VENOUS THROMBOEMBOLISM

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM – January 2024

To the CHI Original Venous Thromboembolism- Issued March 2020

Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AHA	American Heart Association
ALT	Alanine Aminotransferase
APT	Antiplatelet Therapy
aPTT	Activated Partial Thromboplastin Time
ARC-HBR	Academic Research Consortium for High Bleeding Risk
ASA	American Stroke Association
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate Aminotransferase
AVR	Aortic Valve Replacement
BHV	Biological Heart Valve
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CAT	Cancer-Associated Thrombosis
CHI	Council of Health Insurance
COC	Combined Oral Contraceptive
CPG	Clinical Practice Guideline
CrCl	Creatinine Clearance
CRT	Criterion
CT	Computed Tomography
CVC	Central Venous Catheter
CYP	Cytochrome P450
D5W	Dextrose 5% in Water
DAPT	Dual Antiplatelet Therapy
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
EACTS	European Association for Cardio-Thoracic Surgery
EASL	European Association for the Study of the Liver

EMA	European Medicines Agency
ESC	European Society of Cardiology
ESMO	European Society for Medical Oncology
EVD	External Ventricular Drain
FDA	Food and Drug Administration
FVL	Factor V Leiden Mutation
GCS	Graduated Compression Stockings
GI	Gastrointestinal
GR	Grade of Recommendation
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HASBLED	Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly
HIT	Heparin-Induced Thrombocytopenia
HRT	Hormone Replacement Therapy
HTA	Health Technology Assessment
ICH	Intracerebral Hemorrhage
ICP	Intracranial Pressure
IDF	Insurance Drug Formulary
IMiD	Immunomodulatory imide Drug
INR	International Normalized Ratio
IPC	Intermittent Pneumatic Compression
ISTH	International Society on Thrombosis and Haemostasis
IV	Intravenous
IVCF	Inferior Vena Cava Filter
LA	Left Atrium
LE/LOE	Level of Evidence
LV	Left Ventricle
LWMH	Low Molecular Weight Heparin
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
MS	Mitral Stenosis
N/A	Not Applicable

NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NOAC	Non-vitamin K antagonist Oral Anticoagulant
OAC	Oral Anticoagulant
OCEBM	Oxford Centre for Evidence-Based Medicine
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PE	Pulmonary Embolism
PGM	Prothrombin 20210A Gene Mutation
P-gp	P-glycoprotein
PO	Per Os (by mouth)
PT	Prothrombin Time
PTS	Post-Thrombotic Syndrome
RAMS	Risk Assessment and Management System
RCT	Randomized Controlled Trial
SAPT	Single Antiplatelet Therapy
SAVR	Surgical Aortic Valve Replacement
SC	Subcutaneous
SFDA	Saudi Food and Drug Authority
SIHD	Stable Ischemic Heart Disease
SPC	Summary of Product Characteristics
SPVT	Splenic Vein Thrombosis
SVT	Superficial Vein Thrombosis
TAVI	Transcatheter Aortic Valve Implantation
TBI	Traumatic Brain Injury
TIA	Transient Ischemic Attack
TIPS	Transjugular Intrahepatic Portosystemic Shunt
UFH	Unfractionated Heparin
ULN	Upper Limit of Normal
US	Ultrasound
VHD	Valvular Heart Disease
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

Executive Summary

Venous thromboembolism (VTE) is a medical condition characterized by the formation of blood clots within veins. It encompasses two main conditions, namely deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT manifests when a blood clot develops in a deep vein, most commonly in the lower leg, thigh, or pelvis, although it can also occur in the arms, particularly when there is a significant intravenous central line in the vein[1].

The most common triggers for venous thromboembolism are surgery, cancer, immobilization, and hospitalization. Symptoms include swelling, pain, tenderness, skin discoloration, and increased warmth of the affected area.[1]

Complications include clot breaking free to other areas such as the lungs (PE), the heart (heart attack) or the brain (stroke), and postphlebitic syndrome[2].

VTE is a prevalent issue, with up to 600,000 VTE cases reported annually in the United States[1]. The annual incidence rate of the first VTE ranges from 1 to 3 per 1000 in KSA[3].

Annual incident VTE events conservatively cost the US healthcare system $7–10 billion each year for 375,000 to 425,000 newly diagnosed, medically treated incident VTE cases. Subsequent complications are conservatively estimated to increase cumulative costs to $18,000–23,000 per incident case[4].

Pregnancy, associated with the development of a baseline hypercoagulable state, increases the risk of VTE by four to five times. The overall incidence of VTE in pregnancy is estimated between 0.2% to 2% of pregnancies. Increasing maternal age and obesity, combined with higher caesarian section rates have contributed to placing women at higher risk of VTE[5,6]. The American Society of Hematology (ASH), the American College of Obstetricians and Gynecologists (ACOG), and the Royal College of Obstetricians and Gynecologists (RCOG) last issued guidelines between 2015 and 2018 for the management of VTE in pregnancy[7–9]. These guidelines are detailed in the previous CHI report and no updates have since been published.

Mainstay treatment of VTE typically involves anticoagulant therapy (blood thinners).

CHI issued Venous Thromboembolism clinical guidance after thorough review of renowned international and national clinical guidelines in March 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Venous Thromboembolism clinical guidance and seeks to offer guidance for the effective management of Venous Thromboembolism. It provides an **update on the Venous Thromboembolism Guidelines** for CHI Formulary with the ultimate objective of

updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** namely:

1. NCCN **v2.2023** Cancer-Associated Venous Thromboembolic Disease
2. NICE Venous thromboembolic diseases: diagnosis, management, and thrombophilia testing **2023**
3. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report **2021**
4. **2021** ESC/EACTS Guidelines for the management of valvular heart disease Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio – Thoracic Surgery (EACTS)
5. **2020** ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Moreover, **new guidelines are added to the report**:

1. American Society of Hematology **2023** Guidelines for Management of Venous Thromboembolism: Thrombophilia Testing
2. American Society of Hematology **2020** guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism
3. Saudi Critical Care Society clinical practice guidelines on the prevention of venous thromboembolism in adults with trauma: reviewed for evidence-based integrity and endorsed by the Scandinavian Society of Anesthesiology and Intensive Care Medicine **2023**
4. NICE Venous thromboembolism in adults guidelines **2021**
5. The Saudi Consensus for the Management of Cancer-Associated Thromboembolism: A Modified Delphi-Based Study **2023**
6. Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: ASCO Guideline Update **2023**
7. American Society of Hematology **2021** guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer
8. **2020** ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients with Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or with

Atherosclerotic Cardiovascular Disease A Report of the American College of Cardiology Solution Set Oversight Committee

9. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis **2022**
10. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: July **2021** update on post discharge thromboprophylaxis
11. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: May **2021** update on the use of intermediate-intensity anticoagulation in critically ill patients
12. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis for patients with COVID-19: March **2022** update on the use of anticoagulation in critically ill patients
13. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: January **2022** update on the use of therapeutic-intensity anticoagulation in acutely ill patients
14. The use of direct oral anticoagulants for primary thromboprophylaxis in ambulatory cancer patients: guidance from the SSC of the ISTH **2019**
15. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline **2022**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is important to note that it is recommended to delist **Bivalirudin** from the CHI formulary. Additionally, there have been **no newly approved drugs** for the treatment of Venous Thromboembolism, however, there have been **updates** regarding certain previously mentioned drugs in terms of drug information and prescribing edits since March 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the therapeutic management of Venous Thromboembolism.

