NATIONAL CLINICAL GUIDELINE ON VTE (NCG-VTE):

Eve Protocol

Supplementary Appendix

National Clinical Guideline on Venous Thromboembolism (VTE): Prevention, Diagnosis, Acute Treatment and Recovery

Abstract

This supplementary material is linked to sections in the main guideline and referenced in the text and provides detailed information on the evidence used to inform the main guideline including figures, validated instruments, and patient related outcome measures.

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Introduction to the NCG-VTE Supplementary Appendix

This document provides the supplementary material and supporting data accompanying the NCG-VTE (National Clinical Guideline on Venous Thromboembolism (VTE): Prevention, Diagnosis, Acute Treatment and Recovery). This comprises additional information on the evidence used to inform the main guideline, including further information on the figures used and copyright information. The supplementary information/data and figures are linked to chapters and sections within the main guideline for reference. For additional specific guidance for the prevention, diagnosis and management of pregnant patients, refer also to the current National Guideline Recommendations on VTE in pregnancy and postpartum.

PHASE 1 NCG on Venous Thromboembolism: what does this mean?

This document comprises PHASE 1 of a minimum two-phase publication process. In the interests of patient safety, the topics addressed herein have been prioritized for rapid development and publication. This guideline phase is NOT intended to serve as a comprehensive guide to all aspects of VTE care and many additional topics will be addressed in future publications. It is crucial that any patient with a suspected or diagnosed VTE be referred and treated appropriately through existing clinical pathways and governance structures.

1.0 Supplementary information/data linked to NCP-VTE Guideline Executive Summary: Introduction, epidemiology and economic impact of VTE.

1.1 Epidemiology and Impact

VTE comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) and is a major contributor to global disease burden, affecting millions of individuals worldwide every year [1]. The annual incidence is estimated to be 1-2 per 1000 individuals in high-income countries [2-4].

VTE is a common disorder. A nationwide cohort study and a study utilizing data from two large prospective community-based cohort studies have estimated that VTE affects more than **1 in 12 individuals** during their lifetime [4, 5]. In a Danish study, crude VTE incidence rates in women and men were 1.28 (95% confidence interval (CI) 1.27-1.29 and 1.17 (95% CI 1.16-1.18) per 1000 person-years respectively. Incidence rose with age, and reached 4.92-5.73 per 1000 patient-years in people aged ≥80 years [4]. VTE is the leading cause of maternal death in the UK & Ireland and can challenge care for menopausal people and those requiring contraception.

1.2 Clinical Impact

Long-term consequences of VTE affect up to 40-50% of all VTE survivors, and include post-thrombotic syndrome (following DVT), chronic thromboembolic pulmonary hypertension, post-pulmonary embolism syndrome, posttraumatic stress disorder/panic syndrome [6], recurrent VTE and anticoagulant-associated bleeding [3, 7-12].

Despite the incidence, mortality and long-term health impact of VTE, awareness of this condition in the general population is poor. A US survey reported that 75% of respondents had never heard of DVT and that fewer than 1 in 10 had an awareness of DVT symptoms [13]. This is a major clinical and societal risk that should be urgently addressed, given the missed opportunities to prevent death and long term disability.

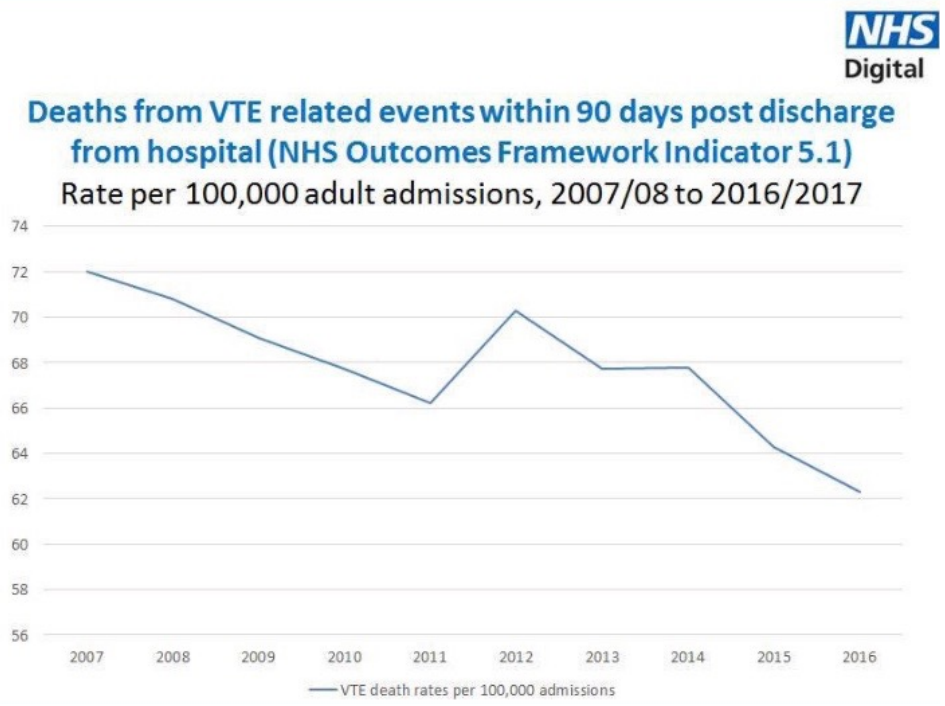
VTE prevention strategies save lives and improve long term health: the data below (**Suppl. Figure 1.1**) are a direct result of implementation of VTE risk assessment strategies at a national level in the UK.

Up to 50-60 percent of all VTE cases occurring during or after hospitalization, such that VTE is a leading preventable cause of hospital death [3, 14, 15]. Recently published Irish data reported a VTE incidence of 1.44 (95% CI 1.36 to 1.51) per 1000 per annum, of which 47% were secondary/ hospital-acquired VTE [16].

The relative risk of VTE has been reported to significantly increase during and after hospitalization compared with community rates [17, 18]. In the U.K, HA-VTE has been significantly reduced following the implementation of a National VTE prevention programme [19]. These and other data demonstrate that HA-VTE is potentially preventable through strategies that may include raised awareness (including awareness of the signs and symptoms of VTE amongst patients), VTE risk assessment and implementation of appropriate thromboprophylaxis [15, 19].

A UK national quality initiative to increase the number of hospitalised patients assessed for risk of VTE, based upon UK National Institute for Health and Care Excellence (NICE) recommendations has resulted in a reduction in VTE mortality [15, 19] (**Suppl. Figure 1.1**). Anticoagulant thromboprophylaxis has also been reported to significantly reduce fatal PE in medical patients with significant VTE risk factors in other developed countries [20-23].

Long term care of patients after a PE diagnosis also improves health, reduces disability and saves costs: PE is a leading cause of death and, importantly, long term disability and poor quality of life [3]. This disability includes a spectrum of symptoms, functional limitation and diminished quality of life that can occur following an acute PE despite appropriate treatment. Growing recognition of this group of symptoms has led to the coining of the term “post-PE syndrome” [24, 25]. Features of this “post-PE syndrome” are common, ranging from 20-75% in recent studies [3, 9, 12, 26].



Suppl. Figure 1.1: Deaths from VTE-related events within 90 days post discharge from hospital (NHS Outcomes Framework 5.1). Rate per 100,000 adult admissions, 2007/08 to 2016/17

1.3 Economic Impact

Long term care of patients after a Pulmonary embolism (PE) diagnosis improves health, reduces disability and is cost-saving. The Post-PE syndrome is common [3, 9, 12, 26]. Associated costs are estimated to be €3,500- 20,000 per patient [27].

VTE is a major burden for health care systems worldwide. The incidence rate of PE is rising in Europe and the United States [28].

- Prevention of hospital-acquired VTE has a major potential economic benefit: It is estimated that in the US, approximately 1600 USD per discharge is saved by appropriate thromboprophylaxis [29]
- 2008 American College of Chest Physicians (ACCP) guidelines reported that pharmacological prophylaxis resulted in net cost savings of approximately $2,900 per patient compared to no prophylaxis, mainly due to reduced VTE-related treatment costs [30].
- In keeping with ISTH data, a 2016 Europe-wide study calculated total, hospital-associated and preventable VTE-related costs ranging from **€1.5-13.2 billion**, €1.0-9.7 billion, €0.5-7.3 billion and €0.2-6.1 billion, respectively, demonstrating that VTE costs have a large financial impact upon the EU-28's healthcare systems and that significant savings could be realised if better preventive and long-term health management measures are applied [31].
- A Danish nationwide population-based cohort study reported that permanent work-related disability pensions were granted to 4,415 individuals with VTE and 9,237 comparison cohort members (incidence rates 17.8 and 6.2 per 1,000 person years, respectively). VTE was associated with a 3-fold (HR 3.0, 95% CI: 2.8-3.1) higher risk of receiving a disability pension [32]. Post-PE and DVT long term pathways could impact this economic burden.
- A large European prospective registry study with a bottom-up approach based on data from the PREFER in VTE registry (Prevention of Thromboembolic Events-European Registry in Venous Thromboembolism) calculated direct and indirect costs of an acute PE event. Disease-specific costs in the first year of follow-up were **€9135-10,620** [28]. Post-PE long term pathways could impact this economic burden.
- A 2020 cost-effectiveness analysis showed that evidence-based diagnostic strategies are associated with potential of cost savings of >$80 million per year for the United States health care system. On average, On average, costs per patient were lower in the evidence based strategy mainly because of the decreased use of radiological imaging [33].
- A 2022 systematic review that informed American Society of Haematology guidelines showed that for DVT diagnosis, studies supporting strategies with D-dimer and/or ultrasound were cost-effective, supporting the recommendation that for patients at low (unlikely) VTE risk, using D-dimer as the initial test reduces the need for diagnostic imaging [34].
- An OECD report states that interventions to reduce VTE harm represent one of the greatest value for money opportunities [35]. VTE is cited in this report as being the 2nd costliest adverse event type [35, 36].

1.4 Impact on admissions and hospital bed days

Patients presenting with acute DVT of PE are traditionally admitted to the hospital for acute management. However, recently published guidelines and consensus statements suggest that, when appropriate infrastructure and appropriate care pathways exist, many of these patients may be managed as outpatients [3]. This approach supports Sláintecare in the development of outpatient and community-based services, and re-orientation of care to the community to reduce the demand for in-patient acute hospital services. A lean, rapid-access (<4 hours), community-based deep vein thrombosis (DVT) diagnostic pathway can deliver significant bed day savings. In Denmark, such a strategy was safe and effective and was associated with a ~60% decrease in resource utilization in comparison to the previous pathway [37].

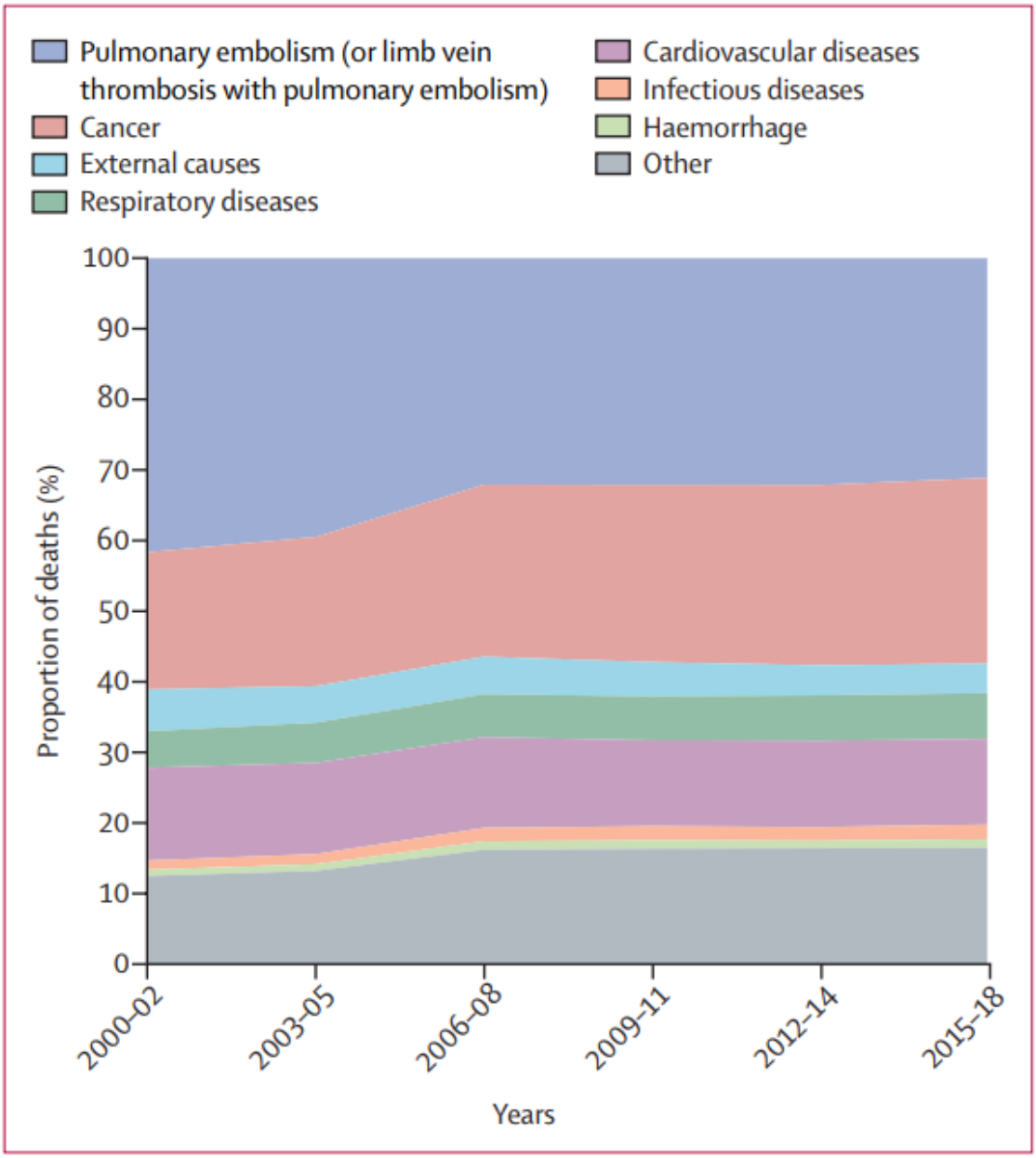
1.5 Patient Safety

VTE prevention strategies save lives and improves long term health. In the U.K., hospital-associated VTE has been significantly reduced following the implementation of a National VTE prevention programme [19]. These and other data demonstrate that HA-VTE is potentially preventable in many cases through VTE risk assessment and implementation of appropriate thromboprophylaxis [15, 19].

[1]HA-VTE, defined as a VTE event occurring either during or up to 90 days following hospitalization

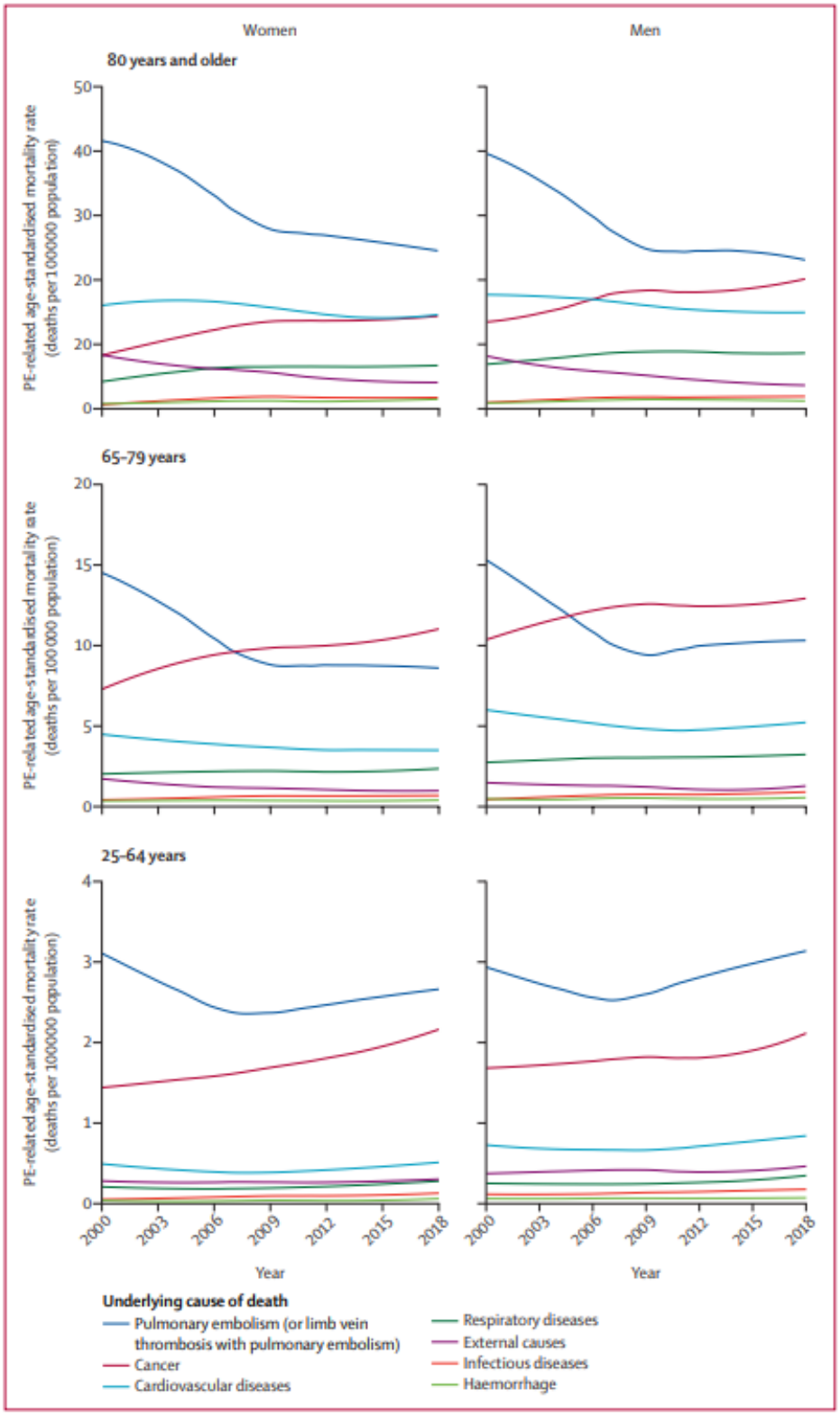
2.0 Supplementary information/data linked to NCP-VTE Guideline Section 2: Acute Diagnosis and Immediate Management of DVT and PE

A missed VTE diagnosis can be fatal or can impose health consequences that may have been avoided by timely diagnosis and treatment. Age-standardised mortality from PE is reported to be higher than that of cancer or cardiovascular disease, especially in women under 65 (**Suppl. Figures 2.1, 2.2**). Implementation of validated diagnostic strategies is therefore important for patient quality of care and for efficient resource utilization.



