thrombus removal. There was no increase in major bleeding rates. The results suggested that there may be a benefit in reducing the risk of moderate to severe PTS, although there was still a higher than expected PTS rate in patients treated by early thrombus removal.[233] However, no benefit was observed in patients with femoropopliteal DVT.[234]

There are several limitations identified with the ATTRACT and CAVA trials. Given the lack of statistical power for the stratified analyses, the ATTRACT investigators recommended that these findings should be confirmed in future research. The withdrawal of consent and screen failures compromised the power of CAVA to meet its primary end point and like ATTRACT, the study was compromised by a low technical success for the delivery of lytic therapy. This may be due to the aforementioned failure of ultrasound assisted CDT to confer any benefit over CDT alone.[218] The low rate of technical success (and, by extension, high rate of occluded venous segments in both groups) can be used to argue both for and against the value of these studies, and many questions therefore remain unanswered.

The significant challenge presented by the CaVenT and ATTRACT trials is the relatively low rate of stenting (17% in CaVenT and 39% in ATTRACT) principally due to the lack of clear consensus among treating physicians regarding the indications for stenting, the absence of defined surveillance follow up (which should be considered standard practice) to demonstrate a patent vein (the so called “open vein hypothesis”), and the significant advances in technology since the trials were performed. One of the devices used in ATTRACT is no longer commercially available and the second has been superseded by an improved device, therefore suggesting that current “best practice” is not represented in the trials. Nevertheless, there is no evidence for the superiority of one treatment modality over another.

The overall results from CaVent, ATTRACT, and CAVA are therefore contradictory, with a significant benefit demonstrated for early thrombus removal in the former and no benefit in the latter. ATTRACT and CAVA suffer from relatively shorter follow ups, with CaVenT suggesting a stronger overall advantage for early thrombus removal strategies as follow up is extended. This principle reinforces the accepted perception that there is a long development phase for PTS.

A meta-analysis of the four RCTs on early thrombus removal (TORPEDO, CaVenT, ATTRACT, and CAVA) is shown in Figs. 4—6. It is evident that although early thrombus

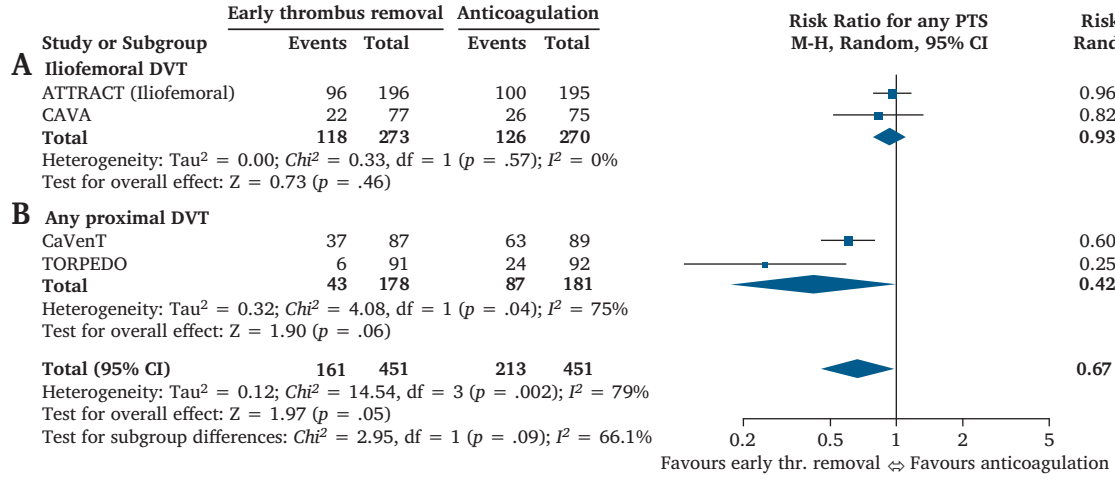


Figure 4. Forest plot analysis of randomised controlled trials comparing early thrombus (thr.) removal techniques with anticoagulation alone regarding the outcome of any post-thrombotic syndrome (PTS) in patients with (A) iliofemoral deep vein thrombosis (DVT) or (B) any proximal DVT. PTS incidence was lower with early thrombus removal techniques than anticoagulation alone. Risk ratio is based on fixed Mantel–Haenszel (M-H) method. There was no significant subgroup difference. CI = confidence interval; ATTRACT = Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis; CAVA = CAtheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT; TORPEDO = Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion.

removal techniques are more effective than anticoagulation alone in preventing any PTS (RR 0.67, 95% CI 0.45 − 1.00; $p = .05$ [Fig. 4]) and, particularly, moderate to severe PTS (RR 0.59, 95% CI 0.44 − 0.80; $p < .001$ [Fig. 5]), there is a significantly increased risk of major bleeding (RR 5.68, 95% CI 1.27 − 25.33; $p = .02$ [Fig. 6]). However, it should be noted that femoropopliteal DVT was included in TORPEDO and CaVenT. Furthermore, there were no heterogeneity or significant subgroup difference among trials regarding the outcome of moderate to severe PTS.

There are no trials offering direct comparison between stenting and no stenting after early thrombus removal, nor are there any comparative trials to allow for a decision between CDT alone or the adjunctive use of PCDT or purely mechanical devices. The latter two options offer the potential benefit of a reduction in, or elimination of, the thrombolytic, which is the principal cause of bleeding complications. Selection of patients for thrombus removal therapies over anticoagulation alone should therefore still be limited to those at highest risk of developing PTS (i.e., extensive clot

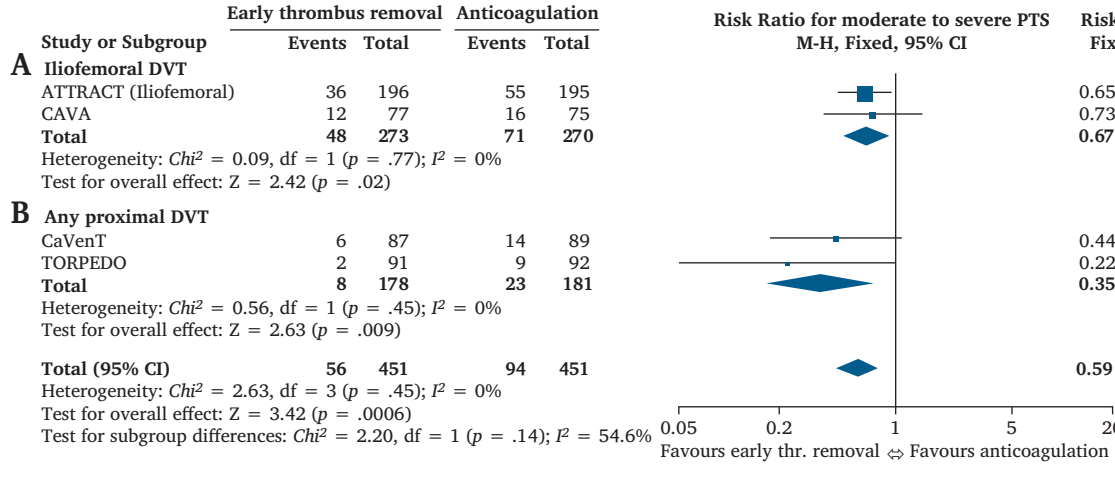


Figure 5. Forest plot analysis of randomised controlled trials comparing early thrombus (thr.) removal techniques with anticoagulation alone regarding the outcome of moderate to severe post-thrombotic syndrome (PTS) in patients with (A) iliofemoral deep vein thrombosis (DVT) or (B) any proximal DVT. PTS incidence was lower with early thrombus removal techniques than anticoagulation alone. Risk ratio is based on fixed Mantel–Haenszel (M-H) method. There was no heterogeneity or significant subgroup difference. CI = confidence interval; ATTRACT = Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis; CAVA = CAtheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT; TORPEDO = Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion.

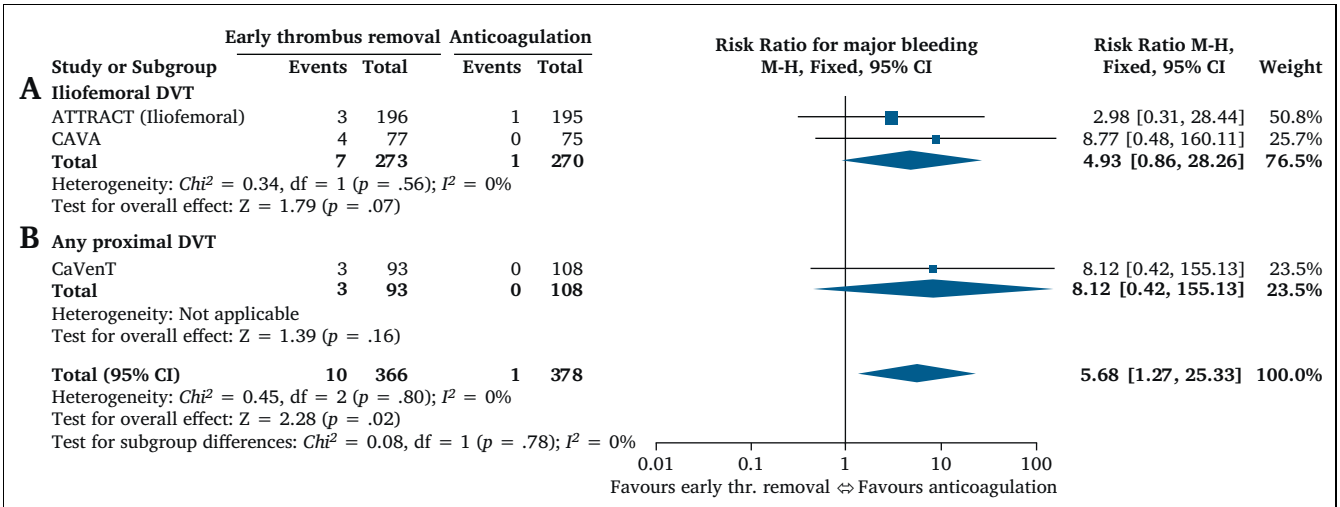


Figure 6. Forest plot analysis of randomised controlled trials comparing early thrombus (thr.) removal techniques with anticoagulation alone regarding the outcome of major bleeding in patients with (A) iliofemoral deep vein thrombosis (DVT) or (B) any proximal DVT. Unlike the analyses in Figs. 4 and 5, TORPEDO (Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion) did not categorise the three bleeding events reported and was not included in the meta-analysis. The incidence of major bleeding was higher with early thrombus removal techniques than anticoagulation alone. There was no heterogeneity or significant subgroup difference. Risk ratio is based on fixed Mantel–Haenszel (M-H) method. CI = confidence interval; ATTRACT = Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis; CAVA = CAtheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT.

burden, including the iliofemoral level), with a high chance of technical success (i.e., within two weeks of onset and no obvious post-thrombotic lesions) and low bleeding risk.[217]

2.8.3. Adjuvant procedures and post-intervention anticoagulation. Relatively disappointing medium and long term iliac vein patency rates (such as 65.9% venous patency at six months post-thrombolysis in the CaVenT trial) were attributed to the fact that residual iliac venous stenosis/scarring after thrombus removal was usually managed conservatively. In recent years, stenting of residual venous outflow stenotic lesions has been advocated increasingly, with the specific aim of reducing early re-thrombosis and improving medium and long term deep vein patency and QoL.

The ideal anticoagulation regimen after deep venous stenting procedures is controversial. In a systematic review of patients with chronic deep vein obstruction, > 10 different anticoagulation regimens were reported, varying in the medication used, duration, and whether adjuvant antiplatelet medications were added.[235] In the context of iliac venous stenting after early thrombus removal for symptomatic iliofemoral DVT, no trials have focused specifically on anticoagulation post-stenting. There is therefore no evidence to support one strategy over another for post-stenting anticoagulation and further studies are required.[236] However, the strategy that would apply to the same DVT managed conservatively should probably apply. Specifically, there is no evidence that stenting the iliac vein reduces the need for anticoagulation.

Recommendation 34

In selected patients with symptomatic iliofemoral deep vein thrombosis, early thrombus removal strategies should be considered.

Class	Level	References
IIa	A	Enden *et al.* (2012),[222] Vedantham *et al.* (2017),[223] Notten *et al.* (2020),[226] Sharifi *et al.* (2012),[230] Comerota *et al.* (2019),[233] Kahn *et al.* (2020)[237]

Recommendation 35

For patients with deep vein thrombosis limited to femoral, popliteal, or calf veins, early thrombus removal is not recommended.

Class	Level	Reference
III	B	Kearon *et al.* (2019)[234]

Recommendation 36

For patients with deep vein thrombosis treated by early thrombus removal, with or without stenting, it is recommended that the duration of anticoagulation should be at least as long as if the patients were treated by anticoagulation alone and at the discretion of the treating physician.

Class	Level	References
I	C	Kearon *et al.* (2019),[234] Eijgenraam *et al.* (2014)[236]

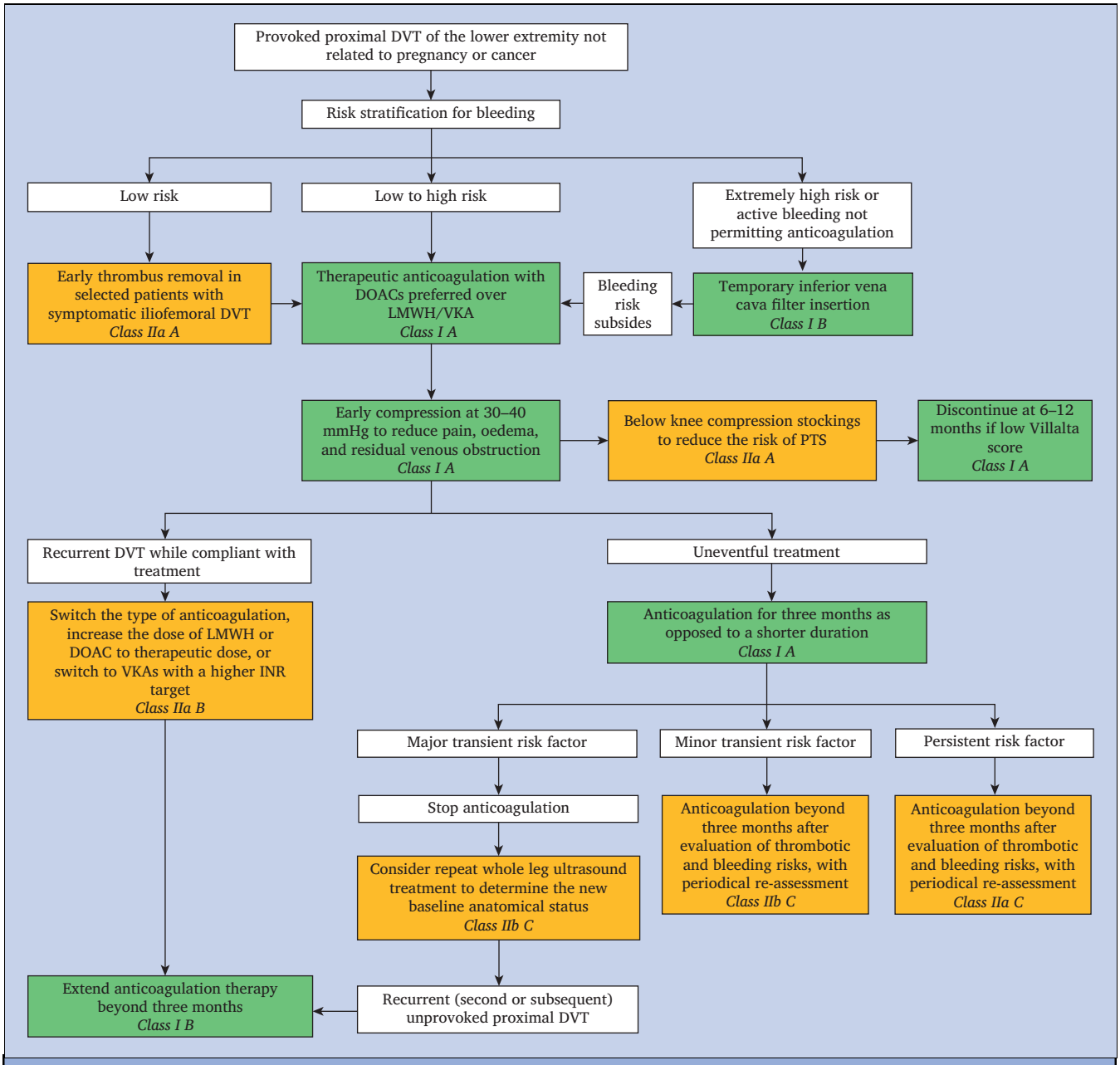


Figure 7. Flowchart of recommendations on treatment for provoked deep vein thrombosis (DVT). PTS = post-thrombotic syndrome; DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; VKA = vitamin K antagonist; INR = international normalised ratio.