Below is a table summarizing the major changes based on the different Venous Thromboembolism treatment guidelines used to issue this report:

Table 1. General Recommendations for the Management of Venous Thromboembolism

Management of Venous Thromboembolism		
General Recommendations	**Level of Evidence/ Grade of Recommendation**	**Reference**
For patients with DVT and/or PE, the ASH guideline panel does not suggest one DOAC over another. Factors, such as a requirement for lead-in parenteral anticoagulation, once- vs twice-daily dosing, and out-of-pocket cost may drive the selection of specific DOACs. Other factors, such as renal function, concomitant medications (e.g., need for a concomitant drug metabolized through the CYP3A4 enzyme or P-glycoprotein), and the presence of cancer, may also impact DOAC choice.	Conditional recommendation, very low certainty in the evidence of comparative effects ⨁◯◯◯	ASH 2020 Guidelines[10]
For patients with extensive DVT in whom thrombolysis is considered appropriate, the ASH guideline panel suggests using catheter-directed thrombolysis over systemic thrombolysis	Conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯	ASH 2020 Guidelines[10]
For patients with proximal DVT and significant preexisting cardiopulmonary disease, the ASH guideline panel suggests anticoagulation alone rather than anticoagulation plus insertion of an inferior vena cava (IVC) filter	Conditional recommendations, low certainty in the evidence of effects ⨁⨁◯◯	ASH 2020 Guidelines[10]
For primary treatment of patients with DVT and/or PE, whether provoked by a transient risk factor or by a chronic risk factor or unprovoked, the ASH guideline panel suggests using a shorter course of anticoagulation for primary treatment (3-6 months) over a longer course of anticoagulation for primary treatment (6-12 months)	Conditional recommendations, moderate certainty in evidence of effects ⨁⨁⨁◯	ASH 2020 Guidelines[10]

Offer either apixaban or rivaroxaban to people with confirmed proximal DVT or PE. If neither apixaban nor rivaroxaban is suitable offer: • LMWH for at least 5 days followed by dabigatran or edoxaban or • LMWH concurrently with a vitamin K antagonist (VKA) for at least 5 days, or until the international normalized ratio (INR) is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.	Not graded	NICE 2023 Guideline[11]

Offer people with confirmed proximal DVT or PE and renal impairment (estimated creatinine clearance between 15 ml/min and 50 ml/min) one of:
• Apixaban
• Rivaroxaban
• LMWH for at least 5 days followed by:
  o Edoxaban or
  o Dabigatran if estimated creatinine clearance is 30 ml/min or above
• LMWH or UFH, given concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.
	Not graded	NICE 2023 Guideline[11]

Offer people with confirmed proximal DVT or PE and established renal failure (estimated creatinine clearance less than 15 ml/min) one of: • LMWH • UFH • LMWH or UFH concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own	Not graded	NICE 2023 Guideline[11]
Consider using the HAS-BLED score for major bleeding risk to assess the risk of major bleeding in people having anticoagulation treatment for unprovoked proximal DVT or PE. Discuss stopping anticoagulation if the HAS-BLED score is 4 or more and cannot be modified.	Not graded	NICE 2023 Guideline[11]

If the current treatment is not well tolerated, or the clinical situation or person's preferences have changed, consider switching to apixaban if the current treatment is a direct-acting anticoagulant other than apixaban. For people who decline continued anticoagulation treatment, consider aspirin 75 mg or 150 mg daily.	Not graded	NICE 2023 Guideline[11]
Consider an IVC filter for people with proximal DVT or PE when anticoagulation treatment is contraindicated. Remove the IVC filter when anticoagulation treatment is no longer contraindicated and has been established.	Not graded	NICE 2023 Guideline[11]
In patients with VTE diagnosed in the absence of transient risk factor (unprovoked VTE or provoked by a persistent risk factor) who cannot receive a DOAC, the guidelines suggest offering extended-phase anticoagulation with a VKA	Weak recommendation, moderate certainty evidence	CHEST 2021 Guidelines[12]
In patients with cerebral vein/venous sinus thrombosis, the guidelines recommend anticoagulation therapy for at least the treatment phase (first 3 months) over no anticoagulant therapy	Strong recommendation, low-certainty evidence	CHEST 2021 Guidelines[12]
For patients with AF and native valve heart disease (except rheumatic mitral stenosis [MS]) or who received a bioprosthetic valve >3 months ago, a non–vitamin K oral anticoagulant (NOAC) is an effective alternative to VKA anticoagulation and should be administered based on the patient's CHA2DS2-VASc score	COR: 1, LOE: A	ACC/AHA 2020 Guidelines[13]
In adults with trauma who receive pharmacologic VTE prophylaxis, we suggest using LMWH (e.g., enoxaparin, dalteparin) over UFH. UFH is preferred in patients with end-stage renal disease and in those with low creatinine clearance (< 30 ml/min)	Weak, low	Saudi Critical Care Society 2023 Guideline[14]
The NCCN Guidelines Panel for Cancer-Associated Venous Thromboembolic Disease recommends VTE prophylaxis for all patients	Not graded	NCCN 2023 Guidelines[15]

hospitalized with cancer, excluding those with basal/squamous cell skin cancer		
Clinical suspicion of superficial vein Thrombosis (SVT) - Upper extremity SVT (median, basilic, and/or cephalic veins): • Use symptomatic treatment and monitor for progression • If progression symptomatically or on imaging, consider prophylactic dose anticoagulation • Consider initial therapeutic dose anticoagulation if the clot is in close proximity to the deep venous system	Not graded	NCCN 2023 Guidelines[15]
Clinical suspicion of superficial vein Thrombosis (SVT) - Lower extremity SVT (great and small saphenous veins): • Prophylactic dose anticoagulation for at least 6 weeks if: o SVT >5 cm in length o SVT extends above knee • Therapeutic dose anticoagulation for at least 3 months if SVT is within 3 cm of the saphenofemoral junction • Consider repeat US in 7–10 days if SVT <5 cm in length or below knee. If repeat US shows progression, consider anticoagulation	Not graded	NCCN 2023 Guidelines[15]
Consider longer duration anticoagulation in patients with catheters with poor flow, persistent symptoms, or unresolved thrombus. Consider shorter duration of anticoagulation if clot or symptoms resolve in response to anticoagulation and/or catheter removal	Not graded	NCCN 2023 Guidelines[15]
Progression or new thrombosis on therapeutic anticoagulation – alternative coagulant to UFH: • Switch to alternative anticoagulant (DOACs [apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B], LMWH, warfarin, fondaparinux) • Increase dose of UFH	Not graded	NCCN 2023 Guidelines[15]

LMWH is the pharmacological option of choice for the primary prophylaxis of CT and remained predominately used in an inpatient and outpatient setting in Saudi Arabia unless contraindicated	Level of agreement: 83%	Saudi 2023 Consensus[16]
DOACs, LMWH, UFH, or fondaparinux, can be used as initial anticoagulants. Among parenteral agents, LMWH is preferred over UFH in the absence of severe renal impairment	Level of agreement: 100%	Saudi 2023 Consensus[16]
High-risk ambulatory patients should be offered thromboprophylaxis. In Saudi Arabia, DOACs and LMWH is commonly used in this setting unless contraindicated	Level of agreement: 75%	Saudi 2023 Consensus[16]
For long-term anticoagulation, DOACs or LMWH for at least 6 months is preferred over VKA. VKAs are less effective but may be used if DOACs or LMWH are not accessible	Level of agreement: 100%	Saudi 2023 Consensus[16]
Catheter-directed pharmaco-mechanical thrombolysis can be considered for DVT in patients at low risk for bleeding but at risk for limb loss or severe persistent symptoms despite anticoagulation	Level of agreement: 100%	Saudi 2023 Consensus[16]
Incidental VTE should be treated in the same manner as symptomatic VTE	Level of agreement: 100%	Saudi 2023 Consensus[16]
It is suggested that outpatient anticoagulant thromboprophylaxis not be used for patients with COVID-19 who are being discharged from the hospital and do not have suspected or confirmed venous thromboembolism (VTE) or another indication for anticoagulation	Conditional recommendation, very low certainty in the evidence about effects ⨁◯◯◯	ASH 2021 Guideline[17]
The American Society of Hematology (ASH) guideline panel suggests using prophylactic-intensity over intermediate-intensity anticoagulation in patients with COVID-19–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE)	Conditional recommendation, low certainty in the evidence about effects ⨁⨁◯◯	ASH 2021 Guideline[18]

