

Consensus on Management of Deep Vein Thrombosis with Emphasis on NOACs (Non-Vitamin K Antagonist Oral Anticoagulants): Recommendations from Inter-Disciplinary Group of Indian Experts

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Abstract

It is estimated that around 2.5 lac patients are identified as having an acute venous thrombo-embolic event in India annually. This includes patients with deep vein thrombosis and pulmonary embolism, and is estimated to result in more than 3.7 lacs deaths each year in European countries. The 'Consensus on Management of Deep Vein Thrombosis with Emphasis on NOACs (Non-Vitamin K Antagonist Oral Anticoagulants): Recommendations from Inter-Disciplinary Group of Indian Experts' position paper was developed to assist clinicians and institutions with an evidence-based approach to the diagnosis and treatment of acute deep vein thrombosis patients. Key to the evaluation of patients with suspected deep vein thrombosis is the use of the clinician's clinical evaluation with the help of pre-test probability tools as well as judicious use of objective diagnostic tests. Our hope is that we have supplemented clinicians' clinical acumen, and assisted them and their health systems in developing best practice approaches to this ever-interesting population of patients.

The Deep Vein Thrombosis Consensus Working Group welcomes your inputs on how improvements might be made on this paper in the future.

all races, age groups, and both genders. DVT in the lower extremity can be classified as (a) proximal (the popliteal vein or thigh veins are involved) or (b) distal (the calf veins are involved). And etiologically, it can be classified as provoked (when the risk factor is known) and unprovoked (when the risk factor is unknown).¹ Various hereditary as well as acquired factors predispose to the development of VTE (Table 1).²

The global burden of VTE shows overall annual incidences of 0.75-2.69 per 1000 population and 2-7 per 1000 in elderly (≥ 70 years of age).³ The overall age adjusted incidence rate of VTE is higher for men (114 per 100,000) than women (105 per 100,000) with male to female sex ratio of 1.2:1.^{4,5} The true incidence of VTE is hard to estimate because of the often silent nature of the condition. In Prospective Registry on Venous Thromboembolic Events (PROVE) conducted in 19 countries, 667 patients with symptomatic DVT from India were included. In this study, proximal plus calf DVTs were found in 54%, proximal DVT in 17 %, and calf DVT in 13 % of Indian patients, compared with 52,

Aims

1. To improve accurate diagnosis and treatment of deep vein thrombosis
2. To prevent progression or recurrence of thromboembolic disease.
3. To safely use anticoagulants to reduce the likelihood of patients

harm and complications of anticoagulation therapy.

Introduction

"Venous thromboembolic (VTE) disease" is a term used to describe both deep vein thrombosis (DVT) and pulmonary embolism (PE). Venous thromboembolism (VTE) is a global health problem as it affects

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Table 1: Risk factors for venous thromboembolism²

Acquired risk factors
Surgery
Trauma (major trauma or lower – extremity injury)
Immobility, lower – extremity paresis
Cancer (active or occult)
Cancer therapy (hormonal, chemotherapy, angiogenesis inhibitors, radiotherapy)
Venous compression (tumor, hematoma, arterial abnormality)
Previous VTE
Increasing age
Pregnancy and the postpartum period
Estrogen-containing oral contraceptives or hormone replacement therapy
Selective estrogen receptor modulators
Erythropoiesis-stimulating agents
Acute medical illness
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Obesity
Central venous catheterization
Inherited risk factors
Factor V Leiden Mutation (most common)
Prothrombin gene mutation (20210A)
Protein S Deficiency
Protein C Deficiency
Antithrombin III Deficiency
Hyper-homocysteinemia

18, and 24 per cent in the global PROVE population, respectively.⁶ The SMART study involving 2420 Asian patients undergoing major orthopaedic surgeries without thromboprophylaxis showed that the incidence of symptomatic VTE is comparable to that of the western countries.⁷ In the ENDORSE study, a multinational cross-sectional survey, out of 68,183 patients in acute hospital beds across 32 countries, 51.8% were at risk for developing VTE according to ACCP guidelines.⁸ In this study, chronic pulmonary disease, heart failure and complete immobilization were the most common risk factors before and during hospitalization, respectively.⁸ The subset of ENDORSE study showed that in India, 53.6% of hospitalized patients [surgical (61.3%), medical (44.7%)] were at-risk for VTE, still >80% of these

Table 2: Clinical features of deep vein thrombosis¹²

Symptoms	Percentages
Calf tenderness	94
Calf pain	90
Ankle swelling	76
Calf swelling	42
Dilated superficial veins	33

patients did not receive American College of Chest Physicians (ACCP) recommended thromboprophylaxis.⁹ About 30% of VTE patients develop recurrence within next 10 years and is highest within first 6 to 12 months of presentation.^{10,11}

Diagnosis of Deep Vein Thrombosis

Symptoms and signs of DVT (Table 2)¹² are not specific and have different possible causes which may warrant further evaluation.¹³ The diagnosis of DVT can be often missed, even in high-risk patients, with a history and physical examination alone.¹³

It is also important to ascertain the diagnosis of DVT accurately to minimize the risk of thromboembolic complications and the potential risk of bleeding due to anticoagulant therapy.¹⁴ Studies have shown that only 20–40% of patients presenting with symptoms of DVT, actually have confirmed diagnosis of the condition.^{15–17} Now, It has been established that a combination of signs, symptoms and clinical prediction rules can be useful to categorise suspected DVT patients as low, moderate or high risk of DVT, and aid further management of such patients.¹³ Following clinical prediction rules can assist in diagnosis of DVT.

Clinical Prediction Rules for Deep Vein Thrombosis

Validated clinical prediction rules reliably predict the pre-test probability of DVT, which guide the interpretation of subsequent diagnostic tests. The usefulness of various diagnostic tests and imaging studies in predicting the presence of DVT depends on the likelihood of disease in each risk

group. For example, a negative test may rule out DVT in a low-probability patient but not in a high-probability patient when applied. Many patients have an intermediate probability of DVT, in such cases; clinical judgment plays an important role in making the decision to treat.¹⁸ Of the available clinical prediction rules for DVT, modified Wells score seems to be more useful because of its reproducibility in predicting the pre-test probability of DVT in outpatient settings (Table 3).^{19–21} The pre-test probability of DVT in three risk group category is 5% (low risk), 17% (moderate risk) and 53% (high risk) respectively while in the two risk category it is 6% (DVT unlikely) and 28% (DVT likely) respectively.^{20,21}

Medical patients have a heterogeneous risk of VTE therefore evaluation of thromboprophylaxis strategies in such patients in two different strata, low risk and high risk is suggested by the guidelines. Several Risk Assessment Models have been proposed to estimate the baseline risk of VTE in hospitalized medical patients. Of which, the Padua prediction score seems to be useful for VTE risk assessment of hospitalized medical patients (Table 4).²² In a prospective observational study, 1180 hospitalized medical patients using this score were, categorized as low risk (<4 points; 60.3% of patients) or high risk (≥4 points; 39.7% of patients) for VTE and followed for symptomatic VTE for 90 days. VTE occurred in 11.8% of high-risk patients who did not receive thromboprophylaxis vs 2.2% of high-risk patients who received thromboprophylaxis. Among 711 low-risk patients, two (0.3%) developed VTE (1 PE, 1 PE with DVT). The ACCP 9th edition guidelines for 'Prevention of VTE in Nonsurgical Patients' mentions that 'this model provides the best available basis for judging hospitalized patients' risk.²³

In patients undergoing general and abdominal-pelvic surgery, the risk of VTE varies depending on both patient-specific and procedure-specific factors. The recommendations for deep vein

Table 3: Modified Wells score¹⁹⁻²¹

Parameter	Score
Active cancer (treatment ongoing, or within 6 months or currently receiving palliative treatment)	1
Paralysis, paresis or recent plaster immobilization of lower extremities	1
Recently bedridden for ≥ 3 days or major surgery within past 12 weeks under general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling more than 3 cm compared with asymptomatic leg	1
Pitting edema (greater than asymptomatic leg)	1
Previous DVT documented	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis (at least as likely as DVT)	-2
Interpretation:	
3 risk group: Patients with score 0 to -2 are considered to be at low risk, between 1-2 at moderate and ≥ 3 are at high risk	
2 risk group: patients are stratified as DVT unlikely (Wells score < 2) or DVT likely (Wells score > 2).	

Table 4: The Padua Prediction Score²²

Parameter	Score
Active cancer (local or distant metastases and/or in whom chemotherapy/radiotherapy in previous 6 months)	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility (Bed rest with bathroom privileges due to patient's limitations or on physicians order) for ≥ 3 days.	3
Already known thrombophilic condition (Carriage of defects of Anti-thrombin, Protein C or S, Factor V Leiden, G20210A Prothrombin mutation, Anti-phospholipid syndrome)	3
Recent (≤ 1 month) trauma and/or surgery	2
Elderly patient with age ≥ 70 years	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥ 30 kg/m ²)	1
Ongoing hormonal treatment	1
Interpretation:	
If the score is <4: Low risk of VTE	
If the score if ≥ 4 : High risk of VTE	

Table 5: Recommendations for deep vein thrombosis risk assessment

- We suggest the use of Modified Wells Score for pretest probability assessment in outpatients with clinical suspicion of DVT.
- In hospitalized patients considered to be at high risk of DVT, we suggest the use of PADUA score, for DVT risk assessment.
- In patients who are undergoing general and abdominal-pelvic surgery, we suggest the use of Caprini score to assess the risk of DVT.

thrombosis risk assessment are summarized in Table 5. Although several models for risk stratification exist, all have important limitations. One such model is the Caprini score, which estimates VTE risk by adding points for various VTE risk factors. With this model, VTE risk is categorized as being very low (0-1 point), low (2 points), moderate (3-4 points), or high (5 points). It is relatively easy to use and appears to

discriminate reasonably well among patients at low, moderate, and high risk for VTE.^{24,25}