Recommendation 37		
For patients with iliofemoral deep vein thrombosis who undergo early thrombus removal, it is recommended that the choice of therapy is based on the judgement of the treating physician.		
Class	**Level**	**Reference**
IIa	C	Consensus

Flowcharts on the integrated treatment of provoked and unprovoked DVT are shown in Figs. 7 and 8, respectively.

2.9. Calf deep vein thrombosis

2.9.1. Risk factors and natural history. Calf DVT (or isolated distal DVT as opposed to proximal DVT) is defined as involving the deep calf veins. It may affect the axial deep calf veins, usually the peroneal or posterior tibial veins, the calf muscle veins (gastrocnemius or soleal veins), or a combination of

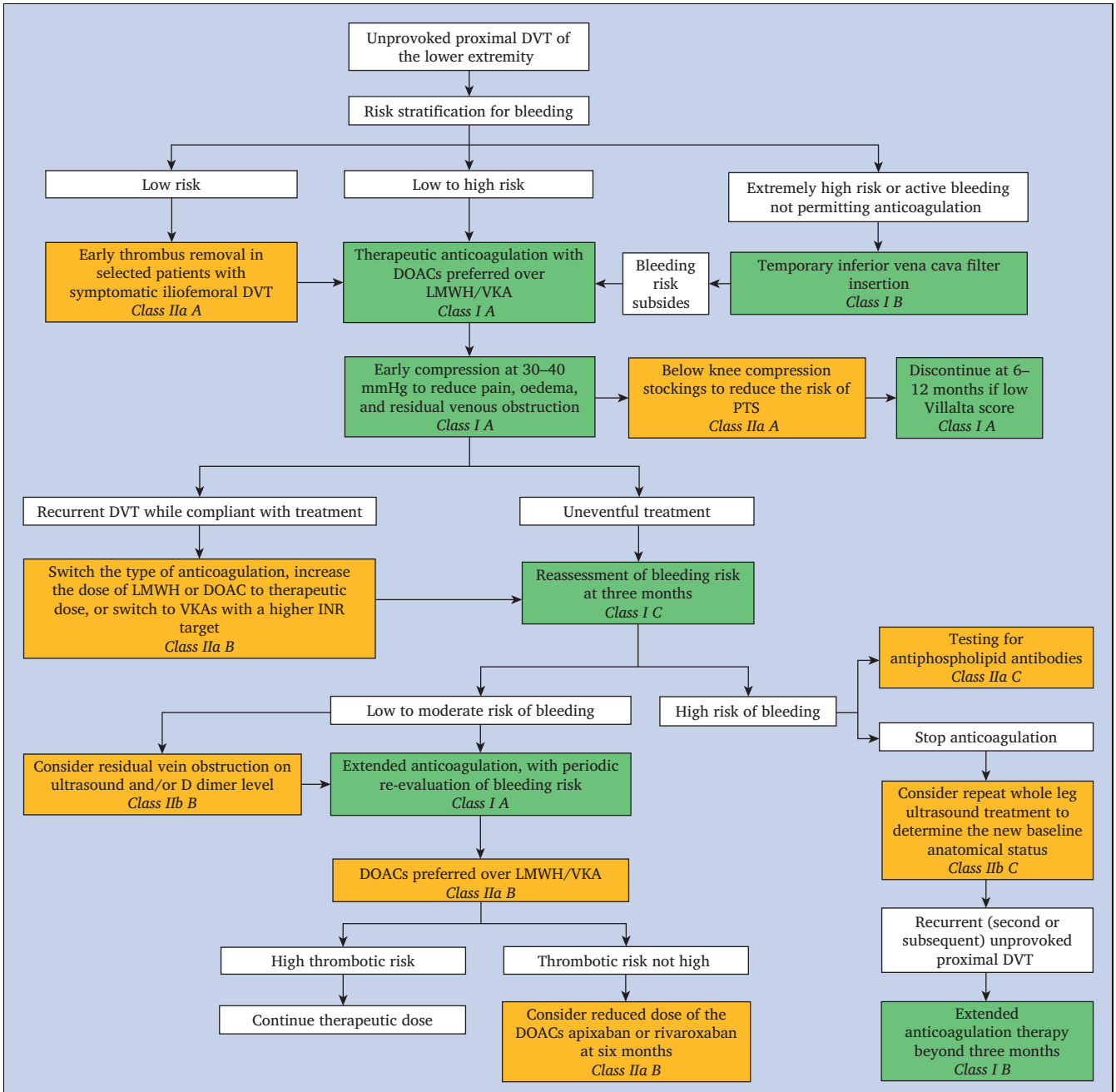


Figure 8. Flowchart of recommendations for treatment of unprovoked deep vein thrombosis (DVT). PTS = post-thrombotic syndrome; DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; VKA = vitamin K antagonist; INR = international normalised ratio.

these. In general, calf DVT shares the same risk factors as proximal DVT.[126] In the OPTIMEV study (*OPTimisation de l'Interrogatoire pour la Maladie thromboEmbolique Veineuse*), isolated calf DVT was more often associated with transient risk factors and events like recent surgery, plaster placement for a limb fracture, or travel, whereas proximal DVT was significantly more often associated with chronic conditions such as active cancer, congestive heart failure, respiratory failure, and age > 75 years.[238]

Investigations performed for calf DVT are the same as for proximal DVT presented in Chapter 2.2.1. Usually less symptomatic than proximal DVT, calf DVT may escape diagnosis if not suspected on patient assessment and ruled out by detailed WLUS. A repeat, WLUS should be performed if an initial limited examination has been performed to exclude proximal DVT.[239] Historically, isolated calf DVT has received little attention because of the perception that it is less clinically significant, owing to the lower risk of recurrent VTE, particularly proximal DVT and PE, and the ongoing debate about whether a diagnosis of calf DVT alters patient outcomes.[240] However, a recent systematic review estimated the rate of propagation of calf DVT to the popliteal

Table 18. Randomised controlled trials including patients with calf deep vein thrombosis (DVT)

Study	Pts − *n*	Population	Intervention	Control	Design	Outcome measures	Main results
Lagerstedt *et al.*[244]	51	Calf vein thrombosis, excluding recurrent and cancer associated DVT	UFH/warfarin for 3 mo	No AC	Open label	VTE recurrence, clinical and/or revealed on imaging	Fewer recurrent VTE episodes at 3 mo and 1 y with warfarin
Nielsen *et al.*[245]	16	Calf vein thrombosis	UFH/ phenprocoumon for 3 mo	No AC	Open label	Propagation or development of new VTE	No clinical VTE at 3 mo in either group
Schwarz *et al.*[247]	107	Muscle vein thrombosis	Nadroparin for 10 d	No AC	Open label	Progression into the deep veins and clinical PE	No difference at 3 mo
Horner *et al.* (ACT)[248]	70	Calf vein thrombosis excluding cancer associated DVT	Dalteparin/ VKA for 3 mo	No AC	Open label	Proximal propagation with or without symptoms, symptomatic PE, VTE related sudden death, or major bleeding	No difference at 3 mo
Righini *et al.* (CACTUS)[249]	259	Axial or muscle calf vein thrombosis, excluding recurrence and cancer associated DVT	Nadroparin for 6 w	Placebo	Double blind	Extension of calf DVT to proximal veins, contralateral proximal DVT, or symptomatic PE	No difference at 6 w and 3 mo
Pinede *et al.* (DOTAVK)[126]	197	Calf vein thrombosis, excluding recurrence and cancer associated DVT	VKA for 12 w	VKA for 6 w	Open label	Recurrent VTE and haemorrhage	No difference in outcome rates up to 15 mo
Schulman *et al.* (DURAC)[127]	347	Distal deep vein thrombosis, excluding recurrence and cancer associated DVT	VKA for 6 mo	VKA for 6 w	Open label	Recurrent VTE at 2 y	A non-significant trend towards reduced VTE rates with 6 mo treatment
Ferrara *et al.*[246]	192	Post-operative calf vein thrombosis	VKA for 12 w	VKA for 6 w	Open label	Extension of calf DVT to proximal veins, symptomatic PE, and major bleeding at 12−16 w	In patients with single vessel DVT there was no significant difference between the two subgroups, whereas in patients with DVT involving ≥2 vessels, a statistically significant difference was observed

UFH = unfractionated heparin; AC = anticoagulation; VTE = venous thromboembolism; PE = pulmonary embolism; ACT = anticoagulation of calf thrombosis project; VKA = vitamin K antagonist; CACTUS = anticoagulant therapy for symptomatic calf deep vein thrombosis trial; DOTAVK = *Durée Optimale du Traitement AntiVitamines K*; DURAC = Duration of Anticoagulation trial; Pts = patients.

vein or above to be around 9% and the rate of PE to be around 1.5%.[241] This risk is equally distributed over a three month period.[242]

2.9.2. Summary of clinical trials. Because of the relatively small risk of VTE without anticoagulation and also the small risk of bleeding with anticoagulation, a conservative approach with observation and repeat scanning to rule out progression to the popliteal vein was advocated in the past, particularly before trial evidence became available. A recent meta-analysis of 20 case control or cohort trials and RCTs included 2 936 patients with calf DVT and concluded that a reduction in recurrent VTE rates was seen in patients who received anticoagulation *vs.* those who did not (either therapeutic or prophylactic; OR 0.50, 95% CI 0.31 − 0.79), without an increase in the risk of major bleeding (OR 0.64, 95% CI 0.15 − 2.73).[243] PE rates were also lower with anticoagulation than in controls (n = 1 997; OR 0.48, 95% CI 0.25 − 0.91). A lower rate of recurrent VTE was observed in patients who received > 6 weeks of anticoagulation than in those who received six weeks of anticoagulation (four studies, 1 136 patients; OR 0.39, 95% CI 0.17 − 0.90).

A Cochrane review identified eight RCTs reporting on 1 239 patients (Table 18).[126,127,244−250] In five of these trials, patients were randomised to anticoagulation for up to three months *vs.* no anticoagulation or placebo.[244,245,247−249] The meta-analysis of these trials regarding the outcome of VTE, which included PE, symptomatic recurrence, or extension to the proximal veins, and also asymptomatic extension to the proximal veins on imaging, is presented in Fig. 9.[250]

Anticoagulation with a VKA for three months was associated with a reduced frequency of recurrent VTE during follow up (1.5%) *vs.* 18.6% in patients receiving no anticoagulation (RR 0.13, 95% CI 0.02 − 0.65; p = .01).[244,245,248] The NNT was six. Conversely, anticoagulation with nadroparin for ≤ 6 weeks *vs.* no anticoagulation failed to reach significance (RR

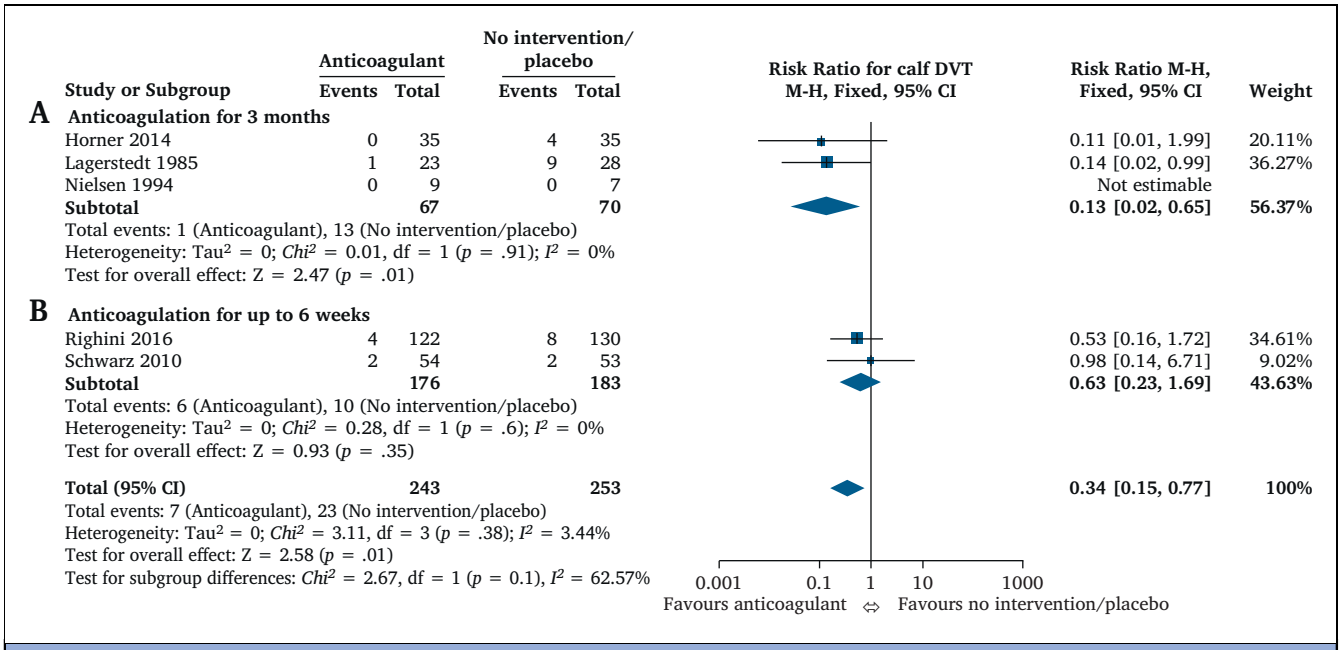


Figure 9. Forest plot analysis of randomised controlled trials comparing anticoagulation for (A) three months or (B) up to six months with no anticoagulation for calf deep vein thrombosis (DVT), stratified by treatment time, regarding the outcome of venous thromboembolism. CI = confidence interval; M−H = Mantel-Haenszel. Reproduced with permission from Kirkilesis *et al.*, 2020.[250]

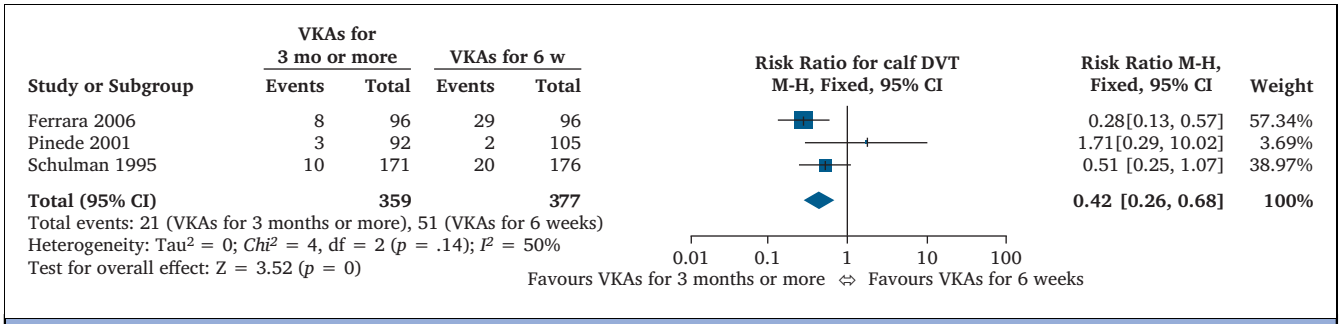


Figure 10. Forest plot analysis of randomised controlled trials comparing anticoagulation duration (standard, i.e., 3 − 6 months *vs.* short, i.e., 6 weeks) for calf deep vein thrombosis (DVT), regarding the outcome of venous thromboembolism. CI = confidence interval; M-H = Mantel−Haenszel; VKA = vitamin K antagonist. Reproduced with permission from Kirkilesis *et al.*, 2020.[250]

0.63, 95% CI 0.23 − 1.69; $p = .35$).[247,249] Major bleeding occurred in 0.4% in the treatment group *vs.* 0.8% in the control group ($p = .77$). In addition to these five RCTs comparing anticoagulation with no anticoagulation, the remaining three RCTs on 736 patients compared six weeks of anticoagulation with three to six months of anticoagulation (Table 18).[126,127,246,250] The results from this Cochane review on these trials are presented in Fig. 10, which showed a significant difference in favour of the standard treatment duration. Anticoagulation with a VKA for three to six months reduced the incidence of recurrent VTE to 5.8% *vs.* 13.5% in patients treated for six weeks (RR 0.42, 95% CI 0.26 − 0.68; $p < .001$). The NNT was 14. Major bleeding occurred in about 0.5% in patients treated for six weeks *vs.* 1.6% in patients treated for 12 weeks ($p = .28$). The number needed to harm was 92.[126,246] Of note, in patients with single vessel postoperative calf DVT there was no significant difference between six and 12 weeks of treatment.[246]

2.9.3. Risk factors for recurrent calf deep vein thrombosis.

Risk factors for short term recurrence of calf DVT (as opposed to general risk factors presented in Chapter 2.3.7.6) include inpatient status,[242] advanced age,[242] and active cancer.[251] Long term risk of recurrence after calf DVT is approximately half that observed for proximal DVT.[252] Risk factors for long term recurrence after calf DVT are presented in Table 19. Long term outcomes after isolated symptomatic calf CAVT were assessed in a multicentre study, which included 308 patients with malignancy, which was metastatic in 48%. During a mean follow up of 13.9 months, the annual rate of recurrent VTE while being treated with anticoagulants was 13.2% and the annual incidence of major bleeding was 2.0%.[253] The anatomic location (muscle *vs.* axial vein) had no effect on short or long term recurrence rates.[249,252] In another observational study in patients with CAVT, calf DVT and proximal DVT had a similar prognosis for VTE recurrence.[254]

Table 19. Risk factors for recurrent venous thromboembolism in patients with calf deep vein thrombosis

Clinical parameter	Annual recurrence rate (95% CI) − %	aHR (95% CI)	*p*
Age >50 y[252]	3.8 (2.6−5.5) *vs.* 0.9 (0.3−2.3) for <50 y	3.7 (1.0−10.6)	
Male sex[251]	–	4.73 (1.55−14.5)	.006
Multiple unilateral thromboses[252]	4.9 (3.1−7.8) *vs.* 1.8 (1.1−2.9) for single unilateral thrombosis	2.9 (1.4−6.1)	
Bilateral DVT[252]	8.9 (3.7−21.4) *vs.* 1.8 (1.1−2.9) for single unilateral thrombosis	4.0 (1.4−11.1)	
Unprovoked DVT[252]	3.8 (2.6−5.6) *vs.* 1.44 (0.7−2.9) for provoked	3.1 (1.4−6.9)	
Cancer[251]	34 (15−50) *vs.* 9 (5−13)*	5.47 (1.76−17.6)	.003*

CI = confidence interval; aHR = adjusted hazard ratio; DVT = deep vein thrombosis.
* Proximal deep vein thrombosis/pulmonary embolism.