The ASH guideline panel suggests using therapeutic-intensity over prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation	Conditional recommendation, very low certainty in the evidence about effects ⨁◯◯◯	ASH 2022 Guideline[19]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Venous Thromboembolism clinical and therapeutic management.** Additionally, **appendices** are provided for treatment algorithms and further information on the topic.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Venous Thromboembolism report, while the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the March 2020 CHI Venous Thromboembolism Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
American society of hematology (ASH) 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and non-hospitalized medical patients	N/A*
The Saudi clinical practice guideline for the prophylaxis of venous thromboembolism in long-distance travelers **[2017] & the Saudi clinical practice guideline** for the prophylaxis of venous thromboembolism in medical and critically ill patients **[2016]**	N/A*
National institute for health care and excellence (NICE) guidelines for venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism **[2018]**	N/A*
American society of hematology 2019 guidelines for management of venous thromboembolism: prevention of venous	N/A*

thromboembolism in surgical hospitalized patients	
European guidelines on perioperative venous thromboembolism prophylaxis **[2017]**	N/A*
American society of hematology (ASH) 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy	N/A*
ACOG practice bulletin: thromboembolism in pregnancy **[2018]**	N/A*
Royal college of obstetricians and gynecologists (RCOG) guidelines for reducing the risk of venous thromboembolism during pregnancy and the puerperium **[2015]**	N/A*
The Saudi clinical practice guidelines: venous thromboembolism prophylaxis and treatment in patients with cancer **[2015]- adopted from the American Society of Clinical Oncology (ASCO) clinical practice guideline updated [2019]**	N/A*
2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer- **the international initiative on thrombosis and cancer (ITAC) endorsed by the international society on thrombosis and hemostasis (ISTH)**	N/A*
NCCN Clinical Practice Guidelines in Oncology: Cancer-associated venous thromboembolism **[2019]**	**NCCN v2.2023** Cancer-Associated Venous Thromboembolic Disease
Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the **European Society of Cardiology (ESC) working groups of aorta and peripheral vascular diseases and**	N/A*

pulmonary circulation and right ventricular function [2017]	
American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy	N/A*
2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with **the European Respiratory Society (ERS) The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC)**	N/A*
New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism **[2019]**	N/A*
NICE guidelines for Venous thromboembolic diseases: diagnosis, management, and thrombophilia testing **[2012]**	**NICE** Venous thromboembolic diseases: diagnosis, management and thrombophilia testing **2023**
Saudi Clinical Practice Guideline on the Treatment of Venous Thromboembolism **[2014] & The Saudi Clinical Practice Guideline** for the treatment of venous thromboembolism inpatient vs. outpatient management **[2015]**	N/A*
Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: **American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [2012]**	Antithrombotic Therapy for VTE Disease: Second Update of the **CHEST** Guideline and Expert Panel Report **2021**
2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation A Report of the American College of Cardiology/American Heart	N/A*

Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society	
2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease- A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines	**2020 ACC/AHA** Guideline for the Management of Patients with Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines
2017 ESC/EACTS Guidelines for the management of valvular heart disease: The Task Force for the Management of Valvular Heart Disease of the **European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)**	**2021 ESC/EACTS Guidelines** for the management of valvular heart disease Developed by the Task Force for the management of valvular heart disease of the **European Society of Cardiology (ESC) and the European Association for Cardio – Thoracic Surgery (EACTS)**
American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia	N/A*
Diagnosis and management of heparin-induced thrombocytopenia: a consensus statement from **the Thrombosis and Haemostasis Society of Australia and New Zealand HIT Writing Group [2019]**	N/A*
American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism	N/A*

*****: *No updated versions available*

1.1.1 National Comprehensive Cancer Network (NCCN) Cancer-Associated Venous Thromboembolic Disease (v 2.2023)

The guidelines recommend the following[15]:

- The NCCN Guidelines Panel for Cancer-Associated Venous Thromboembolic Disease recommends VTE prophylaxis for all patients hospitalized with cancer, excluding those with basal/squamous cell skin cancer. Although multiple risk

assessment models (RAMs) have been developed for patients hospitalized for medical or surgical care, none of these RAMs have been validated in prospective management studies conducted in patients hospitalized with cancer.

- Contraindications to prophylactic anticoagulation:
    1. Active bleeding
    2. Thrombocytopenia (platelet count < 50,000/μL or clinical judgment)
    3. Underlying hemorrhagic coagulopathy (e.g., abnormal PT or aPTT excluding a lupus inhibitor/anticoagulant) or known bleeding disorder in the absence of replacement therapy (e.g., hemophilia, von Willebrand disease)
    4. Indwelling neuraxial catheters (contraindication for apixaban, dabigatran, edoxaban, fondaparinux, rivaroxaban, or enoxaparin dose exceeding 40 mg daily)
    5. Neuraxial anesthesia/lumbar puncture
    6. Interventional spine and pain procedures
    7. Current or previous heparin-induced thrombocytopenia (HIT) (contraindication for LMWH and UFH)

Table 3 details VTE prophylaxis options in medical oncology inpatients, and table 4 details options for ambulatory medical oncology patients and patients post-medical oncology discharge. Tables 5 and 6 list VTE prophylaxis options in surgical oncology inpatients as well as post-discharge prophylaxis for surgical oncology patients.

Table 3. VTE Prophylaxis Options for Medical Oncology Inpatients (NCCN 2023 Guidelines)

Agent	Standard dosing	Renal dose	Dosing for Body Mass Index (BMI) ≥ 40 kg/m^2	Dosing for Actual Body Weight (ABW) 25-50 kg
Dalteparin	5000 units SC daily (category 1)	Avoid if estimated creatinine clearance (CrCl) < 30 mL/min	Consider 7500 units SC daily OR 5000 units SC every 12 hours OR 40-75 units/kg SC daily	Consider 2500 units SC daily OR 100 units/kg SC daily
Enoxaparin	40 mg SC daily (category 1)	Recommend 30 mg SC daily if CrCl < 30 mL/min	BMI > 40 kg/m^2: Consider 40 mg SC every 12 hours OR 0.5 mg/kg actual body weight SC daily BMI >50 kg/m^2: Consider 60 mg SC every 12 hours OR 0.5 mg/kg actual body weight SC daily	ABW 25-40 kg: consider 20 mg SC daily (avoid if CrCl < 30 mL/min) OR ABW 41-50 kg: consider 30 mg SC daily (avoid if CrCl < 30 mL/min)
Fondaparinux	2.5 mg SC daily (category 1)	Caution if CrCl 30-49 mL/min; avoid if CrCl < 30 mL/min	Consider 5 mg SC daily	Contraindicated for body weight < 50 kg
UFH	5000 units SC every 8-12 hours (category 1)	Same as standard dose	Consider 7500 units SC every 8 hours	Weight < 40 kg: 5000 units SC every 12 hours

Table 4. VTE Prophylaxis Options for Ambulatory Medical Oncology Patients and Patients Post-Medical Oncology Discharge (NCCN 2023 Guidelines)

Agent	Standard Dosing	Renal Dose	Other Dose Modifications
Apixaban	2.5 mg PO twice daily	Avoid if CrCl < 30 mL/min	Avoid if platelet count <50,000/µL Avoid if weight <40 kg
Rivaroxaban	10 mg PO once daily	Avoid if CrCl < 30 mL/min	Avoid if platelet count <50,000/µL
Dalteparin	200 units/kg SC daily x 1 month, then 150 units/kg SC daily x 2 months	Avoid if CrCl < 30 mL/min	Avoid if platelet count <50,000/µL
Enoxaparin	1 mg/kg SC daily x 3 months, then 40 mg SC daily	Avoid if CrCl < 30 mL/min	Avoid if platelet count <50,000/µL
Recommendations derived from clinical trials of ambulatory patients with cancer with high thrombosis risk (>18 years, Khorana VTE Risk Score of ≥2, initiating new course of chemotherapy) and are not included in product labeling. Prophylaxis duration should be 6 months or longer if risk persists. **Apixaban is absorbed in the stomach, proximal small bowel, and colon. Patients who have had significant resections of these portions of the intestinal tract may be at risk for suboptimal absorption.** **DOACs are absorbed primarily in the stomach and proximal small bowel, so they may not be appropriate for patients who have had significant resections of these portions of the intestinal tract.** Data supports the use of prophylactic dalteparin and enoxaparin for patients with advanced unresectable and metastatic pancreatic cancer.			