Investigations for Deep Vein Thrombosis

Basic laboratory investigations, D-dimer assessment and imaging are useful in diagnosis of DVT. Basic laboratory investigations include complete blood count, coagulation

profile, electrolyte levels, liver function tests and kidney function tests.²⁶

D-dimer, a degradation product of cross-linked fibrin is commonly elevated in patients with thromboembolism. However, one needs to bear in mind that D-dimer test does not necessarily help in diagnosis of VTE, but rather helps in ruling out thrombotic conditions. Its levels may be elevated in other conditions like malignancy, disseminated intravascular coagulation, infection, acute inflammation, stroke, atrial fibrillation, following surgery or trauma.²¹ In a systematic review, total 217 D-dimer test evaluations for DVT were analysed. In this study, the ELFA (Enzyme Linked Immunofluorescence Assay), microplate ELISA and latex quantitative assays were found to have higher sensitivities (96%, 94% and 93% respectively) compared to the whole-blood D-dimer assay (83%), latex semi quantitative assay (85%) and latex qualitative assay (69%) respectively.²⁷ Based on these data, the ELFA (Enzyme Linked Immunofluorescence Assay), microplate ELISA and latex quantitative assays are considered as "highly sensitive" whereas, the whole-blood D-dimer assay, latex semi quantitative assay and latex qualitative assays are considered as "moderately sensitive" D-dimer assays.²¹ Compression ultrasonography is preferred over venography for the diagnosis of DVT due to its wider availability, non-invasive nature and relatively economical advantage.²¹ The findings of a meta-analysis do not support the use of magnetic resonance venography over ultrasound as a first-line imaging method; however, it may be useful in the diagnosis of DVT where ultrasound is difficult (e.g. leg casting, excessive subcutaneous tissue or fluid preventing adequate assessment of compressibility) or non-diagnostic.^{21,28} Similarly, CT venography is also useful to diagnose DVT in such patients.²¹ Recurrent VTE requires investigations for thrombophilia.²⁶ The American

Table 6: Recommended initial diagnostic tests for acute deep vein thrombosis²¹

Pretest probability	Recommended initial test
Low	Moderately sensitive D-dimer test (preferred) or compression ultrasound of proximal veins
Moderate	Highly sensitive D-dimer test (preferred), proximal compression ultrasound, or whole-leg ultrasound examination
High	Proximal compression (preferred) or whole-leg ultrasound examination

Table 7: Recommendations for parenteral anticoagulation in acute deep vein thrombosis treatment

- Initial treatment with parenteral anticoagulant is recommended for patients with acute DVT, over no such treatment.
- We recommend the use of LMWH/fondaparinux over UFH for treatment in patients with acute DVT due to lack of need for routine aPTT monitoring and ease of administration.
- We recommend weight based dosing of LMWH in all patients for the treatment of acute DVT.
- In case intravenous UFH is preferred, we recommend aPTT monitoring every 6 hourly until two consecutive therapeutic levels are achieved and then 24 hourly for the treatment of acute DVT.
- We recommend platelet count monitoring at baseline and every 2 or 3 days between days 4-14 (or until UFH/LMWH is stopped) of UFH/LMWH therapy for early detection and management of HIT (Heparin Induced Thrombocytopenia).

College of Chest Physicians 9th Ed guideline suggests classification of suspected DVT patients into low, moderate and high pretest probability based on the clinical assessment for guiding the diagnostic procedures in case of first lower extremity DVT.²¹ The recommended diagnostic tests for respective pretest probability are given in Table 6.

Treatment of Acute Deep Vein Thrombosis

Early, accurate diagnosis of DVT is important because treatment with anticoagulants reduces the risk of PE, relieves acute symptoms (e.g., leg pain), prevents DVT in a distal calf vein from extending to proximal veins (e.g., femoral), and may decrease the incidence of PTS²⁹ extension and PE. The anticoagulant therapy for DVT has evolved from inpatient administration of intravenous unfractionated heparin (UFH) to outpatient therapy with low molecular weight heparin (LMWH), warfarin and non-Vitamin-K antagonist oral anticoagulants (NOACs). The duration of anticoagulant therapy is defined as acute (0-7 days), long term (first 3 months of therapy) and extended therapy (beyond 3 months).³⁰ Heparin and warfarin need routine monitoring of anticoagulation profile through aPTT and INR respectively, hence

limiting their use.

Parenteral Anticoagulation for Acute Deep Vein Thrombosis

Heparin use has been a tradition in the management of acute DVT episode. Heparin therapy prevents extension of thrombus and subsequently reduces (but doesn't eliminate) the risk of non-fatal and fatal PE. However, complete clot lysis with heparin therapy has been seen in less than 10% of acute DVT patients in venography studies after treatment. Unfractionated heparin was the standard of care for initial treatment of acute DVT until the introduction of LMWH (Low Molecular Weight Heparin). A meta-analysis of eight clinical trials has shown that subcutaneous UFH is more effective than and at least as safe as continuous intravenous UFH administration for the initial treatment of DVT. Low Molecular Weight Heparin provides better anti-Xa activity, has longer half-life, and better predictability of anticoagulant response than UFH. LMWH can be given once or twice daily s.c. without need of aPTT monitoring. Also, the rate of heparin-induced thrombocytopenia with LMWH is less compared to UFH.³¹ In two meta-analyses, fixed-dose s.c. LMWH was found to be at least as effective and

safe as adjusted-dose intra venous UFH for treatment of patients with acute VTE.^{32,33} Fondaparinux is a synthetic and selective inhibitor of factor Xa which was found to be at least as effective and safe as enoxaparin in the initial treatment of symptomatic deep vein thrombosis in a randomized controlled trial. The recommendations for parenteral anticoagulation in acute deep vein thrombosis treatment are summarized in Table 7.³⁴

Bleeding is the most common adverse effect of anticoagulant therapy. UFH/LMWH therapy may also be associated with non-haemorrhagic adverse effects such as HIT (Heparin Induced Thrombocytopenia), osteoporosis. They are caused by the nonspecific protein binding of UFH and are less common with LMWH, owing to decreased molecular charge. Heparin Induced Osteoporosis is an adverse effect of long-term UFH or LMWH therapy.³⁵ This is not a major concern in most patients with DVT, who receive only short-term treatment; however, long-term heparin therapy may be associated with substantial bone loss.

Oral Anticoagulants

Vitamin K Antagonists

Warfarin acts by inhibiting vitamin K epoxide reductase (VKORC) responsible for the cyclic inter-conversion of vitamin K₁ and vitamin K epoxide. Inhibition of vitamin K epoxide reductase reduces the activation of coagulation factors II, VII, IX, and X production by the liver.³⁶ The structure (racemic mixture) and pharmacokinetic properties (hepatic metabolism, high protein binding) makes warfarin more prone for the drug interactions. Warfarin has two isomers S-isomer and R-isomer, of which "S" form is more potent. Both the isomers are metabolized primarily by CYP2C9 (S-isomer), and CYP1A2 and 3A4 (R-isomer) isozymes.³⁶ Warfarin has several limitations like slow onset and off set of action, drug-food and drug-drug interactions (Figure 1), genetic polymorphism leading to variable response. Due to such

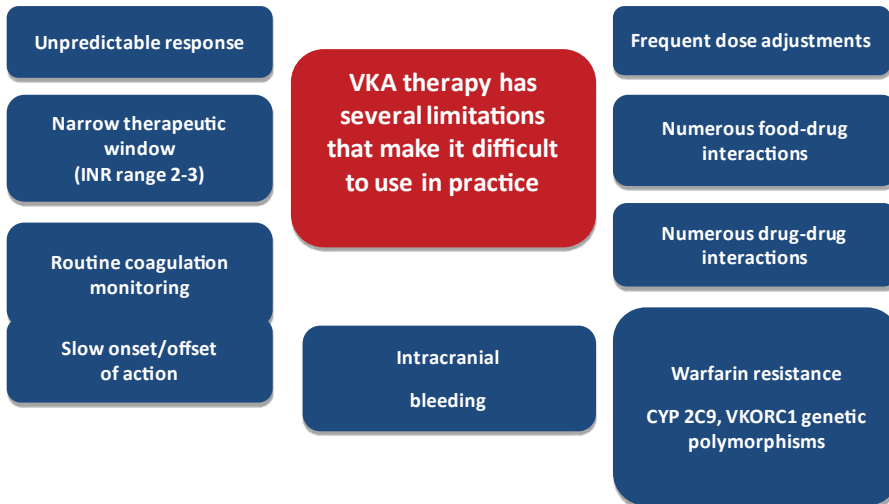


Fig. 1: Limitations of Vitamin K antagonists

limitations, warfarin requires frequent monitoring with INR to keep balance between effectiveness and safety in clinical practice.³⁶ Warfarin has some issues peculiar to Indians. The dietary habit of Indians differ that from their Western counterparts because of which they are prone to various drug-food interactions. For example, eating green leafy vegetables like cabbage, cauliflower, spinach and other foods rich with vitamin K in diet would interfere target INR on patients with warfarin/acenocoumarol and cause labile INR values. Habitual intake of over the counter medications [e.g. nonsteroidal anti-inflammatory drugs (NSAIDs)/tramadol] or alternative herbal products/foods (e.g. garlic, fenugreek) for various disorders would increase the OAC action of the VKA and may cause bleeding. Paracetamol is a frequently unrecognized cause of over anticoagulation in India. Concomitant use of anti-tubercular drugs like isoniazid (INH) or rifampicin can also alter INR values and result in over or under anticoagulation. Indians with low body weight and body mass index (BMI) require lesser doses of VKA to achieve target INR compared to their Western counterparts and are more prone to bleeding. Smoking also causes enzyme induction and lowers INR. Another issue in India is INR monitoring on VKA therapy. One Indian study had shown poor outpatient VKA

anticoagulant control with high proportion of sub therapeutic PT/INR values and high complication rates.³⁷ Another Indian study showed unsatisfactory knowledge base of clinicians in terms of OAC targets with a tendency to under coagulate in view of the perceived risk of bleeding.³⁸ To address such challenges with VKAs, Time in Therapeutic Range (TTR) could be a suitable option. TTR is a measure of intensity of anticoagulation control, which estimates the percentage of time INR values within therapeutic range (i.e. VTE treatment target INR should be 2-3) for patients on VKAs.³⁹ TTR is calculated by Rosendaal method, and it should be >60% to be effective for VKAs. TTR helps the physician to maintain the quality of anticoagulation control over a therapeutic period as well as to minimize the risk of adverse events. i.e. thromboembolic or bleeding on VKA therapy.³⁹ In order to achieve better patient compliance and target INR values as per the recommended guidelines for OAC there is a pressing need for better patient education and physician/local practitioner update of the various issues involved.