Suppl Figure 2.1: Prevalence of conditions listed as the underlying cause of death on death records of patients with PE in the USA, 2000–18 [38].

Data from the Multiple Cause of Death Database. Number of deaths by the underlying cause and proportion of cases among those listing PE codes. PE=pulmonary embolism. Reproduced with permission from Elsevier Science &Technology Journals.



Suppl. Figure 2.2: Trends in age-standardised mortality according to the underlying cause of death on records listing PE among the causes of death in the USA, 2000–18 [38].

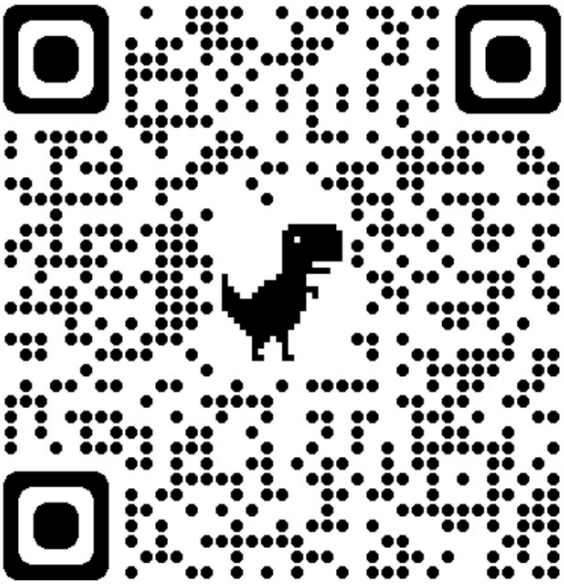
Data from the Multiple Cause of Death Database. Locally weighted scatterplot smoother lines for the annual age-standardised pulmonary embolism-related mortality rate (number of deaths per 100000 population). PE=pulmonary embolism. Age-standardised mortality: This measure accounts for differences in the age distribution of populations and their changes over time. Age-standardised PE-related mortality rates in the US (here) are based on 5-year age groups using the 2013 European standard population to allow comparison with a previous analysis of the European Region. Reproduced with permission from Elsevier Science &Technology Journals.

Supplementary information/data linked to Section 2.1-2.4 Primary and prehospital care:

What does “good care” mean to patients presenting to primary care or other forms of pre-hospital care and to their care providers? Access to timely diagnostic strategies to avoid lengthy waits in the emergency department, emergency department avoidance if possible, timely (emergency) treatment where necessary, reassurance, education, pain management, avoidance of wasted time have all been cited by patients, their families and primary care providers including prehospital emergency care staff. The NCP-VTE, working under the HSE Chief Clinical Officer and National Director and lead for Integrated Care and Clinical Design and innovation, supports the development of business cases to deliver an integrated community-based model of care for patients with suspected VTE to support early identification of VTE, provide best practice initiatives, improve patient safety and improve patient outcomes. In the pre-hospital setting, for a patient with symptoms or signs of VTE presenting in the community, referral, diagnosis and treatment pathways may be operationalized differently by each Regional Executive Officer (REO). Each REO should ensure that a pathway for DVT diagnosis is clearly identified so that general practitioners can access care for their patients in a timely manner. In most cases, immediate referral to the emergency department is appropriate, unless community-based diagnostic pathways have been resourced and safely operationalized. Clinical decision making should guide which patients require immediate (ambulance) transfer, such as in cases where severe PE is suspected.

Pre-hospital emergency care

In collaboration with the Ireland East Hospital Group (IEHG; now HSE Dublin and Southeast) VTE working group, the National Ambulance Service and Dublin Fire Brigade recently conducted Ireland's first prehospital VTE awareness survey, aiming to improve VTE awareness among prehospital practitioners serving a population of 5.1m. In April 2023, this **A**mbulance **S**ervice PE **Surve**y (**“ASSURE”**) survey (10 questions) was disseminated. The background of respondents, awareness of risk factors, complications, treatments, previous experience, and comfort level of making a presumptive diagnosis of VTE was collected, with 500 responses by May 2023. The survey revealed that respondents were aware of VTE and highlighted opportunities for improvement. Co-design with patient partners lead to the launch in September 2023 of a video aimed at improving awareness from a clinical and patient perspective (**Suppl. Figure 2.3**) **[39].** This initiative not only provided critical insights into prehospital VTE awareness but also demonstrated the potential of educational interventions in enhancing prehospital care. Following cascading of the video, a second survey was issued which received 200 response and demonstrated improved awareness of risk factors, treatments, and potential complications, leading to improved comfort levels around making a working diagnosis of PE [39]. The video is now included at training and revalidation programmes. This initiative underscores the effectiveness of targeted educational interventions in bridging knowledge gaps and improving clinical awareness.



Suppl. Figure 2.3: QR code linking to an educational video on VTE awareness aimed at pre-hospital emergency practitioners.
Developed by the National Ambulance Service, Dublin Fire Brigade and Ireland East Hospital Group (now HSE Dublin/ South East) Ambulance Service PE Survey ("ASSURE") study group **[39]**.

Supplementary information/data linked to NCP-VTE Guideline Sections 2.1 and 2.4: Deep Vein Thrombosis (DVT) diagnosis and Immediate Treatment

NCP-VTE recommendations on DVT diagnosis are based primarily upon the Irish Association of Emergency Medicine DVT guidance document [40], a joint consensus statement of the European Society of Cardiology (ESC) [41], a guideline published by the UK National Institute for Health and Care Excellence (NICE) [42], a British Medical Journal (BMJ) "Best Practice" statement, updated in March 2022 [43] and guidelines published by the American Society of Haematology [44]. Diagnosis and immediate treatment (with interim anticoagulation- referring to existing HSE guidelines [45] and anticoagulant product Summary of Product Characteristics https://www.hpra.ie/ - where necessary) is crucial because DVT can extend or progress to pulmonary embolism and also result in long-term complications such as post-thrombotic syndrome [46]. Conversely, ruling out DVT in a timely manner in people who don't have it avoids unnecessary anticoagulation (with its associated risks), and potentially prolonged stays in the emergency department or hospital ward. Systematic reviews have reported the economic benefit of excellent DVT diagnostic strategies and their rigorous implementation [34, 47, 48]. Inclusivity in co-design of DVT pathways is crucial. For example, VTE risk is known to be increased in the setting of social deprivation [49-51].

In the pre-hospital setting, for a patient with symptoms or signs of DVT presenting in the community, referral, diagnosis and treatment pathways may be operationalized differently by each Regional Executive Officer (REO). Each REO should ensure that a pathway for DVT diagnosis is clearly identified so that general practitioners can access care for their patients in a timely manner. In some circumstances, where delays may be experienced in accessing diagnostics, anticoagulation in the community can be risk assessed.

DVT is usually (but not always) unilateral and should be suspected based on the patient's clinical presentation, particularly (but not only) if risk factors for VTE are also present [41-44]. Symptoms and signs of DVT are typically (but not always) unilateral, and may include a combination of those outlined in [52] and in the **Main NCP-VTE Guideline, Central Figure 1; Section 2.1**.

These symptoms and signs are nonspecific and objective testing is required to confirm or exclude a diagnosis of DVT [53].

All healthcare professionals involved in the diagnosis of deep vein thrombosis should use a validated diagnostic pathway. Diagnostic strategies for DVT include validated combinations of clinical prediction rules (such as the **Wells score** [54]**, Main NCP-VTE Guideline, Central Figure 1; Section 2.1**), D-dimer assays and compression ultrasonography (CUS).

D-dimer, a degradation product of fibrin, is usually increased when DVT is present. The D-dimer assay is extremely sensitive, meaning that (when used in the context of validated diagnostic algorithms), it can be useful for DVT rule-out when its levels are NOT elevated. However, a common error is to misunderstand the relevance of a positive (elevated) D-dimer. D-dimers are very often elevated in common conditions associated with infection, inflammation, malignancy and systemic illness and therefore this finding is nonspecific. Consequently, additional testing is mandatory if it is positive or if the clinical pre-test probability is not low [55]. A D-dimer measurement is recommended in patients with a "DVT unlikely" pretest clinical probability patients as this may exclude DVT in a subset of patients (**Main NCP-VTE Guideline, Central Figure 1; Section 2.1) but only for patients presenting from the community. The D-dimer assay has not been validated for admitted inpatients.**

Compression Ultrasound (CUS) evaluates the compressibility of a segment of a vein and a colour Doppler is very often combined with compression to assess blood flow. Thrombus (in acute DVT) causes distention of the vein and therefore compressibility is lost [56]. "Proximal CUS" refers to limiting CUS to the proximal lower limb veins while "whole-leg CUS" involves performing US on the entire leg. The decision to choose one modality over the other depends on local availability of each technique and of serial ultrasound if the algorithm mandates it.

A systematic review reported the pooled estimates for sensitivity and specificity of proximal CUS (in any suspected DVT) as 90.1% (95% confidence interval [CI], 86.5- 92.8) and 98.5% (95% CI, 97.6-99.1), respectively. For whole-leg US, pooled estimates were 94.0% (95% CI, 91.3-95.9) and 97.3% (95% CI, 94.8-98.6); for serial US they were 97.9% (95% CI, 96.0-98.9) and 99.8% (95% CI, 99.3-99.9) and for D-dimer, they were 96.1% (95% CI, 92.6-98.0) and 35.7% (95% CI, 29.5-42.4) [57].

Sensitivity and specificity of clinical symptoms are low on their own but when they are combined into validated prediction rules, this allows pre-test clinical probability classification into two (DVT unlikely or likely) or three categories (low-, intermediate-, or high-clinical probability) with the higher categories associated with increasing disease prevalence [54, 58]. The NCP-VTE recommends

performing a clinical prediction rule (such as the two-level modified Wells score [59], given its ease of use) in patients with suspected lower limb DVT (**Main NCP-VTE Guideline, Central Figure 1; Section 2.1**). CUS is recommended as first line imaging method for DVT diagnosis. Alternative imaging should also be considered if CUS is negative (e.g. CTV/MRV, especially if the patient's whole leg is swollen) or interim repeat ultrasound following discussion with a specialist.

In patients with suspected DVT (without PE symptoms), anticoagulation may be safely withheld in people with a single normal whole-leg CUS [41], as the 3-month VTE occurrence has been reported to be very low (0.57%; 95% CI 0.25%-0.89%) after a negative whole-leg CUS [60] (assuming iliac DVT is not clinically suspected- Central Figure 1). For proximal CUS, anticoagulation may be withheld only if there are systems in place to ensure that the proximal CUS can be repeated, and integrated in a diagnostic strategy including clinical probability and D-dimer assessment [61]. Both strategies are reported to have similar safety in randomized trials [62, 63]. Although both CUS and whole-leg CUS are safe to exclude suspected symptomatic DVT, each approach has different advantages and limitations, and their applicability varies accordingly. CUS is quicker, simpler, has better reproducibility, and is readily available, because comprehensive venous ultrasound skills are not needed [43]. Conversely, detailed investigation of the whole leg may permit prompt identification of other pathological conditions.

A novel emerging strategy is point-of care US (POCUS), typically performed by emergency physicians using proximal CUS. A systematic review including 16 studies included and 2,379 patients suggested acceptable performance, with sensitivity and specificity of 96.1% and 96.8% respectively when compared to the reference imaging test [64]. POCUS may be considered in the future following validation in prospective clinical management studies and integration in a validated diagnostic strategy. Moreover, comparison of two-point CUS to full lower-limb ultrasonography has demonstrated efficacy and safety, when implemented in the context of a robust diagnostic algorithm [62].

Supplementary information/data linked to NCP-VTE Guideline Section 2.4.2: Diagnostic Strategies/ Practical Assessment Pathway for DVT (and Section 5.0: Recommendations for REOs)

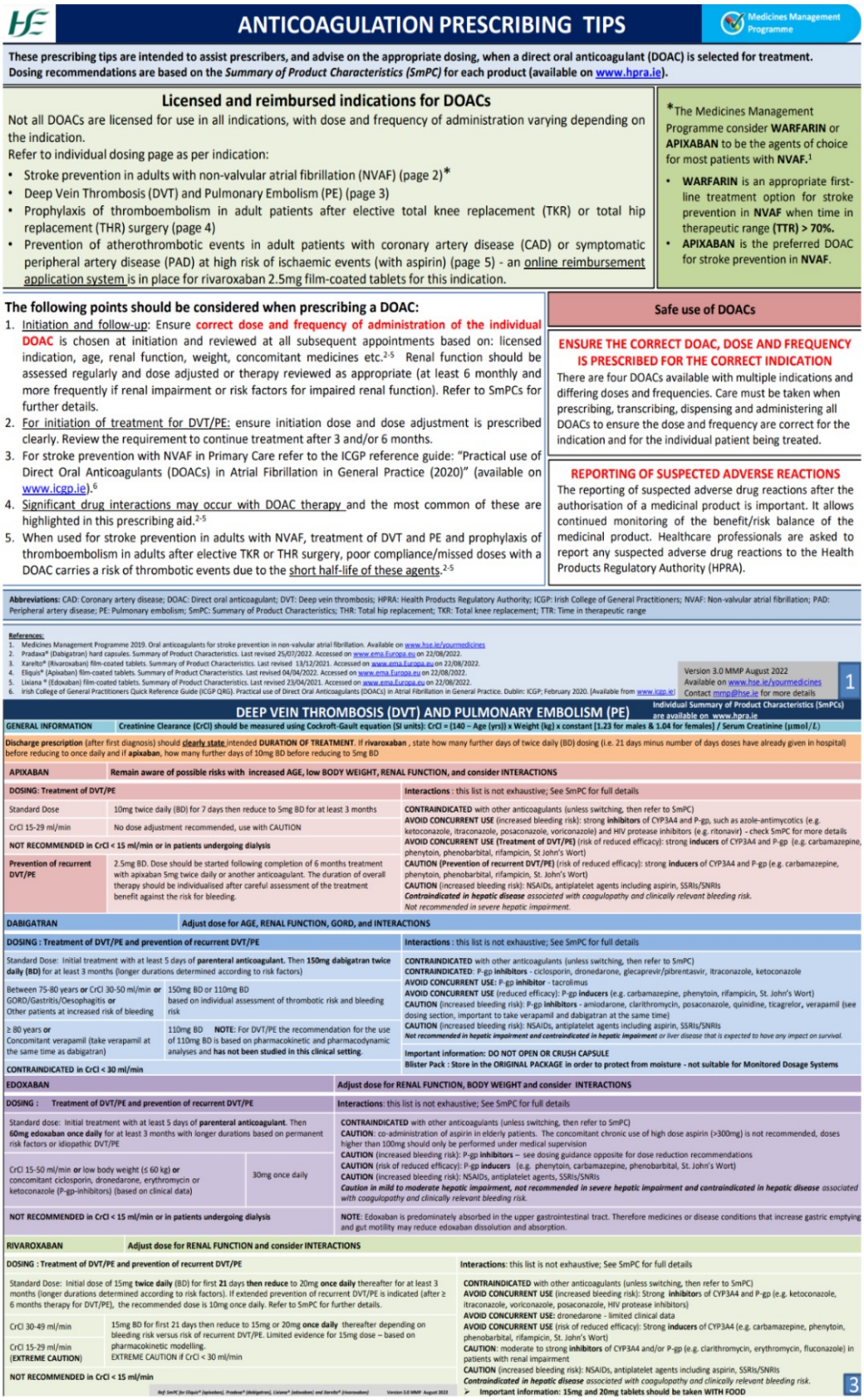
Through hospital and regional VTE working groups, and through resourcing pathways, efforts should be made to minimise the duration of time from presentation to CUS. If a CUS in not available in less than 4 hours, people with a low pre-test probability and a high d-dimer should be offered therapeutic interim anticoagulation [42, 43].

The development of services and best practice initiatives is demonstrated in, *The DVT Nurse-Led Service at University Hospital Limerick (UHL) model*. The service was established in 2019 as part of an admissions-avoidance initiative and has improved the diagnosis and management of patients with Deep Venous Thrombosis (DVT) and pulmonary embolism (PE). The value of nurse-led venous thromboembolism (VTE) management in Ireland is demonstrated by improved outcomes including:

1. **Reduced Hospital Admissions**: Since inception, the DVT service has reviewed 5,730 patients, with only 2.4% requiring admission
2. **Efficient and Timely Care**: With an average patient stay of 2-4 hours, the service ensures rapid diagnosis and treatment. Collaborative efforts with radiology and the Medical Assessment Unit enable prompt access to Doppler ultrasounds.
3. **Virtual Clinics**: The introduction of virtual nurse-led clinics has further streamlined care. Patients on long-term anticoagulation therapy are also reviewed yearly through these virtual clinics.
4. **Multidisciplinary Integration**: The amalgamation of the DVT and Warfarin services in 2020 under the Rapid Acute Medical Unit (RAMU) has allowed for more streamlined care, leading to improved collaboration across teams.
5. **High-Quality Patient-Centred Care**: The service places a strong emphasis on holistic care, with newly diagnosed DVT/PE patients being reviewed by clinical lead consultants in a weekly anticoagulation clinic.
6. **Public and Staff Education and Awareness**: These campaigns further enhance the quality of care and patient safety.

Supplementary information/data linked to NCP-VTE Guideline Section 2.5: Immediate and interim anticoagulation (PATIENTS WITH DVT AND/OR PE)

If a CUS is not available in less than 4 hours, people with a high pre-test probability should be considered for therapeutic interim anticoagulation, referring to existing HSE guidelines [45] ; (**Suppl. Figure 2.4**) and anticoagulant product Summary of Product Characteristics (https://www.hpra.ie/). When using interim therapeutic anticoagulation for suspected proximal DVT or PE, it is suggested to carry out baseline blood tests which may include full blood count, renal and hepatic function, prothrombin time (PT) and activated partial thromboplastin time (APTT), but this should not delay anticoagulation. Where bleeding risk factors are present (such as a low platelet count, renal impairment or other conditions), then a personalized risk assessment should be performed.



ANTICOAGULATION PRESCRIBING TIPS

Medicines Management Programme

These prescribing tips are intended to assist prescribers, and advise on the appropriate dosing, when a direct oral anticoagulant (DOAC) is selected for treatment. Dosing recommendations are based on the *Summary of Product Characteristics (SmPC)* for each product (available on www.hpra.ie).

Licensed and reimbursed indications for DOACs

Not all DOACs are licensed for use in all indications, with dose and frequency of administration varying depending on the indication.
Refer to individual dosing page as per indication:

- Stroke prevention in adults with non-valvular atrial fibrillation (NVAF) (page 2)*
- Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) (page 3)
- Prophylaxis of thromboembolism in adult patients after elective total knee replacement (TKR) or total hip replacement (THR) surgery (page 4)
- Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events (with aspirin) (page 5) - an online reimbursement application system is in place for rivaroxaban 2.5mg film-coated tablets for this indication.