Table 5. VTE Prophylaxis Options for Surgical Oncology Inpatients (NCCN 2023 Guidelines)

Agent	Standard Dosing	Renal Dose	Dosing for BMI ≥ 40 kg/m²	Dosing for ABW 25-50 kg
Dalteparin	5000 units SC the evening prior to surgery, then 5000 units SC daily OR 2500 units SC 1–2 hours prior to surgery and 2500 units SC 12 hours later, then 5000 units SC daily beginning postoperative day (POD) 1	Avoid if CrCl < 30 mL/min	Consider 7500 units SC daily OR 5000 units SC every 12 hours OR 40–75 units/kg SC daily	No dose adjustment available
Enoxaparin	40 mg SC 10–12 hours prior to surgery, then 40 mg SC daily or 40 mg SC daily with first dose 6–12 hours postoperative	Recommend 30 mg SC daily if CrCl < 30 mL/min	Consider 40 mg SC every 12 hours OR 0.5 mg/kg SC daily	ABW 25-40 kg: consider 20 mg SC daily (avoid if CrCl < 30 mL/min) OR ABW 41-50 kg: consider 30 mg SC daily (avoid if CrCl < 30 mL/min)
Fondaparinux	2.5 mg SC daily no earlier than 6–8 hours postoperative Avoid in patients weighing	Caution if CrCl 30–49 mL/min Avoid if CrCl < 30 mL/min	Consider 5 mg SC daily	No dose adjustment available
UFH	5000 units SC 2–4 hours prior to surgery, then 5000 units SC every 8 hours through POD 1	Same as standard dose	Consider 7500 units SC every 8 hours postoperative	Weight < 40 kg: 2500 units SC every 8-12 hours
Apixaban	UFH 5000 units SC 30 minutes prior to surgery and every 8 hours through POD 1, then	Avoid if CrCl < 30 mL/min	No dose adjustment available	No dose adjustment available

	apixaban 2.5 mg PO every 12 hours			
Rivaroxaban	LMWH prophylaxis in standard doses for first week then rivaroxaban 10 mg daily for 3 additional weeks	Avoid if CrCl < 30 mL/min	No dose adjustment available	No dose adjustment available
Limited to no data available to support recommendations on dosing for BMI ≥ 40 kg/m^2. Recommended doses are derived from non-oncology populations. Dosing recommendations for patients weighing 25–40 kg are included as guidance and based on expert opinion. Available data suggest administration of standard VTE prophylaxis doses to patients in this weight range results in over-exposure and increased bleeding, but there are very limited data available to inform dose reduction strategies. Obtain LMWH anti-Xa level 3–5 hours after the third dose to assess dosing. Adjustments may be needed to the dose according to anti-Xa levels, with a recommended target of 0.2 to 0.4 IU/mL for peak levels or 0.1 to 0.2 IU/mL for trough levels. Apixaban is absorbed in the stomach, proximal small bowel, and colon. Patients who have had significant resections of these portions of the intestinal tract may be at risk for suboptimal absorption.				

Table 6. VTE Prophylaxis Options for Post-Discharge Prophylaxis for Surgical Oncology Patients (NCCN 2023 Guidelines)

Agent	Standard Dosing	Renal Dose	Other Dose Modifications
Apixaban	2.5 mg PO every 12 hours x 28 days	Avoid if CrCl < 30 mL/min	Avoid if platelet count < 50,000/µL Avoid if weight < 40 kg
Rivaroxaban	10 mg daily for 21 days		Avoid platelet count < 50,000/µL
Dalteparin	5000 units SC daily x 28 days		
Enoxaparin	40 mg SC daily x 28 days		

- Clinical suspicion of superficial vein thrombosis (SVT) - upper extremity SVT (median, basilic, and/or cephalic veins):
    - Use symptomatic treatment and monitor for progression.
    - If progression symptomatically or on imaging, consider prophylactic dose anticoagulation.
    - Consider initial therapeutic dose anticoagulation if the clot is in close proximity to the deep venous system.
- Clinical suspicion of SVT - lower extremity SVT (great and small saphenous veins):
    - Prophylactic dose anticoagulation for at least 6 weeks if:
        - SVT > 5 cm in length
        - SVT extends above knee.
    - Therapeutic dose anticoagulation for at least 3 months if SVT is within 3 cm of the saphenofemoral junction.
    - Consider repeat US in 7–10 days if SVT < 5 cm in length or below knee. If repeat US shows progression, consider anticoagulation.

➔ Prophylactic dose anticoagulation with rivaroxaban 10 mg PO daily and fondaparinux 2.5 mg SC daily have been shown to be effective in some studies that included a limited number of patients with cancer.

➔ If SVT is within 3 cm from the saphenofemoral junction, treat with therapeutic dose anticoagulation.

- Consider longer duration anticoagulation in patients with catheters with poor flow, persistent symptoms, or unresolved thrombus. Consider shorter duration of anticoagulation if clot or symptoms resolve in response to anticoagulation and/or catheter removal.
- Chronic, portal, mesenteric, and/or splenic vein thrombosis: considering TIPS or surgical shunt was added as an option.
    - Consider TIPS as one of the management options for patients with SPVT and portal hypertension.
    - If thrombectomy expertise is not available, consider consultation with a tertiary medical center.
- Enoxaparin 1 mg/kg SC every 12 hours (BMI <40 kg/m2) or 0.8 mg/kg SC every 12 hours (BMI ≥40 kg/m2) (can consider decreasing intensity to 1.5 mg/kg daily after first month)

- There is limited data on long-term use of LMWH in patients with CrCl <30 mL/min.
- Contraindications – DOACs:
    - Pregnancy or breast feeding were added.
    - Active/clinically significant liver disease:
        - Apixaban: Child-Pugh Class B or C or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) > 3x upper limit of normal (ULN); total bilirubin > 2x ULN
        - Rivaroxaban: Child-Pugh class B or C or ALT/AST > 3x ULN
        - Dabigatran: Child-Pugh class C or ALT/AST > 2x ULN or active/acute hepatitis or cirrhosis
        - Edoxaban: Child-Pugh class B or C or AST/ALT > 3x ULN and bilirubin >2x ULN, cirrhosis, or active hepatitis
        - Strong dual inhibitors/inducers of CYP3A4 and P-gp: see prescribing information for rivaroxaban and apixaban.
- DOACs and GI tract surgery considerations:
    - DOACs are absorbed primarily in the stomach and proximal small bowel (with the exception of apixaban, which is also partially absorbed in the colon), so they may not be appropriate for patients who have had significant resections of these portions of the intestinal tract.
    - Due to limited data, consider checking a drug-specific anti-Xa level for Xa-inhibitors or a dabigatran level to ensure adequate absorption.
- Enteral feeding tube administration of DOACs
    - Apixaban: For nasogastric/gastric feeding tube administration, crushed tablets may be suspended in 60 mL of water or D5W followed by immediate delivery. Crushed tablets are stable in water and D5W for up to 4 hours. Bioavailability is reduced if administered distal to the stomach.
    - Rivaroxaban: For nasogastric/gastric feeding tube administration, crushed tablets may be suspended in 50 mL of water and administered within 4 hours of preparation. Follow administration of the 15 mg and 20 mg tablets immediately with enteral feeding (2.5 mg and 10 mg tablets may be administered without regard to food). Avoid administration distal to the stomach, which can result in reduced absorption. A commercially prepared oral suspension formulation with

an accompanying measuring syringe is also available for pediatric patients.