2.9.4. Practical recommendations. Considering the high risk of proximal extension and/or PE in patients with calf DVT managed without anticoagulation (> 10%),[241] and the results of meta-analyses,[243,250] there is a clear argument in favour of anticoagulation for three months, unless there is a contraindication. Patients with calf DVT not receiving anticoagulation should undergo a repeat WLUS after one week, along with clinical re-assessment. Patients with single vein post-operative calf DVT may be treated for six weeks if a decision to anticoagulate is being made. The use of DOACs has not been investigated in patients with calf DVT, as most large trials of DOACs excluded patients with calf DVT or included a negligible number.[120,130−133] The risk of major bleeding with DOACs in these RCTs was about 1.1% at a mean follow up of around six months. Therefore, the risk of a three month course of DOACs for calf DVT may be extrapolated to be around 0.5%. Given their improved safety and effectiveness profile in proximal DVT and PE,[129] DOACs are preferable over VKAs for the management of acute calf DVT for most patients, with the exception of those with pregnancy related thrombosis. There is a paucity of evidence evaluating the role of extended treatment (beyond three months) for patients with calf DVT. However, in patients with persistent significant risk factors or unprovoked DVT and risk factors for recurrence, extended therapy should be considered.

Recommendation 38

For patients with calf deep vein thrombosis, a decision to anticoagulate based on symptoms, risk factors for progression, and bleeding risk should be considered.

Class	Level	Reference
IIa	C	Consensus

Recommendation 39

For patients with symptomatic calf deep vein thrombosis requiring anticoagulant treatment, three months of therapy is recommended over shorter durations.

Class	Level	References
I	A	Franco *et al.* (2017),[243] Kirkilesis *et al.* (2020)[250]

Recommendation 40

For patients with calf deep vein thrombosis requiring anticoagulation, direct oral anticoagulants are recommended over low molecular weight heparin followed by vitamin K antagonists.

Class	Level	Reference
I	C	Kakkos *et al.* (2014)[129]

Recommendation 41

For patients with symptomatic calf deep vein thrombosis and active cancer, anticoagulation beyond three months should be considered.

Class	Level	Reference
IIa	C	Galanaud *et al.* (2017)[254]

Recommendation 42

For patients with symptomatic calf deep vein thrombosis not receiving anticoagulation, clinical re-assessment and repeat whole leg ultrasound after one week is recommended.

Class	Level	Reference
I	B	Garry *et al.* (2016)[241]

2.10. Phlegmasia alba dolens and phlegmasia cerulea dolens

Phlegmasia describes two clinical conditions due to extensive DVT. Phlegmasia alba dolens (white/milk leg) is typically seen with thrombus in the major deep veins and therefore identical to the majority of iliofemoral DVTs. Phlegmasia cerulea dolens "blue leg" describes an uncommon, very severe form of iliocaval or iliofemoral DVT, causing total outflow obstruction with rapid extension of thrombosis into all deep and superficial veins, as well as collaterals over a few hours causing sudden severe ischaemic pain, massive congestion of the limb, cyanosis, function loss, tachycardia, and shock. It may be complicated by massive PE, compartment syndrome and, potentially, lead to venous gangrene. Cancer and hypercoagulable states may play a major role in the development of this rare condition. CT or MRI can complement ultrasound by excluding alternative diagnoses, but must not delay treatment, which may be associated with amputation rates of up to 50% and

mortality rates of up to 40% for patients treated with anticoagulation alone.[255]

For phlegmasia cerulea dolens, initial management is with weight adjusted heparin (UFH or LMWH) initiated as promptly as possible and delivered in combination with aggressive leg elevation and fluid rescuscitation. Case series have suggested that aggressive strategies including CDT, PCDT and surgical thrombectomy, possibly with iliac stenting and if indicated preceded by fasciotomy, may reduce amputation and mortality rates.[255–257]

Thus, early thrombus removal for both clinical conditions can be performed according to the recommendations in Chapter 2.8.

2.11. Superficial vein thrombosis

2.11.1. Pathophysiology. Thrombosis of the superficial veins can be the result of an injury or trauma affecting normal veins or varicosities, but more commonly follows placement of an IV cannula. However, most cases of SVT are spontaneous, usually in patients with varicose veins. Venous stasis inside the varicosities or the dilated and incompetent main saphenous trunks results in thrombus formation that may extend into adjacent veins, including the deep venous system. SVT of a normal vein may be the result of thrombophilia or Buerger's disease (thromboangiitis obliterans) in younger patients or malignancy in older patients.

2.11.2. Clinical presentation. Typically, SVT of the leg presents as a painful and tender lump or cord, with redness and heat, located in an area of pre-existing varicose veins, particularly along the course of the great saphenous vein (GSV). The clinical appearance of SVT resembles an inflammatory process that is responsible for the term "thrombophlebitis". Misdiagnosis as an infective process is common and frequently results in the unjustified use of antibiotics.

2.11.3. Diagnosis and workup. The diagnosis of SVT is made on clinical grounds where history and physical findings are sufficient. Information from duplex ultrasound may help with the diagnosis in equivocal cases, where incompressible, usually dilated or varicose, superficial veins are identified, lacking augmented luminal flow. A WLUS, bilaterally (as opposed to a two or three point compression test), is required to rule out DVT, which may be a calf DVT or a thrombus not contiguous with the segment of SVT in 50% and 42%, respectively.[258] Similarly, duplex ultrasound should map the superficial and deep veins to characterise superficial venous incompetence that can be treated accordingly, after the acute phase.

2.11.4. Thromboembolic risk associated with superficial vein thrombosis

2.11.4.1. Short term outcomes. Approximately 25% of patients with SVT in the Prospective Observational Superficial Thrombophlebitis (POST) study already had extension of thrombus to the deep venous system or PE at the time of the initial diagnosis.[258] Additionally, in the POST study, 10.2% of patients with SVT developed thromboembolic complications during the first three months of follow up, including DVT, PE, and progressing or recurrent SVT.[258] Recurrent SVT or extension in the POST study was relatively rare, occurring in about 5%.[258] Other studies have shown that during the first three months, recurrent thromboembolic events may occur in 6.2% — 22.6% of patients,[259–262] with recurrent events being VTE in 1.5% — 6.2%.[259–262] A shorter duration of anticoagulation is associated with a higher risk of recurrent events.[259] It is clear from these studies that the risk of thromboembolic events persists for the entire three months after SVT is diagnosed, although the risk may be higher during the first month and gradually decrease.[259] These observations have discredited the widely held perception that SVT is a benign condition. The thromboembolic risk may be higher in subgroups with cancer or extensive thrombosis, particularly if located at thigh level, affecting the GSV or at the popliteal fossa affecting the small saphenous vein (SSV), or extending near the junction with the deep venous system.[261,263–266]

2.11.4.2. Long term outcomes. Several studies have investigated the long term (> 3 months) thromboembolic risks following an episode of SVT. These risks may be associated with ongoing venous stasis in patients with varicose veins, if not treated by stripping or ablative methods, or other risk factors like thrombophilia or malignancy. In one study with a one year follow up, thromboembolic events after three months occurred at an annualised rate of 4.5%, with half of events affecting the deep venous system.[261] In the French OPTIMEV study, which had three years of follow up, VTE recurrence rates were comparable for patients with a first isolated SVT and proximal DVT (5.4% and 6.5% per patient year, respectively; adjusted HR [aHR] 0.9, 95% CI 0.5 — 1.6).[267] For patients with an isolated SVT, recurrent VTE events were six times more likely to be recurrent isolated SVT (2.7% *vs.* 0.6% per patient year; aHR 5.9) and 2.5 times less likely to be a deep venous event (2.5% *vs.* 5.9% per patient year; aHR 0.4). The presence of varicose veins did not influence the risk or the type of VTE recurrence and involvement of a saphenous junction by isolated SVT was not associated with a higher annual risk of recurrence (5.2% *vs.* 5.4%) but was associated with deep venous events.

In the Italian ICARO study (Internal Carotid ARtery Occlusion) of patients with SVT, an annual VTE rate of 4.4% in patients not on anticoagulation was reported.[268] In a Danish study of patients with SVT, the risk of DVT and PE persisted for three decades, although a reduction in risk over time was seen.[269] It is unclear if treatment of the underlying superficial venous disease reduces or abolishes this risk. An alternative explanation for this continued risk may be the presence of undetected DVT at baseline, including DVT in the contralateral leg.

2.11.5. Antithrombotic treatment for superficial vein thrombosis. An extensive overview of the currently available evidence is provided in the most recent update of the Cochrane review on the treatment of SVT of the leg.[270] The heterogeneity of the evidence with anticoagulation precluded a formal meta-analysis. This was because a variety of

LMWHs (and also UFH and warfarin) were given at variable dosages and for a variable duration. Most studies were small and thus underpowered for the outcome measures of DVT and PE. Consequently, studies were probably only adequately powered for the outcome of SVT recurrence. However, studies have consistently observed a "catch up" phenomenon, with a relatively high incidence of SVT recurrence after the end of treatment. Anti-inflammatory medications are frequently used to alleviate pain but have no effect on thromboembolic risks in patients with SVT.

2.11.5.1. Intensity of anticoagulation. In the STENOX study (Superficial Thrombophlebitis Treated by Enoxaparin), which enrolled patients with SVT of at least 5 cm length on ultrasound, enoxaparin given in therapeutic or prophylactic doses for 12 days reduced the risk of SVT recurrence and/or proximal extension from 29.5% with placebo to 5.7% (therapeutic dose) and 8.2% (prophylactic dose).[271] During follow up to 97 days, additional events were seen in all groups, but the differences were largely maintained.

2.11.5.2. Duration of anticoagulation. The optimum duration and dosage of LMWH was investigated in an RCT of patients with SVT of at least a 4 cm in length, randomised to receive either parnaparin 8 500 IU (o.d., intermediate dose) for 10 days followed by placebo for 20 days or 8 500 IU o.d. for 10 days followed by 6 400 IU o.d. for 20 days (intermediate doses) or 4 250 IU o.d. (prophylactic dose) for 30 days.[259] The primary outcome measure was the composite of symptomatic and asymptomatic DVT, PE, and SVT recurrence in the first 33 days. Of 664 randomised patients, the primary outcome occurred in 15.6% with the 10 day intermediate dose, in 1.8% with the 30 day intermediate dose, and in 7.3% with the 30 days prophylactic doses. These results indicated that an intermediate dose of parnaparin for 30 days is superior to either a 30 day prophylactic dose or a 10 day intermediate dose, considering that major bleeding was not observed. The NNT was seven and 12 for the 30 day intermediate dose of parnaparin *vs.* the prophylactic dose and the 10 day intermediate dose, respectively. During an additional 60 day follow up period, the frequency of new events was, on average 7.5%, and similar across the study groups.

Patients with SVT $\geq$ 5 cm in length with a higher than usual thromboembolic risk, such as those with SVT that is extensive, recurrent, is located at the thigh level, affects the GSV or SSV, extends near the junction with the deep venous system ($<$ 3 cm from the junction with the deep system), or is related to malignancy or thrombophilia, may receive a therapeutic or intermediate anticoagulant dose for a longer period, or, alternatively, be switched to prophylactic anticoagulation after 30 $-$ 45 days of intial treatment, for a total of three months of anticoagulant treatment.[261] However, there is little evidence to suggest the routine use of this approach. A similar lack of evidence applies to SVT of short length ($<$ 5 cm), where patients with a higher than usual thromboembolic risk may receive anticoagulant treatment instead of expectant management.

2.11.5.3. Factor Xa inhibitors in superficial vein thrombosis treatment. The CALISTO trial (Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo) randomised 3 002 patients with SVT $\geq$ 5 cm in length, which was located $\geq$ 3 cm away from the junction with the deep veins, to either subcutaneous fondaparinux 2.5 mg b.d., or placebo for 45 days.[262] The primary efficacy outcome, which was a composite of death from any cause or symptomatic VTE events (PE, DVT, SVT extension to junction, and SVT recurrence at day 47), occurred in 13 of 1 502 patients (0.9%) in the fondaparinux group and 88 of 1 500 patients (5.9%) in the placebo group (RR reduction with fondaparinux, 85%; $p < .001$). The rate of DVT or PE was 85% lower in the fondaparinux group than in the placebo group (0.2% *vs.* 1.3%; $p < .001$). Major bleeding occurred in one patient in each group. An advantage of fondaparinux is the lack of HIT, so that there is no need to monitor the platelet count. A recent systematic review and meta-analysis showed that fondaparinux achieved the lowest rate of DVT or PE (1.4 events per 100 patient years of follow up), and that for other treatments there was low quality evidence preventing firm conclusions about the optimal treatment for SVT.[272]

In SURPRISE, an open label, non-inferiority phase IIIb RCT, 472 patients with symptomatic SVT were randomised to receive 10 mg oral rivaroxaban or 2.5 mg subcutaneous fondaparinux o.d. for 45 days.[260] Inclusion criteria were symptomatic SVT, location above the knee, extension of at least 5 cm, and at least one additional risk factor (age $>$ 65 years, male sex, previous VTE, cancer, autoimmune disease, and thrombosis of non-varicose veins). The primary efficacy outcome (composite of symptomatic DVT, PE, progression or recurrence of SVT, and all cause mortality at 45 days) was non-significantly higher (3%) in the rivaroxaban group than the fondaparinux group (2%; $p = .003$ for non-inferiority). There were no major bleeds in either group. The SURPRISE investigators concluded that rivaroxaban was non-inferior to fondaparinux for the treatment of SVT, was not associated with more major bleeding, and could offer patients with symptomatic SVT an oral treatment option, which may be preferable to subcutaneous injection. However, SVT is not a licensed indication for rivaroxaban at present and an RCT comparing it with placebo was terminated because of slow recruitment rates.

2.11.6. The role of surgery to prevent superficial vein thrombosis recurrence. Superficial venous intervention eliminates the source of venous stasis and varicose veins with the aim of reducing the risk of recurrent SVT and secondary VTE. High ligation of the saphenofemoral junction was frequently used in the past to treat SVT approaching the deep venous system. However, anticoagulation is a less expensive and possibly safer method, and has largely replaced this strategy.[273] In a RCT, elastic compression alone was compared with early high ligation (with elastic compression), early stripping (with elastic compression), and anticoagulation followed by delayed surgery (with elastic compression).[274] Elastic compression alone and early high ligation had a significantly higher frequency of SVT extension (41% and 14%, respectively) than early stripping (0%), followed by LMWH (5.2%), which was

also better than elastic compression. The study was underpowered for VTE outcomes, although there was a trend for higher incidence of DVT in patients randomised to elastic compression alone. Although surgery or ablation performed early after an SVT event may eliminate the probability of extension through a junction into the deep venous system, this approach is not without risk. As it may not be feasible to remove large segments of the GSV and/or SSV, and in combination with a potentially generalised prothrombotic state, the possibility of a post-procedural VTE exists.[274] Prolonged thromboprophylaxis may be a pragmatic solution to this concern. Elimination of superficial vein incompetence by surgical or endovascular methods, including sclerotherapy, may be recommended after the acute phase, i.e., three months after the most recent SVT episode. Although rational and commonly practised, this approach is not evidence based.