*The Medicines Management Programme consider **WARFARIN** or **APIXABAN** to be the agents of choice for most patients with **NVAF.**[1]

- **WARFARIN** is an appropriate first-line treatment option for stroke prevention in **NVAF** when time in therapeutic range **(TTR) > 70%.**
- **APIXABAN** is the preferred DOAC for stroke prevention in **NVAF.**

The following points should be considered when prescribing a DOAC:

1. Initiation and follow-up: Ensure **correct dose and frequency of administration of the individual DOAC** is chosen at initiation and reviewed at all subsequent appointments based on: licensed indication, age, renal function, weight, concomitant medicines etc.[2-5] Renal function should be assessed regularly and dose adjusted or therapy reviewed as appropriate (at least 6 monthly and more frequently if renal impairment or risk factors for impaired renal function). Refer to SmPCs for further details.
2. For initiation of treatment for DVT/PE: ensure initiation dose and dose adjustment is prescribed clearly. Review the requirement to continue treatment after 3 and/or 6 months.
3. For stroke prevention with NVAF in Primary Care refer to the ICGP reference guide: "Practical use of Direct Oral Anticoagulants (DOACs) in Atrial Fibrillation in General Practice (2020)" (available on www.icgp.ie).[6]
4. Significant drug interactions may occur with DOAC therapy and the most common of these are highlighted in this prescribing aid.[2-5]
5. When used for stroke prevention in adults with NVAF, treatment of DVT and PE and prophylaxis of thromboembolism in adults after elective TKR or THR surgery, poor compliance/missed doses with a DOAC carries a risk of thrombotic events due to the short half-life of these agents.[2-5]

Safe use of DOACs

ENSURE THE CORRECT DOAC, DOSE AND FREQUENCY IS PRESCRIBED FOR THE CORRECT INDICATION

There are four DOACs available with multiple indications and differing doses and frequencies. Care must be taken when prescribing, transcribing, dispensing and administering all DOACs to ensure the dose and frequency are correct for the indication and for the individual patient being treated.

REPORTING OF SUSPECTED ADVERSE REACTIONS

The reporting of suspected adverse drug reactions after the authorisation of a medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse drug reactions to the Health Products Regulatory Authority (HPRA).

Abbreviations: CAD: Coronary artery disease; DOAC: Direct oral anticoagulant; DVT: Deep vein thrombosis; HPRA: Health Products Regulatory Authority; ICGP: Irish College of General Practitioners; NVAF: Non-valvular atrial fibrillation; PAD: Peripheral artery disease; PE: Pulmonary embolism; SmPC: Summary of Product Characteristics; THR: Total hip replacement; TKR: Total knee replacement; TTR: Time in therapeutic range

References:
1. Medicines Management Programme 2019. Oral anticoagulants for stroke prevention in non-valvular atrial fibrillation. Available on www.hse.ie/yourmedicines
2. Pradaxa® (Dabigatran) hard capsules. Summary of Product Characteristics. Last revised 25/07/2022. Accessed on www.ema.Europa.eu on 22/08/2022.
3. Xarelto® (Rivaroxaban) film-coated tablets. Summary of Product Characteristics. Last revised 13/12/2021. Accessed on www.ema.Europa.eu on 22/08/2022.
4. Eliquis® (Apixaban) film-coated tablets. Summary of Product Characteristics. Last revised 04/04/2022. Accessed on www.ema.Europa.eu on 22/08/2022.
5. Lixiana ® (Edoxaban) film-coated tablets. Summary of Product Characteristics. Last revised 23/04/2021. Accessed on www.ema.Europa.eu on 22/08/2022.
6. Irish College of General Practitioners Quick Reference Guide (ICGP QRG). Practical use of Direct Oral Anticoagulants (DOACs) in Atrial Fibrillation in General Practice. Dublin: ICGP; February 2020. [Available from www.icgp.ie]

Version 3.0 MMP August 2022
Available on www.hse.ie/yourmedicines
Contact mmp@hse.ie for more details

1

DEEP VEIN THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE)

Individual Summary of Product Characteristics (SmPCs) are available on www.hpra.ie

GENERAL INFORMATION — **Creatinine Clearance (CrCl) should be measured using Cockroft-Gault equation (SI units): CrCl = (140 – Age (yrs)) x Weight (kg) x constant [1.23 for males & 1.04 for females] / Serum Creatinine (μmol/L)**

Discharge prescription (after first diagnosis) should **clearly state** intended **DURATION OF TREATMENT**. If **rivaroxaban** , state how many further days of twice daily (BD) dosing (i.e. 21 days minus number of days doses have already given in hospital) before reducing to once daily and if **apixaban**, how many further days of 10mg BD before reducing to 5mg BD

APIXABAN

Remain aware of possible risks with increased AGE, low BODY WEIGHT, RENAL FUNCTION, and consider INTERACTIONS

DOSING: Treatment of DVT/PE

Standard Dose	10mg twice daily (BD) for 7 days then reduce to 5mg BD for at least 3 months
CrCl 15-29 ml/min	No dose adjustment recommended, use with CAUTION
NOT RECOMMENDED in CrCl < 15 ml/min or in patients undergoing dialysis	
Prevention of recurrent DVT/PE	2.5mg BD. Dose should be started following completion of 6 months treatment with apixaban 5mg twice daily or another anticoagulant. The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

Interactions : this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to SmPC)
AVOID CONCURRENT USE (increased bleeding risk): strong **inhibitors** of CYP3A4 and P-gp, such as azole-antimycotics (e.g. ketoconazole, itraconazole, posaconazole, voriconazole) and HIV protease inhibitors (e.g. ritonavir) - check SmPC for more details
AVOID CONCURRENT USE (Treatment of DVT/PE) (risk of reduced efficacy): strong **inducers** of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St John's Wort)
CAUTION (Prevention of recurrent DVT/PE) (risk of reduced efficacy): strong **inducers** of CYP3A4 and P-gp (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St. John's Wort)
CAUTION (increased bleeding risk): NSAIDs, antiplatelet agents including aspirin, SSRIs/SNRIs
Contraindicated in hepatic disease *associated with coagulopathy and clinically relevant bleeding risk.*
Not recommended in severe hepatic impairment.

DABIGATRAN

Adjust dose for AGE, RENAL FUNCTION, GORD, and INTERACTIONS

DOSING : Treatment of DVT/PE and prevention of recurrent DVT/PE

Standard Dose: Initial treatment with at least 5 days of **parenteral anticoagulant.** Then **150mg dabigatran twice daily (BD)** for at least 3 months (longer durations determined according to risk factors)	
Between 75-80 years **or** CrCl 30-50 ml/min **or** GORD/Gastritis/Oesophagitis **or** Other patients at increased risk of bleeding	150mg BD or 110mg BD based on individual assessment of thrombotic risk and bleeding risk
≥ 80 years **or** Concomitant verapamil (take verapamil at the same time as dabigatran)	110mg BD **NOTE**: For DVT/PE the recommendation for the use of 110mg BD is based on pharmacokinetic and pharmacodynamic analyses and **has not been studied in this clinical setting.**
CONTRAINDICATED in CrCl < 30 ml/min	

Interactions : this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to SmPC)
CONTRAINDICATED: P-gp **inhibitors** - ciclosporin, dronedarone, glecaprevir/pibrentasvir, itraconazole, ketoconazole
AVOID CONCURRENT USE: P-gp **inhibitor** - tacrolimus
AVOID CONCURRENT USE (reduced efficacy): P-gp **inducers** (e.g. carbamazepine, phenytoin, rifampicin, St. John's Wort)
CAUTION (increased bleeding risk): P-gp **inhibitors** - amiodarone, clarithromycin, posaconazole, quinidine, ticagrelor, verapamil (see dosing section, important to take verapamil and dabigatran at the same time)
CAUTION (increased bleeding risk): NSAIDs, antiplatelet agents including aspirin, SSRIs/SNRIs
Not recommended in hepatic impairment and contraindicated in hepatic impairment *or liver disease that is expected to have any impact on survival.*

Important information: DO NOT OPEN OR CRUSH CAPSULE
Blister Pack : Store in the ORIGINAL PACKAGE in order to protect from moisture - not suitable for Monitored Dosage Systems

EDOXABAN

Adjust dose for RENAL FUNCTION, BODY WEIGHT and consider INTERACTIONS

DOSING : Treatment of DVT/PE and prevention of recurrent DVT/PE

Standard dose: Initial treatment with at least 5 days of **parenteral anticoagulant.** Then **60mg edoxaban once daily** for at least 3 months with longer durations based on permanent risk factors or idiopathic DVT/PE	
CrCl 15-50 ml/min **or** low body weight (≤ 60 kg) **or** concomitant ciclosporin, dronedarone, erythromycin or ketoconazole (P-gp-inhibitors) (based on clinical data)	30mg once daily
NOT RECOMMENDED in CrCl < 15 ml/min or in patients undergoing dialysis	

Interactions: this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to SmPC)
CAUTION: co-administration of aspirin in elderly patients. The concomitant chronic use of high dose aspirin (>300mg) is not recommended, doses higher than 100mg should only be performed under medical supervision
CAUTION (increased bleeding risk): P-gp **inhibitors** – see dosing guidance opposite for dose reduction recommendations
CAUTION (risk of reduced efficacy): P-gp **inducers** (e.g. phenytoin, carbamazepine, phenobarbital, St. John's Wort)
CAUTION (increased bleeding risk): NSAIDs, antiplatelet agents, SSRIs/SNRIs
Caution in mild to moderate hepatic impairment, not recommended in severe hepatic impairment and contraindicated in hepatic disease *associated with coagulopathy and clinically relevant bleeding risk.*

NOTE: Edoxaban is predominately absorbed in the upper gastrointestinal tract. Therefore medicines or disease conditions that increase gastric emptying and gut motility may reduce edoxaban dissolution and absorption.

RIVAROXABAN

Adjust dose for RENAL FUNCTION and consider INTERACTIONS

DOSING : Treatment of DVT/PE and prevention of recurrent DVT/PE

Standard Dose: Initial dose of 15mg **twice daily** (BD) for first **21** days **then reduce** to 20mg **once daily** thereafter for at least 3 months (longer durations determined according to risk factors). If extended prevention of recurrent DVT/PE is indicated (after ≥ 6 months therapy for DVT/PE), the recommended dose is 10mg once daily. Refer to SmPC for further details.	
CrCl 30-49 ml/min	15mg BD for first 21 days then reduce to 15mg or 20mg **once daily** thereafter depending on bleeding risk versus risk of recurrent DVT/PE. Limited evidence for 15mg dose – based on pharmacokinetic modelling. EXTREME CAUTION if CrCl < 30 ml/min
CrCl 15-29 ml/min (**EXTREME CAUTION**)	
NOT RECOMMENDED in CrCl < 15 ml/min	

Interactions: this list is not exhaustive; See SmPC for full details

CONTRAINDICATED with other anticoagulants (unless switching, then refer to SmPC)
AVOID CONCURRENT USE (increased bleeding risk): Strong **inhibitors** of CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors)
AVOID CONCURRENT USE: dronedarone - limited clinical data
AVOID CONCURRENT USE (risk of reduced efficacy): Strong **inducers** of CYP3A4 (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St. John's Wort)
CAUTION: moderate to strong **inhibitors** of CYP3A4 and/or P-gp (e.g. clarithromycin, erythromycin, fluconazole) in patients with renal impairment
CAUTION (increased bleeding risk): NSAIDs, antiplatelet agents including aspirin, SSRIs/SNRIs
Contraindicated in hepatic disease *associated with coagulopathy and clinically relevant bleeding risk.*
➢ **Important information: 15mg and 20mg tablets should be taken WITH FOOD**

3

Suppl. Figure 2.4: HSE guidance on anticoagulation with Direct Oral Anticoagulation. Linked to NCP-VTE Guideline section 2.5 Interim anticoagulation (PATIENTS WITH DVT AND/OR PE) of the main guideline:

Adapted from [45]; These prescribing tips are intended to assist prescribers, and advise on the appropriate dosing, when a direct oral anticoagulant (DOAC) is selected for treatment. Dosing recommendations are based on the Summary of Product Characteristics (SmPC) for each product (available on www.hpra.ie).

Supplementary information/data linked to NCP-VTE Guideline Section 2.2 and 2.6: Pulmonary Embolism Diagnosis and Immediate Treatment

PE is a leading cause of death and long-term disability [3]. Therefore, excellent pathways for diagnosis, treatment and long-term management are of crucial importance [9]. European Society of Cardiology (ESC) guidelines provide an evidence-based framework for PE diagnosis and management [3]. This framework has been adapted here for implementation in Ireland.

At the heart of the ESC guideline is a risk-adapted management strategy, outlined in **Main NCP-VTE Guideline, Figure 3**. The components of this pathway are outlined next.

Acute PE interferes with circulation and gas exchange, causing death mainly through right ventricular (RV) failure as a result of acute pressure overload [3]. If >30-50% of the pulmonary arterial bed is obstructed, pulmonary artery pressure (PAP) increases, causing increased pulmonary vascular resistance (PVR). This is associated with vasoconstriction and anatomical obstruction [65]. Next, RV dilation, altered contractility, and increased wall tension occur, which prolong RV contraction and cause bowing of the interventricular septum to the left, impairing left ventricular filling and reducing cardiac output [66]. Increased levels of biomarkers of myocardial injury reflect RV ischemia during acute PE. Systemic hypotension happens towards the most severe end of the spectrum [3].

Acute right ventricular (RV) failure is characterized by systemic congestion due to impaired RV filling or reduced flow output. Acute RV failure is a key factor in the severity and outcome of acute PE [67]. Clinical signs of RV failure and haemodynamic instability indicate a high risk of early mortality. High-risk PE, which is defined very specifically by haemodynamic instability (**Main NCP-VTE Guideline Table 1**), needs immediate diagnostic and therapeutic measures. Even without haemodynamic instability, there can still be underlying RV dysfunction. This situation needs further assessment to determine risk levels and to guide management.

Accurate diagnosis of PE according to evidence-based algorithms is essential to avoid unnecessary morbidity and mortality. Pathways differ, depending on whether the patient with suspected PE is categorized into a low, intermediate or high-risk category (**Main NCP-VTE Guideline Figure 6**).

Supplementary information/data linked to NCP-VTE Guideline Section 2.6.1: Clinical features of PE

Acute PE can present with non-specific symptoms such as dyspnoea, chest pain, presyncope or syncope, and haemoptysis. Haemodynamic instability indicates severe PE, often linked to syncope and RV dysfunction [68]. PE can also be asymptomatic or it can be incidentally discovered. The severity of dyspnoea varies with PE location. Chest pain often results from pleural irritation [69]. This can result in the classic "pleuritic" type chest pain, in which an intake of breath causes severe sharp pain in the area. Predisposing factors for VTE can help to ensure that PE is suspected, but **40% of PE cases lack identifiable risk factors**. Hypoxaemia and hypocapnia (due to hyperventilation) are common, and chest X-rays help rule out other conditions [70]. Severe PE shows electrocardiographic signs of RV strain, while milder cases may only exhibit sinus tachycardia. Atrial arrhythmias, especially atrial fibrillation, can also occur [71].

Supplementary information/data linked to NCP-VTE Guideline Section 2.6.2: Pre-test probability assessment for PE

The classification of patients with suspected PE into categories of clinical or pre-test probability is essential for diagnosis. Pre-test probability is a process that combines symptoms, clinical findings, and predisposing factors for VTE. This pre-test assessment is done either through clinical judgment or validated prediction rules like the Wells or revised Geneva rule (**Main NCP-VTE Guideline, Central Figure 2; Suppl. Table 2.1**) and it influences the post-test probability of PE after imaging. These rules categorize patients into low, moderate, or high-probability groups (or simplified categories) [72, 73].

Items	Clinical decision-rule points:	
	Original [74]	**Simplified [75]**
Previous PE or DVT	3	1
Heart Rate: 75-94 bpm ≥95 bpm	 3 5	 1 2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation & unilateral oedema	4	1
Age >65 years	1	1
Clinical Probability		
Three-level score		
Low	0-3	0-1
Intermediate	4-10	2-4
High	≥11	≥5
Two-level score		
PE-unlikely	0-5	0-2
PE-likely	≥6	≥3

Suppl. Table 2.1: The revised Geneva clinical prediction rule for pulmonary embolism
Bpm: beats per minute; DVT: deep vein thrombosis; PE: pulmonary embolism

Supplementary information/data linked to NCP-VTE Guideline Section 2.6.3: D-dimer testing in the diagnostic algorithm for suspected PE

D-dimer testing is highly effective in ruling out PE when results are normal, but less useful for confirming PE when they are elevated [3]. D-dimer levels are often higher in cancer patients, hospitalized patients, and people with severe infections or during pregnancy. Various D-dimer assays, particularly ELISA, can exclude PE in low or intermediate-risk patients with high sensitivity [76]. Age-adjusted D-dimer cut-offs (discuss with local laboratory first if implementing) improve specificity in older patients, in other words increasing the number of patients in whom PE is excluded without false negatives [77]. The 'YEARS' clinical decision rule has been reported to further refine exclusion criteria based on D-dimer levels and specific clinical signs [78].

Supplementary information/data linked to NCP-VTE Guideline Section 2.6.4: Diagnostic imaging for suspected PE (radiological imaging and echocardiography)

Computed Tomographic Pulmonary Angiography (CTPA)

CTPA is the an excellent imaging method for diagnosis of PE because of its ability to visualize pulmonary arteries down to the subsegmental level [79]. The PIOPED II study reported a sensitivity of 83% and specificity of 96% for CTPA in PE diagnosis [80]. The study also highlighted the importance of pre-test clinical probability on CTPA's predictive value. A negative CTPA effectively rules out PE in patients with low or intermediate clinical probability but is less reliable in high-probability patients. Conversely, a positive CTPA is highly predictive in intermediate and high-probability cases but less so in low-probability patients. Further testing is warranted if clinical judgment and CTPA results differ.

Lung Scintigraphy

Lung scintigraphy, particularly the planar ventilation/perfusion (V/Q) scan, is another established diagnostic tool for suspected PE. V/Q scans have an advantage due to lower radiation exposure [3]. V/Q scanning is particularly suitable for outpatients with low clinical probability, young women, patients with contrast medium allergies, and people who have severe renal failure. Single-Photon Emission Computed Tomography (SPECT) imaging, with or without low-dose CT, may reduce the rate of non-diagnostic V/Q scans. Results to date are promising, suggesting high accuracy and low non-diagnostic rates, however less validation has been performed to date than for standard lung scintigraphy [81].

Magnetic Resonance Angiography (MRA)

While MRA has potential for PE diagnosis, large-scale studies have shown that it is not yet ready for clinical practice because of low sensitivity, a high rate of inconclusive scans, and low availability in emergency settings. Ongoing research is investigating whether a negative MRA combined with the absence of proximal DVT on CUS can safely exclude clinically significant PE [3].