  - Edoxaban: Crushed tablets may be suspended in 2 to 3 ounces of water and immediately administered through a gastric tube.
  - Dabigatran: Should not be administered through an enteral feeding tube.

- Management of anticoagulation for VTE in patients with chemotherapy-induced thrombocytopenia:
  - The patient's risk for recurrent thromboembolism and the patient's risk of bleeding including the anticipated depth and duration of thrombocytopenia should be considered.
  - For patients at high risk of recurrent thromboembolism, management options include:
    - Continuation of therapeutic dose anticoagulation while maintaining platelet count ≥ 50,000/μL with platelet transfusions
    - Placement of a retrievable IVC filter and discontinuation of anticoagulation until platelet recovery.
  - For patients at lower risk for recurrent thromboembolism, management options include:
    - Lower dose anticoagulation (table 7)
    - Removal of central venous catheter in patients with central venous catheter-associated DVT
    - Monitoring of distal DVT with serial US surveillance while patient is off anticoagulation (if clot extends to proximal venous system, then manage as acute high-risk).

Table 7. Enoxaparin Dose Modifications in the Setting of Thrombocytopenia (NCCN 2023 Guidelines)

Platelet Count	Dose Adjustment	Suggested Dose of Enoxaparin	Alternative Once-Daily Dosing Regimen
> 50,000/μL	Full-dose enoxaparin	1 mg/kg twice daily	1.5 mg/kg once daily
25,000-50,000/μL	Half-dose enoxaparin	0.5 mg/kg twice daily	-
< 25,000/μL	Temporarily hold enoxaparin		

- Progression or new thrombosis on therapeutic anticoagulation – alternative coagulant to UFH:
    - Switch to alternative anticoagulant (DOACs [apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B], LMWH, warfarin, fondaparinux)
    - Increase dose of UFH
- LMWH (anti-Xa) levels may be considered in patients with body weight extremes, renal impairment, or for whom adherence is a concern. Obtain LMWH anti-Xa level 3-5 hours after the third dose to assess dosing. Adjustments may be needed to the dose according to anti-Xa levels, with a recommended peak of 0.6-1.0 units/ml (1 mg/kg twice daily dosing) or peak of 1-2 units/mL (1.5 mg/kg once daily dosing).
- Reversal of anticoagulation
    - In the event of life-threatening bleeding or the need for urgent/emergent invasive procedures, anticoagulant effect must be reversed promptly.
    - UFH: Follow aPTT or anti-Xa levels in accordance with institutional SOP closely, was added.
    - In the event of ongoing bleeding and persistent drug levels, consider a second dose of protamine for both UFH and LWMH.
    - DOACs: Drug-specific anti-Xa assays should not be used to assess reversal of direct factor Xa inhibitors after administration of andexanet alfa, as they are not interpretable, was added.
    - Andexanet alfa dosing and administration:

Table 8. Andexanet Alfa Dosing and Administration (NCCN 2023 Guidelines)

Medication	Last Dose	Dosing Strategy Based on Time Since Last Dose	
		Last Dose < 8 Hours Prior or Unknown	**Last Dose ≥ 8 Hours Prior**
Rivaroxaban	≤ 10 mg	Low-dose	Low-dose
	> 10 mg or unknown	High-dose	Low-dose
Apixaban	≤ 5 mg	Low-dose	Low-dose
	> 5 mg or unknown	High-dose	Low-dose
Edoxaban	≤ 30 mg	Low-dose	Low-dose

	> 30 mg	High-dose	Low-dose

Table 9. Andexanet Alfa Low- and High-Dose Strategies and Administration Instructions

Dose	Initial IV Bolus (administered at a rate of 30 mg/min)	IV Infusion
Low-dose	400 mg	480 mg administered over 120 minutes (4 mg/min)
High-dose	800 mg	960 mg administered over 120 minutes (8 mg/min)
All patients should receive an initial IV bolus followed immediately by IV infusion as outlined above. The safety and efficacy of repeat dosing or extension of infusion beyond this time frame have not been evaluated. Note, the IV infusion dosing recommendations above differ from the package insert prescribing information to round doses to the closest available vial size.		

Workup and management for suspected hit: A “low” pre-test probability score combined with a negative antibody test is useful in ruling out a diagnosis of HIT; a positive test increases the suspicion for HIT. In patients without cancer with 4T scores of 1–3, the risk of HIT is small but not zero, but this has not been validated in patients with cancer. Based on clinical judgment, HIT antibody testing and initiation of argatroban/bivalirudin or fondaparinux in place of UFH/LMWH may be warranted in select patients.

1.1.2 National Institute for Health and Care Excellence (NICE) Guideline on Venous Thromboembolic Diseases: Diagnosis, Management and Thrombophilia Testing (2023)

This guideline covers diagnosing and managing venous thromboembolic diseases in adults. It aims to support rapid diagnosis and effective treatment for people who develop deep vein thrombosis (DVT) or pulmonary embolism (PE). It also covers testing for conditions that can make a DVT or PE more likely, such as thrombophilia (a blood clotting disorder) and cancer. The guideline does not cover pregnant women. The guidelines recommend the following[11]:

If DVT is suspected, use the 2-level DVT Wells score (table 10) to estimate the clinical probability of DVT.

Table 10. Two-Level DVT Wells Score (NICE 2023 Guideline)

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2
Clinical probability simplified score	
DVT likely	≥ 2
DVT unlikely	≤ 1

DVT likely (Wells score 2 points or more)

- If a proximal leg vein ultrasound scan result cannot be obtained within 4 hours, offer people with a DVT Wells score of 2 points or more:
    - a D-dimer test, **then**
    - interim therapeutic anticoagulation **and**
    - proximal leg vein ultrasound scan with the result available within 24 hours
- For people with a negative proximal leg vein ultrasound scan and a positive D-dimer test result:
    - stop interim therapeutic anticoagulation, but do not stop:
        - long-term anticoagulation when used for secondary prevention, or
        - short-term anticoagulation when used for primary VTE prevention in people with COVID-19
    - offer a repeat proximal leg vein ultrasound scan 6 to 8 days later and:

        - If the repeat scan result is positive, follow the actions in below sections.
        - If the repeat scan result is negative, follow the actions in below sections.
- For people with a negative proximal leg vein ultrasound scan and a negative D-dimer test result:
    - Stop interim therapeutic anticoagulation, but do not stop:
        - long-term anticoagulation when used for secondary prevention, or
        - short-term anticoagulation when used for primary VTE prevention in people with COVID-19
    - Think about alternative diagnoses.
    - Tell the person that it is not likely they have DVT. Discuss with them the signs and symptoms of DVT and when and where to seek further medical help.

DVT unlikely (Wells score 1 point or less)

- Offer people with an **unlikely** DVT Wells score (1 point or less):
    - A D-dimer test with the result available within 4 hours or
    - If the D-dimer test result cannot be obtained within 4 hours, offer interim therapeutic anticoagulation while awaiting the result.
- If the D-dimer test result is positive, offer:
    - A proximal leg vein ultrasound scan, with the result available within 4 hours if possible, or
    - Interim therapeutic anticoagulation and a proximal leg vein ultrasound scan with the result available within 24 hours.
- If the proximal leg vein ultrasound scan is negative:
    - Stop interim therapeutic anticoagulation, but do not stop:
        - long-term anticoagulation when used for secondary prevention, or
        - short-term anticoagulation when used for primary VTE prevention in people with COVID-19
    - Think about alternative diagnoses.