For venous thrombosis prevention after hip and major gynaecological surgeries, warfarin (INR 2-3) has been found to be effective with modest risk of clinically relevant bleeding.⁴⁰ In a meta-analysis of LMWH, UFH and warfarin for prophylaxis of thrombo-embolism

in orthopaedic surgery, warfarin had significantly lower risk of minor bleeding compared with LMWH [RR for LMWH vs. warfarin 3.28, $p < 0.05$].⁴¹ For the treatment of acute DVT, initial therapy with VKA alone is not recommended because VKA alone was found to be associated with more recurrent symptomatic and asymptomatic VTE in a randomized trial. When acute VTE is suspected initial parenteral anticoagulation for at least 5 days along with VKA is given and once the INR reaches 2-3, parenteral anticoagulation should be discontinued.⁴² DURAC⁴³ and WODIT trials⁴⁴ demonstrated that oral anticoagulation therapy with VKA for 6 months and 1 year is better than 6 weeks and 3 months of therapy for prevention of recurrent VTE in patients who had first episode of VTE and idiopathic proximal DVT respectively.

Need for Newer Oral Anticoagulants

Need for frequent laboratory monitoring is a challenge for outpatient management with VKAs especially in India. Therefore, an oral anticoagulant with wide therapeutic window without routine laboratory monitoring would be a good alternative to VKAs in the treatment as well as secondary prevention of DVT.

Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)

The NOACs are broadly classified into two major categories: direct thrombin (factor IIa) inhibitors and direct Factor Xa inhibitors. Dabigatran is a direct thrombin inhibitor while other three i.e. rivaroxaban, apixaban, and edoxaban are direct factor Xa inhibitors.³⁶ The NOACs offer advantages of predictable pharmacokinetic profile and lesser food and drug interactions compared to warfarin. Moreover NOACs do not require routine monitoring. The NOACs have been extensively studied in the treatment of acute VTE and prevention of VTE. Dabigatran, rivaroxaban, apixaban and edoxaban have shown to be effective and at least comparable in safety with the conventional treatment of acute VTE. They are associated with lower risk of

Table 8: Pharmacology of NOACs

	Dabigatran ⁴⁶	Rivaroxaban ⁴⁹	Apixaban ⁵⁶	Edoxaban ⁵⁵
Mechanism of action	Competitive, direct thrombin inhibitors	Selective inhibitor of FXa	Selective inhibitor of FXa	Selective inhibitor of FXa.
Time to peak concentration (T-max)	1 - 3 hours	2 to 4 hours	3 to 4 hours	1-2 hours
Plasma protein binding	35%	92-95%,	Approximately 87%	About 55%
Renal elimination	80%	About 51% recovered as inactive metabolites (urine 30 and feces 21%)	Renal excretion is about 27% of total clearance	Renal clearance is about 50% of total clearance
Metabolism	Not a substrate, inhibitor, or inducer of CYP450	Major metabolism via CYP3A4/5 and CYP2J2 and hydrolysis	Substrate of transport proteins: P-gp	Minimal metabolism via hydrolysis, conjugation, and oxidation by CYP3A4.
Half-life	12-17 hours	5-9 hours	12 hours	10 to 14 hours

intracranial or intracerebral bleeding compared to warfarin.⁴⁵

Dabigatran

Dabigatran etexilate, an oral prodrug is rapidly converted by esterases to dabigatran which competitively inhibits both free and fibrin-bound thrombin.³⁶ In 2014, dabigatran received approval in India for the treatment and secondary prevention of DVT and PE in patients who have been treated with a parenteral anticoagulant (UFH or LMWH/fondaparinux) for 5-10 days. Its use is also approved to reduce the risk of recurrence of DVT and PE in patients who have been previously treated and for the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery.⁴⁶ The approval is based on four clinical trials which examined the effects of dabigatran in venous thromboembolism (VTE). Dabigatran can be given as a simple, fixed-dose regimen without need for routine laboratory monitoring. The RE-COVER studies compared dabigatran versus warfarin in patients with acute VTE who initially received parenteral anticoagulation therapy.^{47,48} Dabigatran was found to be non-inferior to warfarin for the primary outcome of recurrent VTE and related deaths, and major bleeding rates were found to be less with dabigatran compared to warfarin in individual studies.^{47,48} The pooled analysis of RE-COVER

and RE-COVER-II studies also showed non-inferiority of dabigatran for the primary efficacy outcome of recurrent symptomatic VTE and related deaths, and significantly lower bleeding rates compared to warfarin in the treatment of acute VTE.⁴⁸

Rivaroxaban

Rivaroxaban is a selective and reversible direct oral FXa inhibitor.³⁶ In 2011, the USFDA approved rivaroxaban to reduce the risk of DVTs and PEs from occurring after knee or hip replacement surgery. In November 2012, the USFDA approved it for the treatment of acute DVT or PE, and to reduce the risk of recurrent DVT and PE following initial treatment.^{49,50} Rivaroxaban can be given as a simple, fixed-dose regimen without need for routine laboratory monitoring.⁵¹ The efficacy of rivaroxaban was evaluated in the EINSTEIN studies (EINSTEIN-DVT and EINSTEIN-PE) for the treatment of acute DVT/PE respectively.^{51,52} These studies showed that compared with LMWH/VKA treatment, rivaroxaban was non-inferior for recurrent VTE and had similar or fewer major haemorrhages.^{51,52}

Apixaban

Apixaban is also a selective and reversible direct oral factor Xa inhibitor.³⁶ The AMPLIFY study compared apixaban versus subcutaneous enoxaparin, followed by warfarin in the treatment of acute

VTE.⁵³ For primary efficacy outcome of recurrent symptomatic VTE or VTE related death, apixaban was non-inferior to the conventional therapy. For major bleeding and the composite outcome of major bleeding and clinically relevant non-major bleeding, apixaban was superior compared to conventional therapy.⁵³

Edoxaban

Edoxaban is an oral, selective Factor Xa inhibitor.³⁶ Edoxaban is administered once daily and has a rapid onset of action.⁵⁴ Edoxaban is approved by the USFDA for the treatment of DVT and PE following 5 to 10 days of initial parenteral anticoagulation therapy.⁵⁵ In the Hokusai-VTE study, edoxaban therapy for 3 to 12 months was compared with warfarin in patients with acute VTE, who had initially received heparin therapy for 5-10 days.⁵⁴ In this study, it was found to be non-inferior to warfarin for primary efficacy outcome of recurrent symptomatic VTE.⁵⁴ The principal safety outcome of major or clinically relevant non-major bleeding was significantly less with edoxaban compared to warfarin.⁵⁴ Detailed pharmacological characteristics, drug interactions and study characteristics of all NOACs are elucidated in Table 8, 9 and 11, respectively.

Drug interactions of NOACs:

NOACs can also interact with other medications. The recommendations for dose adjustment/contraindications are given in Table 9.⁵⁶

Monitoring NOACs Anticoagulant Effect

Routine monitoring of anticoagulant effect of NOAC is not required. However, monitoring of NOAC anticoagulant effect might be useful in certain situations: (i) serious bleeding, (ii) emergency surgery or intervention, (iii) suspected overdose, (iv) patients with renal or hepatic insufficiency, (v) potential drug-drug interactions. Monitoring assays for NOACs are summarized in Table 10.⁵⁶

Table 9: Drug interactions^{46,49,55,56,57}

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban	
Amiodarone	+12-60 %	No PK data	+40 %	Minor effect (use with caution if CrCl <50 ml/min)	
Antacids	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment	
Atorvastatin	No dose adjustment	No data yet	No dose adjustment	No dose adjustment	
Clarithromycin/ Erythromycin	No dose adjustment	No data yet	Reduce NOAC dose by 50 %	+30-54 %	
Cyclosporin/ Tacrolimus	Not recommended	No data yet	+73 %	Extent of increase unknown	
Digoxin	No dose adjustment	No data yet	No dose adjustment	No dose adjustment	
Diltiazem	No dose adjustment	+40 %	No data yet	Minor effect (use with caution if CrCl 15-50 ml/min)	
Dronedaron	Contraindicated	No PK/PD data; caution	Reduce NOAC dose by 50 %	Moderate effect but no PK/PD data: caution and try to avoid	
HIV protease inhibitors	No data yet	Strong increase	No data yet	Contraindicated	
Ketoconazole, Itraconazole, Voriconazole, Posaconazole	Contraindicated	Contraindicated	Reduce NOAC dose by 50 %	Contraindicated	
Carbamazepine, Phenytoin, Phenobarbitone, Rifampicin	Minus 66 %	Minus 54 %	Minus 35 %	Up to minus 50 %	
Quinidine	+53 %	No data yet	+77 %	Extent of increase unknown	
Verapamil	+12-180 %	No PK data	+53 % (Slow release)	Minor effect (use with caution if CrCl 15-50 ml/min)	
Contraindicated	Dose reduction required	Consider dose reduction if ≥ 2 yellow is present	No dose adjustment required	Reduction in NOAC plasma levels. This may also constitute a contraindication for simultaneous use	Decrease in plasma level but not clinically relevant. Avoid if possible

Table 10: Monitoring assays for NOACs⁵⁷

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
aPTT	✓	✗	✗	⊙*
TT, dTT	✓	✗	✗	✗
ECT	✓	✗	✗	✗
Anti-Fxa assays	✗	✓ [†]	✓ [‡]	✓ [†]
PT	✗	✓ [¶]	✗	✓*
INR	✗	✗	✗	✗

*Prolonged, but no known relationship to bleeding risk; †No data on threshold values for bleeding or thrombosis; ‡No data yet; ¶Influenced by rivaroxaban in a dose-dependent way with a close correlation to plasma concentrations only if Neoplastin is used. aPTT = activated partial thromboplastin time; dTT = diluted thrombin time; ECT = ecarin clotting time; Fxa = Factor Xa; INR = international normalized ratio; PT = prothrombin time; TT = thrombin time

Table 11: Important clinical trials with NOACs

	Dabigatran ^{47,48}	Rivaroxaban ^{51,52}	Apixaban ⁵³	Edoxaban ⁵⁴
Study name	RE-COVER I and II	EINSTEIN-DVT EINSTEIN-PE	AMPLIFY	Hokusai-VTE
Total number of patients	5128	8282	5400	8292
Dosage	Dabigatran 150 mg twice daily for 6 months	Rivaroxaban: 15 mg twice daily for 3 weeks, followed by 20 mg once daily for 12 months	Apixaban 10 mg twice daily for first 7 days, followed by 5 mg twice daily for 6 months	Edoxaban 60 mg once daily, or 30 mg once daily (e.g., Crcl 30 to 50 ml per minute or a body weight <60 kg) for 3 to 12 months

Acute Treatment of Deep Vein Thrombosis

The efficacy and safety of NOACs have been evaluated in large phase III clinical trials versus warfarin or parenteral anticoagulation plus warfarin (Table 11, Figures 2 and 3) for treatment of acute venous thromboembolism. In these phase III clinical trials, NOACs have been found to be non-inferior in reducing recurrence VTE with less major and major plus clinically relevant non-major bleeding compared to warfarin or parenteral anticoagulant plus warfarin.^{47,48,53,54,58} The recommendations for OACs in acute deep vein thrombosis treatment are summarized in Table 12.