2.11.7. Superficial vein thrombosis unrelated to venous stasis. Excluding the most common causes of SVT (stasis, venous trauma, or cannulation), SVT of a normal vein can occur in patients with a history of VTE, as reported in 29% in a series of 42 patients.[275] VTE may have been the result of a known thrombophilia in 48% – 77%,[276,277] mostly factor V Leiden mutation,[275,277] or be idiopathic. Investigation in this patient group may reveal malignancy in about 5%,[275] which may be much more common in patients with multiple unprovoked SVT events.[276] However, in another study of 277 patients, a single episode of unprovoked SVT diagnosed by a family physician was not associated with an increased risk of subsequent cancer.[278] Other causes of SVT of a normal vein include systemic prothrombotic conditions (e.g., rheumatological or inflammatory diseases) that may not be apparent or known at the time of presentation, including ulcerative colitis, systemic lupus erythematosus, Buerger's disease and pernicious anaemia.[275] A high rate of recurrence has been reported,[275] and this seems to be higher than in patients with SVT due to venous stasis.[279]

Recommendations and a flowchart (Fig. 11) on diagnosis, investigations, and treatment for SVT are shown below.

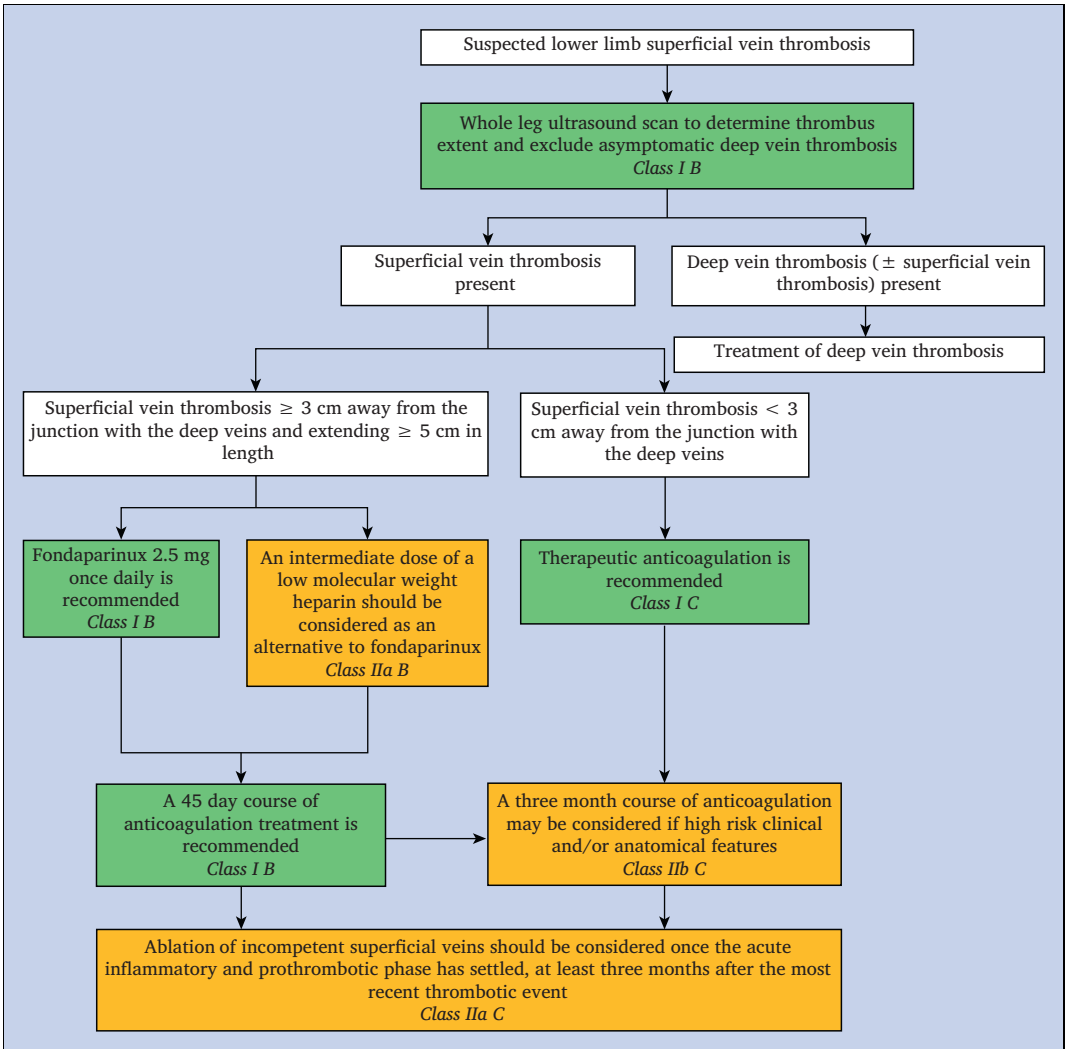


Figure 11. Flowchart of recommendations on treatment for superficial vein thrombosis.

Recommendation 43

For patients with suspected lower limb superficial vein thrombosis, a whole leg ultrasound scan is recommended to determine thrombus extent and exclude asymptomatic deep vein thrombosis.

Class	Level	References
I	B	Decousus *et al.* (2010),[258] Di Minno *et al.* (2016),[280] Jorgensen *et al.* (1993)[281]

Recommendation 44

For patients with isolated lower limb superficial vein thrombosis < 5 cm in length on ultrasound and lacking high risk features, such as malignancy, thrombophilia, or proximity to the deep venous system, anticoagulation is not recommended.

Class	Level	Reference
III	C	Consensus

Recommendation 45

For patients with lower limb superficial vein thrombosis ≥ 3 cm away from the junction with the deep veins and extending ≥ 5 cm in length, fondaparinux 2.5 mg once daily is recommended.

Class	Level	Reference
I	B	Decousus *et al.* (2010)[262]

Recommendation 46

For patients with lower limb superficial vein thrombosis ≥ 3 cm away from the junction with the deep veins and extending ≥ 5 cm in length, an intermediate dose of a low molecular weight heparin should be considered as an alternative to fondaparinux.

Class	Level	References
IIa	B	Cosmi *et al.* (2012),[259] Decousus *et al.* (2010),[262] Duffett *et al.* (2019)[272]

Recommendation 47

For patients with lower limb superficial vein thrombosis extending ≥ 5 cm in length on ultrasound and extending ≥ 3 cm from the junction with the deep veins, 45 days of anticoagulation treatment is recommended.

Class	Level	References
I	B	Cosmi *et al.* (2012),[259] Decousus *et al.* (2010)[262]

Recommendation 48

For patients with lower limb superficial vein thrombosis ≤ 3 cm from the junction with the deep veins, therapeutic anticoagulation is recommended.

Class	Level	Reference
I	C	Consensus

Recommendation 49

For patients with superficial vein thrombosis of the leg, which exhibits high risk clinical and/or anatomical features, a three month course of anticoagulation may be considered.

Class	Level	Reference
IIb	C	Nikolakopoulos *et al.* (2018)[261]

Recommendation 50

For patients with lower limb superficial vein thrombosis, acute superficial venous intervention is not recommended.

Class	Level	Reference
III	C	Lozano & Almazan (2003)[273]

Recommendation 51

For patients with lower limb superficial vein thrombosis, ablation of incompetent superficial veins should be considered once the acute inflammatory and prothrombotic phase has settled, at least three months after the most recent thrombotic event.

Class	Level	Reference
IIa	C	Consensus

3. SPECIFIC TYPES OF VENOUS THROMBOSIS

3.1. Upper extremity deep vein thrombosis

3.1.1. Diagnosis. Approximately 10% of all cases of DVT occur in the upper extremities, which affect 4 — 10 per 100 000 population.[282] Two different types of UEDVT are recognised. Primary effort thrombosis (Paget—Schroetter disease), often triggered by strenuous effort, and secondary UEDVT, which is usually related to the use of a central venous catheter (CVC), the latter being far more frequent (see Chapter 3.3). In the Global Anticoagulant Registry in the FIELD — Venous Thromboembolism (GARFIELD-VTE) registry, patients with UEDVT were significantly more likely to have a CVC than those with lower extremity DVT and had a higher rate of active cancer or recent hospitalisation than patients with lower extremity DVT.[283] In a recent meta-analysis, the proportion of PTS was higher in patients with unprovoked UEDVT than secondary, whereas recurrence was higher in secondary UEDVT.[284]

3.1.1.1. Clinical characteristics. The most common signs and symptoms of UEDVT are venous distention (100%), swelling of the arm (93%), bluish discoloration (77%), and aching or pain aggravated by exercise (66%). Occasionally, symptomatic PE may be the first feature of UEDVT. While these manifestations may raise the possibility of UEDVT, clinical evaluation has a low specificity (30% — 64%) and the diagnosis should be confirmed by additional diagnostic investigation.[285]

3.1.1.2. D dimers. Plasma D dimers are well established in the diagnostic work up of lower extremity DVT. However,

the role of D dimer in the diagnosis of UEDVT has not been widely investigated. Many patients with UEDVT have additional comorbidities associated with elevated D dimer levels, limiting their use in the diagnostic work up.[286] In a more recent study including 239 patients with a clinical suspicion of UEDVT, UEDVT was detected with ultrasound in 24 patients, sensitivity, and specificity of D dimer were 92% and 60%, respectively. It appears that D dimer is suboptimal as a single test approach to rule out UEDVT.[287]

3.1.1.3. Imaging modalities. Compression ultrasound is the most commonly used imaging initial test for the diagnosis of UEDVT with use of colour duplex to assess the subclavian vein. In a systematic review of 11 studies that compared ultrasound with venography the pooled sensitivity and specificity for compression ultrasound was 91% and 93%, respectively. These results should be interpreted with caution as the studies had small numbers of patients and had methodological limitations.[288] Venography has been long considered the gold standard for the investigation of a suspected UEDVT. However, it is rarely used as a diagnostic modality with the exception of the investigation of the patient with a strong clinical suspicion of UEDVT and an inconclusive ultrasound scan. There are limited data on the use of CTV in suspected UEDVT. It is not known whether this modality provides additional advantages over venography in the diagnosis of UEDVT, but it is less invasive. For patients for whom surgery for thoracic outlet decompression is contemplated, potential sources of compression have to be investigated, as this can guide management approaches.[289] CT scanning, chest and cervical spine X rays may reveal the presence of a cervical rib or other bony abnormalities, and MRI can show soft tissue structures, such as fibrous bands, responsible for vein compression,[289] to be eliminated by future surgery.

In a single study of 31 patients with suspected UEDVT, contrast venography was performed, which confirmed the presence of UEDVT in 11 patients. Twenty-one of these patients underwent MRI, which was inconclusive owing to suboptimal imaging in three. The sensitivities and specificities were 71% and 89% for time of flight and 50% and 80% for gadolinium enhanced MRV, respectively.[290] MRV is expensive and time consuming, and on the basis of the current limited evidence, cannot be recommended in the diagnostic work up of a suspected UEDVT.

3.1.2. Treatment. The main objective of treatment of UEDVT is the prevention of DVT propagation and PE. Another aim is the prevention of recurrent UEDVT, as well as encouraging rapid recovery and improving patient QoL. A long term objective is the prevention of the development of upper extremity PTS. The initial treatment is anticoagulation. Owing to limited data from studies regarding the management of UEDVT, some of the recommendations are from extrapolation of studies on DVT in the lower extremities. It has been shown that during the course of anticoagulation patients with UEDVT had similar outcomes (PE, recurrence, or major bleeding) to those with lower extremity DVT.[291]

3.1.2.1. Anticoagulation. All patients with UEDVT should receive anticoagulation unless there are major contraindications. Traditionally, LMWH in a therapeutic dose is provided, followed by a VKA. There are no studies on the optimal duration of the anticoagulation. Based on extrapolation from lower extremity DVT and small cohort studies of patients with UEDVT, ACCP guidelines recommend anticoagulation for at least three months.[64] Data from the Swedish national anticoagulation registry were retrospectively evaluated in 55 patients with UEDVT who were treated with DOACs (rivaroxaban in 84%). During a six month period there was only one DVT recurrence. This report concluded that DOACs are safe and effective in the treatment of UEDVT.[292] Similar good results were obtained in another study on 30 patients treated with rivaroxaban.[293] A more recent case control study comparing apixaban ($n = 63$) or rivaroxaban ($n = 39$) with LMWH and/or warfarin ($n = 108$) concluded that DOACs appeared to be as safe and effective as LMWH and/or warfarin.[294]

For patients with cancer associated UEDVT, long term LMWH monotherapy is preferred over the administration of VKAs. Anticoagulation therapy should be continued as long as the cancer remains active if the thrombotic event was not related to a CVC. After the first three to six months, anticoagulation therapy may be switched to a VKA or DOAC (see Chapter 4.3.2). For patients with catheter associated UEDVT (with or without cancer), anticoagulation therapy can be discontinued after three months if the CVC is removed (see also Chapter 3.3.3); if the catheter is not removed, it has been suggested that anticoagulation therapy should be considered for a minimum of three months,[295,296] or continued as long as the catheter remains (see also Chapter 3.3.3).[297]

3.1.2.2. Thrombus removal strategies. Thrombolytic therapy in the acute phase is effective in eliminating the thrombus and relieving symptoms. Systemic thrombolysis has been abandoned and, in most reports, CDT is the preferred thrombus removal strategy. Venous access can be obtained by puncturing a deep vein distal to the obstruction in the upper extremity and the catheter is placed within the thrombus under fluoroscopic guidance. In a recent meta-analysis including 3 550 patients in 60 studies, major bleeding occurred in patients with UEDVT in 5% after anticoagulation alone and 3.8% after thrombolysis and/or surgery.[284] Thrombolysis is most effective when it is used within the first two weeks from the development of the UEDVT. Organised thrombus older than two weeks is less responsive to thrombolysis.[285]

CDT has been compared with PCDT in a small retrospective series of 43 patients. The clinical outcomes were similar. PCDT required shorter hospital stay and less intensive surveillance leading to lower total cost.[298] In a non-randomised retrospective analysis of 103 patients who had 110 first rib resections, 45 subclavian veins underwent thrombolysis with or without venoplasty prior to first rib resection and were compared with 65 subclavian veins treated by pre-operative anticoagulation alone. Around 91% of veins were patent in asymptomatic patients at the 16 month follow up in each of the two groups. The authors concluded that pre-operative endovascular intervention offered no benefit over simple anticoagulation; however, thrombolysis was performed late, on average 3.8 months after the initial presentation.[299]

3.1.2.3. Surgery for thoracic outlet decompression. Many clinicians advocate thoracic outlet decompression after thrombolysis for primary UEDVT, although there is no clear evidence and the timing of decompression remains controversial. Some clinicians advocate a conservative approach for patients who do not develop subclavian vein stenosis with arm abduction. Others suggest thoracic outlet decompression only on patients with persistent upper extremity symptoms, after thrombolysis and one to three months of anticoagulation therapy.[300] The appropriate selection of patients for thoracic outlet decompression has never been evaluated in RCTs and any recommendations are based on small institutional series only. In a systematic review of 12 case series, patients were divided in three groups according to treatment after thrombolysis. Symptom relief was significantly more likely in the 448 patients treated by first rib resection (95%) and the 68 patients who underwent first rib resection plus venoplasty (93%) than in the 168 patients in the group in whom the first rib was not removed (54%), as was patency of the subclavian vein (98%, 86%, and 48%, respectively).[301] More than 40% of patients in the group in whom the first rib was not removed eventually required rib resection for recurrent symptoms. First rib resection is associated with a significant risk of serious complications in approximately 25% of patients. Complications of first rib resection include haemopneumothorax, brachial plexus injury, haematoma requiring re-operation, and recurrence of the thrombosis.[302]

In a case control study, 45 consecutive patients who had been treated within two weeks of presentation for primary UEDVT received either oral anticoagulant therapy only ($n = 14$, group 1); thrombolysis followed by anticoagulant therapy ($n = 14$, group 2); or thrombolysis, transaxillary first rib resection and anticoagulant therapy ($n = 17$, group 3). End points were persisting symptoms and QoL. Patients in groups two and three had significantly less pain, swelling and fatigue in the affected limb at six weeks. There was no difference in pain, swelling, fatigue, functional impairment, recurrence, or QoL between groups at the end of follow up (mean follow up 57 $\pm$ 46 months). Treatment strategy was not predictive of QoL ($p = .91$, analysis of variance). There were no differences in long term symptoms or QoL between patients with successful and unsuccessful thrombolysis. The authors concluded that thrombolysis with or without first rib resection does not appear to contribute to lasting symptom reduction and improvement of QoL.[303]

Following the first rib resection, venography may be performed. A significant post-operative residual stenosis can be treated by balloon venoplasty. In a small series of 25 patients who required post-operative balloon venoplasty, assessment of functional outcome using the validated DASH questionnaire, showed a similar DASH score in patients who had a successful ($n = 18$) or unsuccessful ($n = 7$) post-operative venoplasty.[304] However, the management of intrinsic residual venous defects is controversial and not evidence based. Proponents of an anticoagulation alone approach stress the high failure rates of angioplasty and point out that many or most such lesions will remodel with time once bony decompression and venolysis has taken place. There has never been a comparison of open surgical venoplasty *vs.* endovascular venoplasty.