    - Tell the person that it is not likely they have DVT. Discuss with them the signs and symptoms of DVT and when and where to seek further medical help.
- If possible, choose an interim anticoagulant that can be continued if DVT or PE is confirmed.
- When using interim therapeutic anticoagulation for suspected proximal DVT or PE:
    - Carry out baseline blood tests including full blood count, renal and hepatic function, prothrombin time (PT) and activated partial thromboplastin time (APTT)
    - Do not wait for the results of baseline blood tests before starting anticoagulation treatment.
    - Review, and if necessary, act on the results of baseline blood tests within 24 hours of starting interim therapeutic anticoagulation.
- Offer anticoagulation treatment for at least 3 months to people with confirmed proximal DVT or PE.
- When offering anticoagulation treatment, take into account comorbidities, contraindications and the person's preferences.
- Offer either apixaban or rivaroxaban to people with confirmed proximal DVT or PE. If neither apixaban nor rivaroxaban is suitable offer:
    - LMWH for at least 5 days followed by dabigatran or edoxaban or
    - LMWH concurrently with a vitamin K antagonist (VKA) for at least 5 days, or until the international normalized ratio (INR) is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.
- Do not routinely offer unfractionated heparin (UFH) with a VKA to treat confirmed proximal DVT or PE unless the person has renal impairment or established renal failure or an increased risk of bleeding.
- Consider anticoagulation treatment with regular monitoring of therapeutic levels for people with confirmed proximal DVT or PE who weigh less than 50 kg or more than 120 kg, to ensure effective anticoagulation.

  Note the cautions and requirements for dose adjustment and monitoring in the medicine's summary of product characteristics (SPC) and follow locally agreed protocols or advice from a specialist or multidisciplinary team.
- For people with confirmed PE and hemodynamic instability, offer continuous UFH infusion and consider thrombolytic therapy.

- Offer people with confirmed proximal DVT or PE and renal impairment (estimated creatinine clearance between 15 ml/min and 50 ml/min) one of:
    - Apixaban
    - Rivaroxaban
    - LMWH for at least 5 days followed by:
        - edoxaban or
        - dabigatran if estimated creatinine clearance is 30 ml/min or above.
    - LMWH or UFH, given concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own. Note the cautions and requirements for dose adjustment and monitoring in the medicine's SPC and follow locally agreed protocols or advice from a specialist or multidisciplinary team.
- Offer people with confirmed proximal DVT or PE and established renal failure (estimated creatinine clearance less than 15 ml/min) one of:
    - LMWH
    - UFH
    - LMWH or UFH concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own. Note the cautions and requirements for dose adjustment and monitoring in the medicine's SPC and follow locally agreed protocols or advice from a specialist or multidisciplinary team.
- Offer people with active cancer and confirmed proximal DVT or PE anticoagulation treatment for 3 to 6 months. Review at 3 to 6 months according to clinical need.
- When choosing anticoagulation treatment for people with active cancer and confirmed proximal DVT or PE, take into account the tumor site, interactions with other drugs including those used to treat cancer, and the person's bleeding risk.
- Consider a DOAC for people with active cancer and confirmed proximal DVT or PE.
- If a DOAC is unsuitable consider LMWH alone or LMWH concurrently with a VKA for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.
- Offer people with confirmed proximal DVT or PE and an established diagnosis of triple positive antiphospholipid syndrome LMWH concurrently with a VKA

for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.

- If anticoagulation treatment fails:
    - Check adherence to anticoagulation treatment.
    - Address other sources of hypercoagulability.
    - Increase the dose of anticoagulant or change to an anticoagulant with a different mode of action.
- Assess and discuss the benefits and risks of continuing, stopping or changing the anticoagulant with people who have had anticoagulation treatment for 3 months (3 to 6 months for people with active cancer) after a proximal DVT or PE.
- Consider stopping anticoagulation treatment 3 months (3 to 6 months for people with active cancer) after a provoked DVT or PE if the provoking factor is no longer present and the clinical course has been uncomplicated. If anticoagulation treatment is stopped, give advice about the risk of recurrence, and provide:
    - Written information on symptoms and signs to look out for.
    - Direct contact details of a healthcare professional or team with expertise in thrombosis who can discuss any new symptoms or signs, or other concerns.
    - information about out-of-hours services they can contact when their healthcare team is not available.
- Consider continuing anticoagulation beyond 3 months (6 months for people with active cancer) after an unprovoked DVT or PE. Base the decision on the balance between the person's risk of VTE recurrence and their risk of bleeding. Discuss the risks and benefits of long-term anticoagulation with the person and take their preferences into account.
- Explain to people with unprovoked DVT or PE and a low bleeding risk that the benefits of continuing anticoagulation treatment are likely to outweigh the risks.
- Do not rely solely on predictive risk tools to assess the need for long-term anticoagulation treatment.
- Consider using the HAS-BLED score for major bleeding risk to assess the risk of major bleeding in people having anticoagulation treatment for unprovoked proximal DVT or PE. Discuss stopping anticoagulation if the HAS-BLED score is 4 or more and cannot be modified.

- Take into account the person's preferences and their clinical situation when selecting an anticoagulant for long-term treatment.
- For people who do not have renal impairment, active cancer, established triple positive antiphospholipid syndrome or extreme body weight (less than 50 kg or more than 120 kg):
    - Offer continued treatment with the current anticoagulant if it is well tolerated or
    - If the current treatment is not well tolerated, or the clinical situation or person's preferences have changed, consider switching to apixaban if the current treatment is a direct-acting anticoagulant other than apixaban.
- For people with renal impairment, active cancer, established triple positive antiphospholipid syndrome or extreme body weight (less than 50 kg or more than 120 kg), consider carrying on with the current treatment if it is well tolerated.
- For people who decline continued anticoagulation treatment, consider aspirin 75 mg or 150 mg daily.
- Review general health, risk of VTE recurrence, bleeding risk and treatment preferences at least once a year for people taking long-term anticoagulation treatment or aspirin.
- Be aware that heparins are of animal origin and that apixaban and rivaroxaban contain lactose from cow's milk. For people who have concerns about using animal products because of a religious or ethical belief, or a food intolerance.
- Do not offer an inferior vena caval (IVC) filter to people with proximal DVT or PE unless:
    - It is part of a prospective clinical study or
    - Anticoagulation is contraindicated or a PE has occurred during anticoagulation treatment.
- Consider an IVC filter for people with proximal DVT or PE when anticoagulation treatment is contraindicated. Remove the IVC filter when anticoagulation treatment is no longer contraindicated and has been established.
- Consider an IVC filter for people with proximal DVT or PE who have a PE while taking anticoagulation treatment only after taking the steps outlined in the recommendation on treatment failure.

- Before fitting an IVC filter, ensure that there is a strategy in place for it to be removed at the earliest possible opportunity. Document the strategy and review it if the clinical situation changes.
- For people with unprovoked DVT or PE who are not known to have cancer, review the medical history and baseline blood test results including full blood count, renal and hepatic function, PT and APTT, and offer a physical examination.
- Do not offer further investigations for cancer to people with unprovoked DVT or PE unless they have relevant clinical symptoms or signs.
- Do not offer testing for hereditary thrombophilia to people who are continuing anticoagulation treatment.
- Consider testing for antiphospholipid antibodies in people who have had unprovoked DVT or PE if it is planned to stop anticoagulation treatment but be aware that these tests can be affected by anticoagulants and specialist advice may be needed.
- Consider testing for hereditary thrombophilia in people who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment but be aware that these tests can be affected by anticoagulants and specialist advice may be needed.