Echocardiography

Echocardiography can detect RV PE-associated pressure overload and dysfunction (**Main NCP-VTE Guideline Figure 7; Suppl Figure 2.5**). Although it cannot reliably exclude PE on its own, it can provide useful information for risk stratification and differential diagnosis in people with suspected PE [82]. Specific echocardiographic signs, such as the 60/60 sign and McConnell sign, are suggestive of PE but are only present in a minority of patients. Echocardiography is particularly useful in hemodynamically unstable patients to guide emergency treatment decisions if immediate CTPA is not feasible [83].

Compression Ultrasonography

Compression ultrasonography (CUS) is very often used to diagnose DVT, which is the primary source of PE. In suspected PE cases, detection of lower limb DVT (focusing on the groin and popliteal fossa) can be especially useful for patients who cannot undergo CTPA due to contraindications like severe renal failure or iodine allergy [3].

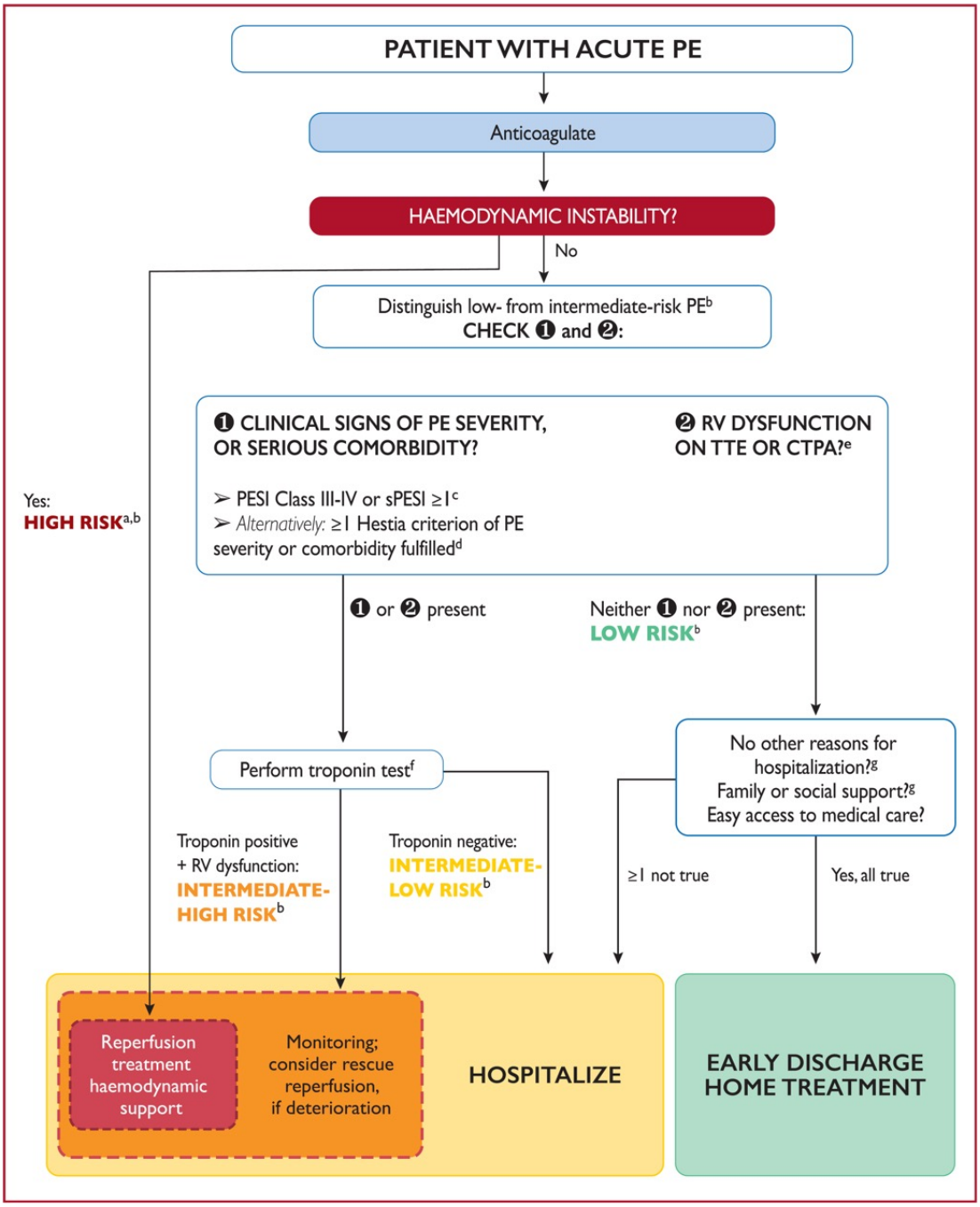
Supplementary information/data linked to NCP-VTE Guideline Section 2.6.5: Risk stratification (in terms of probability of complications) during diagnostic assessment of patients with acute PE

A full evaluation of clinical signs, echocardiographic and CTPA findings and biomarkers is essential for risk stratification and initial treatment decisions in acute PE [3]. We include this here because it should take place simultaneously during the diagnostic pathway. Initial risk assessment focuses on clinical signs of **hemodynamic instability (HIGH-RISK PE: Main NCP-VTE Guideline Table 1 and Central Figure 2**), which predicts a high risk of early death, therefore **an emergency algorithm including reperfusion (thrombolysis) is indicated (Main NCP-VTE Guideline Central Figure 2**). For patients without these signs, further risk stratification involves evaluating clinical, imaging, and laboratory indicators of PE severity and identifying comorbidities or other conditions that could worsen the prognosis.

Acute right ventricular (RV) failure is a key outcome predictor in acute PE [67]. Clinical signs including tachycardia, low systolic blood pressure, respiratory insufficiency, and syncope are linked to a poor short-term prognosis [67]. Echocardiographic assessment of RV size and function is crucial; an RV/LV diameter ratio ≥ 1.0 and a tricuspid annular plane systolic excursion (TAPSE) < 16 mm are in particular associated with an unfavourable prognosis [84].

CTPA also plays an important role and in particular, RV enlargement has been associated with adverse outcomes [85]. In meta-analysis of 49 studies including >13,000 PE patients, an RV/LV ratio of ≥1.0 on CT was associated with a 2.5-fold increased risk for all-cause mortality (OR 2.5, 95% CI 1.8-3.5), and a 5-fold risk for PE-related mortality (OR 5.0, 95% CI 2.7-9.2) [86]. This ratio, along with other volumetric heart analyses and contrast reflux to the inferior vena cava, provides critical prognostic information.

Laboratory biomarkers such as elevated troponin and B-type natriuretic peptide (BNP) levels indicate myocardial injury and RV dysfunction, respectively, and help in predicting mortality and adverse outcomes [3].



Copy of Figure 3, Main NCP-VTE Guideline: Risk-adapted management strategy for acute PE. Hemodynamic instability is defined in **main NCP-VTE Guideline Table 1 (copied in this document below)**. "a": Refer to emergency management algorithm (**Main NCP-VTE Guideline Central Figure 2 and Figure 7 (copied in this document below)**); "b": Refer to Main NCP-VTE Guideline Figure 6 (Copied in this document below) for definition of high, intermediate-high-, intermediate-low-, and low-risk PE; "c" Cancer, heart failure and chronic lung disease are included in the PESI and sPESI (**Main NCP-VTE Guideline Table 3; (copied in this document below)**); "d" The Hestia criteria are described in **Suppl Table 2.2**; "e" Prognostically relevant imaging (TTE or CTPA) findings in patients with acute PE, are shown in **Suppl Figure 2.5**; "f" A cardiac troponin test may already have been performed during initial diagnostic work-up. "g" This information is included in the Hestia criteria (**Suppl Figure 2.5**).

CTPA: computed tomography pulmonary angiography/angiogram; PE: pulmonary embolism; PESI: Pulmonary Embolism Severity Index; RV: right ventricular; sPESI; simplified Pulmonary Embolism Severity Index; TTE: transthoracic echocardiogram. Konstantinides et al., 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS), European Heart Journal, 2019, Figure 6, pg. 573, doi: 10.1093/eurheartj/ehz405, www.escardio.org/Guidelines, Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.

<table>
<tr><th colspan="2" rowspan="2">Early mortality risk</th><th colspan="4">Indicators of risk</th></tr>
<tr><th>Haemodynamic instability[a]</th><th>Clinical parameters of PE severity and/ or comorbidity: PESI class III–V or sPESI ≥I</th><th>RV dysfunction on TTE or CTPA[b]</th><th>Elevated cardiac troponin levels[c]</th></tr>
<tr><td colspan="2">High</td><td>+</td><td>(+)[d]</td><td>+</td><td>(+)</td></tr>
<tr><td rowspan="2">Intermediate</td><td>Intermediate–high</td><td>-</td><td>+[e]</td><td>+</td><td>+</td></tr>
<tr><td>Intermediate–low</td><td>-</td><td>+[e]</td><td colspan="2">One (or none) positive</td></tr>
<tr><td colspan="2">Low</td><td>-</td><td>-</td><td>-</td><td>Assesment optional; if assessed, negative</td></tr>
</table>

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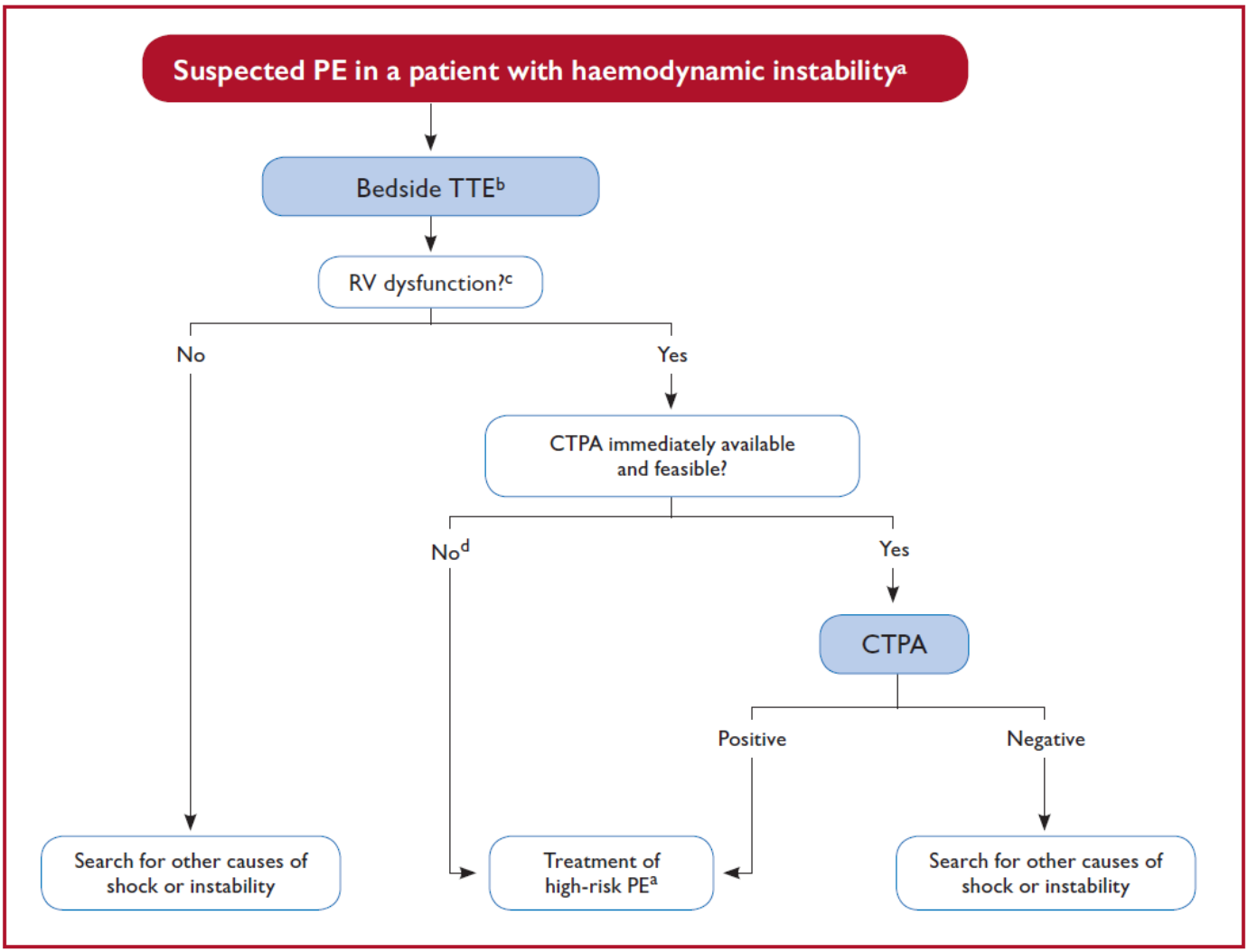
Copy of Main NCP-VTE Guideline Figure 6: Classification of pulmonary embolism severity and the risk of early (in-hospital or 30 day) death (linked to Main NCP-VTE Guideline, Figure 3, above).

CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism; RV: right ventricular; (s)PESI: (simplified) Pulmonary Embolism Severity Index; TTE: transthoracic echocardiogram.

“a” Defined in **Main NCP-VTE Guideline Table 1**; “b” Prognostically relevant imaging (TTE or CTPA) findings in patients with acute PE, and the corresponding cut-off levels, are available in [3] but are beyond the scope of this guideline; “c” Do not use other biomarkers until validated; “d” Haemodynamic instability, combined with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE, is sufficient to classify a patient into the **high-risk** PE category. **In these cases, neither calculation of the PESI nor measurement of troponins or other cardiac biomarkers is necessary**; “e” Signs of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of I-II or an sPESI of 0. Until the implications of such discrepancies for the management of PE are fully understood, these patients should be classified into the intermediate-risk category [3].

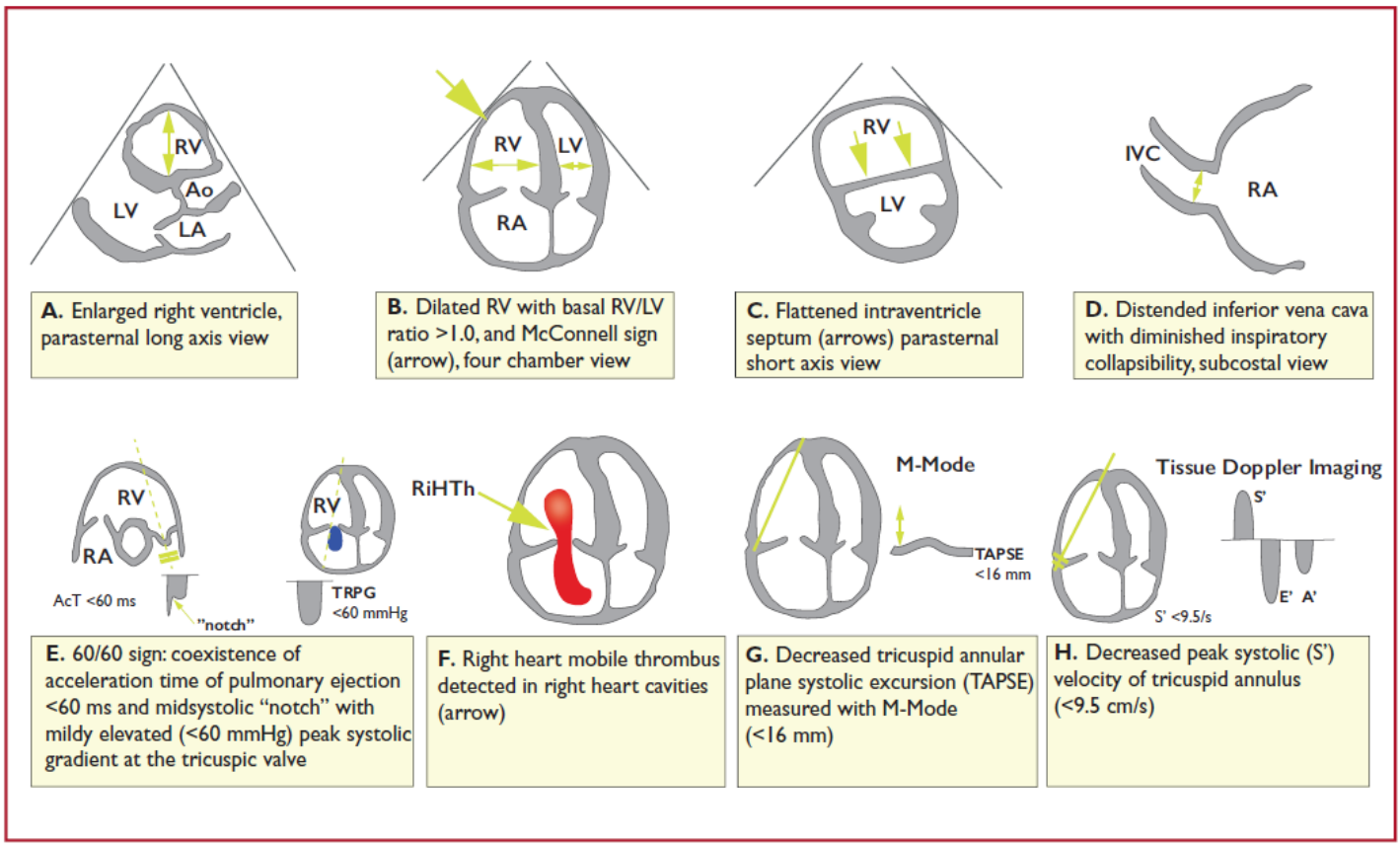
Konstantinides et al., 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS), European Heart Journal, 2019, Table 8, pg. 563, doi: 10.1093/eurheartj/ehz405, www.escardio.org/Guidelines, Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.



Copy of Main NCP-VTE Guideline Figure 7: Diagnostic algorithm for patients with suspected high-risk pulmonary embolism presenting with haemodynamic instability (linked to Main NCP-VTE Guideline Figure 3).

CTPA: computed tomography pulmonary angiography; CUS: compression ultrasonography; DVT: deep vein thrombosis; LV: left ventricle; PE: pulmonary embolism; RV: right ventricle; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiogram. “a” See **Main NCP Guideline, Table 1** for definition of haemodynamic instability and high-risk PE. “b” Ancillary bedside imaging tests may include TOE, which may detect emboli in the pulmonary artery and its main branches; and bilateral venous CUS, which may confirm DVT and thus VTE.
“c” In the emergency situation of suspected high-risk PE, this refers mainly to a RV/LV diameter ratio >1.0; the echocardiographic findings of RV dysfunction are graphically presented in **Suppl Figure 2.5**. “d” Includes the cases in which the patient’s condition is so critical that it only allows bedside diagnostic tests. In such cases, echocardiographic findings of RV dysfunction confirm high-risk PE and emergency reperfusion therapy is recommended.

Konstantinides et al., 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS), European Heart Journal, 2019, Figure 4, pg. 570, doi: 10.1093/eurheartj/ehz405, www.escardio.org/Guidelines, Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.