Another approach is to perform delayed venography and balloon venoplasty after allowing several weeks for the endothelium to recover from the thrombosis and thrombolysis.[305] There is a general agreement that the placement of a stent in the thoracic outlet, even after first rib resection, for the management of residual stenosis, is associated with a high incidence of stent fracture and thrombosis. Therefore, the use of stents is not recommended.[282,285] The timing of thoracic outlet decompression is another area of controversy. Immediate decompression has the potential advantage of early reduction of recurrence risk, while a delayed approach may avoid invasive surgery for some patients who remain asymptomatic. Also, delayed surgery may be associated with lower risks compared with surgery immediately after thrombolysis.

Recommendation 52

For patients with suspected upper extremity deep vein thrombosis, ultrasound is recommended as the initial imaging investigation.

Class	Level	Reference
I	C	Kraaijpoel *et al.* (2017)[288]

Recommendation 53

For patients with primary upper extremity deep vein thrombosis, anticoagulation therapy for three months is recommended.

Class	Level	References
I	C	Montiel *et al.* (2017),[292] Schastlivtsev *et al.* (2019)[293]

Recommendation 54

In most patients with symptomatic primary upper extremity deep vein thrombosis, early thrombus removal is not recommended.

Class	Level	Reference
III	C	Guzzo *et al.* (2010)[299]

Recommendation 55

In selected young and active patients with upper extremity deep vein thrombosis with severe symptoms, thrombolysis may be considered within the first two weeks.

Class	Level	References
IIb	C	Bosma *et al.* (2011),[303] Illig & Doyle (2010)[305]

Recommendation 56

For patients with upper extremity deep vein thrombosis treated by early thrombus removal, first rib resection may be considered if there is clear evidence of venous thoracic outlet syndrome.

Class	Level	Reference
IIb	C	Lugo *et al.* (2015)[301]

3.2. Deep vein thrombosis in unusual sites

Any part of the venous system can be affected by thrombosis, including cerebral, jugular, abdominal, and pelvic vein thrombosis. This heterogeneity in location is reflected in the clinical presentation, pathophysiology, and prognosis of these cases. The majority of information is derived from case reports or case series; therefore, treatment recommendations are only supported by low quality evidence.[306]

Some DVTs in unusual sites are strongly associated with local factors, like CVC induced jugular vein thrombosis, local inflammation, or trauma.[307] Local precipitating factors for splanchnic vein thrombosis include solid abdominal cancers, liver cirrhosis, intra-abdominal inflammation, and surgery. However, systemic DVT precipitants in unusual sites include hormonal therapy, assisted reproduction technology causing ovarian hyperstimulation syndrome, haematological disorders, autoimmune diseases, and especially acquired and hereditary thrombophilic disorders.[308]

The choice of imaging is dependent on the location of DVT and testing for thrombophilia or malignancy should be initiated in many such cases. Unless there are contraindications, immediate anticoagulation is recommended. In the acute phase LMWH and UFH are most commonly used in the literature followed by LMWH monotherapy or VKA for three months in patients with transient risk factors. Indefinite anticoagulation is recommended for permanent risk factors.[306,309,310] Treatment of mesenteric vein thrombosis is described in the ESVS guidelines on the management of diseases of mesenteric arteries and veins.[311]

3.3. Catheter related deep vein thrombosis

Numerous types of CVC are in widespread use, including tunnelled or non-tunnelled catheters, dialysis catheters, implanted ports, and peripherally inserted central catheters.[312] Vessel injury during insertion, venous stasis, and ongoing catheter motion in the vein, as well as hypercoagulability, can lead to catheter related thrombosis (CRT).[313,314] CRT may result in recurrent DVT, PTS, PE, and sepsis.[285] Studies screening patients with CVC using venography or ultrasound report CRT in 16% — 18% of patients.[315,316] Symptomatic CRT (symptoms ranging from minor pain and tenderness to superior vena cava syndrome) is uncommon and seen in only 1% — 5%.[317–319]

3.3.1. Risk factors for catheter related thrombosis. A meta-analysis of risk factors for CRT in 5 636 patients with cancer reported that the CVC insertion site (femoral > subclavian > jugular), tip location (proximal to superior vena cava > superior vena cava/right atrium junction), and type of CVC (peripherally inserted central catheter > implanted ports), as well as previous DVT were predictors of CRT.[320] Consistently, studies in patients with cancer report metastatic disease as the most important risk factor for CRT.[313] Hereditary thrombophilias such as factor V Leiden (OR 4.6, 95% CI 2.6 — 8.1) and prothrombin gene mutation (OR 4.9, 95% CI 1.7 — 14.3) were also associated with increased risk.[321]

3.3.2. Prevention of catheter related thrombosis. Current evidence is unable to guide which patients may benefit from prophylactic anticoagulation. The use of anticoagulation for the prevention of CRT in patients with cancer was reported in a 2014 systematic review analysing 12 RCTs. UFH was associated with a significant reduction in the incidence of symptomatic UEDVT (RR 0.48, 95% CI 0.27 — 0.86), without an impact on mortality, or major or minor bleeding.[322] The use of different locking solutions for CVCs was reported in several studies, but the benefit in terms of CRT risk remains uncertain.[323,324]

3.3.3. Treatment of catheter related thrombosis. The treatment of CRT varies in clinical practice and combinations of anticoagulation, catheter removal, and replacement have been described.[325] Regarding the duration of anticoagulation there are no RCTs, but a systematic review described outcomes in patients treated by anticoagulation with UFH or VKA ranging from eight days to more than six months. PE was reported in 2.8%, recurrent DVT in 7%, and major haemorrhage in 2.8% of patients receiving anticoagulation with a median follow up between one and five years.[326] In an analysis of the RIETE registry (*Registro Informatizado de Enfermedad TromboEmbólica*), 67% of isolated CRT and 49% of CRT with PE were treated with long term LMWH *vs.* 27% and 47% treated with VKA for a median of 3.5 months in isolated CRT and 4.5 months in CRT with PE.[327] There are only few retrospective reports of the use of rivaroxaban.[328,329] Data on thrombolytic therapy are limited and thrombolysis should only be used where the risk of thrombosis is greater than the risk of bleeding.[295] Several consensus statements recommend catheter removal only when it is not needed, not functional, anticoagulation is contraindicated, symptoms are not resolving, or the thrombosis is limb or life threatening.[64] On the basis of retrospective data and two prospective cohort studies anticoagulation with either LMWH or VKA for three months after catheter removal is recommended for patients with CRT.[295,296] Future comparative trials between anticoagulants for the treatment of CRT are needed.

Recommendation 57

For patients with catheter related thrombosis, catheter removal should be considered, when (1) it is not needed; (2) it is not functional; (3) anticoagulation is contraindicated; (4) symptoms are not resolving with anticoagulation; or (5) the thrombosis is limb or life threatening.

Class	Level	Reference
IIa	C	Baumann Kreuziger *et al.* (2015)[327]

Recommendation 58

For patients with catheter related thrombosis, anticoagulation with low molecular weight heparin or low molecular weight heparin followed by vitamin K antagonists should be considered for a minimum of three months.

Class	Level	References
IIa	C	Debourdeau *et al.* (2013),[295] Barco *et al.* (2017)[296]

4. SPECIFIC PATIENT POPULATIONS

4.1. Deep vein thrombosis in children

Overall, the incidence of VTE is much lower in children (< 1 per 10 000 per annum) than in adults (0.5 − 1 per 1 000 per annum).[330] VTE is thought to affect one in 200 hospitalised paediatric patients. The incidence is increasing, possibly due to the increasingly invasive support of critically ill patients with CVCs.[331] Paediatric patients with VTE may differ from adults in a number of ways. The principal differences relate not only to the epidemiology and natural history of VTE events, but also to the pharmacodynamics of antithrombotic medications. The majority of DVT events in paediatric patients are related to CVCs.[332]

4.1.1. Anticoagulation for deep vein thrombosis in children. While a detailed description of all the treatment options for VTE in paediatric patients is beyond the remit of this guideline document, the need for monitoring of anticoagulation (APTT ratio, anti-Xa levels, etc.) is greatly increased compared with adult patients. The role of DOACs in the treatment of children with DVT has been subject to significant debate. In the phase III EINSTEIN-Jr trial, 500 children with VTE were treated with a body-weight adjusted 20 mg equivalent dose of rivaroxaban and compared with standard anticoagulants (heparin treatment or switched to a VKA).[333] The two treatments were found to be equally effective and safe. Furthermore, rivaroxaban resulted in a reduced thrombotic burden compared with standard anticoagulants ($p = .012$). Further studies of DOACs in the paediatric population are awaited.

4.1.2. Thrombolysis for deep vein thrombosis in children. Although several case series have reported positive outcomes after thrombolysis for acute DVT in children, high quality evidence reporting outcomes or safety data are scarce. Therefore, the use of thrombolysis should be reserved for cases with limb or life threatening features. As the presence of a CVC is a far more common provoking factor in paediatric DVT, compared with adults, this is worthy of specific further comment. The time of CVC removal has been suggested to be a particularly high risk period for venous embolisation.[334] Some guidelines have specifically recommended three to five days of anticoagulation therapy before removal of the central venous access device.[335] If the catheter is still required and functioning, then this can be left *in situ* while anticoagulation therapy is given. The management of children with cancer and DVT may present a complex challenge. In the absence of RCTs, clinical practice in this group is guided by indirect appraisal of the evidence and expert opinion. Clearly, the specific bleeding and thrombosis risks for each individual child will need careful assessment to guide practice. This further emphasises the importance of involving a paediatric haematology specialist in the care of this patient group.

Recommendation 59		
The management of children with deep vein thrombosis should be guided by clinicians with specific expertise in paediatric thrombosis and haemostasis.		
Class	**Level**	**References**
I	C	Monagle *et al.* (2012),[335] Monagle *et al.* (2020)[336]

4.2. Deep vein thrombosis in pregnancy

4.2.1. Epidemiology and pathophysiology. Compared with healthy women of the same age, VTE is 10 times more common antenatally and 25 times more common postnatally.[337–339] This increased risk of VTE arises early in pregnancy and extends to 12 weeks postpartum with an OR of VTE of 12 (95% CI 7.9 − 18.6) in the first six weeks postpartum and 2.2 (95% CI 1.4 − 3.3) for the period between seven and 12 weeks postpartum.[340,341] The UK Confidential Enquiries reports into Maternal Deaths show that VTE is the leading cause of direct maternal death,[342,343] despite increased use of thromboprophylaxis. The increased prevalence of obesity,[344] and the rising average maternal age, are probable factors contributing to this high rate.

Hypercoagulability in pregnancy results from increased levels of the coagulation factors, particularly factor VIII and fibrinogen, reduced levels of protein S, increased resistance to activated protein C, and altered fibrinolysis, partly owing to the placental production of plasminogen activator inhibitor 2. Lower limb blood flow is reduced by up to 50% by 29 weeks' gestation. The third component of Virchow's triad, endothelial changes occur as a result of the hormonal changes of pregnancy, and endothelial damage can arise during delivery.

4.2.2. Presentation and assessment of suspected deep vein thrombosis in pregnancy. The clinical assessment of DVT is more unreliable in pregnancy than in non-pregnant patients. This is due to confounding factors that may mimic the symptoms and signs of DVT, such as leg swelling, which is commonly found in normal pregnancy. As a consequence, the specificity of clinical diagnosis is < 10%.[339,345] The majority of DVTs in pregnancy occur in the left leg,[339,345] probably reflecting extrinsic compression of the left common iliac vein by the right common iliac artery and the ovarian artery, which cross the vein. Over 70% of DVTs in pregnancy arise in the iliac and femoral veins rather than the calf veins,[346] whereas in non-pregnant patients < 10% arise in the iliofemoral area.[347] Therefore, non-specific symptoms such as lower abdominal pain and/or back pain and/or swelling of the entire limb need to be recognised as potential DVT features in addition to more classical symptoms.

D dimer levels increase physiologically through pregnancy and increase further in the presence of other complications of pregnancy, such as pre-eclampsia. A large multicentre study (DiPEP [Diagnosis of PE in Pregnancy]) showed that

expert derived pre-test probability and clinical decision tools such as the Wells and Geneva scores and candidate biomarkers, including D dimers, were all unreliable in diagnosing PE in pregnancy.[348] Importantly, a negative D dimer did not exclude VTE. Therefore, these commonly used clinical decision tools and D dimer measurements should not be used in the diagnosis or exclusion of DVT in pregnancy. Alternative prediction rules like the "LEFt" rule (symptoms in the left leg [L], calf circumference difference of two cm or over [E for edema] and first trimester presentation [Ft]) may be used to exclude DVT when the pre-test probability is low, defined as none of the "LEFt" being present.[349,350]

4.2.3. Investigation of suspected deep vein thrombosis in pregnancy. Ultrasound, ideally WLUS of the lower extremity venous system, is the recommended primary imaging modality. If ultrasound is negative and a high level of clinical suspicion still exists, then repeat WLUS with visualisation of the iliac veins can be performed, or an alternative diagnostic test offered. If repeat testing is negative, anticoagulant treatment can then be withheld.[339,345] For the diagnosis of iliac vein thrombosis, unenhanced MRV, magnetic resonance direct thrombus imaging, or conventional contrast venography may also be considered.[339] However, there are concerns of potential risks to the foetus exerted by the acoustic noise and the heating effects from radio-frequency pulses.[351]

Almost half of patients with VTE in pregnancy will have a thrombophilia.[352] However, performing thrombophilia testing during the acute thrombosis may yield misleading results and is not recommended. Levels of physiological anticoagulants may fall, particularly if thrombus is extensive. In addition, protein S levels are low in normal pregnancy and an acquired APC resistance is found with the APC sensitivity ratio test in around 40% of pregnancies, due to the physiological changes in the coagulation system. As in non-pregnant individuals the results of thrombophilia testing will not influence the immediate management of acute VTE unless the patient has AT deficiency, which will affect the efficacy of LMWH. The finding of aPL antibodies will indicate the need for more intensive foetal monitoring as the antibody can cause placental dysfunction.[78] In summary, routine thrombophilia testing is not recommended in pregnancy outside of aPL testing and also considering measuring AT levels in those with a strong family history of VTE.

4.2.4. Treatment of deep vein thrombosis in pregnancy. Anticoagulant therapy should be started as soon as possible where DVT is suspected, even before imaging, if imaging is delayed. Before initiation of anticoagulation, a full blood count, coagulation screen, urea, electrolytes, and liver function tests should be checked. LMWH is the anticoagulant of choice in pregnancy. A systematic review has confirmed its efficacy and safety.[353] Compared with UFH, LMWH is associated with a lower risk of haemorrhage and osteoporosis.[338,345] Neither UFH nor LMWH cross the placenta and are safe for breastfeeding mothers (heparins cross into the breast milk in small amounts, but heparins are not absorbed from the gastrointestinal tract).[354] In view of improved CrCl during pregnancy, a twice daily dosage regimen was initially recommended. However, pharmacokinetic and observational data suggest similar efficacy and safety with once daily dosing.[339,345]

Owing to the predictable pharmacokinetics of LMWH, satisfactory anti-Xa levels (aiming for a peak anti-Xa activity, three hours after injection, of 0.5 − 1.2 IU/mL) are reliably achieved using a weight based dosing regimen. There may be a case for monitoring levels at extremes of body weight ($<$ 50 kg and $\geq$ 90 kg), and in patients with renal disease. Platelet count monitoring is not usually required as HIT is extremely rare in pregnancy.[355] Continuation of the full dose is advised throughout pregnancy.[338]

VKAs should be avoided in pregnancy as they cross the placenta and are associated with increased foetal loss, a specific embryopathy associated with VKA use in the first trimester, as well as foetal haemorrhage (especially intracerebral), at any stage of pregnancy. DOACs are contraindicated in pregnancy or breastfeeding mothers as their use has not been adequately investigated in pregnancy, and because animal studies suggest teratogenicity. It should be noted that such small molecules may be transferred to the fetus or in breast milk to nursing infants.[356,357] Finally, women who became pregnant while on extended treatment with oral anticoagulants (i.e., a VKA or a DOAC) for a past DVT should switch to a LMWH.