1.1.3 CHEST Guideline and Expert Panel Report on Antithrombotic Therapy for VTE Disease – Second Update (2021)

Certainty of evidence was based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach and categorized as high, moderate, low, or very low[12].

Initial management

- In patients with acute isolated distal DVT of the leg who are treated with serial imaging, the guidelines
    (i) Recommend no anticoagulation if the thrombus does not extend (strong recommendation, moderate-certainty evidence),
    (ii) Suggest anticoagulation if the thrombus extends but remains confined to the distal veins (weak recommendation, very low-certainty evidence), and
    (iii) Recommend anticoagulation if the thrombus extends into the proximal veins (strong recommendation, moderate-certainty evidence).

- In patients with subsegmental pulmonary embolism (PE) (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a
    (i) low risk for recurrent VTE, the guidelines suggest clinical surveillance over anticoagulation (weak recommendation, low-certainty evidence) or
    (ii) high risk for recurrent VTE, the guidelines suggest anticoagulation over clinical surveillance (weak recommendation, low-certainty evidence).
- In patients with cerebral vein/venous sinus thrombosis, the guidelines recommend anticoagulation therapy for at least the treatment phase (first 3 months) over no anticoagulant therapy (strong recommendation, low-certainty evidence).
- In patients with acute DVT of the leg the guidelines suggest anticoagulant therapy alone over interventional (thrombolytic, mechanical, or pharmacomechanical) therapy (weak recommendation, moderate-certainty evidence).
- In patients with acute DVT of the leg, the guidelines recommend against the use of an inferior vena cava (IVC) filter in addition to anticoagulants (strong recommendation, moderate-certainty evidence).
- In patients with acute proximal DVT of the leg and a contraindication to anticoagulation, the guidelines recommend the use of an IVC filter (strong recommendation, moderate-certainty evidence).
- In patients with VTE (DVT of the leg or PE) the guidelines recommend apixaban, dabigatran, edoxaban, or rivaroxaban over VKA as treatment-phase (first 3 months) anticoagulant therapy (strong recommendation, moderate-certainty evidence).
- In patients with acute VTE in the setting of cancer (cancer-associated thrombosis) the guidelines recommend an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and treatment phases of therapy (strong recommendation, moderate-certainty evidence).
- In patients with confirmed antiphospholipid syndrome being treated with anticoagulant therapy, the guidelines suggest adjusted-dose VKA (target international normalized ratio [INR] 2.5) over DOAC therapy during the treatment phase (weak recommendation, low-certainty evidence).
- In patients with superficial venous thrombosis (SVT) of the lower limb at increased risk of clot progression to DVT or PE, the guidelines suggest the use of anticoagulation for 45 days over no anticoagulation (weak recommendation, moderate certainty evidence).

- In patients with SVT who are treated with anticoagulation, the guidelines suggest fondaparinux 2.5 mg daily over other anticoagulant treatment regimens such as (prophylactic- or therapeutic-dose) LMWH (weak recommendation, low-certainty evidence).
- In patients with SVT who refuse or are unable to use parenteral anticoagulation, the guidelines suggest rivaroxaban 10 mg daily as a reasonable alternative for fondaparinux 2.5 mg daily (weak recommendation, low-certainty evidence).

Duration of treatment phase of anticoagulation

- In patients with acute VTE who do not have a contraindication, the guidelines recommend a 3-month treatment phase of anticoagulation (strong recommendation, moderate-certainty evidence).

Extended-phase therapy

- In patients with VTE diagnosed in the setting of a major transient risk factor, the guidelines recommend against offering extended-phase anticoagulation (strong recommendation, moderate-certainty evidence).
- In patients with VTE diagnosed in the setting of a minor transient risk factor, the guidelines suggest against offering extended-phase anticoagulation (weak recommendation, moderate-certainty evidence).
- In patients with VTE diagnosed in the absence of transient provocation (unprovoked VTE or provoked by persistent risk factor), the guidelines recommend offering extended-phase anticoagulation with a DOAC (strong recommendation, moderate-certainty evidence).
- In patients with VTE diagnosed in the absence of transient risk factor (unprovoked VTE or provoked by a persistent risk factor) who cannot receive a DOAC, the guidelines suggest offering extended-phase anticoagulation with a VKA (weak recommendation, moderate certainty evidence).
- In patients offered extended-phase anticoagulation, the guidelines suggest the use of reduced-dose apixaban or rivaroxaban over full-dose apixaban or rivaroxaban (weak recommendation, very low certainty evidence).
- In patients offered extended-phase anticoagulation, the guidelines recommend reduced-dose DOAC over aspirin or no therapy (strong recommendation, low-certainty evidence) and suggest rivaroxaban over aspirin (weak recommendation, moderate-certainty evidence).
- In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, the

guidelines suggest aspirin over no aspirin to prevent recurrent VTE (weak recommendation, low-certainty evidence).

Complications of VTE

- In patients with acute DVT of the leg, the guidelines suggest against using compression stockings routinely to prevent PTS (weak recommendation, low-certainty evidence).

1.1.4 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) Guidelines for the Management of Valvular Heart Disease (2021)

The guidelines published the below recommendations which are graded as outlined below[20]:

Table 11. Classes of Recommendations (ESC/EACTS 2021 Guidelines)

	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 12. Levels of Evidence (ESC/EACTS 2021 Guidelines)

Level	Definition
A	Data derived from multiple randomized clinical trials or meta-analyses.
B	Data derived from a single randomized clinical trial or large non-randomized studies.

C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

New and revised recommendations related to pharmacotherapy are summarized below:

- Management of atrial fibrillation in patients with native VHD: For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs in patients with aortic stenosis, aortic and mitral regurgitation (Class I)
- Recommendations for prosthetic valve selection:
    - A bioprosthesis may be considered in patients already on long-term NOACs due to the high risk for thromboembolism. (Class: IIb)
    - A bioprosthesis is recommended when good-quality anticoagulation is unlikely (adherence problems, not readily available), contraindicated because of high bleeding risk (previous major bleed, comorbidities, unwillingness, adherence problems, lifestyle, occupation) and in those patients whose life expectancy is lower than the presumed durability of the bioprosthesis.
- Management of antithrombotic therapy in the perioperative period:
    - Bridging of OAC, when interruption is needed, is recommended in patients with any of the following indication (Class I):
        - Mechanical prosthetic heart valve.
        - AF with significant mitral stenosis.
        - AF with a CHA2DS2-VASc score >_3 for women or 2 for men.
        - Acute thrombotic event within the previous 4 weeks.
        - High acute thromboembolic risk.
    - It is recommended that VKAs are timely discontinued prior to elective surgery to aim for an INR <1.5. (Class: I)
    - In patients undergoing surgery, it is recommended that aspirin therapy, if indicated, is maintained during the periprocedural period. (Class: I)
    - In patients who have undergone valve surgery with an indication for postoperative therapeutic bridging, it is recommended to start either UFH or LMWH 12-24 hours after surgery. (Class: I)
    - In patients with MHVs, it is recommended to (re)- initiate VKAs on the first postoperative day. (Class: I)

- In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery, in the absence of an indication for OAC, it is recommended to resume the P2Y12 inhibitor postoperatively, as soon as there is no concern over bleeding. (Class: I)
- In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery, in the absence of an indication for OAC, bridging P2Y12 inhibitors with glycoprotein IIb/IIIa inhibitors or cangrelor may be considered. (Class: IIb)