Bleeding Risk Assessment for Patients on Anticoagulation

Various risk stratification tools prepared by considering parameters such as age, comorbid conditions (e.g. renal disease, anemia, liver disease, hypertension, malignancy etc.), past history of bleeding, and anemia are available for assessment of bleeding risk in patients on anticoagulants.

HAS-BLED score: Major bleeds occurred in 11/537 patients (2.0%, 5.2/100 person years, 95% CI 2.8-9.2). Cumulative incidences of major bleeds were 1.3% (95% CI 0.1-2.5) in the non-high (HAS-BLED < 3) and 9.6% (95% CI 2.2-17.0) in the high-risk group (HAS-BLED ≥ 3), (p < 0.0001 by Log-Rank test), with a HR of 8.7 (95% CI 2.7-28.4).⁵⁸

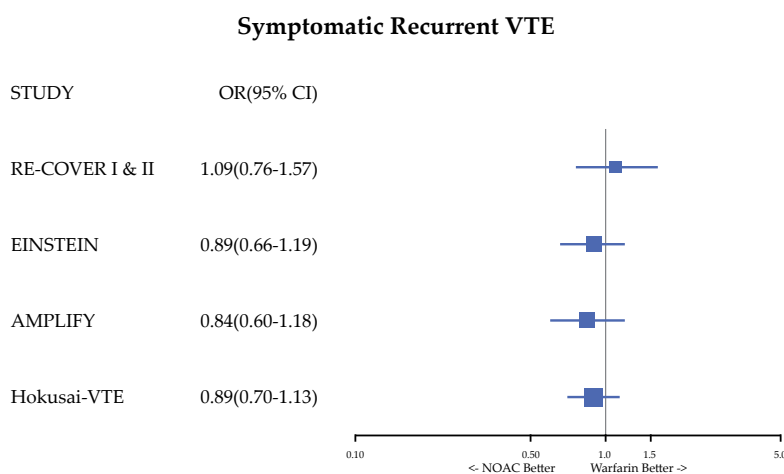
Acute VTE patients with a HAS-BLED score ≥ 3 points (Tables 13 and 14) are at increased risk of major bleeding. These results warrant for correction of the potentially reversible risk factors for major bleeding and careful International Normalized Ratio monitoring in acute VTE patients with a high HAS-BLED score.⁵⁸

Extended Therapy in Deep Vein Thrombosis

The duration of extended anticoagulant therapy in deep vein thrombosis depends on the risk of recurrent VTE (fatal/non-fatal) and bleeding complications. The RIETE

Table 12: Recommendations for OACs in acute deep vein thrombosis treatment

- In patients with proximal DVT, at least 3 months anticoagulant therapy is recommended over no therapy and use of NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) is suggested over VKA therapy.
- In case VKA therapy is considered, concomitant (on the same day) parenteral anticoagulation is recommended in the initial phase of DVT treatment for at least 5 days or till INR >2.
- We recommend percentage TTR (Time in Therapeutic Range) of >60 % in case of VKA therapy.
- If dabigatran or edoxaban is considered, parenteral anticoagulation for 5-10 days should be used in the initial DVT treatment, with no overlap.
- In case of isolated distal DVT of the leg, if the patient is decided to be treated with anticoagulant, therapy should be given for 3 months.

**Fig. 2: Efficacy outcome of NOACs RCTs in the management of acute VTE^{47,48,53,54,58}**

registry data of 41,826 patients with mean duration of anticoagulation therapy for 7.8 months showed 16.1% case fatality rate (CFR) of recurrent VTE during first three months compared, to 2.0% beyond this period while the case fatality rate (CFR) of major bleeding was 20.2% during the first three months, compared to 18.2% beyond this period. These findings suggest reduction in CFR of recurrent VTE over time with no major change in bleeding risk with continued use of anticoagulant.⁵⁹ In one meta-analysis of seven randomized trials, 2925 patients with a first episode of VTE who received different durations of anticoagulation were followed up for 24 months after stopping the anticoagulation therapy.⁶⁰ This study showed a higher recurrence of VTE if anticoagulation was stopped at 1.0 or 1.5 months compared with at 3 months or later, and similar recurrence of VTE if anticoagulation was stopped at 3 months compared with at 6 months or later.⁶¹ Current

ACCP 10th (American College of Chest Physicians) guidelines recommend long term (at least 3 months) anticoagulant therapy for patients with DVT (proximal or distal) or PE over no such therapy.³⁰ Decision to further extend anticoagulant therapy should be at physician's discretion based on the benefit versus the risk of its continuation considering patients' profile.

Deep Vein Thrombosis Recurrence Risk Assessment

The assessment of risk of VTE recurrence is important because of its potential impact on the duration of anticoagulant treatment. The VTE recurrence risk is more in unprovoked cases compared to those with provoked risk factors, and the duration of treatment is longer in the former cases compared to the later.⁶² Three scores have been proposed to identify patients who carry a high recurrent risk and require extended anticoagulant treatment, the HERDOO2, the DASH score,

Table 13: HAS-BLED risk criteria⁵⁹

HAS-BLED risk criteria	Score
Hypertension	1
Abnormal renal or liver function (1 or 2 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (e.g. age >65 years)	1
Drugs or alcohol (1 point each)	1 or 2

INR, international normalized ratio. Hypertension' is defined as systolic blood pressure >160 mmHg. Abnormal kidney function is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200 mmol/L. Abnormal liver function is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin 2 _ the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase. 3 _ upper limit normal, etc.). Bleeding refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anemia, etc. Labile INRs refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, nonsteroidal anti-inflammatory drugs, or alcohol abuse, etc.

Table 14: Recommendation for bleeding risk assessment for patients on OAC

We recommend the use of HAS-BLED score for assessing the risk of bleeding in anticoagulated DVT patients.

and the Vienna prediction model (Table 15). In all, male sex and elevated D-dimer levels have been identified as important risk factors for recurrence. However, there are some differences among these scoring systems. The HERDOO2 score includes D-dimer levels measurement during anticoagulation and age more than 65 as a risk factor for recurrence, whereas the DASH score considers age less than 50 as a higher risk.⁶² The Vienna Prediction Model is a simple and useful scoring system to assess the recurrence risk in patients with a first unprovoked VTE. It was first validated on a prospective cohort study of 929 patients with a first unprovoked VTE. In this study, a total of 176 patients (18.9%) had recurrent VTE. The risk of recurrence was higher in men vs. women, with proximal DVT and PE vs. distal DVT, and with elevated levels of D-dimer after

Major Bleeding

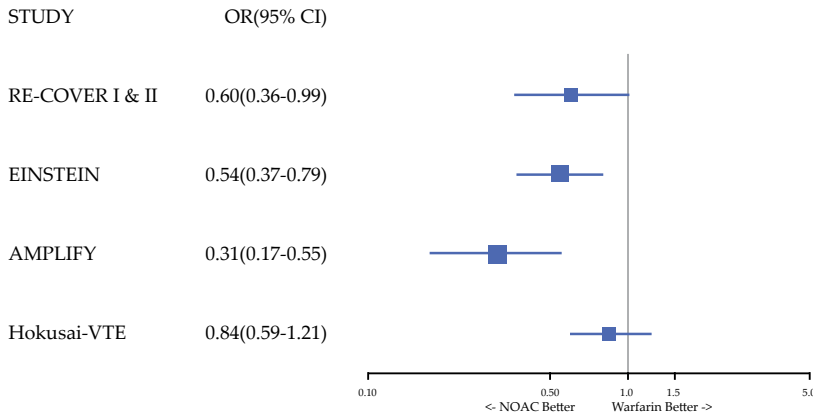


Fig. 3A: Safety outcomes of NOACs RCTs in the management of acute VTE^{47,48,53,54,58}

Major and Clinically Relevant Non-Major Bleeding

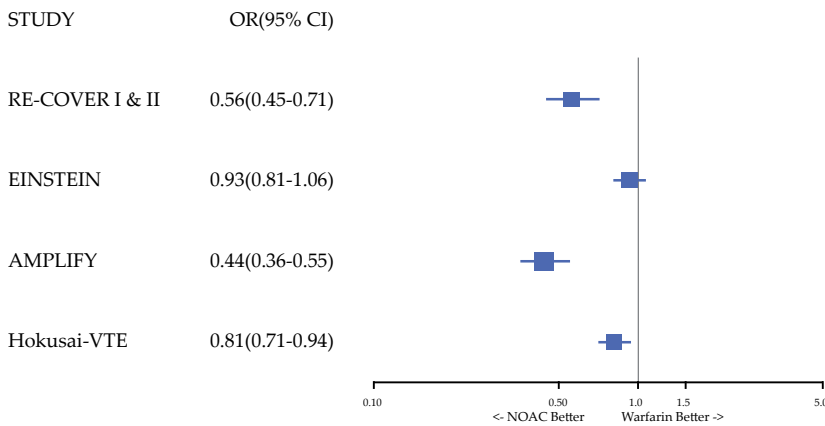


Fig. 3B: Safety Outcomes of NOACs RCTs in the management of acute VTE^{47,48,53,54,58}

Table 15: Vienna prediction model⁶⁴

Parameter	Points
Male	60 points
Female	0 points
Proximal DVT	70 points
Distal DVT	0 points
PE	90 points
D-dimer level (0-100 mcg/l- "0" points based on the level)	100 mcg/l- "0" points 2000mcg/l- "100" points

*Patients at low risk [rate of recurrence of 4.4% (95% CI 2.7–6.2%)] when points (according to nomogram) are 180 or less.⁶⁴

to reduce risk of recurrence. The extension studies have proved efficacy and safety of NOACs in patients with VTE. All NOACs have been evaluated for extended therapy versus placebo.⁶⁶⁻⁶⁸ They were found to be superior to placebo in reducing the risk of primary efficacy end point of symptomatic recurrent VTE or death from VTE. The incidence of major bleeding was low with all NOACs. However as expected all the NOACs significantly increased the risk of clinically relevant non major bleeds and total bleeds in comparison to placebo. Additionally, dabigatran (150 mg BD) was compared with dose adjusted warfarin (INR 2-3) for extended therapy for VTE prevention in 2866 patients with a longest period of treatment up to 36 months. In this study, less major bleeding, significantly less major or clinically relevant bleeding and significantly less any bleeding events were seen with dabigatran with non-inferior rates of VTE and VTE related deaths compared to dose adjusted warfarin.⁶⁶ One systematic review and network meta-analysis of efficacy and safety of oral anticoagulants and antiplatelets for secondary prevention of VTE showed that oral anticoagulants are more efficacious and safe compared to aspirin or observation alone (Table 16).⁶⁹ The recommendations for extended therapy in deep vein thrombosis are summarized in Table 17.