4.2.5. Management at delivery and in the postpartum period. A planned induction of labour or caesarean section minimises the risk of delivery for patients on therapeutic anticoagulation. The dose of LMWH can be reduced to a thromboprophylactic dose the day before and omitted until the baby has been delivered. Regional anaesthetic techniques should not be used until 24 hours after the last therapeutic LMWH dose. The epidural cannula should not be removed within 12 hours of the most recent injection,[345] and after removal of the epidural catheter, LMWH should not be given for at least four hours.

If a woman develops a DVT less than two weeks before her anticipated delivery date, the risks of extension of the DVT and/or PE are high. Therefore, elective delivery and the use of IV UFH may be preferable to minimise the window without anticoagulation. A temporary IVC filter may be considered,[358] and should be removed as soon as possible after delivery.[338]

Owing to the prothrombotic state of the puerperium, anticoagulation should be continued for at least six weeks postpartum and possibly longer to ensure a total treatment period of at least three months. Breastfeeding is safe in mothers receiving both heparin and/or warfarin and some mothers may prefer to switch to warfarin. Neonatal vitamin K is recommended in babies of mothers receiving warfarin. PTS is found in $>$ 60% of patients with pregnancy related

DVT, possibly due to the higher prevalence of iliofemoral thrombosis in this population.[359,360]

Recommendation 60		
In pregnant women with suspected deep vein thrombosis, the use of D dimer and Wells score is not recommended.		
Class	**Level**	**Reference**
III	B	Goodacre *et al.* (2018)[348]

Recommendation 61		
In pregnant women with deep vein thrombosis, therapeutic doses of low molecular weight heparin are recommended during pregnancy for at least three months and for at least six weeks postpartum.		
Class	**Level**	**Reference**
I	B	Greer & Nelson-Piercy (2005)[353]

Recommendation 62		
In pregnant women with deep vein thrombosis less than two weeks before the anticipated date of delivery, a temporary inferior vena cava filter filter may be considered.		
Class	**Level**	**Reference**
IIb	B	Harris *et al.* (2016)[358]

4.3. Cancer associated deep vein thrombosis

4.3.1. Epidemiology and pathophysiology. Although malignancy has been recognised as a risk factor for DVT for over a century, an increased risk of recurrent VTE during anticoagulant treatment in such patients *vs.* those without malignancy had not been described until relatively recently.[361] In an observational study of 842 patients, including 181 with known cancer at entry, treated by anticoagulation of variable duration, the 12 month cumulative incidence of recurrent VTE in patients with cancer was 20.7% *vs.* 6.8% in patients without cancer (HR 3.2).[361] The risk was higher in patients with lung or gastrointestinal cancer. Anticoagulation for CAVT is additionally challenging because of an increased risk of bleeding complications. The 12 month cumulative incidence of major bleeding in this study was 12.4% in patients with cancer and 4.9% in patients without cancer (HR 2.2).[361] Recurrence and bleeding were both related to cancer severity and occurred predominantly during the first month of anticoagulant therapy. Of note, recurrent thrombosis and bleeding complications could not be solely explained by under or over-anticoagulation. At the time of recurrence, the anticoagulation levels were in or greater than the therapeutic range in a higher proportion of patients with cancer (83.3%) than in patients without cancer (57.6%; $p = .030$). At the time of bleeding, the level of anticoagulation was above the therapeutic range in similar proportions of patients with cancer (23.5%) and without cancer (34.8%; $p = .50$). In a recent population based cohort study on the epidemiology of first and recurrent VTE in patients with active cancer treated by anticoagulation for a variable period of time, a high incidence of recurrent DVT was reported (8.8 cases per 100 person years).[362] This rate was 20.2 for the first six months, dropping to 8.4 between six and 12 months, to 6.2 during the second year and to approximately three to four cases per 100 person years for the following three years. A remarkable 64.5% one year mortality rate was reported to be due to the advanced stage of their cancer.

A detailed presentation of the pathophysiology and risk factors of CAVT is beyond the scope of this guideline and can be found elsewhere.[363] In brief, risk factors for CAVT can be grouped into tumour related factors (including type of malignancy, time since diagnosis, and stage), patient related factors (including history of VTE or varicose veins), treatment related factors (e.g., pharmacological, surgical, or radiation therapies), and the presence of specific biomarkers (e.g., D dimer).[363]

4.3.2. Treatment of cancer associated venous thrombosis

4.3.2.1. Results of meta-analyses of randomised controlled trials. The relative efficacy and safety of LMWHs, DOACs, and VKAs for the treatment of CAVT was investigated in a network meta-analysis of 10 RCTs that included 3 242 patients with cancer.[364] In the indirect network comparison of DOACs with LMWHs, a comparable efficacy was demonstrated (RR 1.08; $p = .81$), and a non-significant RR towards improved safety with DOACs (RR 0.67). It should be noted that in the original trials, treatment with LMWH or a DOAC was assessed only for a period of about six months, while the number of patients with cancer was a limited percentage of all patients enrolled in the trials. Also, cancer status at the time of enrollment in the DOACs trial was not reported.

A recent meta-analysis identified 23 RCTs with 6 980 patients.[365] LMWHs were more effective than VKAs in preventing recurrent VTE (RR 0.58, 95% CI 0.45 — 0.75) and DVT (RR 0.44, 95% CI 0.29 — 0.69). DOACs were more effective than VKAs in preventing recurrent VTE (RR 0.65, 95% CI 0.45 — 0.95), but equivalent regarding overall mortality or bleeding. However, anti-Xa DOACs were more effective than VKAs (RR for VTE 0.64, 95% CI 0.42 — 0.97) and caused less bleeding, although major bleeding was reduced only with DOACs not requiring initial parenteral anticoagulation with heparin, i.e., rivaroxaban and apixaban (RR 0.45, 95% CI 0.21 — 0.97).

4.3.2.2. Results of randomised controlled trials comparing low molecular weight heparins with direct oral anticoagulants. Direct comparison between LMWHs and DOACs is the only rational way to provide level A evidence and inform anticoagulation practice in this field. At the time of writing, four RCTs have reported findings. In the first open label, non-inferiority trial, the Hokusai VTE Cancer Investigators randomly assigned 1 050 patients with cancer who had acute symptomatic or incidental VTE to receive either LMWH for at least five days followed by oral edoxaban (60 mg once daily) or subcutaneous dalteparin (200 IU/Kg for one month reduced to 150 IU/kg, once daily).[366] Treatment was given for 6 — 12 months. The primary

outcome (composite of recurrent VTE or major bleeding at one year) occurred in 12.8% in the edoxaban group and in 13.5% in the dalteparin group (HR 0.97; p = .006 for non-inferiority and $p = .87$ for superiority). Recurrent VTE occurred in 7.9% and 11.3% in the edoxaban and dalteparin groups, respectively ($p = .09$). Major bleeding occurred in 6.9% and 4.0% in the edoxaban and dalteparin groups, respectively ($p = .04$); however, the frequency of major bleeding categorised as an emergency was similar in the two groups, considering that the study was probably underpowered for this end point. In a subsequent analysis, the excess of major bleeding with edoxaban was confined to patients with gastrointestinal cancer.[367]

In SELECT-D, an open label pilot trial, 406 patients with active cancer who had VTE were allocated to dalteparin (same doses as in Hokusai VTE Cancer) or rivaroxaban (15 mg twice daily for three weeks, then 20 mg once daily).[368] Treatment was given for six months. The six month cumulative VTE recurrence rate was 11% with dalteparin and 4% with rivaroxaban (HR 0.43, 95% CI 0.19 — 0.99). The six month cumulative rate of major bleeding was 4% for dalteparin and 6% for rivaroxaban (a non-significant HR of 1.83, 95% CI 0.68 — 4.96). However, clinically relevant non-major bleeding rates were 4% and 13%, respectively (HR 3.76, 95% CI 1.63 — 8.69).

In a third open label RCT comparing apixaban (10 mg twice daily for seven days followed by 5 mg twice daily) and dalteparin (same doses as in the previous two trials) in patients with active cancer who developed VTE (Apixaban and Dalteparin in Active Malignancy [ADAM] VTE trial), 300 patients were randomised and 287 were analysed.[369] Unlike the two previous RCTs, patients with UEDVT or splanchnic vein thrombosis were also included and comprised about 30% of patients. Recurrent VTE occurred in 0.7% of apixaban *vs.* 6.3% of patients on dalteparin (HR 0.099; $p = .028$). Major bleeding occurred in 0% of patients receiving apixaban *vs.* 1.4% of patients receiving dalteparin ($p = .14$). Major bleeding or clinically relevant non-major bleeding rates were 6% for both groups.

In a fourth open label non-inferiority RCT comparing apixaban with dalteparin in patients with cancer (CARAVAGGIO) who had symptomatic or incidental acute proximal DVT or PE, 32 of 576 patients (5.6%) receiving apixaban and 46 of 579 patients (7.9%) receiving dalteparin developed recurrent VTE (HR 0.63; p < .001 for non-inferiority).[370] Major bleeding rates were similar in the two study groups (3.8% *vs.* 4.0%; HR 0.82 [$p = .60$]). Of note, CARAVAGGIO included a small number of patients with malignancies of the upper gastrointestinal tract, associated, among others, with an increased risk of bleeding.

A meta-analysis of these four RCTs is shown in Figs. 12 and 13. It is evident that although anti-Xa DOACs are more effective than dalteparin in preventing VTE recurrence, there is a non-significant trend for increased major bleeding, without a significant difference between the three types of DOAC; it should be noted that VTE events by far outnumber major bleedings and that cancer types responsible for excessive bleeding were not excluded, which prompts for an individual patient data meta-analysis.

A few additional, albeit small, RCTs are still ongoing and their results are awaited.[363,371]

4.3.2.3. Practical considerations. Anticoagulation with LMWH, fondaparinux, rivaroxaban, apixaban, or UFH are acceptable therapeutic options for initial anticoagulation in patient with CAVT, while anticoagulation with LMWH, fondaparinux, DOACs (rivaroxaban, apixaban, or

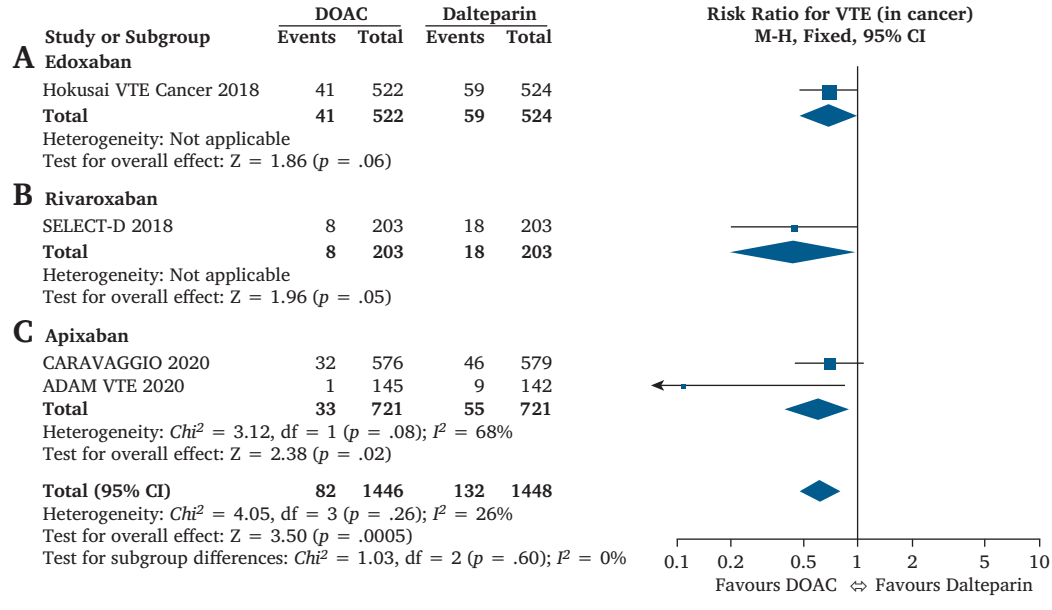


Figure 12. Forest plot analysis of randomised controlled trials comparing a direct oral anticoagulant (DOAC), (A) edoxaban, (B) rivaroxaban, or (C) abixaban, with dalteparin for cancer associated venous thrombosis, regarding the outcome of venous thromboembolism (VTE). M-H = Mantel–Haenszel; CI = confidence interval; ADAM = Apixaban and Dalteparin in Active Malignancy.

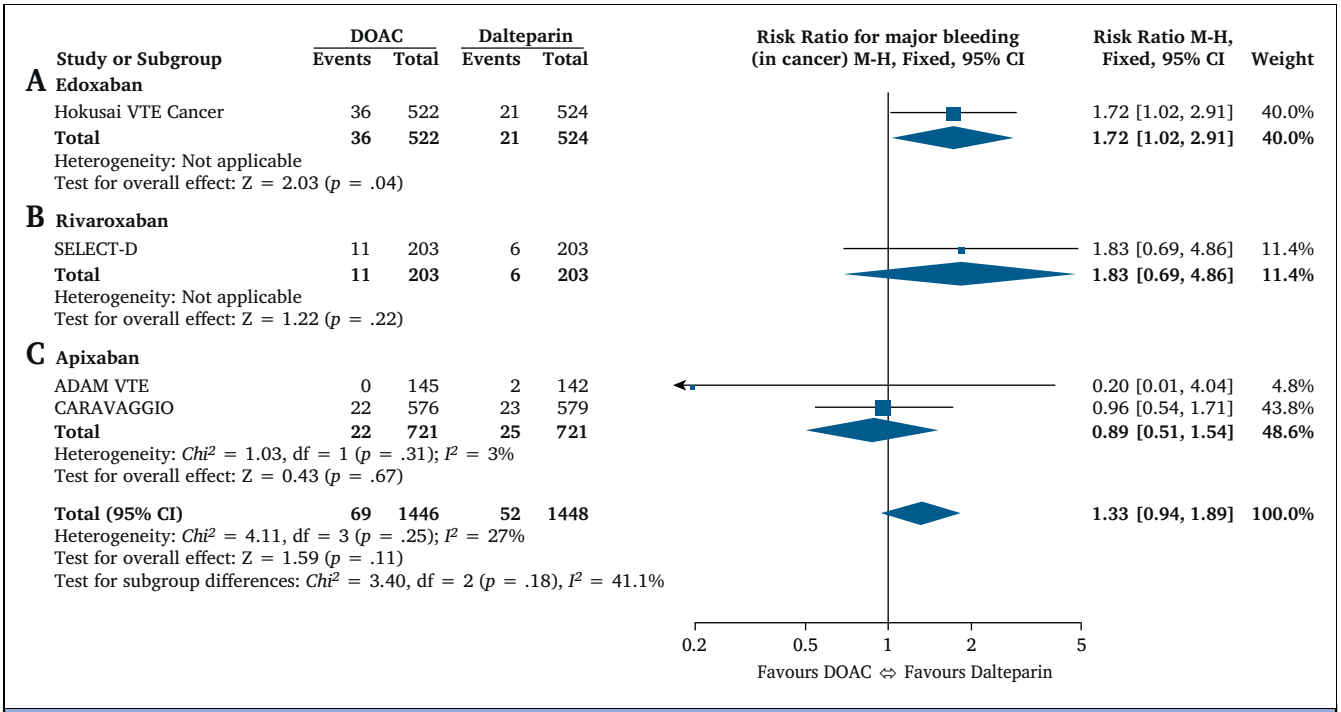


Figure 13. Forest plot analysis of randomised controlled trials comparing a direct oral anticoagulant (DOAC), (A) edoxaban, (B) rivaroxaban, or (C) abixaban, with dalteparin for cancer associated venous thrombosis, regarding the outcome of major bleeding. M-H = Mantel–Haenszel; CI = confidence interval; VTE = venous thromboembolism; ADAM = Apixaban and Dalteparin in Active Malignancy.

edoxaban), UFH, or VKAs are acceptable therapeutic options for principal anticoagulation.[365,369] See also sections 2.3.3, 4.6 for patients with renal impairment, and 4.7 for patients with extreme body weight. In general, for patients with CAVT, anticoagulation should be continued for as long as the cancer is active, considering that rates of late recurrence, after two to three years, are generally much lower than observed in the first two years.[362] The evidence supporting low dose DOAC therapy in a patient with active cancer is lacking,[140,154] and the GWC suggest that patients with active cancer should not be offered a reduced DOAC dose for extended treatment, pending results of ongoing RCTs. Because of considerations regarding the extended use of LMWH beyond six months (risk of osteoporosis or HIT), it is common practice to switch to a VKA. Patients with DVT and an active non-gastrointestinal or genitourinary cancer without thrombocytopenia, liver, or renal failure, who are not on chemotherapy or have a low risk of interaction with chemotherapy agents, should be considered for a DOAC instead of a VKA for the principal treatment phase. This is owing to the safety profile of the DOACs, particularly anti-Xa DOACs not requiring initial parenteral anticoagulation with heparin (i.e., rivaroxaban or apixaban).[365] Management of recurrent VTE in patients with cancer follows the principles provided elsewhere in the document, with additional consideration of mechanical compression from tumour masses.[372]

Recommendation 63

For patients with cancer associated deep vein thrombosis, a low molecular weight heparin is recommended for initial and principal phase anticoagulation.