Suppl Figure 2.5: Graphic representation of transthoracic echocardiographic parameters in the assessment of right ventricular pressure overload. (Linked to Main NCP-VTE Guideline, Figure 3)

Ao: aorta; IVC: inferior vena cava; LA: left atrium; LV : left ventricle; RA: right atrium; RV: right ventricle/ventricular; AcT: right ventricular outflow Doppler acceleration time; TRPG= tricuspid valve peak systolic gradient; RiHTh: right heart thrombus (or thrombi); TAPSE= tricuspid annular plane systolic excursion; S': peak systolic velocity of tricuspid annulus by tissue Doppler imaging; E': peak early diastolic velocity of tricuspid annulus by tissue Doppler imaging; A': peak late diastolic (during atrial contraction) velocity of tricuspid annulus by tissue Doppler imaging.

Konstantinides et al., 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS), European Heart Journal, 2019, Figure 3, pg. 558, doi: 10.1093/eurheartj/ehz405, www.escardio.org/Guidelines, Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.

Cardiac arrest	Obstructive shock	Persistent Hypotension
Need for CPR	Systolic BP <90 mmHg or Vasopressors needed for BP ≥90 mmHg* *AND* End-organ hypoperfusion$	Systolic BP <90 mmHg or systolic BP drop ≥40 mmHg**

Copy of main NCP-VTE Guideline Table 1: Definition of haemodynamic instability in acute high-risk PE [3] linked to Main NCP-VTE Guideline Central Figure 2 and Figure 3 (Risk-adapted management strategy for acute PE)

CPR: cardiopulmonary resuscitation
*Despite adequate filling status
** Lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis
$ altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate

Supplementary information/data linked to NCP-VTE Guideline Section 2.6.6: Integration of data during early PE diagnosis

To assess overall mortality risk and early outcomes in acute PE, it is essential that we integrate clinical, imaging as well as laboratory findings along with baseline parameters of aggravating conditions/comorbidities. This allows risk stratification and guides early management in order to improve outcomes. The Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) (**Main NCP-VTE Guideline Table 3 and copied below**) are validated tools that combine these to estimate a patient's 30-day mortality risk [87-90]. The Hestia exclusion criteria for assisting in identification of patients who might be suitable for outpatient management is detailed in **Suppl Table 2.2 and linked to Main NCP-VTE Guideline Figure 3**.

The presence of concomitant DVT is an adverse prognostic factor which is independently predictive of increased mortality within three months of acute PE [91].

Risk stratification begins with the initial suspicion and diagnosis of PE. The focus is on identifying high-risk patients who need immediate intervention (**Main NCP-VTE Guideline Central Figure 2, Table 1 and Figure 3**). For people without hemodynamic instability, additional stratification is essential to determine the need for hospitalization or monitoring (for example in a critical care or monitored environment; **Main NCP-VTE Guideline Figure 6**).

Patients who are classified as intermediate risk PE but who have both RV dysfunction and increased cardiac biomarkers are categorized as having intermediate-high risk PE. RV dysfunction can be detected using echocardiography or CTPA. Patients with intermediate-high risk PE **should be closely monitored in case of hemodynamic collapse, usually by admission to a high or intensive dependency/care unit**. Patients without these findings fall into the intermediate-low risk category (**Main NCP-VTE Guideline Figures 3 and 6**). Patients with signs of RV dysfunction or elevated cardiac biomarkers should be reclassified as intermediate-low risk due to their higher mortality risk, even if they have a low PESI or sPESI score [3].

<table>
<tr><th>Parameter</th><th colspan="3">Original version [89]</th><th colspan="2">Simplified version [90]</th></tr>
<tr><td>Age</td><td colspan="3">Age in years</td><td colspan="2">1 point (if age >80 years)</td></tr>
<tr><td>Male sex</td><td colspan="3">+10 points</td><td colspan="2">-</td></tr>
<tr><td>Cancer</td><td colspan="3">+30 points</td><td colspan="2">1 point</td></tr>
<tr><td>Chronic heart failure</td><td colspan="3">+10 points</td><td colspan="2" rowspan="2">1 point</td></tr>
<tr><td>Chronic pulmonary disease</td><td colspan="3">+10 points</td></tr>
<tr><td>Pulse rate ≥110 bpm</td><td colspan="3">+20 points</td><td colspan="2">1 point</td></tr>
<tr><td>Systolic BP <100 mmHg</td><td colspan="3">+30 points</td><td colspan="2">1 point</td></tr>
<tr><td>Respiratory rate >30 breaths/min</td><td colspan="3">+20 points</td><td colspan="2">-</td></tr>
<tr><td>Temperature <36^{0}C</td><td colspan="3">+20 points</td><td colspan="2">-</td></tr>
<tr><td>Altered mental status</td><td colspan="3">+60 points</td><td colspan="2">-</td></tr>
<tr><td>Arterial O_2 Saturations <90%</td><td colspan="3">+20 points</td><td colspan="2">1 point</td></tr>
<tr><td rowspan="7"></td><td colspan="3">RISK STRATA[a] (CLASS)</td><td colspan="2">RISK STRATA[a]</td></tr>
<tr><td>Class</td><td>Points</td><td>Mortality[b]</td><td>Points</td><td>Mortality[b]</td></tr>
<tr><td>I</td><td>≤65</td><td>0-1.6%</td><td rowspan="5">0

≥1</td><td rowspan="5">1.0% (CI 0.0-2.1%)

10.9% (CI 8.5-13.2%)</td></tr>
<tr><td>II</td><td>66-85</td><td>1.7-3.5%</td></tr>
<tr><td>III</td><td>86-105</td><td>3.2-7.1%</td></tr>
<tr><td>IV</td><td>106-125</td><td>4.0-11.4%</td></tr>
<tr><td>V</td><td>>125</td><td>10-24.5%</td></tr>
</table>

Copy of Main NCP-VTE Guideline Table 3: Original and simplified Pulmonary Embolism Severity Index [89, 90].

BP: blood pressure; b.p.m.: beats per minute; br/min: breaths per minute; O2: Oxyhaemoglobin; CI: 95% confidence interval; “a” Based on the sum of points; “b”: “Mortality”= 30 day mortality risk.

Criterion/question
Is the patient haemodynamically unstable?[a]
Is thrombolysis or embolectomy necessary?
Active bleeding or high risk of bleeding?[b]
Has the patient needed >24 hours of oxygen to maintain oxygen saturations >90%?
Has PE been diagnosed during anticoagulant treatment?
Severe pain needing IV pain medication for >24 hours?
Medical/social reason for treatment in hospital for >24 hours?*
Does the patient have a CrCl of <30 ml/min?[c]
Does the patient have severe liver impairment?[d]
Is the patient pregnant?
Does the patient have a documented history of heparin-induced thrombocytopenia?

Suppl Table 2.2: Hestia exclusion criteria for outpatient management [92] (Referenced in Main GL, Figure 3)

If the answer to one or more of the questions is 'yes', then the patient cannot be treated at home.

BP: blood pressure; b.p.m.: beats per minute; CrCl: creatinine clearance; i.v.: intravenous; PE: pulmonary embolism; IV: intravenous; *for example, infection, malignancy or no support system. "a": Includes the following criteria (and at the discretion of the clinician): systolic BP <100 mmHg with heart rate >100 b.p.m.; condition requiring admission to an intensive care unit. "b" Gastrointestinal bleeding in the preceding 14 days, recent stroke (<4 weeks ago), recent operation (<2 weeks ago), bleeding disorder or thrombocytopenia (platelet count <75 x 109/L), or uncontrolled hypertension (systolic BP >180 mmHg or diastolic BP >110 mmHg). "c" Calculated CrCl according to the Cockroft-Gault formula. "d" Left to the discretion of the clinician.

Supplementary information/data linked to NCP-VTE Guideline Section 2.6.7: Immediate management considerations during initial PE assessment:

During the diagnostic and prognostic workup of patients with suspected PE, some aspects of treatment have to be delivered in parallel. Therefore, they will be briefly discussed here, with additional information and long-term therapeutic strategies outlined in the chapter dealing with VTE treatment.

For patients with a high or intermediate clinical probability of pulmonary embolism (PE), anticoagulation should begin while awaiting diagnostic test results (**Suppl. Figure 2.4**) This initial treatment often involves subcutaneous, weight-adjusted low-molecular-weight heparin (LMWH) or intravenous unfractionated heparin (UFH). Direct oral anticoagulants (DOACs) have shown non-inferior efficacy in clinical trials using higher doses of apixaban or rivaroxaban [3]. LMWH is preferred over UFH in most scenarios due to the lower risk of major bleeding and heparin-induced thrombocytopenia. UFH is primarily used for patients with haemodynamic instability, serious renal impairment, or severe obesity [3].

Thrombolytic therapy provides rapid improvement in pulmonary obstruction and right ventricular function in PE patients, especially when initiated within 48 hours of symptom onset [3]. Thrombolysis can reduce mortality and recurrent PE in high-risk patients but carries risks of severe bleeding and intracranial hemorrhage. For intermediate-high risk PE, systemic thrombolysis was shown in the “Pulmonary Embolism Thrombolysis” (PEITHO) trial to decrease the risk of haemodynamic decompensation but also to increase bleeding risks and is therefore not recommended in non-high risk patients [93]. In younger patients, <75 years, the OR was 0.33 (0.12-0.85) versus >75 years (OR 0.63 (0.23 -1.66)). Catheter-directed treatments (CDT) and surgical embolectomy are not currently considered standard of care but in certain circumstances (and where expertise exists), can occasionally provide alternative reperfusion strategies in challenging patient groups [3], for example, if use of systemic thrombolysis is not possible due to extremely high bleeding risk. Randomized trials with clinically-important outcomes evaluating CDT [94, 95] and reduced-dose systemic lysis [96] in intermediate-high risk acute PE respectively are ongoing.

The use of multidisciplinary pulmonary embolism response teams (PERTs) is increasingly recommended [3]. PERTs bring together specialists from various fields to enhance decision-making and treatment implementation in real-time, potentially improving outcomes for patients with severe PE [97, 98]. This collaborative approach aligns with modern healthcare needs, providing structured and immediate responses to acute PE cases [99].

It should be noted that the practice of requesting bilateral lower limb dopplers routinely for patients with acute PE is not evidence-based and is not routinely recommended.

Upper extremity DVT (UEDVT) and cerebral vein thrombosis (CVT)

Upper extremity DVT (UEDVT) may involve the radial, ulnar, brachial, axillary, subclavian, internal jugular or brachiocephalic veins and accounts for 4 to 10% of all cases of DVT [100]. Primary UEDVT comprises one third of the cases and this group includes unprovoked UEDVT, effort-related thrombosis (sometimes termed “Paget-Schroetter Syndrome”), and thrombosis due to the thoracic outlet syndrome. Secondary UEDVT is associated with risk factors such as central venous catheters (CVCs), pacemakers, or cancer. Over 40% of patients with UEDVT have a co-existing malignancy and approximately 70% of secondary UEDVT are diagnosed in association with the use of a CVC. Acute complications of include PE, loss of venous access and difficulty in arm function. Presenting symptoms are similar to lower extremity DVT and include pain and swelling of the affected limb [100].

Another rarer type of venous thrombotic complication is cerebral vein and sinus thrombosis (CVST). CVS/CVST presents with typically variable symptoms, with the most common being a severe headache, which is reported by 60–90% of patients [101]. Some people report a “thunderclap headache”. Acute symptomatic seizures affect 30–40% of patients.

CVT symptoms and signs typically group into four patterns [101]:

1. **Isolated intracranial hypertension** with headache, nausea, papilledema, visual impairment, and tinnitus.
2. **Focal neurological deficits** from superficial venous thrombosis, often with seizures.
3. **Diffuse encephalopathy**, leading to mental status changes or coma.
4. **Cavernous sinus thrombosis** with orbital pain, chemosis, proptosis, and ophthalmoplegia.

CVT affects primarily young and middle-aged adults, particularly women. Heparin is the first-line treatment, even if intracerebral haemorrhage is present . Crucially, symptoms can be missed and a high index of suspicion should be maintained. European Stroke Organization Guidelines suggest use of magnetic resonance or computed tomographic angiography for confirming the diagnosis of CVT/CVST in patients with suspected CVT (with low quality of associated evidence and weak recommendation strength) [102].

If UEDVT or CVST are suspected, immediate referral for diagnostic imaging is recommended. Specialist multidisciplinary input is likely to be required, especially in severe cases and should be sought urgently by the receiving clinician.

The detailed management of these conditions (beyond immediate anticoagulation with LWMH) are outside the scope of this current guideline phase and should be guided by the immediate involvement of multidisciplinary specialists.

Supplementary information/data linked to NCP-VTE Guideline Section 2.8: Patient education and information at the time of VTE diagnosis)

It is widely accepted to be important that patients with a new DVT or PE diagnosis receive information on these conditions. The NCP-VTE have developed the patient education material (Appendices) including those that are relevant to patients with a new VTE diagnosis.

These NCP-VTE educational materials also ensure that patients who are commencing anticoagulant treatment receive written information about:How to use anticoagulants.

- How long to take anticoagulants.
- Possible side effects of anticoagulants and what to do if these occur.
- How other medications, foods and alcohol can affect oral anticoagulation treatment.
- Any monitoring needed for their anticoagulant treatment.
- How anticoagulants may affect their dental treatment.
- Taking anticoagulants if they are planning pregnancy or become pregnant.
- How anticoagulants may affect activities such as sports and travel.
- When and how to seek medical help.
- Heavy menstrual bleeding may be a side-effect of anticoagulation.
- The NCP-VTE PIL on anticoagulation (Appendices) should be provided.

3.0 Physical and psychological recovery following VTE: What is important in addition to anticoagulation?

Supplementary information/data linked to NCP-VTE Guideline Section 3.1: Post Thrombotic Syndrome (PTS) following DVT

Post Thrombotic Syndrome (PTS) represents a form of chronic venous insufficiency following DVT [103]. PTS is characterised by symptoms of pain, fullness and cramping coupled with signs of ongoing lower limb swelling, dependent cyanosis, erythema and venous ectasia that occurs due to ongoing venous hypertension post-DVT, caused by caused either by residual venous obstruction, valvular damage, or both. PTS can affect up to 50% of individuals following proximal DVT.

Although PTS is not fatal, it has a detrimental effect on quality of life that is similar to that of other chronic illnesses like diabetes mellitus or heart failure [104, 105]. PTS is a clinical diagnosis that requires assessment of both symptoms and signs. Diagnosis should not take place until ~3-6 months after the DVT event. There are three scales that have been specifically developed for DVT (Villalta, Ginsberg and Brandjes), however the NCP-VTE suggests use of the Villalta scale (**Suppl. Table 3.1**), which is endorsed by the International Society of Thrombosis and Hemostasis (ISTH) and the American Heart Association (AHA), due to its ease of use and clinician familiarity [106].

Established PTS unfortunately has no proven treatment, thus the best way to manage PTS is to prevent its occurrence after DVT. In order to prevent PTS, optimal anticoagulation is essential [103]. Although there is disagreement on their benefits for preventing PTS, elastic compression stockings (ECS) may be useful in managing acute DVT symptoms [103, 107, 108]. Meta-analyses have reported a low level of evidence with high heterogeneity, suggesting clinical equipoise, and supporting clinician judgement and patient preference in the use of ECS [103].

Patients with ilio-femoral DVT who are at low risk of bleeding may experience a reduction in the long-term risk of moderate-to-severe PTS when using catheter-directed procedures to treat their DVT: In the landmark ATTRACT RCT, 692 people with acute femoro-popliteal DVT or iliofemoral DVT were randomized to pharmacomechanical catheter-directed therapy (PCTD) or anticoagulation alone [109]. No significant difference in the primary outcome of PTS at 2 years was reported (47% vs. 48%), and there were significantly higher rates of bleeding complications noted in the PCDT group compared to the control group (1.7% vs. 0.3%). The proportion of people who experienced moderate to severe PTS was reduced upon analysis of secondary outcomes (18% vs. 24%; p = 0.04), especially in people with iliofemoral DVT (18% vs. 28%; p = 0.02) [109].

A small trial including 43 people with PTS who were randomized to a structured 6-month exercise program or control reported significant improvements in quality of life (VEINES-QOL [110]) scores (mean difference 4.6 points; p=0.03) but no change in Villalta scores [111]. The NCP-VTE suggest early mobilisation and exercise (including provision of an NCP-VTE exercise leaflet) in patients following DVT, and we suggest leg elevation, weight loss, and exercise as examples of lifestyle modifications in patients with PTS [103].

Clinical Feature	Score 0 (None)	Score 1 (Mild)	Score 2 (Moderate)	Score 3 (Severe)
Pain	None	Mild	Moderate	Severe
Cramps	None	Mild	Moderate	Severe
Heaviness	None	Mild	Moderate	Severe
Paresthesia (tingling)	None	Mild	Moderate	Severe
Pruritus (itching)	None	Mild	Moderate	Severe
Pretibial edema (swelling)	None	Mild	Moderate	Severe
Skin Induration (hardening)	None	Mild	Moderate	Severe
Hyperpigmentation	None	Mild	Moderate	Severe
Redness	None	Mild	Moderate	Severe
Venous Ectasia (dilated veins)	None	Mild	Moderate	Severe
Pain upon calf compression	None	Mild	Moderate	Severe

Scoring & Classification:

1. **0 – 4 points:** No PTS
2. **5 – 9 points:** Mild PTS
3. **10 – 14 points:** Moderate PTS
4. **≥15 points or presence of venous ulcer**: Severe PTS

Suppl. Table 3.1: The Villalta scale for postthrombotic syndrome (PTS)[106]: linked to section 6.6; Recommendations VTE recovery and long-term management

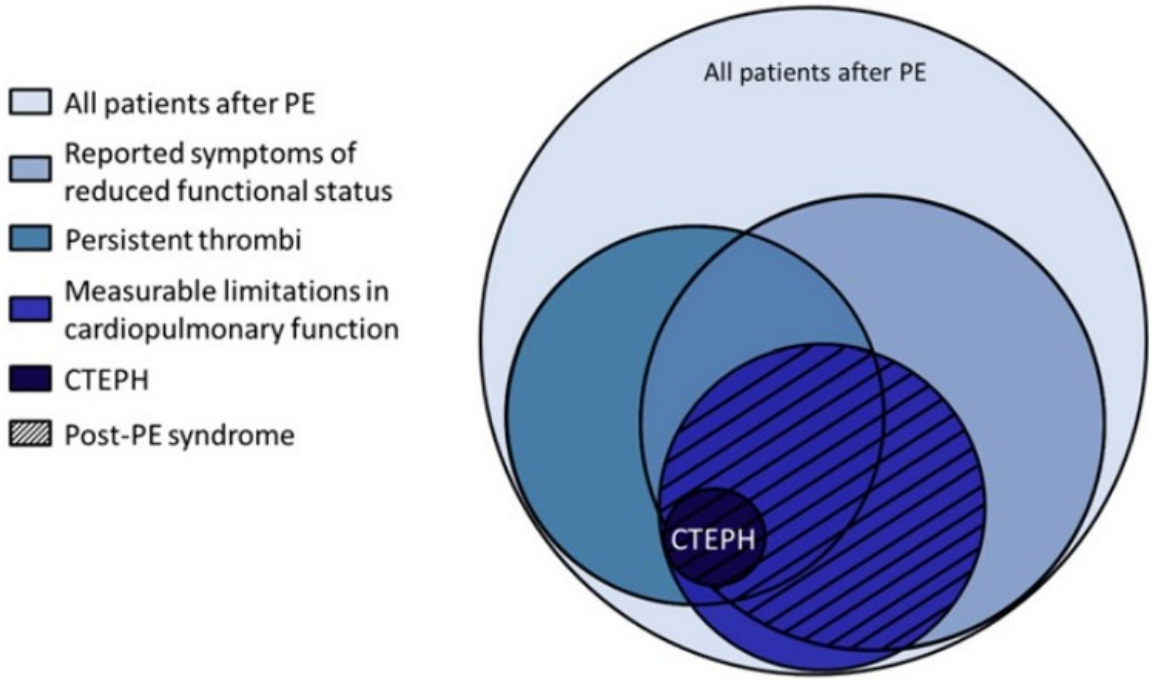
Each sign is assigned a score (from 0 (absent) to 3 (most severe)). Symptoms are also scored out of 3, including pain, cramps, heaviness, paresthesia and pruritus. Scores of 5–9, 10-14 and ≥ 15 indicated mild, moderate and severe PTS respectively, and the presence of a venous ulcer immediately classifies a patient as having severe PTS.