Switching between Anticoagulant Regimens

Switching between different anticoagulant regimens should consider two important things:

discontinuation of anticoagulation, Based on this study, a nomogram to compute the risk of recurrence has been developed.⁵⁰ The risk factors along with their assigned points are given in Table 15. The total score is calculated by adding points assigned to each variable which is then mapped against expected cumulative recurrence risk at 12 and 60 months.⁶³

It has been validated externally enrolling 904 older patients (median age, 68 years) where it underestimated the observed cumulative recurrence rates at 12 months.⁶⁴ The updated Vienna Prediction Model is an improved version of the original Vienna Prediction Model which allows prediction of recurrence at several

different time points after stopping anticoagulation.⁶⁵ It was developed in a prospective cohort of 553 patients with unprovoked VTE with the same clinical parameters (ie, sex, location of VTE, and a quantitative D-dimer level determined by ELISA between 3 weeks and 15 months after discontinuation of anticoagulation) to estimate the risk of recurrent VTE up to 60 months.⁶⁵

NOACs in Extended Therapy for Deep Vein Thrombosis Prevention

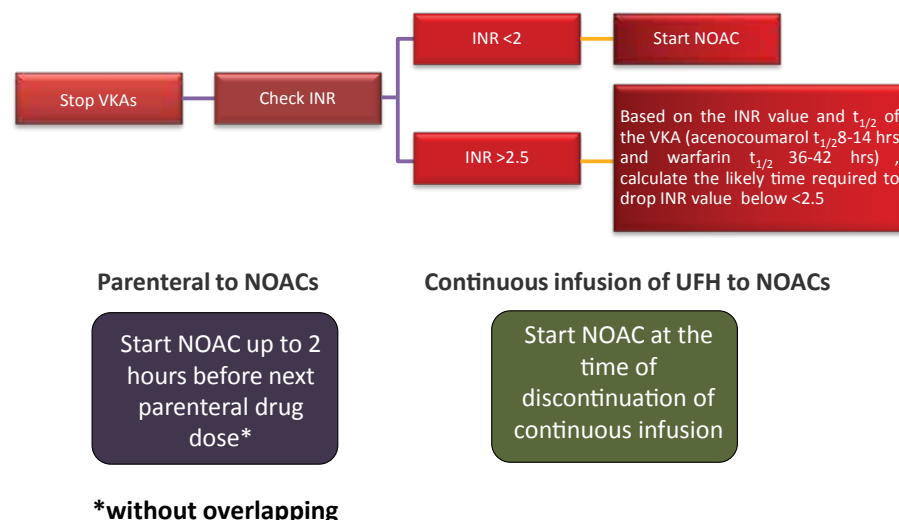
Long-term anticoagulant treatment is effective in the treatment of acute VTE. However, the risk of recurrence remains once the therapy is discontinued. The risk of recurrence can be 5-10 % during the first year.⁵¹ Extended therapy with anticoagulants is an option

Table 16: Absolute risk of recurrent VTE and major bleeding per 100 patients treated each year

	Placebo or Observation	Vitamin K antagonist (dose adjusted)	Dabigatran (150 mg BD)	Rivaroxaban (20 mg OD)	Apixaban (5 mg BD)	Aspirin (100 mg/day)
Absolute risk of recurrent VTE	10/100	1/100	2/100	2/100	2/100	7/100
Absolute risk of major bleeding	1/100	2/100	1/100	6/100	1/100	1/100

Table 17: Recommendations for extended therapy in deep vein thrombosis

- At least 3 months treatment with anticoagulant is recommended in patients with venous thromboembolism due to first provoked event while extended therapy is required for patients with a first unprovoked event.
- The risk of ongoing anticoagulation therapy for extended duration should be assessed after every 3 months of therapy to look at the benefit risk profile.
- An unprovoked DVT of the leg requires anticoagulation for at least 3 months after which the patient should be evaluated for the risk-benefit ratio of extended anticoagulant therapy.
- If the first VTE is an unprovoked proximal DVT of the leg with low or moderate bleeding risk, then extended anticoagulant therapy is suggested.
- If the first VTE is an unprovoked proximal DVT of the leg with high bleeding risk, then at least 3 months of anticoagulant therapy is suggested with close monitoring.
- In patients with second unprovoked VTE with low bleeding risk, extended anticoagulant therapy over three months is recommended while for moderate bleeding risk, extended anticoagulant therapy over three months is suggested with close monitoring.

**Fig. 4: Switching between anticoagulant regimen³⁶**

(1) Maintenance of optimal anticoagulant effect, and (2) Minimizing the bleeding risk at the same time.³⁶

Switching to and from VKA to NOAC

Switching from VKA to NOAC should start with discontinuation of VKA followed by check INRs. Once the INR reaches < 2 , NOAC should be started immediately. For INR > 2 , consider actual INR value and half-life of VKA to calculate the approximate time for INR to

reach below threshold of 2 after which NOAC can be initiated.⁵⁷ While switching from a NOAC to warfarin, consider bridging with a short-acting parenteral agent (rivaroxaban, apixaban)^{49,56} or a lower dose (edoxaban)⁵⁵ of the NOAC. For switching from dabigatran to VKA check creatinine clearance first. If it is ≥ 50 ml/min, start VKA 3 days before discontinuation of dabigatran, and if CrCL is ≥ 30 - < 50 ml/min, start VKA 2 days before the

discontinuation of dabigatran.⁴⁶

Switching to and from Parenteral Anticoagulant to NOAC

NOAC should be initiated up to 2 h before the next dose of the parenteral agent when transitioning from a parenteral agent to a NOAC and vice versa. The prescribing information of each of the NOACs describes the strategy for switching between these therapies. Figure 4 summarizes the transition between different treatment regimens.³⁶

Approach to pharmacological management of DVT is shown in Figure 5.

Complications of Deep Vein Thrombosis

Complications of DVT include recurrence, pulmonary embolism (i.e. proximal DVT of leg), death due to massive pulmonary embolism, post thrombotic syndrome, chronic thromboembolic pulmonary hypertension (i.e. survivors of acute PE).^{70,71} Recurrence of VTE may occur in about one third population with a decade.⁷² Overall, VTE results in more than 100,000 deaths every year.⁷³ Pulmonary embolism can lead to three month all-cause mortality rate of up to 30%.⁷³ It is generally believed that proximal DVT in the leg is associated with an increased risk for PE while calf DVT with post thrombotic syndrome.⁷⁴ The seriousness of calf DVT lies in the fact that 15- 25% of them may progress to become proximal DVT.⁷⁴ Symptomatic chronic thromboembolic pulmonary hypertension (CTEPH) is a common and serious complication of PE which may occur in about 4% patients at 2 years.⁷¹

Post-thrombotic Syndrome

Post-thrombotic Syndrome is often ignored, but an important complication of DVT seen in about 30% of patients. Chronic pain and swelling in the affected extremity are the typical clinical features of the post-thrombotic syndrome, formerly known as post-phlebotic syndrome. Post-thrombotic syndrome results in dermatological changes, venous stasis and sometimes venous ulcer and