Class	Level	Reference
I	A	Kirkilesis *et al.* (2019)[365]

Recommendation 64

For patients with active cancer associated deep vein thrombosis, switching from a low molecular weight heparin to an oral anticoagulant is recommended after three to six months of treatment for extended treatment.

Class	Level	Reference
I	C	Consensus

Recommendation 65

In selected patients with cancer associated deep vein thrombosis, with the malignancy not located in the gastrointestinal or genitourinary systems, an approved direct oral anticoagulant for initial, principal, and extended treatment should be considered.

Class	Level	References
IIa	A	Posch *et al.* (2015),[364] Kirkilesis *et al.* (2019),[365] Kraaijpoel *et al.* (2018),[367] McBane *et al.* (2020),[369] Agnelli *et al.* (2020)[370]

4.4. Deep vein thrombosis in patients with thrombophilia

4.4.1. General management of deep vein thrombosis in patients with thrombophilia. Details of testing for hereditary and acquired thrombophilias are provided in Chapter 2.2.5.

The term thrombophilia is conventionally used to describe a propensity for developing thrombosis owing to the presence of hereditary and/or acquired prothrombotic abnormalities.[75,373] The hereditary thrombophilias can be classified as either (1) loss of function of natural coagulation inhibitors (i.e., AT, protein C, and protein S deficiencies); or (2) gain of function with mutations in clotting proteins (i.e., factor V Leiden and prothrombin G20210A mutations).[374,375] The accurate planning of anticoagulant therapy necessitates a thoughtful comprehension of VTE pathogenesis. Clinical thrombophilia includes (1) patients with a strong family history and a confirmed thrombotic episode and (2) patients who have more than one first degree relative with VTE. Such a clinical thrombophilia is associated with identified genetic prothrombotic anomalies in about 50% of cases. The most important acquired hypercoagulable states leading to VTE are APS, acquired deficiency of coagulation inhibitors (e.g., liver failure, nephrotic syndrome, and L-asparaginase treatment), myeloproliferative syndromes with JAK2V617F mutation, and PNH. Their prevalence and relative risks for development of VTE are shown in Table 20. APS is a systemic autoimmune disorder characterised by thrombotic and/or obstetric complications and persistently positive aPL antibodies.[376] In reality, VTE is related to a complex synergistic multifactorial process associating genetic and epigenetic factors with environmental triggering factors (surgery, trauma, pregnancy, immobilisation, acute medical illness, cancer, etc.) and various lifestyle parameters (obesity, smoking, stress, sedentary lifestyle, etc.). Therefore, even in the presence of thrombophilia, holistic identification of risk factors is recommended on an individual basis to optimise treatment duration.[75]

Owing to the lack of RCTs, the recommendations for VTE treatment in patients with thrombophilia are based on a low level of evidence. The presence of a thrombophilic defect is only one of many elements that determine risk. Therefore, the utility of thrombophilia testing to inform treatment decisions is controversial.[377] Decisions for extended anticoagulation should be taken on an individual basis regardless of their biological thrombophilia status.[377] The benefits of anticoagulation must outweigh the risk of bleeding, especially in elderly patients and a haematologist experienced in the diagnosis and management of thrombophilias and hypercoagulable disorders should be consulted.[377,378] For patients with hereditary thrombophilia the prolongation of anticoagulant treatment should be considered after careful evaluation of the number of previous VTE episodes, the presence of provoking factors, the proximal extent of the thrombosis, symptom severity, type of thrombophilia, bleeding risk, and patient preferences.[379]

4.4.2. Specific considerations. Observational studies indicate that anticoagulants are equally effective in patients with and without thrombophilia.[377,378] The risk of recurrent VTE after stopping anticoagulant therapy may be higher in patients with thrombophilia.[378] However, the risk of recurrent VTE after stopping anticoagulant therapy is not uniform for all thrombophilias. It is higher in patients with severe hereditary thrombophilia (i.e., AT deficiency, combined deficiencies, homozygous factor V Leiden mutation or FII G20210A mutation, or combined heterozygous factor V Leiden and

Table 20. Prevalence and relative risk of development of venous thromboembolism (VTE) of the most common hereditary and acquired haematological alterations related to clinical thrombophilia[71,380–387]

Thrombophilia deficiency/ mutation	Prevalence in the general population − %	Prevalence in patients with VTE − %	Relative risk of first VTE *vs.* community controls
Heterozygous AT	0.02	1	10–30
Heterozygous PC	0.2–0.5	1–3	10
Homozygous PC			Very high risk
Heterozygous PS	0.1–0.7	1–2	8
Homozygous PS			Very high risk
FV Leiden heterozygous	2–15	10–20	3–7
FV Leiden homozygous	0.06–0.25	–	80
FII G20210A heterozygous	1–2	3–5	3–7
FII G20210A homozygous	Rare	Rare	10–20
Combined heterozygous in FV Leiden and FII G20210A or other genetic risk factor (two or more defects)	Rare	Rare	10–20
FVIII > 150%	11	25	2
MTHFR polymorphisms with hyperhomocysteinaemia	5	10	1.5
Antiphospholipid syndrome	2	4–15	7–10
JAK2 mutation	0.1–0.2	3.2 (mainly with splanchnic vein thrombosis)	2–3
Dysfibrinogenaemia	Rare	Rare	5–7
PNH	1–9/100 000	Rare	3–5

AT = antithrombin; PC = protein C; PS = protein S; FV = factor V; FII = factor II; FVIII = factor VIII; MTHFR = methylenetetrahydrofolate reductase; JAK2 = Janus kinase; PNH = paroxysmal nocturnal haemoglobinuria.

FIIG20210A mutations), as well as in patients with APS *vs.* those with thrombophilia of moderate severity.[380–382]

Hereditary VTE risk depends on the genotype and is highest in those with defects of the natural anticoagulants (AT, protein C, and protein S) or homozygosity for factor V Leiden. VTE risk is also higher in patients with more than one hereditary thrombophilia, and in those with a co-existing acquired thrombophilic risk factor such as pregnancy, puerperium, combined oral contraceptive pill use, surgery, or trauma. Patients with more severe, homozygous, or multiple thombophilic traits often present at a younger age, have thromboses in unusual sites, recurrent VTE, or a clear family history.

4.4.3. Use of direct oral anticoagulants for patients with thrombophilia. The gold standard treatment of a patient with APS with VTE remains VKAs with a target INR of 2 — 3 after an initial overlap with heparin.[376] The use of DOACs in thrombophilia remains controversial owing to the paucity of available data.[388] Only one randomised, double blind, controlled trial evaluated the efficacy of dabigatran in patients with thrombophilia. A post hoc, subgroup analysis was conducted on data from the RE-MEDY trial. Approximately 18% of the patients in each arm (dabigatran and active control) had known thrombophilias at baseline, most commonly factor V Leiden mutation.[141] Dabigatran demonstrated non-inferiority, compared with warfarin in patients with thrombophilia in terms of recurrent VTE or VTE related deaths.[389] Owing to their frequency, it is probable that a significant proportion of patients included in phase III trials had undiagnosed moderate thrombophilias without any efficacy or safety concerns.[389] Small, real world series of patients with thrombophilia receiving DOACs have indicated that these patients can be treated safely and effectively.[141,388–390] A recent meta-analysis has reported that rates of VTE recurrence and bleeding events were both low and comparable in patients with various thrombophilias receiving either treatment, suggesting that DOACs are an appropriate treatment option in this population but, owing to limited data, it is unclear whether these findings apply to specific subgroups such as high risk APS and uncommon thrombophilias.[391] Patients with APS are clinically heterogeneous, and anticoagulation intensity and duration should be decided after consideration of the risk of recurrent thrombosis, bleeding risk, the clinical phenotype, and risk profile.[392] Based on recent RCTs of DOACs compared with VKAs, and a patient level data meta-analysis of observational studies, caution is required in patients with major thrombophilias such as triple positive APS or APS with a history of previous arterial or small vessel thrombosis, in whom DOACs are not recommended.[390,393–397] The question of DOAC use in patients with a history of isolated venous thrombosis and a lower risk aPL profile remains unsolved.[69] DOACs may be considered when there is a known VKA allergy/intolerance or poor anticoagulant control,[392,394] recognising that recurrent VTE episodes while on DOACs are mostly related to non-adherence, which highlights the importance of patient education for such high risk situations. Further, larger, ongoing studies may provide better long term efficacy and safety data on more homogeneous populations before DOACs can be widely recommended.[398]

For catastrophic APS therapy a combination of glucocorticoids, therapeutic UFH, and plasmapheresis or IV immunoglobulins are recommended as the first line therapy.[70]

Recommendation 66

For patients with deep vein thrombosis and high risk thrombophilia (e.g., antiphospholipid syndrome, homozygous factor V Leiden mutation, or deficiencies of protein C or S, or antithrombin), full dose extended anticoagulant therapy is recommended with periodic re-evaluation.

Class	Level	References
I	C	Tektonidou *et al.* (2019),[69] Nicolaides *et al.* (2013)[117]

Recommendation 67

For patients with deep vein thrombosis and antiphospholipid syndrome who are triple positive or have a history of arterial or small vessel thrombosis, direct oral anticoagulants should not be used.

Class	Level	References
III	B	Tektonidou *et al.* (2019),[69] Pengo *et al.* (2018),[395] Malec *et al.* (2020),[396] Ordi-Ros *et al.* (2019)[397]

Recommendation 68

For patients with deep vein thrombosis and triple positive antiphospholipid syndrome, treatment with a vitamin K antagonist titrated to maintain a target international normalised ratio between 2–3 should be considered.

Class	Level	Reference
IIa	B	Pengo *et al.* (2018)[395]

Recommendation 69

For patients with deep vein thrombosis and a high risk thrombophilia, long term follow up by a thrombophilia expert is recommended.

Class	Level	Reference
I	C	Consensus

4.5. Deep vein thrombosis in patients with inferior vena cava developmental anomalies

Normal embryological development of the IVC occurs between four and eight weeks of life, from complex fusion of the three pairs of cardinal veins. Anomalies of the IVC are relatively common, frequently involving the left renal vein or a duplicated IVC system. However, atresia or stenosis of the IVC also occurs and has been described in patients with iliofemoral DVT events, typically in patients aged < 30 years, presenting with uni- or bilateral extensive DVT. There is circumstantial evidence from reported cases that IVC

"atresia" is not always a congenital anomaly, but may also be the consequence of an often undiagnosed (ilio)caval DVT related to CVC insertion in the neonatal period and/or severe disease during the first year of life. It remains unclear whether IVC anomalies predispose to DVT, or DVT recurrence, as the evidence base consists of case reports/series only. It is clear that many people are entirely asymptomatic for many years with fairly extensive and dramatic anomalies.[399] The main implications for patients with iliofemoral DVT may be for acute thrombus removal,[400] and duration of anticoagulation after DVT[399] in patients with IVC anomalies. While early thrombus removal may be entirely feasible, adjuvant stenting procedures may be highly complex if extensive iliocaval stenting is required.

4.6. Deep vein thrombosis in patients with renal impairment

Chronic kidney disease (CKD) is associated with a significant increase in the risk of recurrent VTE.[401] Conversely, DVT treatment in patients with CKD (and similarly with acute kidney injury) is challenging, because of the increased risk of bleeding. For patients with DVT and end stage renal disease (CrCl $<$ 15 mL/minute), LMWHs, fondaparinux, and DOACs are not recommended. A recent meta-analysis reported on five anticoagulation trials in patients with VTE. In the control group of nearly 14 000 patients treated with warfarin, patients with a CrCl between 30 and 50 mL/minute had a higher risk of bleeding than those with a CrCl $>$ 50 mL/minute (RR 1.49; p = .003).[402] Patients with CKD and DVT are traditionally managed with IV UFH followed by a VKA, as the intensity of anticoagulation can be easily titrated. In severe or moderate CKD (CrCl 15 — 59 mL/minute), LMWHs or fondaparinux should be prescribed with caution, at an adjusted dose with monitoring of anti-Xa levels, or not recommended, depending on the formulary and the severity of CKD, to prevent bioaccumulation and bleeding, particularly in advanced CKD (CrCl $<$ 30 mL/minute).[403,404]

LMWHs are used to treat the acute phase of DVT and switched to VKAs, and in patients with cancer they are also recommended for the principal and extended treatment (see Chapter 4.3). The reader is referred to the SPC of the various LMWHs and fondaparinux for further information on dosing and precautions in CKD. In recent years the relative efficacy and safety of DOACs *vs.* VKAs in patients with VTE and with mild to moderate CKD (CrCl 30 — 80 mL/minute) has been confirmed in the initial/principal and extended treatment of DVT.[120,130,131,140,141,405] Rivaroxaban, apixaban, and edoxaban are not recommended in patients with a CrCl $<$ 15 mL/minute, which is raised to 30 mL/minute for dabigatran. However, the GWC acknowledges that this a rapidly moving field, after the USA Food and Drug Administration approved apixaban for treating atrial fibrillation in patients with end stage renal disease, where dose monitoring may play a role in the future in patients with DVT. Periodic re-assessment of renal function in patients with severe or moderate CKD receiving LMWH, fondaparinux or a DOAC could be helpful in preventing bioaccumulation and bleeding.

Recommendation 70

For patients with deep vein thrombosis and chronic kidney disease requiring anticoagulation, monitoring of anticoagulation levels and dose reduction should be considered as most anticoagulants are renally excreted.

Class	Level	Reference
IIa	C	Consensus

Recommendation 71

For patients with deep vein thrombosis and chronic kidney disease treated with a low molecular weight heparin, fondaparinux, or a direct oral anticoagulant, periodic re-assessment of renal function is recommended.

Class	Level	Reference
I	C	Consensus

4.7. Deep vein thrombosis in patients with extremes of body weight

Treatment of DVT in patients with very low or very high body weight may be challenging. In a recent meta-analysis including five trials investigating patients with VTE, patients with a low body weight (defined as $<$ 50 or 60 kg) treated with warfarin had a higher risk of bleeding than those with a normal body weight (RR 1.20; p = .05).[402] Traditionally, the dose of UFH, LMWHs, and fondaparinux is adjusted according to the body weight to reduce bleeding in underweight patients and recurrent VTE in overweight patients; the reader is referred to the SPC of the various agents. Fixed dose rivaroxaban or edoxaban is not associated with an increased risk of major recurrent VTE or bleeding in patients with either a low or high bodyweight.[131,406]

A non-significant trend for higher efficacy of apixaban compared with warfarin in those with a BMI $>$ 30 kg/m^2 (p = .06) has been reported, with no effect on bleeding.[130] In a cohort study of 13 510 obese patients (BMI $\geq$ 30 kg/m^2) with VTE, prescription of rivaroxaban was associated with a significantly reduced risk of recurrent VTE compared with warfarin (HR 0.63 at 12 months), without any effect on major bleeding. The results remained consistent across BMI classes (30.0 — 34.9, 35.0 — 39.9, and $\geq$ 40 kg/m^2).[407] Similar findings for the efficacy of dabigatran have been reported in this specific population, but no results on any potential modulators of bleeding have been presented.[133,141] RCTs on DOACs had no weight restrictions.[120,130,140]

Recommendation 72

For underweight or overweight patients with deep vein thrombosis requiring anticoagulation, it is recommended to adjust the dose of unfractionated heparin, low molecular weight heparins, and fondaparinux.

Class	Level	Reference
I	C	Consensus

5. UNRESOLVED ISSUES

The GWC has identified the following issues, where the available evidence is currently insufficient to guide clinical practice.

5.1. Aetiology of deep vein thrombosis

The cause of racial disparities in the incidence of DVT is largely unknown and deserves further investigation. This observation may be related to the many unknown causes of unprovoked DVT, frequently called "unknown thrombophilias".