Supplementary information/data linked to NCP-VTE Guideline Section 3.2: Post-Pulmonary Embolism recovery and screening for specific complications

Post-PE management should include screening for and recognition of: Post-PE syndrome (PPES), Chronic Thromboembolic Pulmonary Disease (CTEPD) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

PE is a leading cause of death, long term disability and poor quality of life [3]. Long-term disability following PE includes a spectrum including symptoms, functional limitation and diminished quality of life that can occur following an acute PE despite appropriate treatment. Growing recognition of this group of symptoms has led to the coining of the term “post-PE syndrome (PPES)” [24, 25, 112] (**Suppl. Figure 3.1** [112]).

Features of this “post-PE syndrome” are common, ranging from 20-75% in recent studies [3, 9]. The PPES is formally defined as “new or progressive dyspnoea, exercise intolerance, and/or impaired functional or mental status after at least 3 months of adequate anticoagulation following acute PE, which cannot be explained by other (pre-existing) comorbidities” [9].



Suppl. Figure 3.1: Summary of the various chronic consequences two years after PE [112]

This figure suggests that ~50% of patients report symptoms of reduced functional status or quality of life; ~25-33% of patients are diagnosed with persistent thrombi; ~10-30% of patients are found to have persistent/worsening cardiac or pulmonary function and ~0.5-4% of patients are diagnosed with CTEPH. The relative size and overlap of the circles are expected to change over time. Klok et al proposed the presence of the “post-PE syndrome” when patients have measurable limitations of cardiopulmonary function after a PE event, in combination with deterioration of clinical symptoms, functional status or quality of life (stripes).

PE= pulmonary embolism, CTEPH=chronic thromboembolic pulmonary hypertension. Reproduced with permission from Elsevier Science &Technology Journals.

The post-PE syndrome includes chronic thromboembolic pulmonary vascular disease (CTEPD), and persistent right ventricular dysfunction, but also otherwise unexplained new or progressive exercise intolerance after PE [25]. Rarely, long-term disability after PE may manifest as chronic thromboembolic pulmonary hypertension (CTEPH), the most severe form of PPES which is defined by the additional demonstration of pulmonary hypertension in association with ongoing mismatched V/Q deficits [3, 9, 113]. However, a sizeable proportion of patients without CTEPH experience long term symptoms post PE, including dyspnoea and exercise limitations [7, 112]. How to optimally manage non-CTEPH forms of the post-PE syndrome is not yet known, but these patients do need special attention and a follow-up pathway (see below).

Chronic thromboembolic pulmonary vascular disease (CTEPD) is defined by the detection of chronic pulmonary vascular obstruction but, unlike CTEPH, accompanied by normal mean pulmonary artery pressure at rest, and, importantly, by *limitations in exercise tolerance [9]*.

Incomplete thrombus resolution and residual pulmonary vascular obstruction (RPVO) post-acute PE are likely implicated in the development of CTEPD and CTEPH. The reported prevalence of RPVO is influenced by the chosen imaging modality and the time interval post-acute PE and varies from 19% to 57% at 6-8 months post PE [114-118]. Radiologically-diagnosed perfusion defects do not necessarily translate directly to clinical symptoms or syndromes: upon analysis of data from the ELOPE (Evaluation of Long-term Outcomes after PE) study, there was no correlation between the degree of vascular obstruction on imaging and functional limitation at 12 months post-acute PE [119].

Dyspnea and functional limitation post-PE are common and can occur in the absence of perfusion defects, pulmonary hypertension or recurrent PE [10, 120]. Long-term follow-up of patients recruited to the PEITHO (Pulmonary Embolism Thrombolysis) study identified persistent functional limitation in one-third of patients with intermediate-risk PE, despite infrequent CTEPH (2.1% and 3.2% of the thrombolysis and placebo groups respectively) [121]. The term “post-PE-related dyspnea” has been used to reflect a cohort of post-PE patients who experience dyspnea, persistent functional limitation and reduced quality of life without evidence of CTEPD or CTEPH for at least three months post-PE despite adequate anticoagulation [120]. Advanced age, higher BMI, smoking history and cardiopulmonary comorbidities have been identified as independent predictors of exertional dyspnea post PE [10]. Many of these patients will also demonstrate a reduction in objective parameters such as the 6 minute walk test. A recent systematic review and meta-analysis highlighted that PE survivors walked shorter than predicted 6 minute walk distances, scored lower in generic quality of life (QoL) scores (in the 40th percentile) and demonstrated RV dysfunction in 18% [122]. A recent single-center prospective cohort study recruiting 101 consecutive patients with acute PE characterized post-PE symptoms and consequences, and reported dyspnea in 47%, depression in 15.9% and post-pulmonary embolism impairment (PPEI) in 25.3% at 6 months following acute PE [123]. Moreover, the FOCUS study was a prospective multicenter observational cohort study including 1017 patients with acute symptomatic PE in 17 German centers. CTEPH was diagnosed in 16 (1.6%) of patients after a median of 129 days and the estimated 2-year

cumulative incidence was 2.3% (1.2–4.4%). The 2-year cumulative incidence was 16.0% (95% CI 12.8–20.8%). Patients with PPEI had a higher risk of re-hospitalization and death and worse quality of life compared with those without PPEI [124].

Cardiopulmonary exercise testing (CPET) is a practical non-invasive tool to investigate undifferentiated dyspnea and exercise limitation, particularly in the context of comorbidities, as it provides objective information regarding respiratory, cardiovascular, metabolic and muscular responses to physical activity [125]. It has an established role in pulmonary vascular disease, as peak oxygen consumption (peakV′O2) and the minute ventilation (V′E)/carbon dioxide production (V′CO2) relationship are incorporated into the multimodal assessment of PH patients to aid prognostic stratification . Additionally, it has been demonstrated that CPET parameters can be predictive of hemodynamic findings in right heart catheterization in PH [126]. Persistent symptoms, functional limitation and RV abnormalities are common among survivors of PE and CPET is helpful in this population to differentiate intrinsic cardiopulmonary limitation that might be amenable to specific interventions, from alternative etiologies such as general deconditioning [7, 120, 127]. This was exemplified in the ELOPE study, as 46.5% of patients had a reduced peak V′O2 during CPET at one year post-acute PE and none of these patients demonstrated circulatory limitation to exercise; deconditioning was the explanation in the majority of these cases [12]. Potential limitations to wider CPET use are cost, time constraints and the requirement of particular expertise for accurate interpretation.

In addition to persistent physical symptoms, many patients experience emotional distress, depression, anxiety and post thrombotic panic syndrome [6, 32, 46, 128-130]. Measuring all relevant aspects of physical and mental health in VTE patients will lead to earlier detection of the whole range of complications described above, timely referral to relevant healthcare professionals (e.g. CTEPH experts but also rehabilitation specialists, physiotherapist and psychologists) and empower patients

Supplementary information/data linked to NCP-VTE Guideline Section 3.3: Patient-reported outcome measures after VTE (Evaluating recovery using patient-reported outcome measures.)

Supplementary information/data linked to NCP-VTE Guideline Section 3.3.1: What data should be collected?

Quality of life patient-reported outcome data elements have been informed by patient stakeholder engagement and by reference to the International Consortium for Health Outcomes Measurement (ICHOM) venous thromboembolism (VTE) recommendations [8]. ICHOM-VTE brought together patient representatives, clinician leaders, and registry leaders from all over the world to develop a set of Patient-centred Outcome Measures for VTE.

The proposed 7 patient-reported outcome measure (PROM) data elements herein (and recommended by ICHOM) are intended by the NCP-VTE to inform patient care rather than to be used for research purposes. Implementation of PROM measurement is encouraged in centres with the required expertise and with the personnel resources to make it feasible. The tools herein are provided to assist care providers who wish to implement PROM measurement.

Supplementary information/data linked to NCP-VTE Guideline Section 3.3: Patient-reported outcome measures (PROM)

The 7 PROM required to inform patient care are measurable at a minimum (according the ICHOM-VTE standards) with a core set of 4 tools (PVFS; PROMIS GH v1.2; PEmb-QoL, VEINES-QoL) and two questions recommended by ICHOM-VTE [8] (Appendices); Suppl. Figure 3.2; Main NCP-VTE Guideline Figure 8.

1. Functional limitations
    - Post-VTE Functional Status (PVFS) scale (1 item) [25]
2. Quality of life
    - PROMIS Scale v1.2 - Global Health (10 items) [131]
    - Pulmonary Embolism Quality of Life Questionnaire [26] (PEmb-QoL) (40 items)
    - VEINES-QoL (26 items) [111]
3. Pain
    - PROMIS Scale v1.2 - Global Health
    - PEmb-QoL
    - VEINES-QoL
4. Dyspnoea
    - PEmb-QoL
5. Psychosocial wellbeing
    - PROMIS Scale v1.2 - Global Health
    - PEmb-QoL
    - VEINES-QoL
6. Satisfaction with treatment
    - Measured either by the question: “Are you satisfied with your VTE treatment?” (1 item).
7. Changes in life view
    - Measured through the question: “Have you experienced a change in your expectations, aspirations, values, or perspectives on life opportunities since the diagnosis of VTE?” (1 item).

At what timepoints should these data be collected?

- At time of index event (EXCLUDING Quality of life; Treatment satisfaction; Changes in life view).
- 3 months.
- Thereafter for as long as the patient is under care: 6 months, 1 year and then annually.

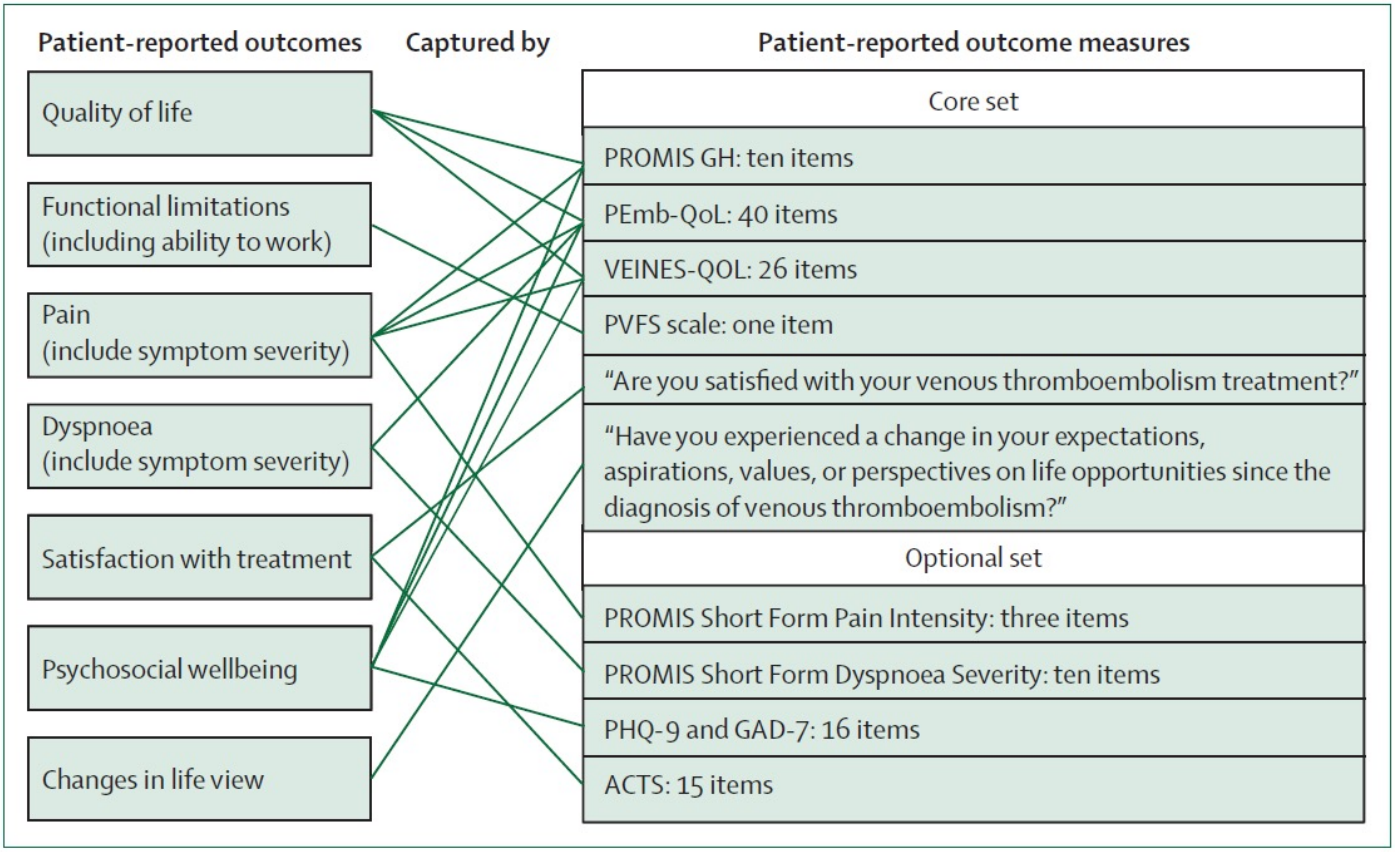
The Pulmonary Embolism Quality of Life Questionnaire (PEmb-QoL) quantifies health-related quality of life across six health dimensions: (1) frequency of complaints, (2) activities of daily living limitations, (3) work-related problems, (4) social limitations, (5) intensity of complaints, and (6) emotional complaints. Two questions are related to the time of the day at which the symptoms appear, and the state of the patient's current condition compared with one year before. These questions don't contribute to the overall score. The six contributing dimensions are summed, weighted, and transformed to a percentage scale (0 to 100), with higher scores indicating worse quality of life. The minimal clinically important difference in PEmb-QoL scores has been determined to be 15 [132]. PEmb-QoL has been translated into several languages [26, 133-137].

The Post-VTE functional status (PVFS) scale [25] interrogates aspects of daily life during follow up after a VTE event (**Suppl. Table 3.2; Main NCP-VTE Guideline, Figure 8**). The PVFS was developed to raise awareness in functional limitations in patients who have experienced a VTE event, whether as a direct consequence of the VTE or not, and to objectively determine the degree of disability. Following the identification of an unmet clinical need, international VTE experts and patients participated in the development of this scale through a Delphi process. The PVFS is currently being utilized in clinical research, including the ongoing Hi-PEITHO RCT (NCT04790370; clinicaltrials.gov).

PVFS scale	grade	Description
0	No functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity. Symptoms, pain and anxiety are absent.
1	Negligible functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity, despite some symptoms, pain, or anxiety.
2	Slight functional limitations	Some usual duties/activities at home or at work are carried out at a lower level of intensity or are occasionally avoided due to symptoms, pain, or anxiety.
3	Moderate functional limitations	Usual duties/activities at home or at work have been structurally modified (reduced) due to symptoms, pain, or anxiety
4	Severe functional limitations	Assistance needed in activities of daily living due to symptoms, pain, or anxiety: nursing care and attention are required.
D	Death	Death occurred before the scheduled assessment.

Suppl. Table 3.2: The Post-VTE functional status (PVFS) scale [25]: linked to section 6.3; Measuring Recovery Using Patient reported outcome measures.

The PVFS asks questions about aspects of daily life during follow up after a VTE event. The post-VTE functional status scale shown in this table was agreed by a Delphi panel and patient focus groups [25]. The last grade ("D") is only relevant for clinical trials.



Suppl. Figure 3.2: Tools for patient-reported outcome measures recommended by the International Consortium of Health Outcome Measures-VTE (ICHOM-VTE) [8]:
linked to 6.3; Measuring Recovery Using Patient reported outcome measures after VTE

The PROMIS short forms Pain Intensity and Dyspnea Severity are triggered by PROMIS short form GH and PEmb-QOL respectively. PHQ-9 and GAD-7 are triggered by PROMIS sort form GH.

ACTS: Anti-Clot Treatment Scale; GAD-7: Generalized Anxiety Disorder-7; GH= Global Health; PEmb-QoL: Pulmonary Embolism Quality of Life; PVFS: Post-Venous thromboembolism Functional Status; PHQ-9: Patient Health Questionnaire-9; PROMIS: Patient-Reported Outcomes Measurement Information System; VEINES-QOL: Venous Insufficiency Epidemiological and Economic Study on Quality of Life.

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Supplementary information/data linked to NCP-VTE Guideline Section 3.4: Ideal Post-PE care pathway

The NCP-VTE post-PE care pathway has been informed by recommendations of the ESC guidelines on acute PE 2019 [3] and of ICHOM-VTE [8]. Upon diagnosis of acute Pulmonary Embolism and initial anticoagulation, patients should be counselled, given a patient information leaflet and told what to expect in terms of follow-up. This follow up may require initial visits before 3-6 months, depending on individual circumstances.

However, it is important that a specific appointment is scheduled for all patients at 3-6 months to screen for post-PE complications. Each hospital should determine the best location and speciality for this clinic visit, depending on local resources and pathways. This clinic visit is an opportunity to screen for CTEPD, psychological symptoms and to evaluate satisfaction with treatment, life expectations and quality of life (**Main NCP-VTE Guideline, Figure 8**)

We recognize that completion of the entire suggested pathway may not be possible in some centres without additional local resources. The pathway below may be adapted to fit with local feasibility and resources where necessary. However, those patients with persistent dyspnea and functional limitations must be referred to a centre with more advance PE expertise, so that investigations for CTEPD can be conducted, in order to ensure that delayed or missed CTEPH diagnosis is avoided.