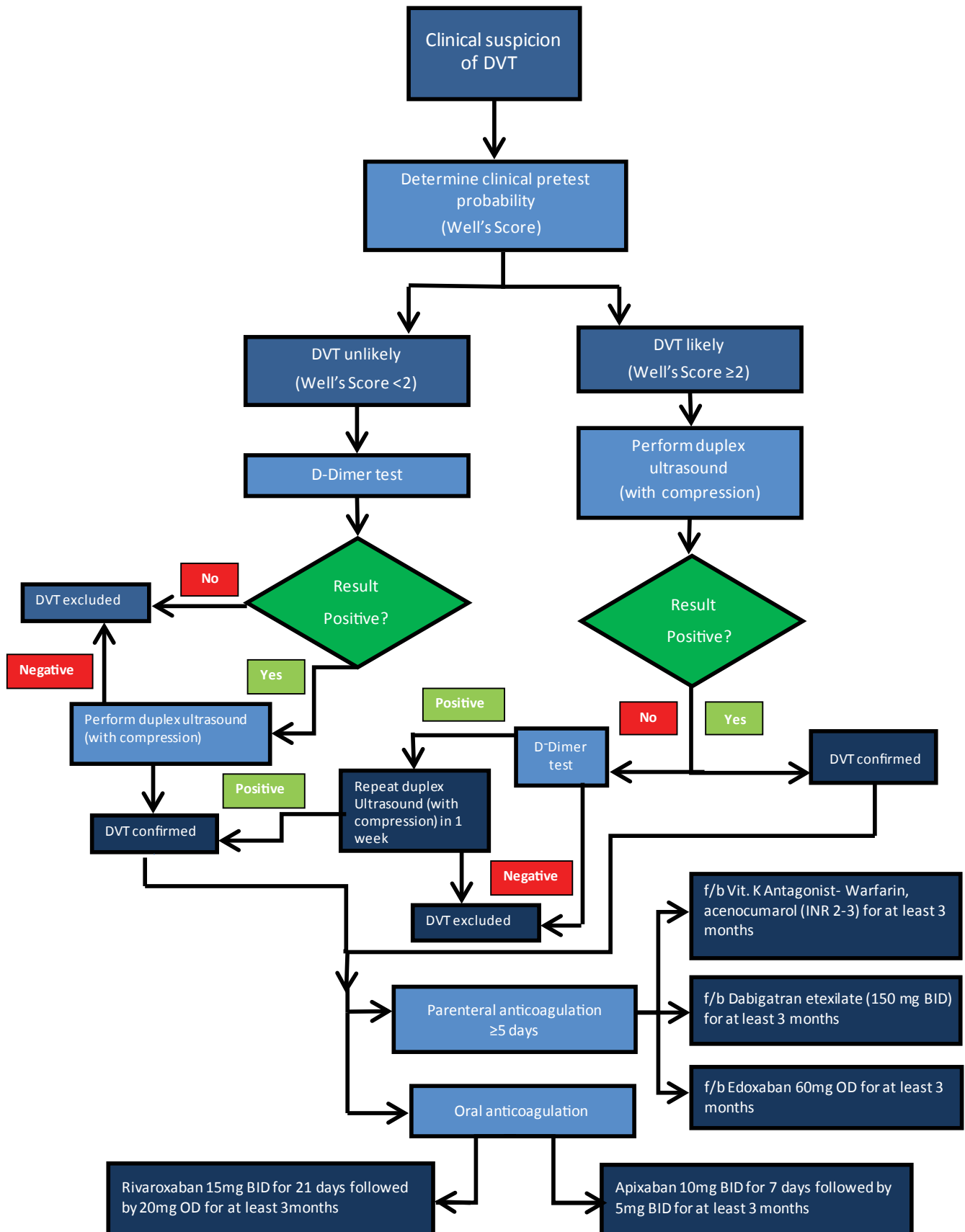


Fig. 5: DVT Management Protocol^{21,30}

Table 18: Recommendations for management of post-thrombotic syndrome⁷⁵

Patient category	Recommendations/suggestions
Patients with DVT	Routine use of elastic compression stockings (ECS) is not recommended for prevention of PTS
Leg swelling due to acute DVT-related	Trial of ECS may be given.
Established PTS	Daily use of 20-30 mm Hg knee-length ECS (stronger pressure stockings, if ineffective)
Moderate-to-severe PTS with inadequate control of symptoms with ECS	Intermittent compression devices/pneumatic compression sleeve
Patients who can tolerate exercise	Supervised exercise training program for ≥6 months may be tried

leads to impaired quality of life.^{73,75} It has been estimated that about half of the people with DVT develop post-thrombotic syndrome.⁷² Deep vein thrombosis should be prevented by pharmacologic or mechanical thromboprophylaxis in high risk patients to avoid development of PTS. The recommendations for the management of PTS (post-thrombotic syndrome) are summarized in Table 18.

Interventions in Deep Vein Thrombosis Treatment

Systemic Thrombolysis for Deep Vein Thrombosis Treatment

Intravenous streptokinase and recombinant tissue plasminogen activator (rt-PA) have been studied in the treatment of DVT.⁷⁶ Thrombolysis can reduce the long-term complications like post-thrombotic syndrome.⁷⁷ An updated Cochrane analysis examining thrombolysis and anticoagulation versus anticoagulation for acute DVT has confirmed that the use of thrombolytics plus anticoagulation can result in complete clot lysis or better improvement in venous patency more often and significantly less occurrence of post-thrombotic syndrome compared to anticoagulation alone; however, significantly more bleeding complications resulted from this therapy.⁷⁸ Streptokinase infusion is not commonly used in the clinical practice because of higher bleeding complications.⁷⁶

Catheter Directed Thrombolysis for Deep Vein Thrombosis Treatment

Catheter-directed thrombolysis (CDT) receives greater acceptance with the treating physicians as compared to intravenous thrombolysis⁷⁸ and there has been a

steady rise in its use in the United States for the treatment of inferior vena cava thrombosis. The data from the Nationwide Inpatient Sample Database (2005 to 2011) comparing CDT plus anticoagulation versus anticoagulation alone showed no significant difference in mortality between two groups. However, CDT group had more bleeding events and resource utilization compared to anticoagulation.⁷⁹ A recent study by Enden et al has shown that long term outcome after CDT plus anticoagulation in acute ilio-femoral deep vein thrombosis as measured by PTS at 24 months and ilio-femoral patency at 6 months was significantly better than conventional therapy.⁸⁰ Allergy may also occur in some patients.⁸¹ Catheter directed thrombolysis can be performed in patients having no contraindications for treatment.⁸¹ Patients with extensive thrombosis, for e.g., ilio-femoral thrombosis have the most to gain in terms of preserving venous function.⁷⁸ Patient selection is important to provide maximum benefit and to keep low risk of bleeding in patients.⁷⁸ From an Indian perspective, catheter-directed thrombolysis has limited acceptance due to perceived risks, time required for lysis, and cost involved. Catheter assisted thrombus removal should be done only by an expert in the presence of resources for acute PE associated with hypotension and high risk of bleeding risk, failed systemic thrombolysis, or severe shock likely to cause death within hours.⁷⁸

Mechanical Thrombectomy for Deep Vein Thrombosis Treatment

Mechanical thrombectomy requires less time for clot lysis compared to catheter directed thrombolysis.⁸² In recent times use

of mechanical thrombolysis as endovascular therapy is increasing. However, it also requires expertise and resources. There are no full-fledged sufficiently powered studies available to provide evidence for the use of mechanical thrombectomy for deep vein thrombosis.

IVC Filters for Deep Vein Thrombosis Treatment

The use of for vena cava filters in treatment of VTE is controversial. In the absence of strong evidence of efficacy in preventing DVT, high cost and difficulty in predicting which patients might benefit, prophylactic IVC filters cannot be recommended. However, some selected patients in very high-risk category might be benefited with optional IVC filters.⁸³ In patients with absolute contraindications for the use of anticoagulation and a high risk of VTE recurrence, IVC filters might be tried.⁸⁴ Recommendations for interventions in deep vein thrombosis treatment are given in Table 19.

Compression Devices for Deep Vein Thrombosis Treatment

Three types of compression devices are available for prevention of DVT. Compression stockings with graduated pressure (highest at the ankle and lower proximally) prevent venous stasis due to pressure difference. Alternate inflation and deflation of the cuffs used in intermittent pneumatic compression are another type of compression devices to prevent venous stasis. The third type of compression device is mechanical foot pumps, which by intermittent plantar compression (IPC) increases the flow of blood in leg veins (Table 20).⁸⁵

Upper Extremity Deep Vein Thrombosis

Upper extremity deep vein thrombosis (UEDVT) comprises 5-10% of VTE. It is either due to primary cause (unprovoked with or without thrombophilia, effort-related and thoracic outlet syndrome)

Table 19: Recommendations for interventions in deep vein thrombosis treatment

Interventions	Recommendations
Systemic Thrombolysis	<ul style="list-style-type: none"> • Routine use of systemic thrombolysis for treatment of acute proximal DVT is not recommended. • We suggest use of anticoagulant therapy alone over systemic thrombolysis in patients with acute proximal DVT. • Intravenous thrombolysis can be considered in the following: <ul style="list-style-type: none"> - Iliofemoral DVT - Symptoms <14 days - Good functional status - Life expectancy of ≥1 year, and - Low risk of bleeding
Catheter Directed Thrombolysis	<ul style="list-style-type: none"> • Routine use of Catheter Directed Thrombolysis is not recommended for treatment of acute proximal DVT. • We suggest use of anticoagulant therapy alone over Catheter Directed Thrombolysis in patients with acute proximal DVT. • Catheter Directed thrombolysis can be considered in the following : <ul style="list-style-type: none"> - Iliofemoral DVT - Symptoms <14 days - Good functional status - Life expectancy of ≥1 year, and - Low risk of bleeding • Catheter directed thrombolysis should be done only by experienced interventionists and in the facilities where resources for management of complications are available
Mechanical Thrombectomy	<ul style="list-style-type: none"> • Routine use of Mechanical thrombectomy is not recommended for treatment of acute proximal DVT. • We suggest use of anticoagulation therapy alone over mechanical thrombectomy in patients with acute proximal DVT. • Mechanical thrombectomy can be considered in the following : <ul style="list-style-type: none"> - Iliofemoral DVT - Symptoms <7 days - Good functional status - Life expectancy of ≥1 year, and - Resources and expertise are available
IVC filters	<ul style="list-style-type: none"> • In patients with acute DVT treated with anticoagulants, use of an inferior vena cava (IVC) filter is not recommended. • We recommend use of an IVC filter in patients with acute proximal DVT of the leg and contraindication to anticoagulation.

Table 20: Recommendation for compression devices for deep vein thrombosis treatment

In patients with acute DVT of the leg, routine use of compression stockings to prevent PTS is not suggested.

Table 21: Recommendation for upper extremity deep vein thrombosis treatment

We suggest anticoagulant therapy alone over thrombolysis in patients with acute UEDVT that involves the axillary or more proximal veins.

and secondary cause (provoked by central venous catheters, pacemakers, or cancer). UEDVT usually occurs in subclavian, axillary or brachial veins and may involve brachiocephalic vein, superior vena cava or internal jugular vein. UEDVT may lead to complications like symptomatic PE (5%), recurrence (8% at 5 years) and PTS of the arm (20%) (Table 21).^{30,86}

Superficial Vein Thrombosis

Superficial veins of the upper extremity include cephalic vein, basilic vein, median cubital vein, accessory cephalic vein, superficial median vein of the forearm, palmar venous plexus, palmar digital veins whereas superficial veins of the lower extremity include great

saphenous vein, small saphenous vein, dorsal venous arch. Superficial vein thrombosis (SVT) characterized by thrombosis and inflammation in a superficial vein most commonly affects the great saphenous vein, sometimes small saphenous vein and rarely upper extremity veins. The etiology of SVT includes trauma or haematologic changes. The complications of SVT include suppuration, thrombosis at different sites, hypercoagulable state⁸⁷ and increased risk of DVT and PE.⁸⁸ The treatment of SVT is directed at alleviation of pain and inflammation and prevention of complications. The treatment approach includes removal of predisposing factors, symptomatic treatment with anti-inflammatory drugs, and warm compression. Superficial vein thrombosis close to saphenofemoral or saphenopopliteal junction may require anticoagulant treatment while varicose veins and reflux may require surgery.⁸⁶ In a randomized double blind study fondaparinux at a dose of 2.5 mg S.C. once a day for 45 days in patients with acute superficial vein thrombosis of lower extremity was found to be effective with serious side effects (Figure 6).⁸⁹

Special Population and Deep Vein Thrombosis

Elderly Patients

Age is an important risk factor for VTE and VTE recurrence. The risks for DVT and PE are 4 to 6 times higher in patients above 70 years old compared to younger patients,^{90,91} and this risk doubles with each decade of aging.⁹² Importantly, elderly patients also exhibit a higher case-fatality rate due to more frequent fatal PE (odds ratio in patients aged >75 years 2.31)⁹³ and coexistent comorbidities. The diagnosis of VTE in the elderly also poses particular challenges, as an atypical presentation and a reduced sensitivity and specificity of both clinical scoring systems and laboratory parameters may impede a timely diagnosis.⁹⁴ In patients treated with warfarin, the rate of VTE recurrence was higher in patients aged ≥75, with a pooled risk ratio of