5.2. Work up in patients with suspected or proven deep vein thrombosis

The benefits of screening for PE in subgroups of patients with DVT, such as those with ECG or CXR abnormalities, free floating thrombus, cardiac biomarkers suggesting possible pulmonary involvement, or increased bleeding risk are not fully understood to guide current practice.

The effectiveness of testing for undiagnosed cancer in people with a first episode of unprovoked DVT in reducing cancer or VTE related morbidity and mortality is currently unclear.

5.3. Treatment of deep vein thrombosis

The interaction and additive effect of risk factors for bleeding is unclear.

The effectiveness and safety of fondaparinux in treating HIT has not been fully studied.

The use of an IVC filter is recommended as the only viable treatment option for patients with DVT in whom anticoagulation is contraindicated; however, the long term effects of IVC filters remain undetermined.

Management of post-intervention thrombosis is an area with very little evidence.

5.4. Prevention of post-thrombotic syndrome

The heterogeneity of the clinical effectiveness of ECS in PTS prevention is heterogeneous and largely unexplored.

High quality randomised trials of thrombus removal strategies are still required owing to flaws in CaVenT and ATTRACT, and changes in devices and international practice since publication.

5.5. Calf deep vein thrombosis.

For patients with calf vein DVT, the decision to prescribe anticoagulation is based on low level evidence due to the almost complete lack of RCTs specific for each clinical scenario.

The suggestion for extended anticoagulation in patients with calf CAVT is merely based on observational data on risk and not on trial evidence.

5.6. Superficial vein thrombosis

For patients with SVT, there is no evidence that intermediate doses of LMWHs reduce VTE (DVT and/or PE) *vs.* placebo.

A paucity of information is recognised for patients with SVT near a junction with the deep veins regarding length of therapeutic anticoagulation.

The suggestion on extending anticoagulation beyond 45 days in selected patients with SVT is based on observational data and not an RCT.

5.6. Specific types of deep vein thrombosis and patient populations

For patients with suspected UEDVT, the relative sensitivity and specificity of the various diagnostic modalities are based on small studies.

The role of first rib resection after UEDVT remains very controversial owing to the lack of high quality prospective and randomised studies.

The use of IVC filters in pregnant women developing DVT less than two weeks before the anticipated date of delivery is not based on trial evidence.

For patients with CAVT, the exact role of DAOCs has not been fully studied.

The relative effectiveness and safety of the various types of anticoagulation in patients with thrombophilia has not been fully studied.

6. RECOMMENDATIONS FOR FUTURE RESEARCH

The GWC has identified the following areas where further research may help the decision making process and better guide clinical practice.

6.1. Aetiology of deep vein thrombosis

The cause of racial disparities in the incidence of DVT deserves further investigation.

Further research to identify the cause of DVT in patients with apparently unprovoked DVT may broaden our knowledge and lead to mechanism specific treatment in the future.

6.2. Work up in patients with suspected or proven deep vein thrombosis

Algorithms employing pre-test probability and D dimer assessment deserve extermal validation in the context of large RCTs, incorporating cost effectiveness analyses to justify CUS instead of WLUS.

The exact place of magnetic resonance direct thrombus imaging and other novel modalities in distinguishing between acute recurrent thrombus and a persisting thrombus in the same location requires further study.

6.3. Treatment of deep vein thrombosis

The interaction and additive effect of risk factors for bleeding requires external validation.

IVC filter use is recommended as the only viable treatment option for patients with deep vein thrombosis in whom anticoagulation is contraindicated; however, the low level of evidence for this indication prompts for further research.

6.4. Prevention of post-thrombotic syndrome

The clinical effectiveness of ECS in PTS prevention is heterogeneous and should be explored to inform clinical practice.

The contradictory results of CaVenT and ATTRACT should be explored in future trials before thrombus removal strategies become the standard of care for patients with iliofemoral DVT.

6.5. Calf deep vein thrombosis

For patients with calf vein DVT, the use of DOACs is based on extrapolation from trials that included almost exclusively patients with proximal DVT, and therefore further specific trials will be required to provide direct evidence required to increase the level of evidence.

6.6. Superficial vein thrombosis

For patients with SVT, further research should investigate the effectiveness of intermediate doses of LMWHs in reducing VTE (DVT and/or PE) *vs.* placebo.

Future studies on patients with SVT should stratify the thrombotic process by GSV involvement.

6.7. Specific types of deep vein thrombosis and patient populations

The exact place of thrombolysis and first rib resection in treating UEDVT requires clarification.

7. INFORMATION FOR PATIENTS

This information has been developed by the European Society for Vascular Surgery (ESVS). The ESVS produces guidelines to help medical professionals involved in the care of patients with a wide range of conditions related to circulation and blood flow. In this document, a specially convened international group of specialists in venous thrombosis and the ESVS guidelines committee have produced a full set of guidelines and recommendations for healthcare professionals.

The following section contains a summary of the information in the full guideline document, presented in a format suitable for non-experts. Details of the process used to create the guidelines and areas where further research is needed are described at the end of this section. Where there is strong evidence to support a particular treatment, or strong evidence to show that a treatment is not effective, details are summarised in this section. Full details of the guideline are not included in this section, but the reader is encouraged to read the relevant section of the full guideline document or speak to their healthcare professional for further information.

7.1. What is venous thrombosis?

Venous thrombosis is the medical term used when there is a blood clot within a vein. The most common type of venous thrombosis is deep vein thrombosis (DVT) of the leg. Around one in every 1 000 adults each year are affected by venous thrombosis. Most patients suffering from DVT have recently been in hospital (known as hospital acquired thrombosis) or have other risk factors for developing thrombosis. However, in some people, there is no obvious reason for venous thrombosis. In these cases, the venous thrombosis may be described as “unprovoked”, rather than “provoked”, which is used to describe venous thrombosis where there is a clear predisposing cause.

When a blood clot forms within a vein, blood can no longer flow in the normal way. Consequently, the tissues that are drained by the vein become very swollen and painful as the blood can no longer escape. The symptoms experienced vary depending on which veins are affected. In the early period after developing venous thrombosis, the main concerns are that the clot may extend, or a part of the clot may break away (known as an embolus) and travel to the lungs (a “pulmonary embolus”, or PE). This is a serious condition, as up to 10% of people with a PE will die without treatment. Most of the treatments for venous thrombosis aim to reduce the risk of PE. The treatment of patients with a PE is a specialist area and not included in this guideline document.

7.2. Why does venous thrombosis occur?

The specific reasons for venous thrombosis vary from individual to individual. Usually, blood clots in the veins occur because of one or more of the following factors:

- reduced flow in the vein
- damage to the wall of the vein
- increased “stickiness” of the blood, making clotting more probably

There are some specific situations that increase the risk of blood clots (due to affecting the mechanisms above), including increased age, immobility, recent surgery or hospital admission, cancer, pregnancy, use of some types of oral contraceptive pill or hormone replacement therapy, obesity, and long distance travel.

7.3. Which veins can be affected by venous thrombosis?

Venous thrombosis can affect any vein in the body, but some veins are affected more commonly than others. The symptoms, investigations, risks, treatments, and outcomes vary depending on which vein is affected. The most common type of venous thrombosis affects the deep veins in the legs and is known as DVT. Around 10% of DVTs affect the deep veins of the arm, rather than the leg.

Sometimes, the superficial veins of the leg (or, less commonly, the arm) can be affected by venous thrombosis. This is sometimes called “phlebitis”, “thrombophlebitis”, or “superficial thrombophlebitis”. In this guideline document, the term “superficial vein thrombosis” (SVT) is used.

Although a different entity to DVT, patients with SVT are at risk of clot progressing into the deep veins (to become a DVT) and potentially PE. Venous thrombosis can also occur in veins where a medical cannula or line has been inserted (in superficial or deep veins).

Finally, venous thrombosis may also occur in veins in the abdomen, head and neck, and other parts of the body. These conditions are less common, often associated with other medical problems, and will not be included in these guidelines.

7.4. What are the symptoms of deep vein thrombosis?

The usual symptoms of DVT in the leg are pain, and redness and swelling in the calf, which is often tender. Sometimes, the whole leg may be affected, particularly when the DVT is more extensive and affects the veins in the abdomen, as well as the leg. However, each individual is different, and in some cases, there may be few or no outward signs of a problem, particularly when the blood clot only occurs in the calf veins. DVT of the arm may result in a swollen, painful, and warm arm, which may appear blue and discoloured.

When there is SVT, there is often a hard, thickened, red, and painful superficial vein in the leg. The skin over the inflamed vein may appear darker and people who develop SVT often have a history of varicose veins.

7.5. How is a deep vein thrombosis diagnosed?

It is often difficult for medical staff to be certain about the diagnosis of DVT. There are certain features and symptoms that make a DVT more likely. The use of a proven scoring system where medical staff can assess the likelihood of DVT for each individual is recommended before arranging scans or other tests (recommendation 1). Medical teams should also use clear pathways to ensure consistent care for people suspected to have a DVT (recommendation 2). A blood test called the D dimer may also be helpful in deciding whether a DVT is likely or not. However, if a DVT is thought to be likely, performing an ultrasound scan before other scans is recommended (recommendation 3).

In some cases, repeat ultrasound or additional, detailed scans such as computed tomography (CT) or magnetic resonance imaging (MRI) may be needed (recommendation 5). Although some patients with a DVT may need tests for PE, to look for cancers or blood clotting disorders, routine testing for all patients is not recommended as studies do not support this approach (recommendations 7 — 9).

7.6. What is the treatment for deep vein thrombosis?

For most patients with DVT, the principal treatment is medication to thin the blood in order to prevent PE and stop the clot from spreading further in the deep veins. Many different types of blood thinning medications are available, each with different advantages and potential risks. Several studies have been performed to see which blood thinning medications work best and the guideline committee evaluated these trials in detail. For people with a clear reason for their DVT (such as hospital admission or surgery), blood thinning medication for a duration of three months is recommended (recommendation 14) using one of the newer blood thinning drugs (known as direct oral anticoagulants, or DOACs) rather than the traditional blood thinner warfarin (recommendation 16).

Where there is not an obvious reason for the DVT, the risk of further DVT after stopping blood thinning medication is relatively high. Therefore, assuming the risk of bleeding is not too high, extending blood thinning treatment beyond three months is recommended (recommendation 21). For some people with a low risk of further DVT, a lower dose of DOAC medication may be suitable (recommendation 23).

In addition to blood thinning medication, the use of tight bandages or stockings on the leg with DVT, applied within 24 hours of the diagnosis and continued for 6 — 12 months is recommended to improve the pain and swelling in the leg (recommendation 31).

7.7. Are there any ways of removing the clot in a deep vein thrombosis and are they recommended?

For many people with DVT treated with blood thinning medication alone, the leg remains painful and swollen for months or years after the DVT. This is called “post-thrombotic syndrome” (PTS) and in severe cases, the leg may become severely discoloured or develop sores or wounds that do not heal (known as venous ulcers). To try and prevent PTS, some doctors have recommended aggressively removing or breaking up the clot in the veins, soon after the diagnosis of DVT. Although not recommended or necessary for every person with a DVT, these techniques to remove or break up the clot may be helpful for some patients with DVT extending into the veins in the lower abdomen (iliac veins) (recommendation 34). Aggressive clot removal is not recommended where the DVT is only in the calf or thigh (recommendation 35). This is primarily because studies have shown that the outcome is no better after aggressive clot removal for most people with DVT in the thigh or calf only.

7.8. What if my deep vein thrombosis is only in the calf veins?

If the clot only affects the smaller veins in the calf, the symptoms in the leg may be much less severe than a DVT affecting the thigh veins, or there may be no symptoms at all. In general, the risks of PE and recurrent DVT is lower for calf vein DVT. Therefore, it is recommended that the decision of whether or not to prescribe blood thinning medication should be made on a case by case basis, taking into account the risks of bleeding (recommendation 38). If blood thinning medication is prescribed, treatment for three months is recommended, using a DOAC medication (recommendation 40).

7.9. If I have had a deep vein thrombosis, what is my risk of having another one?

The risk of having a further DVT depends on a number of different factors. If there was a clear reason for the DVT (such as recent hospitalisation or surgery), then the risk of further DVT is very low, as long as the cause of the DVT is no

longer present. However, the risk of further DVT is much higher if the initial DVT did not have an obvious cause (known as unprovoked DVT). Between a quarter and half of people with an unprovoked DVT will develop a further DVT if blood thinning medication is stopped. For this reason, long term blood thinning medication should be considered.

7.10. What is the best treatment if I have a superficial vein thrombosis?

SVT most commonly occurs in people who have varicose veins, which are dilated and tortuous veins in the legs. As superficial veins in the leg drain blood into deep veins, there is a risk of clot spreading into the deep veins and becoming a DVT. As the risks from SVT are related to the precise location and length of the clot in the superficial veins, it is recommended that all people suspected of having a SVT should have a detailed ultrasound scan of superficial and deep veins of the leg (recommendation 43). If the clot is longer than 5 cm, between 30 days and three months of blood thinning medication is recommended, depending on how close the clot is to the deep veins (recommendation 47, 49). For some people, treatment of the varicose veins may be necessary in a second stage to prevent further episodes of SVT.

7.11. How should I be treated if I have a deep vein thrombosis of the arm?

Around one in 10 of all DVTs occur in the arm and the most common cause is the presence of a cannula or "drip" used to give medications for cancer and other conditions. Some people develop DVT in the arm after strenuous effort or exercise (known as "effort thrombosis"). In people with effort thrombosis, there is thought to be pressure on the deep veins as they leave the arm, which reduces the flow and causes the clot to form. In general, the principles of treatment for DVT of the arm are the same as for DVT in the leg, to prevent PE, reduce the risk of clot spreading in the vein, and prevent long term problems in the affected limb. The committee noted that there were relatively few studies done on patients with DVT of the arm, so many of the recommendations are extrapolated from DVT in the leg.

As with DVT of the leg, it is recommended that people with DVT of the arm should be treated with blood thinning medication for three months (using a DOAC blood thinner). As most people make a good recovery with blood thinning medication alone, aggressive clot removal or breakdown treatments are not recommened for most patients with DVT of the arm (recommendation 54).

7.12. Are there any special circumstances that should be considered when treating deep vein thrombosis?

There are several situations where DVT treatment may be particularly complex and specific guidance is needed. In children, the risk of DVT is much lower than in adults, but most DVTs are caused by a line or "drip" in the vein. Children with DVT are very different from adults with DVT, as the risks and recovery from venous thrombosis vary and children react to blood thinning medications in a different way. Therefore, it is recommended that children with venous thrombosis should be treated by a specific specialist. Another highly complex area is the treatment of DVT in pregnancy. Pregnancy increases the risk of DVT and clots tend to be much more extensive when they do occur. Many of the commonly used blood thinning medications are not suitable for use in pregnancy owing to dangers to the foetus, so it is recommended that pregnant women with DVT should be treated with specific blood thinning injections (low molecular weight heparins, or LMWHs), which are known to be safe (recommendation 61). As the risk of DVT persists beyond childbirth, it is recommended that LMWH injections should continue until six weeks after childbirth (recommendation 61).

7.13. How should I be treated if I have a condition that predisposes me to getting venous thrombosis?

There are several conditions that cause the blood to be more likely to clot and result in venous thrombosis (known as thombophilias). Many of these conditions are inherited, but some may develop without any genetic contribution. Patients should be treated by an expert with specific knowledge of these conditions (recommendation 69). For certain "high risk" thrombophilias, lifelong blood thinning medication is recommended to reduce the risk of venous thrombosis (recommendation 66).

7.14. What are the areas that need further research?

During the development of this guideline document, the committee identified several areas where the current evidence was weak and further research is needed. Some questions that remain unanswered include:

- What is the best treatment pathway to diagnose and treat patients suspected of having venous thrombosis?
- Which patients with DVT should be offered scans to look for cancer or clots in the lungs?
- What is the best way to assess the risk of bleeding when starting blood thinning medication?
- Which patients should be selected for aggressive clot removal or breakdown in DVT of the leg or arm?
- What are the costs and cost effectiveness of different treatments for DVT?

7.15. How was this information developed and what do I need to know before reading the full document?

The information in this section is a summary of the guideline document produced by the ESVS Venous Thrombosis Guidelines Writing Committee. The committee consists of experts from across Europe who reviewed the available medical evidence to make recommendations about how

venous thrombosis should be managed. At a series of meetings, the committee decided whether there was enough robust evidence to make a firm recommendation that health professionals should follow or not. The document was reviewed by another independent group of international specialists, to double check that the recommendations were accurate and up to date with the most recent evidence. Some of these recommendations could change in the future as research and knowledge increase.

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