The NCP-VTE has developed patient educational materials addressing exercise and “looking after your mind” following VTE, which can be given to patients after PE (**Appendices**).

The key tenets of an integrated post-PE care pathway are elegantly summarised in a recent publication, “Optimal follow-up after acute pulmonary embolism” [9]. This document describes the steps that should be taken at the time when patients are diagnosed with VTE, in the first weeks after VTE diagnosis, at 3 (-6) months and during long-term management, to ensure holistic, integrated care that is in line with the recommendations in this chapter. It will be noted that the recommendations are broadly in line with those of **Main NCP-VTE Guideline, Figure 8**.

Supplementary information/data linked to NCP-VTE Guideline Section 3.5: Co-design of a model for a VTE Recovery Programme

Thrombosis Ireland (now the Irish Heart Foundation) Irish Heart Foundation – The National Heart and Stroke Charity and the NCP-VTE propose seeking resourcing for the following patient-centred recovery programme, a 10-step plan which will be updated as further evidence is published (**Suppl. Figure 3.3**).

1. After diagnosis, ensure that the correct anticoagulation drug choice has been selected for your patient, keeping in mind cost implications, sex and the age of your patient.
2. Explain to your patient exactly what has happened to them and that they are now in safe hands (reassure them, don't scare them) and that they can commence their recovery.
3. Consider connecting your patient with Thrombosis Ireland (now the Irish Heart Foundation) through their website Irish Heart Foundation – The National Heart and Stroke Charity. They will then receive peer support and a recovery pack.
4. When anticoagulation is in place, ensure that the patient, their carer or family members understand the reason for and side-effects of the drug they are taking; how it works, how to take it and what to do if they forget to take a dose or if they double up on a dose. Please provide the NCP-VTE DOAC or Warfarin Leaflet (Appendices).
5. Patients with severe ilio-femoral DVT who are at low risk of bleeding may be considered for catheter-directed procedures to treat their DVT (within 2 weeks of symptom onset), following appropriate counselling, particularly if the patient is very symptomatic or is at risk of immediate limb compromise.
6. Once anticoagulation is in place at the correct level and once the patient is safe, please explain how important it is to start exercising immediately and why. After evaluating the patient's individual ability, consider for example starting slowly and building up to one hour walk per day. **Ensure that they understand why this is important**. Provide NCP-VTE Exercise after a blood clot leaflet (Appendices).
7. Consider referral to a Recovery Exercise Programme with Medical Oversight.
8. Acknowledge the psychological impact of a life-threatening health incident with your patient and assess their psychological well-being as in **Main NCP-VTE Guideline, Figure 8** and provide the NCP-VTE Psychological Recovery Leaflets, available at (Appendices).
9. Following an initial check-up, it is important that a specific appointment is scheduled for all patients at 3-6 months to screen for post DVT/PE/CVST complications. Each hospital should determine the best location and speciality for this clinic visit, depending on local resources and pathways. This clinic visit is an opportunity to screen for CTEPD, psychological symptoms, Neurological complications or support needed (in the case of CVST) and to evaluate satisfaction with treatment, life expectations and quality of life.
10. Take action by further specialised referral to ensure your Patient has the ongoing recovery support they need to achieve optimal recovery.



Suppl. Figure 3.3: A model for a patient-centred recovery pathway: Linked to section 6.5: Co-design of a model for a VTE Recovery Programme

Co-designed by Thrombosis Ireland (now the Irish Heart Foundation) Irish Heart Foundation – The National Heart and Stroke Charity and the NCP-VTE, highlighting the ideal model for evidence-based recovery after VTE. This model will be adapted as additional evidence is available.

NCP-VTE: National Venous Thromboembolism programme; Thrombosis Ireland (now the Irish Heart Foundation) Website: Irish Heart Foundation – The National Heart and Stroke Charity

Patient information leaflets are in Appendices; DVT: Deep vein thrombosis; PE: Pulmonary embolism

4.0 Supplementary information/data linked to NCP-VTE Guideline Section 4: Awareness of VTE of signs and symptoms; basics of VTE prevention

Supplementary information linked to NCP-VTE Guideline Section 4.1: VTE Awareness

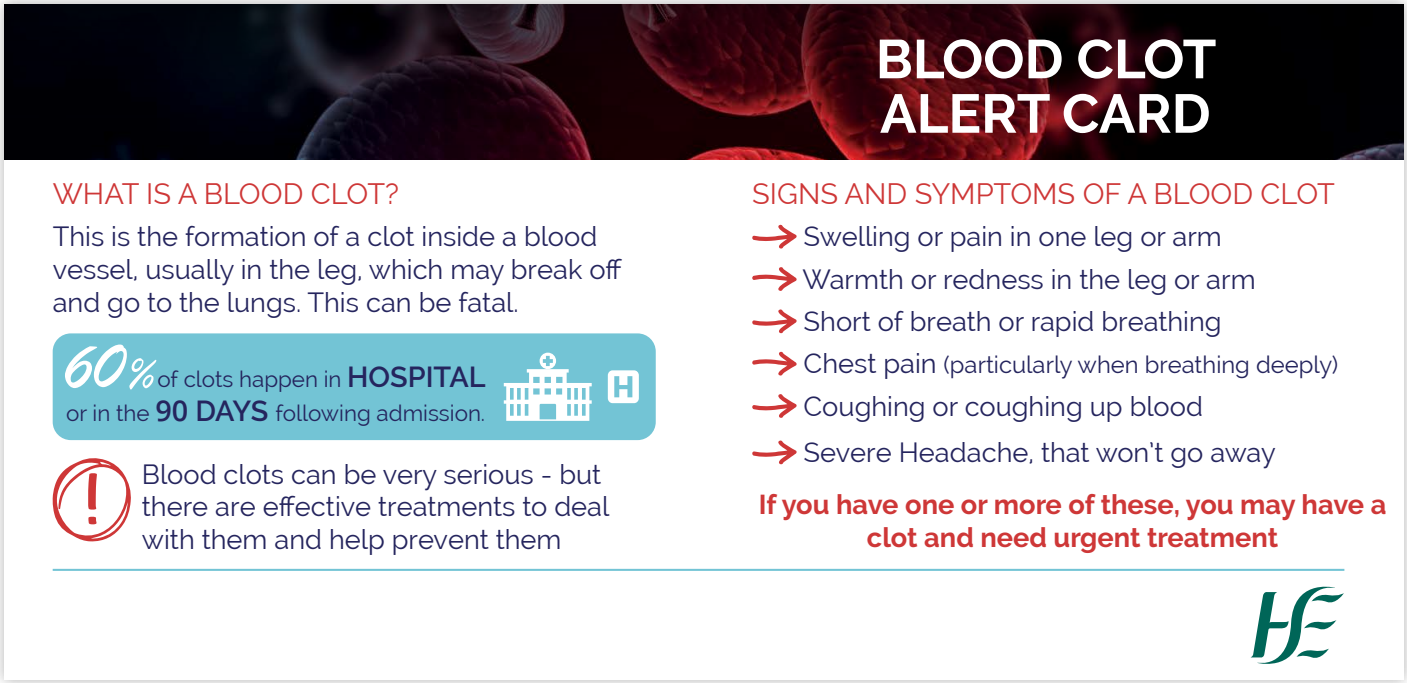
Despite the incidence, mortality and long-term health impact of VTE, awareness of this condition in the general population is very poor. In 2015, the World Thrombosis Day Campaign, under the auspices of the International Society on Thrombosis and Haemostasis, published the results of a survey including 800 respondents from each of Argentina, Australia, Canada, Germany, Japan, Thailand, the Netherlands, the United Kingdom and the United States that had aimed to measure general awareness about thrombosis, including deep vein thrombosis (DVT) and pulmonary embolism (PE) [138]. The authors reported that the proportion of respondents who demonstrated awareness of thrombosis, DVT and PE (68%, 44% and 54%, respectively) was lower than for other thrombotic disorders, such as heart attack and stroke (88% and 85%, respectively), and health conditions such as hypertension, breast cancer, and prostate cancer (90%, 85%, and 82% respectively). Unfortunately, lower awareness was associated with younger age.

More recently, a 2022 US survey reported that 75% of respondents had never heard of DVT and fewer than 1 in 10 had an awareness of DVT symptoms [13].

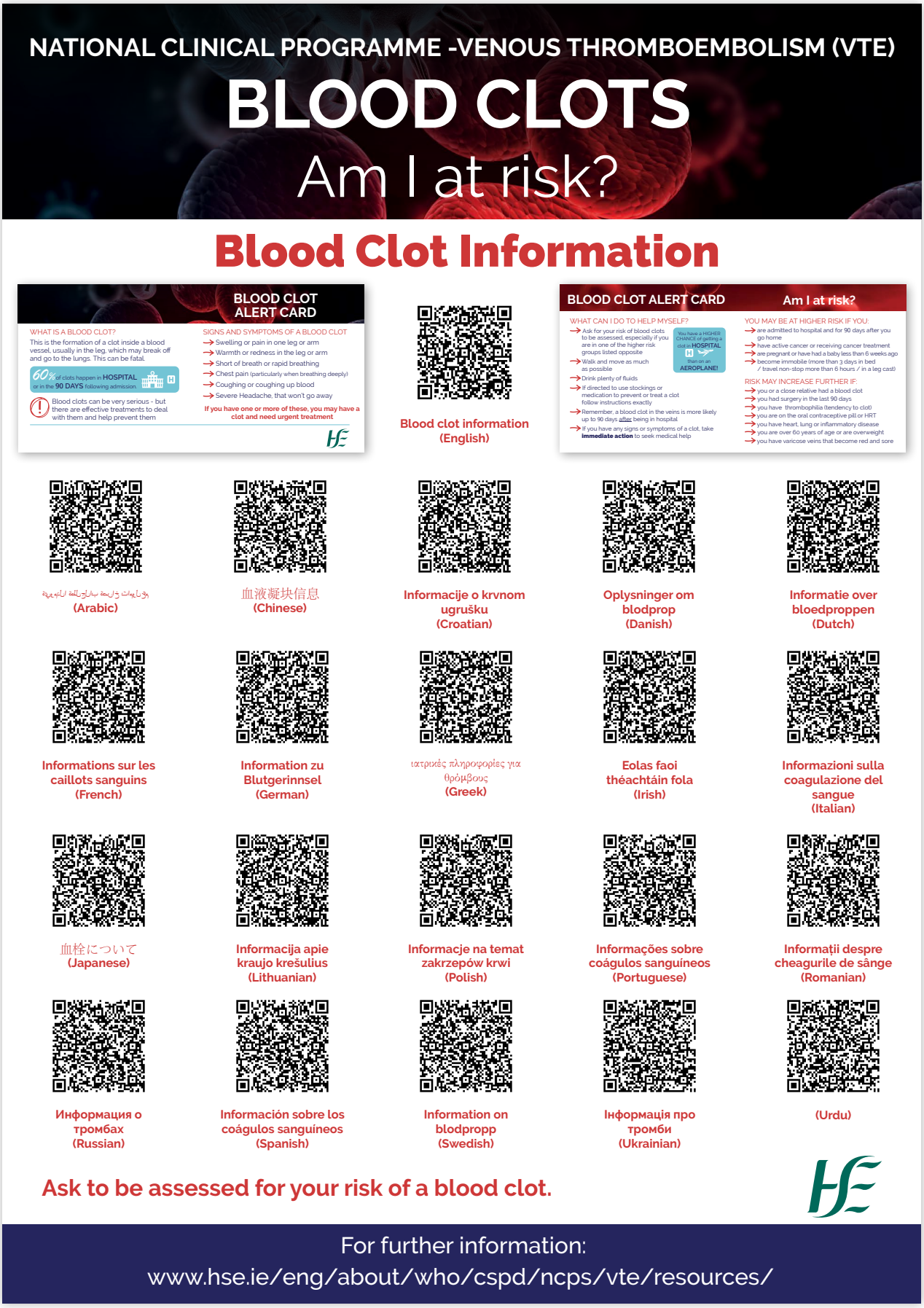
Tragically, lack of basic awareness of VTE signs and symptoms amongst the general community, those most at risk and amongst health care providers can result in missed opportunities to save lives and to prevent long-term disability.

In addition, sometimes the challenge for clinicians is not just lack of awareness that VTE is a serious condition but also that the initial signs and symptoms can be non-specific and often initially mild, including for example persistent coughing, shortness of breath on exertion, and even just feeling a little dizzy. These are symptoms that could easily be caused by a viral illness. Therefore, if we remember “THINK THROMBOSIS”, we are less likely to miss an opportunity to diagnose and treat VTE.

The NCP-VTE, working with Thrombosis Ireland and other HSE colleagues including the National Quality and Patient Safety Directorate, has developed a suite of resources to assist in promoting VTE awareness, including the Thrombosis Ireland/NCP-VTE VTE. These include a “Blood Clot Alert Card” (**Suppl. Figure 4.1**), a Blood Clot Information poster (**Main NCP-VTE Guideline Figure 9, copied below**), simple videos suitable for dissemination on social media, TV or on websites: https://www2.healthservice.hse.ie/organisation/nqpsd/featured-articles/world-thrombosis-day-2024/; https://www.youtube.com/watch?v=BWmJrzHC4uI&list=PLaiYIyOBPuPd4Wa1SIXGNkwLUoB69O4BU. Many make use of QR codes. The World Thrombosis Day Campaign (under the auspices of the International Society on Thrombosis and Haemostasis) also provides a suite of useful resources (https://www.worldthrombosisday.org/).



Suppl. Figure 4.1: Thrombosis Ireland/NCP-VTE Blood Clot Alert Card (Upper panel: Front of card; Lower panel: Back of card)



Copy of Main NCP-VTE Guideline Figure 9: NCP-VTE/Thrombosis Ireland Blood Clot information poster highlighting signs and symptoms of VTE and the risk factors for same, translated into some commonly encountered languages in the Irish health system.

4.0 Supplementary information/data linked to NCP-VTE Guideline Section 4.2 and 4.3: basics of VTE prevention

Risk factors for VTE are outlined in **Main NCP-VTE Guideline, Figure 10** and vary between men and women. Oestrogen-containing combined oral contraceptives (COC), for example, are associated with a 2-6 fold increased VTE risk (depending on the preparation used) [139], but the absolute risk is still very low . Similarly, oral (but not transdermal) use of postmenopausal hormone replacement therapy (HRT) has been reported to increase VTE risk. Risk factors such as thrombophilia, age, smoking, obesity and major provoking risk factors (e.g. major surgery or fractures) further increase VTE risk in users of COC and HRT. Some risk factors are not simply additive but appear to be synergistic in combination, such as COC use and the factor V Leiden mutation [139, 140].

People in the community with VTE risk factors **Main NCP-VTE Guideline, Figure 10** are expected to have a higher probability of developing VTE and this is of great relevance when considering referral for VTE investigations. However rarely is the absolute risk of a patient in the community sufficiently high to warrant outpatient continuous thromboprophylaxis. In contrast, absolute VTE risks in hospitalized patients frequently reach thresholds at which additional prevention strategies should be considered.

Hospital-acquired VTE (HA-VTE, defined as a VTE event occurring either during or up to 90 days following hospitalization) is an important cause of death and disability. Up to 50-60 percent of all VTE cases occurring during or after hospitalization, such that VTE a leading preventable cause of hospital death [1, 14, 15, 19]. In the U.K, HA-VTE has been significantly reduced following the implementation of a National VTE prevention programme. These and other data demonstrate that HA-VTE is a potentially preventable through strategies that may include raised awareness (including awareness of the signs and symptoms of VTE amongst patients), VTE risk assessment and implementation of appropriate thromboprophylaxis [15, 19]. Risk factors for VTE include immobilization, surgery, cancer, pregnancy, certain hormonal therapies, infection, obesity, medical comorbidities and limb fracture [3]. These risk factors must be formally assessed to identify whether a patient is at risk of a VTE event and whether pharmacological thromboprophylaxis is required. Finally, a bleeding risk assessment must be carried out prior to prescription of pharmacological thromboprophylaxis, to ensure that no contraindication exists.

The relative risk of VTE has been reported to increase significantly during and after hospitalization compared with community rates [17, 18]. Randomized clinical trials (RCTs) have shown that pharmacological thromboprophylaxis can reduce the incidence of PE and DVT in medical and surgical patients [1, 20, 141, 142]. However, universal thromboprophylaxis is not recommended due to competing bleeding risks [20, 143]. Therefore, risk assessment of hospitalized patients to identify those with a high VTE risk and a low bleeding risk is essential, followed by targeted appropriate thromboprophylaxis [20, 141]. A UK national quality initiative to increase the number of hospitalised patients assessed for risk of VTE, based upon UK National Institute for Health and Care Excellence (NICE) recommendations has resulted in a reduction in VTE mortality [15, 19].

National guidance on the operationalization of VTE risk assessment and prevention was published in July 2018 by the National Medication Safety Improvement Programme of what was then termed the HSE Quality Improvement Division (now the HSE National Quality and Patient Safety Directorate). This was the “Preventing Blood Clots in Hospitals Improvement Collaborative Report; National Recommendations and Improvement Toolkit" [144]. The key recommendations of this report are summarized below:

Summary of recommendations of essential requirements of the “Preventing Blood Clots in Hospitals Improvement Collaborative Report; National Recommendations and Improvement Toolkit" [144] incorporating additional NCP-VTE implementation recommendations:

Each patient admitted to hospital for an in-patient stay requires:

- Information about any prophylaxis they are receiving, their risk of VTE for 90 days after hospitalization, the signs and symptoms of VTE and what to do if they occur.
- Assessment following the VTE prevention protocol as soon as possible after the decision to admit is made and repeated if clinical situation changes. The protocol comprises standardised VTE risk assessment and bleeding risk assessment
- The VTE protocol should comprise clinical decision support to guide the appropriate choice of prophylaxis, in line with the patient’s VTE risk, bleeding risk, contra-indications to mechanical prophylaxis and any dose adjustment required due to renal impairment or weight. A national protocol is available for adult medical inpatients and those with Covid-19 (**Suppl. Figure 4.2; CD19-120-001 Covid-19 Interim Clinical Guidance -VTE Protocol and patient Information for Acute Hospitals Version 2 - 04.05.2022; updated 2022 [145]**) **linked to section 4.3 (VTE prevention strategies in Ireland**). Future updates will include additional patient groups.
- All of these steps should be completed as soon as possible after admission. The appropriate prophylaxis should be prescribed, administered and/or applied within 14 hours after the decision to admit.