RECOMMENDATION FOR MANAGEMENT OF SUPERFICIAL VEIN THROMBOSIS OF LOWER EXTREMITY

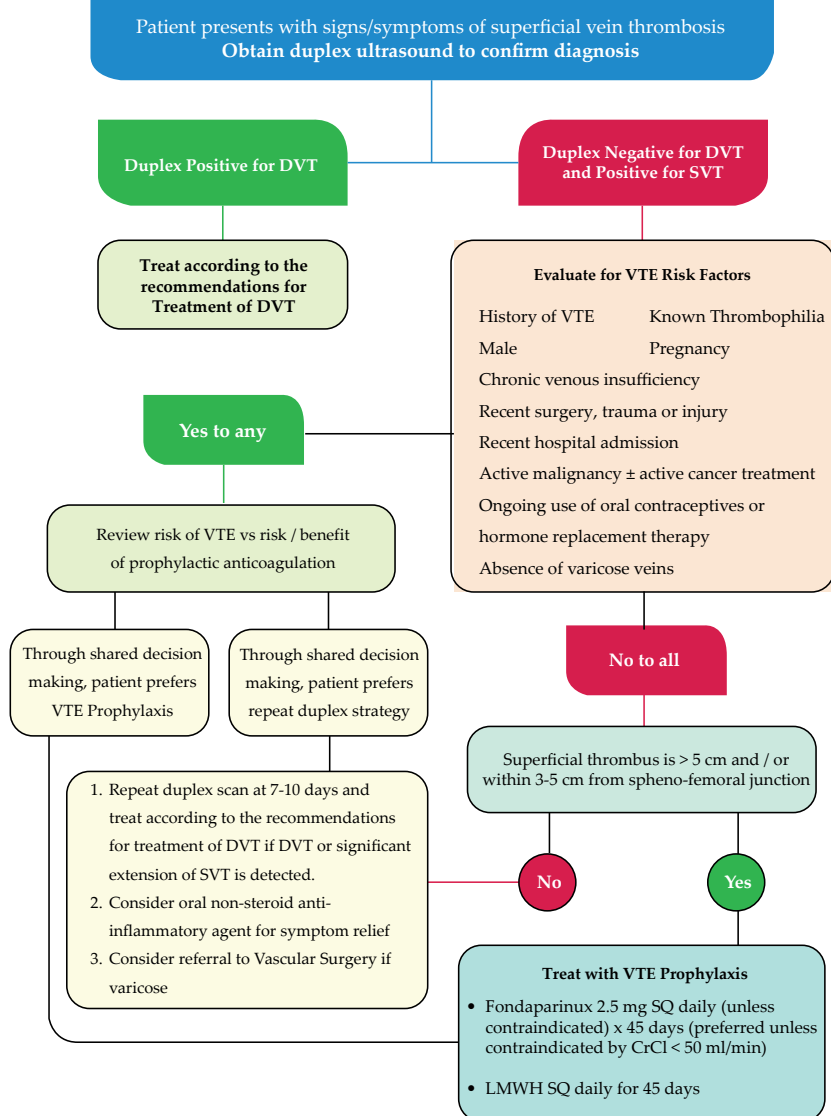


Fig. 6: Superficial vein thrombosis management protocol⁸⁶

1.47 compared to warfarin-treated patients <75 years. In contrast, patients ≥75 treated with NOACs did not have an increased recurrence compared to younger patients. Thus, in a meta-analysis of all patients ≥ 75, NOACs were found to be more effective compared to warfarin.⁹⁵

Patients with Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a clinic-pathological syndrome,⁹⁶ its diagnosis is based on characteristic clinical events and concurrent laboratory detection of HIT antibodies in the setting of

recent heparin therapy. As a result of which there could be increased thrombin generation, which may be associated with arterial or venous thrombosis.⁹⁶ Thrombocytopenia that typically occurs 5 to 10 days after heparin exposure, though it may develop more rapidly in patients previously exposed to heparin within the preceding 100 days.⁹⁶ A decline of 50% from the baseline platelet count should raise clinical suspicion for HIT.⁽⁹⁶⁾ In patients receiving heparin for treatment, both antibody formation and clinical HIT are more common

with UFH than LMWH.⁹⁷ Alternate anticoagulation should be considered if a patient develops HIT. LMWH is not an optimal alternative to UFH because of a high risk of clinically significant cross-reactivity with the HIT antibodies. Warfarin may cause micro thrombosis in patients with HIT. These patients typically present with an international normalized ratio (INR) greater than 4, which corresponds to severe protein C depletion. Initiation of warfarin should be postponed until substantial platelet recovery. Preferably, warfarin should not be started before the platelet count exceeds $150 \times 10^9/L$.^{26,97} If warfarin has already been started, vitamin K should be given.⁹⁸

Thrombophilia, Anti-phospholipid Antibody Syndrome, and Deep Vein Thrombosis

Thrombophilia is a known risk factor for the development of VTE. In the MAISTHRO registry, out of 1490 patients analysed at the time of first VTE, 50.1% patients had at least one thrombophilia.⁹⁹ The hereditary thrombophilia was less common in elderly people compared to younger population. Thrombophilia was more commonly observed in unprovoked VTE compared with risk-associated VTE (57.7% vs. 47.7%; $P = 0.001$).⁹⁹ positivity for anti-phospholipid antibody syndrome (APLAS) are at higher risk for development of thrombotic events.⁹⁹ At the moment, the best anticoagulation regimen for these patients is unknown. Aspirin use as an add-on to low dose warfarin does not provide benefits while short term therapy with warfarin is less useful.¹⁰⁰ In patients with APLAS and DVT, long-term warfarin (INR 3.0-4.0) may seem to be superior compared to warfarin (INR 2.0-3.0).¹⁰⁰ A post-hoc subgroup analysis of thrombophilia patients within the RE-MEDY trial showed that efficacy of dabigatran vs dose adjusted warfarin was not affected by the presence of thrombophilia at baseline.¹⁰¹

Patients with Renal Impairment

Renal impairment was associated with an increased risk of recurrence

Table 22: Recommendations for deep vein thrombosis treatment in special population

Special Population	Recommendations
Elderly (≥ 75 Yrs)	Based on the currently available evidence, we suggest the use of NOACs over VKA therapy in patients' ≥ 75 years.
HIT (Heparin Induced Thrombocytopenia)	In patients with prior history of HIT who have DVT and normal renal function, we suggest the use of fondaparinux as an initial anticoagulation therapy until transition to VKA therapy.
Thrombophilia	The screening for hereditary thrombophilia in VTE patients should be done based on age and other risk factors. Thrombophilia workup may be done for DVT occurring at a younger age (i.e. < 45 years) Unprovoked DVT Recurrent DVT Thrombosis at an unusual site (splanchnic, sinus/cerebral, or renal veins) Unusually extensive spontaneous DVT Family history of DVT Thrombophilia work up to be done Activated protein C resistance Prothrombin gene mutations Protein S, C, and antithrombin III deficiency Antiphospholipid antibodies Factor V Leiden mutation Homocysteine levels
Renal impairment	VKA is the preferred anticoagulant for patients with renal disease and creatinine clearance < 30 mL/min. NOACs and LMWH are contraindicated in patients with severe renal insufficiency (creatinine clearance < 30 mL/min). Assess renal function of the patient before starting NOACs.
Hepatic impairment	Avoid NOACs in moderate to severe hepatic dysfunction.
Active Cancer	In cancer patients having DVT of the leg, long-term (first 3 months) anticoagulant therapy is recommended. LMWH is preferred over VKA or NOACs (dabigatran, rivaroxaban, apixaban or edoxaban) in cancer associated thrombosis. Extended anticoagulant therapy is recommended in patients without high bleeding risk.
Concomitant antiplatelet use	We suggest avoiding concomitant antiplatelet therapy during NOAC therapy unless the potential benefit clearly justifies the increased bleeding risk.

in the warfarin-arms of all trials. Although not significant in most individual trials, pooled data show a significant 71% risk increase in patients with reduced renal clearance. A similar increase in recurrence was noted in patients with reduced renal function treated with apixaban or rivaroxaban, but not in patients treated with dabigatran or edoxaban. A pooled analysis showed no significant difference in relative efficacy between NOACs and warfarin in patients with renal dysfunction.¹⁰²

Patients with Active Cancer

Malignancy is well known risk factor for the development of VTE. Different factors including

hypercoagulable state due to interaction between tumor and host cells, venous stasis, endothelial dysfunction, age of the patient and treatment related components contribute to the risk of VTE. The risk of VTE in active cancer is up to 8-fold higher compared to general population. VTE adversely affect the survival outcome in patients with cancer.¹⁰³

A landmark study comparing dalteparin with an oral anticoagulant therapy in malignancy showed 52% reduction in recurrent VTE without major differences in the rates of major bleeding or mortality.¹⁰⁴ A recent Cochrane review of seven randomized clinical trials comparing LMWH versus VKA therapy showed

53% reduction in recurrent VTE with LMWH with minor difference in the rate of major bleeding.^{47,103} Data on the use of NOACs in cancer patients receiving chemotherapy is limited. The pooled data from two large randomized trials in acute VTE (RECOVER and RECOVER-II showed similar benefits with dabigatran as warfarin. No significant difference in efficacy was seen for cancer at baseline or diagnosed during the study.⁵¹

Patients taking Anti-platelet Agents

The NOAC VTE treatment trials allowed low-dose concomitant aspirin, and dual antiplatelet therapy was allowed in the dabigatran and rivaroxaban trials. The rate of low-dose aspirin use ranged from 8 to 14 % for dabigatran, rivaroxaban, and apixaban, and was not reported in the edoxaban trial.^{47,48,51-54} The recommendations for deep vein thrombosis treatment in special population are summarized in Table 22.