Hospitals should ensure that:

1. Oversight for monitoring and improving VTE prevention is assigned to the appropriate governance committee and is an agenda item at meetings at least twice a year.
2. As improving VTE prevention is a large undertaking, establishing a dedicated hospital Thrombosis Committee or Thrombosis Prevention Committee may be required, with reporting structures to higher levels of governance.
3. There is a standardised hospital VTE prevention protocol, comprising VTE risk assessment, bleeding risk assessment and clinical decision support for choice and dose of prophylaxis according to the patient’s risk, weight, renal function and contra-indications to prophylaxis.

4. Standardised VTE risk assessment following the VTE protocol should be carried out for each inpatient as soon as possible after the decision to admit is made, and appropriate prophylaxis received asap and within 14 hours.
5. Each in-patient should receive information about any VTE prophylaxis they are receiving, their risk of VTE for 90 days after hospitalisation, the signs and symptoms of VTE and what to do if they occur, facilitated by providing the Blood Clot Alert Card (or similar).
6. Responsibilities for prescribing according to the VTE prevention protocol, independently checking prophylaxis and providing patient information prior to discharge is assigned and these healthcare professionals are clearly aware of their responsibility.
7. All staff involved in the processes of risk assessment, prescribing, administering, monitoring and checking VTE prophylaxis have access to the VTE prevention protocol and information about preventing VTE.
8. Monitoring of key metrics takes place at least quarterly and is reviewed at the appropriate governance committee at least twice a year. This includes:

   a. Rate of defined and suspected venous thromboembolism (VTE, blood clots) associated with hospitalisation (National KPI [146]).

   b. Percentage of sampled patients with appropriate prophylaxis (i.e. in line with the hospital's VTE prevention protocol) within 14 hours of the decision to admit. **Standardised sampling, data collection and measurement instructions are available on www.hse.ie/safermeds.**

   c. Percentage of sampled discharged patients who received information about VTE risk and signs and symptoms, for a random sample of 10 patients per quarter or greater.

   d. Hospitals may supplement the above with additional more detailed quantitative and/or qualitative research, audit and measurement for improvement.
9. Hospital-acquired VTE is documented in patient's notes, reported and managed in accordance with the HSE Incident Management Framework, including open disclosure (www.hse.ie/opendisclosure). Where the VTE occurred following treatment in another hospital, that hospital is also informed.
10. Hospital-acquired VTE is listed as a risk on the hospital's risk register.

Audit Standards for VTE prevention

1. **Thromboprophylaxis Administration:**
    - **Standard 1.1: Thromboprophylaxis Assessment**
        - *Criteria:* 100% of patients admitted to the hospital should be assessed for VTE risk within 14 hours.
        - *Measure:* Percentage of patients assessed for VTE risk ≤ 14 hours.
        - *Target:* 100%
    - **Standard 1.2: Appropriate Thromboprophylaxis**
        - *Criteria:* 90% of patients identified as at risk for VTE should receive appropriate thromboprophylaxis according to clinical guidelines.
        - *Measure:* Percentage of at-risk patients receiving appropriate thromboprophylaxis.
        - *Target:* 90%
2. **Patient Information and Education:**
    - **Standard 2.1: Patient Information on VTE**
        - *Criteria:* 90% of patients should receive verbal and written information on VTE signs, symptoms, and prevention strategies during their admission.
        - *Measure:* Percentage of patients provided with VTE information.
        - *Target:* 90%
    - **Standard 2.2: Documentation of Patient Education**
        - *Criteria:* 100% of patient education on VTE should be documented in the patient's medical record.
        - *Measure:* Percentage of patient records with documented VTE education.
        - *Target:* 100%
3. **Clinical Audits and Reporting:**
    - **Standard 4.1: Local and Regional Reporting**
        - *Criteria:* 100% of hospitals should produce quarterly reports on HA-VTE rates, rates of appropriate thromboprophylaxis, and patient education efforts.
        - *Measure:* Frequency and completeness of quarterly reports.
        - *Target:* 100%

- **Standard 4.2: National Reporting**
  - *Criteria:* Annual national reports on HA-VTE should be compiled and made publicly available.
  - *Measure:* Availability and comprehensiveness of the national report.
  - *Target:* 100%

4. **Quality Improvement and Action Planning:**
   - **Standard 5.1: Quality Improvement Initiatives**
     - *Criteria:* 100% of hospitals should develop and implement quality improvement (QI) initiatives based on audit findings to address gaps in VTE prevention and management.
     - *Measure:* Number and scope of QI initiatives implemented.
     - *Target:* 100%

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VTE Prevention Protocol for In-Patients aged 16 or Over with COVID-19 or Medical Conditions

All hospitalized patients are at increased risk for VTE. VTE is associated with increased morbidity and mortality.
Appropriate VTE prevention reduces risk for patients at high risk of VTE.
Assess all patients as soon as possible (within 14 hours) after the decision to admit. Reassess at consultant review and if clinical condition changes.

Step 1: VTE risk assessment VTE risk factors	Padua score	VTE risk factors continued	Padua score
Confirmed or presumed COVID-19		At risk, proceed to step 2	
Medical in-patient without a COVID-19 diagnosis		Assess according to Padua Prediction Score (below)	
Immobility expected for at least 3 days (confined to bed +/- bathroom)	3	Active cancer or treatment (chemo-or radiotherapy within 6 months or metastases)	3
Previous DVT/PE	3	Thrombophilia	3
Trauma and/or surgery in previous 30 days	2	Ischaemic stroke (discuss with stroke team) or Acute MI	1
Heart and/or respiratory failure	1	Aged 70 or over	1
Taking oestrogen-containing contraceptive or oral HRT	1	Acute infection or Acute or chronic rheumatologic disorder	1
BMI 30 or greater (obese)	1	Pregnant or up to 6 weeks post-partum*	4*

Patients with COVID-19: all patients are at risk of VTE; proceed to step 2.
Medical patients: Padua Prediction Score 4 or greater = at risk of VTE; proceed to step 2.
Padua Prediction Score 3 or less = at low risk of VTE; no prophylaxis required.
***Pregnant or post-partum: Medical admission = at risk of VTE, proceed to step 2. Maternity = follow maternity guidance.**

Step 2: Bleeding risk assessment. Any risk factor below = contra-indication to low molecular weight heparin (LMWH) or heparin	
Active bleeding	On anticoagulant at therapeutic levels/dose, e.g. warfarin, dabigatran, rivaroxaban, edoxaban, apixaban, heparin, enoxaparin: No additional prophylaxis except while anticoagulant held
Platelets less than 50 x 10^9/L	Undergoing procedure with high bleeding risk, e.g. neurosurgery, spinal or eye surgery
Bleeding disorder, e.g. haemophilia, Von Willebrand's	History of Heparin-Induced Thrombocytopaenia (HIT): Contact haematology or pharmacy
Acquired bleeding disorder e.g. liver failure with PT over 15	Other bleeding risk: if risk of VTE outweighs bleeding risk, consider pharmacological prophylaxis. If risk of bleeding outweighs risk of VTE, consider mechanical VTE prophylaxis
Acute stroke (discuss with stroke team)	
Blood pressure 230 systolic or 120 diastolic or greater	Note: Dual antiplatelet therapy does not preclude prophylactic dose LMWH. There is a lack of data to support therapeutic dose LMWH in patients with COVID-19 who are receiving dual antiplatelet therapy: Consider prophylactic-intensity anticoagulation as an alternative
Epidural or spinal or lumbar puncture in last 4 hours or expected in next 12 hours	

Step 3: Recommended VTE prevention (or anticoagulation as a "therapeutic" strategy for COVID-19). These recommendations should not be used to guide care for patients with acute venous thromboembolism.				
All patients	Adequate hydration, early mobilisation			
Pharmacological	**Weight 50-100 kg and GFR over 30 mL/min**	**Weight 101-150 kg**	**Weight less than 50 kg**	**GFR less than 30 mL/min**
Prophylactic intensity anticoagulation: All COVID-19 patients not on therapeutic anticoagulation or Medical patients with Padua score ≥4 **And** No C/I to heparin	Tinzaparin 4500 units once daily or Enoxaparin 40 mg once daily	Tinzaparin 4500 units bd or Enoxaparin 40 mg bd	Tinzaparin 3500 units once daily or Enoxaparin 20mg once daily	Heparin 5000 units twice daily or Tinzaparin 3500 units daily (caution) or enoxaparin 20 mg daily (contra-indicated in GFR less than 15 mL/min)
Therapeutic-intensity LMWH* **may be considered** in patients admitted to hospital because of moderate COVID-19** AND **who have a low bleeding risk** This also applies to patients admitted for another reason but who progress to develop moderate COVID-19	Tinzaparin 175 units / kg once daily or Enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily ** Moderate COVID-19 is defined as follows: admission to hospital ward level of care (ie, not to ICU), not already mechanically ventilated, and not imminently requiring mechanical ventilation or critical care. **We suggest that this therapeutic strategy be limited to patients who have oxygen saturations of ≤ 93% on room air due to COVID-19, or who require low-flow oxygen via nasal prongs or face mask to maintain normal oxygen saturations.** The evidence supports prophylactic intensity LMWH for all other patients with COVID-19 (unless contra-indicated), including those with severe COVID-19			Data supporting the use of therapeutic-intensity anticoagulation for patients with COVID-19 and renal impairment are lacking. We suggest against therapeutic anticoagulation (in the absence of a VTE event), if GFR is less than 30ml/min. Consider prophylactic-intensity LMWH instead.
Mechanical				
COVID-19 patient or High-risk medical patient (score 4 or greater) with contra-indication to heparins	Mechanical compression: Anti-embolism stockings* +/- intermittent pneumatic compression devices (IPCD)/ foot pumps * Do not use in suspected or proven peripheral arterial disease, severe dermatitis, massive leg oedema, leg deformity preventing correct fit, peripheral neuropathy, recent skin graft, allergy to fabric or acute stroke. Use caution and clinical judgement if applying stockings over venous ulcers or wounds. Use IPCD if available, particularly in COVID-19 or acute stroke.			
Low-risk medical (score 3 or lower)	No heparin or low molecular weight heparin - No mechanical compression			
Duration: local decision; e.g. until low-risk for VTE or until discharged. May consider prolonged prophylaxis on a case-by-case basis.				

Step 4: Inform the patient about the signs and symptoms of VTE. Prescribe appropriate prophylaxis.

Step 5: As part of the discharge plan, give patients (and family members/carers if appropriate) verbal information and the VTE patient alert card. Give those discharged with prophylaxis information about its importance and how to use it effectively and safely and notify their GP.

Suppl. Figure 4.2: VTE Prevention Protocol for In-Patients aged 16 or Over (updated 2022: CD19-120-001 Covid-19 Interim Clinical Guidance -VTE Protocol and patient Information for Acute Hospitals Version 2 - 04.05.2022) linked to NCP-VTE Guideline section 4.3 Recommendations VTE Risk Assessment and Prevention

6.0 Supplementary information/data linked to NCP-VTE Guideline Section 6: Guideline methodology, Evidence searches and the method of appraisal

GRADE (**G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuations) methodology is a transparent framework for developing and presenting summaries of evidence which provides a systematic approach for making clinical practice recommendations [147-150]. The GRADE methodology was developed in 2011, partly in response to the Institute of Medicine's call for "Guidelines We can Trust" [147-149]. An EtD (Evidence to Decision) framework should also be applied, which is a transparent framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations [150]. PICO (Population, Intervention, Comparator and Outcomes) questions are developed, which define the scope of the guideline by defining inclusion and exclusion criteria for the systematic review of the evidence. Based on the availability of evidence, PICO questions are then categorized and prioritized.

The National VTE guideline panel was not resourced to undertake a full GRADE process, which, as explained above involves a rigorous and resource-intensive procedure including the aforementioned Evidence to Decision (EtD) framework. To streamline our process and maintain high standards, in addition to performing rapid evidence synthesis in line with HSE guidelines, we have in some circumstances adopted recommendations from reputable international guidelines that are based on robust published data. In cases where these recommendations align with our national context, we have implemented them without conducting a de novo GRADE assessment. This approach allows us to provide evidence-based, high-quality recommendations efficiently while adhering to required formats.

6.1 Guidelines and Guidance Documents: What is the difference?

A Clinical Practice Guideline adheres to a formal governance and operational framework as well as a rigorous, structured process to address a topic with moderate-to-high-quality evidence to inform best practises, employs a structured process to summarise the evidence (i.e., systematic review), and provides a standardised method to express a recommendation [151-153]. In contrast, a guidance document addresses a clinically important topic (diagnostic-, therapeutic-, or laboratory-based) of broad clinical interest, in some circumstances where evidence-based guidelines and/or RCTs are lacking or are unlikely to be developed in future [152, 153]. ***We suggest that the material herein, although containing elements of both, more completely aligns to the traditional definition of a guidance document rather than a Clinical Practice Guideline.***

6.2 Evidence synthesis

A systematic review of the literature was undertaken to identify relevant literature on venous thromboembolism (VTE) awareness, prevention, diagnosis, immediate treatment and long-term recovery. Systematic searches of EBSCO Medline, Embase, and EBSCO Cinahl, were completed using (MeSH/Emtree terms).

Inclusion Criteria

Inclusion criteria focused on high-quality studies such as randomized controlled trials (RCTs), systematic reviews, and meta-analyses.

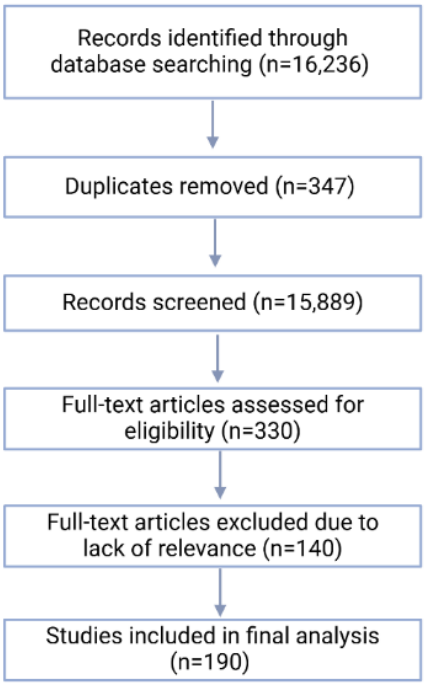
Exclusion Criteria

Exclusion criteria included studies with high risk of bias, small sample sizes, or those not directly relevant to the key questions.

Method of appraising evidence

The Development Group membership comprised of a multidisciplinary taskforce including physicians from various specialities, nursing, physiotherapy, psychology, primary care colleagues, patients and patient representatives. The group followed a rigorous and systematic approach to screen and appraise the evidence. This process ensured that the guidance and recommendations developed are firmly grounded in the best available evidence.

A total of 190 articles were included in the final analysis (**Suppl. Figure 6.1**)



Decision-Making Process

Evidence was reviewed at the Development Group meetings linking evidence to recommendations. Each recommendation in the guideline was explicitly linked to the supporting evidence. The strength of the recommendation was determined based on the quality of the evidence and the balance between benefits and harms. Draft recommendations were reviewed by external experts and stakeholders to ensure validity, reliability and applicability of the recommendations in the context of the evidence.

No.	***VTE AND Prevention Ovid Medline Search Strategy***
1	exp Venous Thromboembolism/ or ("Venous Thromboembolism" or VTE or "HA-VTE" or Thromboprophylaxis or "Deep vein thrombosis" or "DVT" or "Pulmonary embolism" or "PE").ti,ab,kw.
2	(prevention* or "risk assessment*" or "bleeding risk assessment*" or "national guidelin*" or "hospitalized patient*" or "prevention protocol*" or "prevention strateg*" or "risk factor*" or "clinical decision support" or "patient education" or "quality improvement*" or (monitor adj2 audit*) or "national program*" or (HSE adj2 guideline*) or "safety improvement program*" or "hospital governance" or "hospital acquired" or prevention or "pharmacological thromboprophylaxis" or "mechanical prophylaxis" or "anticoagulant thromboprophylaxis").tw.
3	1 and 2
4	limit 3 to (english language and yr="2015 -Current")

No.	***PE & VTE Recovery Search Strategy Ovid Medline***
1	exp Pulmonary Embolism/ or ("Pulmonary Embolism*" or PE or "Post-Pulmonary Embolism Syndrome*" or "PPES" or "Chronic Thromboembolic Pulmonary Hypertension" or "CTEPH" or "Chronic Thromboembolic Pulmonary Disease*" or "CTEPD" or "Residual Pulmonary Vascular Obstruction*" or "RPVO" or "Post-Thrombotic Syndrome*" or "PTS").ti,ab,de.
2	("VTE recovery" or (post adj2 (management or recover)) or ("general VTE" adj2 (recovery or "long term management" or "longterm management")) or ("post VTE" adj2 management) or (VTE adj2 "long-term complication*") or ("chronic complication*" adj2 (VTE or PE)) or (post adj2 care) or "PE sequelae" or recovery or "quality of life" or "QOL" or "functional limitation*" or (post adj2 symptom*) or (post adj2 dyspnea) or "emotional distress" or ("mental health" adj4 VTE) or ("quality of life" adj3 PE) or (emotion* adj3 VTE) or "cardiopulmonary exercise testing" or "CPET" or ("post PE" adj2 depression) or (("post-thrombotic" adj2 "panic syndrome*") or "CTEPD recovery" or ("Pulmonary obstruction" adj3 "after PE") or ("chronic vascular obstruction*" adj3 "post PE") or "Chronic Thromboembolic Pulmonary Hypertension" or "CTEPH" or "chronic thromboembolic pulmonary hypertension" or "CTEPH" or "CTEPH management" or ("Pulmonary hypertension" adj2 "post PE") or "CTEPH prognosis*" or "residual pulmonary vascular obstruction*" or "RPVO" or (("Post-Thrombotic Syndrome" or "PTS") adj3 DVT) or ("post thrombotic syndrome" or "PTS" or "Chronic Thromboembolic Pulmonary Disease" or "CTEPD" or "Chronic thromboembolic pulmonary disease" or CTEPD or (PTS adj2 ("deep vein thrombosis" or DVT)) or "DVT complication*" or ((("Post-VTE functional status" or "PVFS") adj3 scale) or ("chronic venous insufficiency" adj4 ("after DVT" or "post DVT")) or ("PEmb-QoL" or "Pulmonary Embolism Quality of Life" or ("PTS after" adj3 ("after deep vein thrombosis" or DVT))))))).tw.
3	1 and 2
4	limit 3 to (english language and yr="2014 -Current")

No.	
1	exp Venous Thromboembolism/ or ("Venous Thromboembolism" or VTE or "HA-VTE" or "Deep vein thrombosis" or "DVT" or "Pulmonary embolism" or "PE").ti.
2	("diagnostic criteria*" or "diagnostic strategies*" or "clinical prediction*" or "prediction strateg*" or "clinical decision support" or "investigation* or “diagnostic guideline” or “guideline” or “investigation algorithm*).tw.
3	1 and 2
4	limit 3 to (english language and yr="2015 -Current")

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