Deep Vein Thrombosis and Pregnancy

The risk of VTE in pregnancy is five to ten times higher than non-pregnant women of similar age group. During the postpartum period the risk of VTE is even more (15-35 times higher) compared to non-pregnant women of the same age. The risk of VTE is greatest during the first 3 to 6 weeks after delivery.¹⁰⁵ Overall, the rate of VTE in pregnancy ranges between 0.5–2.2 per 1000 deliveries based on different population studies and can result in significant maternal morbidity and mortality.¹⁰⁵⁻¹¹² Treatment and prevention of deep vein thrombosis in pregnancy is of concern due to two reasons. First, the risk involved for mother and the fetus due to both the VTE and drugs used in its management and secondly, absence of high quality pregnancy specific data causing difficulty in providing recommendations. The recommendations are mostly based on observational studies and data extrapolated from non-pregnant patients. Vitamin K antagonists cross the placenta and can cause teratogenicity, miscarriage, fetal bleeding, and neurological

Table 23: Recommendations for treatment of deep vein thrombosis during pregnancy/peripartum/breast feeding**Recommendations for treatment of DVT during pregnancy**

- Women of child bearing potential should avoid pregnancy during treatment with NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) and Vitamin K antagonists, and if pregnancy is planned, use appropriate contraception or switch over to LMWH/UFH as early as possible.
- When pregnant, NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) should be used only if the potential benefit outweighs the potential risk to the mother and fetus.
- Vitamin K antagonists should be avoided during pregnancy because of their known potential risk to the mother and fetus. If pregnant, discontinue VKA and switch to LMWH/UFH before the 6th week of gestation or consider for medical termination of pregnancy according to the potential risk to the mother and fetus.
- LMWH (dalteparin 200 units/kg once daily or 100 units/kg 12 hourly; tinzaparin 175 units/kg once daily; enoxaparin 1 mg/kg 12 hourly; nadroparin 86 units/kg 12 hourly or 171 units/kg once daily) is the drug of choice for treatment and prevention of VTE in pregnancy and postpartum period, except in cases with history or presence of heparin induced thrombocytopenia, or significant kidney dysfunction. In patients with significant kidney dysfunction (GFR < 30 ml/min), UFH is preferred.
- Danaparoid or fondaparinux may be used in pregnant women with severe skin allergies to UFH or LMWH or history or presence of heparin induced thrombocytopenia.
- Outpatient treatment can be considered in clinically stable patients and those having good cardiorespiratory reserve, no major risk factors for bleeding and good social support with easy access to medical care.

Recommendations for treatment of DVT during peripartum period

- Anticoagulant therapy should be discontinued at the onset of spontaneous labor.
- LMWH should be discontinued at least 24 hours before the expected time of epidural analgesia or delivery in case of planned delivery.
- Intravenous UFH should be discontinued at least 4-6 hours before the expected time of epidural analgesia or delivery with check aPTT in case of planned delivery.
- Subcutaneous UFH should be discontinued preferably 24 hours before the expected time of epidural analgesia or delivery with check aPTT in case of planned delivery.
- LMWH/intravenous UFH may be initiated/reinitiated 24 hours after delivery or as soon as haemostasis is achieved.

Recommendation for treatment of DVT in breastfeeding Women

- NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) should be avoided in breastfeeding women, and other alternative anticoagulants i.e. LMWH/UFH/warfarin/acenocoumarol should be considered.

Recommendation for duration of anticoagulation therapy for DVT in pregnancy and postpartum period

- Anticoagulation therapy should continue throughout pregnancy and at least 6 weeks postpartum. Decision to further continue anticoagulation therapy should be based on risk of recurrent VTE versus risk of bleeding.

Table 24: Recommendations for anticoagulation therapy in deep vein thrombosis associated with ART

- No routine thromboprophylaxis for women undergoing ovulation induction needed.
- We recommend thromboprophylaxis with LMWH for woman at increased risk (e.g. previous h/o VTE, h/o asymptomatic thrombophilia, family history of symptomatic thrombophilia and pregnancy related risk factors) of VTE undergoing ART at the time of ovarian stimulation. It has to be stopped 24-48 hrs prior to OPU (oocyte pick-up) and restarted 24 hrs after OPU (oocyte pick-up).
 - In case pregnancy ensues – then continue for first 6 weeks of pregnancy.
 - In absence of pregnancy – can be stopped at a negative UPT (Urine Pregnancy Test).
- In case of severe OHSS due to ART, we recommend thromboprophylaxis with LMWH for at least 8-12 weeks after the resolution of the syndrome.
- We recommend therapeutic anticoagulation for a minimum 3 months for woman with VTE in association with the use of ART who do not conceive in that cycle.
- We recommend therapeutic anticoagulation for a minimum 3 months for woman with VTE in association with the use of ART who conceive in that cycle. After which anticoagulation intensity can be decreased to intermediate or prophylactic dose for the remainder of the pregnancy and for at least 6 weeks postpartum.

developmental defects. Pregnant women were excluded from all non-vitamin K antagonist oral anticoagulants (e.g. dabigatran,

rivaroxaban, apixaban, edoxaban) clinical trials.^{46,49,55,56} These agents are likely to cross the placenta and their risks during pregnancy use are not known.^{46,49,55,56} Fondaparinux crosses placenta in small amount, and its use during pregnancy has been found to be safe.¹¹³⁻¹²⁰ LMWH, UFH and danaparoid do not cross the placenta and have a better safety profile in pregnancy.¹²¹⁻¹²⁴ UFH can be used during pregnancy for both prevention and treatment of thromboembolism though LMWH has a better safety profile than UFH in such patients.¹²⁵ The recommendations for treatment of deep vein thrombosis during pregnancy / peripartum / breast feeding are summarized in Table 23.

Assisted Reproductive Technology and Deep Vein Thrombosis

There is limited data on epidemiology and management of VTE related to Assisted Reproductive Technology (ART). According to a retrospective analysis of data from 2748 in vitro fertilization (IVF) cycles, the risk of thromboembolism in women undergoing IVF is 0.11% per cycle. And in the presence of OHSS (Ovarian Hyper stimulation Syndrome), the risk of thrombosis is as high as 0.78% per cycle involving upper extremity in majority of cases.^{126,127} The VTE risk in OHSS (Ovarian Hyper stimulation Syndrome) may remain for weeks or months even after the resolution of the OHSS. In women with high risk of VTE, thromboprophylaxis might be started at the start of ovarian stimulation, and continued till the completion of ART. In case pregnancy occurs, thromboprophylaxis should be continued during the antepartum period. If the woman undergoing IVF does not have risk factors for the development of VTE, routine thromboprophylaxis is not required. However if she develops severe OHSS, thromboprophylaxis should be used.¹²⁷ The recommendations for anticoagulation therapy in deep vein thrombosis associated with ART are summarized in Table 24.

Table 25: Suggestions for preoperative interruption of NOACs¹²⁸

	Dabigatran (150 mg twice daily) Last dose		Rivaroxaban (20 mg once daily) Last dose		Apixaban (5 mg twice daily) Last dose	
	Low bleeding risk surgery (Hours before surgery)	High bleeding risk surgery (Hours before surgery)	Low bleeding risk surgery (Hours before surgery)	High bleeding risk surgery (Hours before surgery)	Low bleeding risk surgery (Hours before surgery)	High bleeding risk surgery (Hours before surgery)
Normal or mild renal impairment	24 hrs	48–72 hrs	24 hrs	48–72 hrs	24 hrs	48–72 hrs
Moderate renal impairment	48–72 hrs	96 hrs	48 hrs	72 hrs	48 hrs	72 hrs

Table 26: Pharmacological properties of reversal agents¹³⁰

	Idarucizumab	Andexanet alfa	Ciraparantag (PER 977)
Target	Dabigatran	FXa inhibitors	FXa inhibitors, dabigatran and heparins
Mechanism of action	Specific humanized Fab: specifically binds dabigatran	Non-specific recombinant modified activated FX: Competitive affinity for direct FXa inhibitors	Non-specific synthetic small molecule; hydrogen bonds (NOACs): charge-charge interactions (heparin)
Direct prothrombotic signals	Absent	Present (clinically not relevant)	Absent
Administration	IV bolus or short infusion	IV, bolus and/or continuous infusion	IV
Re-initiate anti-coagulation	Possible	No data available	No data available
Inclusion criteria in patient trial	Uncontrolled bleeding or requiring emergency surgery procedure	Uncontrolled bleeding only	No patient trial yet

Peri-procedural Management of Anticoagulants

An important consideration in the perioperative period is the risk of thrombosis with stopping treatment risk of bleeding with ongoing treatment. Unlike warfarin, NOAC may not be required to discontinue for minor procedures, but surgery should be planned to avoid peak drug levels during procedure time. In case of major risk of bleeding, the surgery should be well planned with stoppage of NOAC because of the lack of reversal agents. The properties of short onset and offset of action allows discontinuation of NOAC for shorter period in patients with normal liver and kidney functions. Based on the half-life, suggested timings for interruption of NOACs are given in Table 25.¹²⁸

Resuming NOACs after Surgical Procedure

Hepatic and renal function tests should be assessed and within normal range before starting NOACs postoperatively. For low and high bleeding risk surgery, NOAC can be started 24 hours and 48–72 hours after surgery, respectively.¹²⁸

Bleeding Management with OACs

The major side effect of anti-coagulation is bleeding. The management approach in case of serious bleeding episode with anti-coagulant is generally divided into general measures specific measures and adjuvant therapies. Measures to manage the acute bleeding event whilst on NOACs have been described in details by EHRA 2015 consensus document titled: Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation.⁵⁷

Reversal Agents for NOACs

An increased risk of bleeding is a known possible complication of all anticoagulant therapies. Although NOACs have demonstrated favourable efficacy and safety profile in the absence of a specific reversal agent, certain clinical situations may arise in which rapid reversal of anticoagulant activity is desirable. Due to the short duration of action of the drugs, the discontinuation of the drug is in most cases sufficient to control the problem. However, need for a reversal agent to neutralize these compounds in case of an overdose or serious bleeding, or when a

rapid restoration of haemostasis is required (e.g. perioperative period) has been acknowledged since the clinical use of these anticoagulants began. Following NOAC reversal agents are in development; idarucizumab, which specifically targets dabigatran, andexanetalfa, a Factor Xa inhibitor and PER977 which can block actions of multiple anticoagulants.^{129,130} The details of these agents are summarized in Table 26.

In a recently published prospective study, intravenous idarucizumab (5 gm) normalized the test results in 88–98% of dabigatran treated patients with serious bleeding or who required urgent procedure. The complete reversal of anticoagulant effect of dabigatran was evident within minutes.¹³¹ Currently, none of these agents are approved in India. Once available, they may aid in the usage of NOACs.

Evidence Gaps and Future Research Directions

The utility and validity of the clinical prediction scores and bleeding risk assessment scores in Indian populations has not been studied. Validation studies for these scores are required in Indian patients. Indian studies are awaited on risk of DVT/PE in patients with

superficial venous thrombosis.

Conflicts of Interest

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