- Patients with an indication to concomitant antiplatelet therapy:
  - After uncomplicated PCI or ACS in patients requiring long -term OAC, early cessation (≤1 week) of aspirin and continuation of dual therapy with OAC and a P2Y12 inhibitor (preferably clopidogrel) for up to 6 months (or up to 12 months in ACS) is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used. (Class: I)
  - Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months. (Class: I)
  - In patients treated with a VKA (e.g. MHVs), clopidogrel alone should be considered in selected patients (e.g. HAS-BLED >_3 or ARC-HBR met and low risk of stent thrombosis) for up to 12 months. (Class: IIa)
  - In patients requiring aspirin and/or clopidogrel in addition to VKA, the dose intensity of VKA should be considered and carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65-70%. (Class: IIa)
  - After uncomplicated PCI or ACS in patients requiring both OAC and antiplatelet therapy, triple therapy with aspirin, clopidogrel and OAC for longer than 1 week should be considered when the risk of stent thrombosis outweighs the risk of bleeding, with a total duration (≤1 month) decided according to assessment of these risks and clearly specified at hospital discharge. (Class: IIa)
- Surgical valve replacement
  - NOACs should be considered over VKA after 3 months following surgical implantation of a BHV, in patients with AF. (Class: IIa)
  - In patients with no baseline indications for OAC, low-dose aspirin (75-100 mg/day) or OAC using a VKA should be considered for the first 3 months after surgical implantation of an aortic BHV. (Class: IIa)

    - NOACs may be considered over VKA within 3 months following surgical implantation of a BHV in mitral position in patients with AF. (Class: IIb)
- Transcatheter Aortic Valve Implantation (TAVI)
    - OAC is recommended lifelong for TAVI patients who have other indications for OAC. (Class: I)
    - Revised single anti-platelet therapy (SAPT) may be considered after TAVI in the case of high bleeding risk. (Class: IIb)
    - Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC. (Class: I)
    - Routine use of OAC is not recommended after TAVI in patients with no baseline indication for OAC. (Class: III)
- Bioprosthetic thrombosis: Anticoagulation should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients, at least until resolution. (Class: IIa)

1.1.5 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Management of Patients with Valvular Heart Disease (2020)

The focus of this guideline is the diagnosis and management of adult patients with valvular heart disease (VHD). For the purpose of this report, only recommendations focusing on the use of prophylactic antithrombotic therapy have been included. The guidelines recommend the following[13]:

- Recommendations for anticoagulation for atrial fibrillation (AF) in patients with VHD:
    - For patients with AF and native valve heart disease (except rheumatic mitral stenosis [MS]) or who received a bioprosthetic valve >3 months ago, a non–vitamin K oral anticoagulant (NOAC) is an effective alternative to VKA anticoagulation and should be administered on the basis of the patient's CHA2DS2-VASc score (COR: 1, LOE: A).
    - For patients with AF and rheumatic MS, long-term VKA oral anticoagulation is recommended (COR: 1, LOE: C-EO).
    - For patients with new-onset AF ≤3 months after surgical or transcatheter bioprosthetic valve replacement, anticoagulation with a VKA is reasonable (COR: 2a, LOE: B-NR)
    - In patients with mechanical heart valves with or without AF who require long-term anticoagulation with VKA to prevent valve thrombosis, NOACs are not recommended (COR: 3 Harm, LOE: B-R).

- Recommendations for choice of mechanical versus bioprosthetic aortic valve replacement (AVR):
    - For patients of any age requiring AVR for whom VKA anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired, a bioprosthetic AVR is recommended (Class: 1, LOE: C-EO).
    - For patients < 50 years of age who do not have a contraindication to anticoagulation and require AVR, it is reasonable to choose a mechanical aortic prosthesis over a bioprosthetic valve (Class: 2a, LOE: B-R).
    - For patients 50 to 65 years of age who require AVR and who do not have a contraindication to anticoagulation, it is reasonable to individualize the choice of either a mechanical or bioprosthetic AVR with consideration of individual patient factors and after informed shared decision-making (Class: 2a, LOE: B-NR).
- Recommendations for medical therapy in patients with rheumatic MS:
    - In patients with rheumatic MS and 1) AF, 2) a prior embolic event, or 3) an LA thrombus, anticoagulation with a VKA is indicated (Class: 1, LOE: C-LD)
- Recommendations for diagnosis and follow-up of prosthetic valves:
    - For patients of any age requiring valve replacement for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired, a bioprosthetic valve is recommended (Class: 1, LOE: C-EO)
    - For patients < 50 years of age who do not have a contraindication to anticoagulation and require AVR, it is reasonable to choose a mechanical aortic prosthesis over a bioprosthetic valve (Class 2a, LOE: B-NR).
    - For patients 50 to 65 years of age who require AVR and who do not have a contraindication to anticoagulation, it is reasonable to individualize the choice of either a mechanical or bioprosthetic AVR, with consideration of individual patient factors and after informed shared decision-making (Class 2a, LOE: B-NR)
    - For patients < 65 years of age who have an indication for mitral valve replacement, do not have a contraindication to anticoagulation, and are unable to undergo mitral valve repair, it is reasonable to choose a mechanical mitral prosthesis over a bioprosthetic valve (Class 2a, LOE: B-NR)

- Recommendations for antithrombotic therapy for prosthetic valves:
    - In patients with a mechanical prosthetic valve, anticoagulation with a VKA is recommended (Class: 1, LOE: A)
    - For patients with a mechanical bileaflet or current-generation single-tilting disk AVR and no risk factors for thromboembolism, anticoagulation with a VKA to achieve an INR of 2.5 is recommended (Class 1, LOE: B-NR)
    - For patients with a mechanical AVR and additional risk factors for thromboembolism (e.g., AF, previous thromboembolism, LV dysfunction, hypercoagulable state) or an older-generation prosthesis (e.g., ball-in-cage), anticoagulation with a VKA is indicated to achieve an INR of 3.0. (Class 1, LOE: B-NR)
    - For patients with a mechanical mitral valve replacement, anticoagulation with a VKA is indicated to achieve an INR of 3.0 (Class 1, LOE B-NR)
    - For patients with a bioprosthetic TAVI, aspirin 75 to 100 mg daily is reasonable in the absence of other indications for oral anticoagulants (Class 2a, LOE B-R)
    - For all patients with a bioprosthetic surgical aortic valve replacement (SAVR) or mitral valve replacement, aspirin 75 to 100 mg daily is reasonable in the absence of other indications for oral anticoagulants (Class 2a, LOE B-NR)
    - For patients with a bioprosthetic SAVR or mitral valve replacement who are at low risk of bleeding, anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and for as long as 6 months after surgical replacement (Class 2a, LOE B-NR)
    - For patients with a mechanical SAVR or mitral valve replacement who are managed with a VKA and have an indication for antiplatelet therapy, addition of aspirin 75 to 100 mg daily may be considered when the risk of bleeding is low (Class 2B, LOE B-R)
    - For patients with a mechanical On-X AVR and no thromboembolic risk factors, use of a VKA targeted to a lower INR (1.5–2.0) may be reasonable starting ≥ 3 months after surgery, with continuation of aspirin 75 to 100 mg daily. (Class: 2b, LOE: B-R)
    - For patients with a bioprosthetic TAVI who are at low risk of bleeding, dual antiplatelet therapy with aspirin 75 to 100 mg and clopidogrel 75 mg may be reasonable for 3 to 6 months after valve implantation (Class: 2b, LOE: B-NR)

- For patients with a bioprosthetic TAVI who are at low risk of bleeding, anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after valve implantation (Class: 2b, LOE: B-NR)
- For patients with bioprosthetic TAVI, treatment with low-dose rivaroxaban (10 mg daily) plus aspirin (75–100 mg) is contraindicated in the absence of other indications for oral anticoagulants (Class: 3 Harm, LOE: B-R)
- For patients with a mechanical valve prosthesis, anticoagulation with the direct thrombin inhibitor, dabigatran, is contraindicated (Class: 3 Harm, LOE: B-R)
- For patients with a mechanical valve prosthesis, the use of anti-Xa direct oral anticoagulants has not been assessed and is not recommended. (Class: 3 Harm, LOE: C-EO)

- Recommendations for bridging therapy during interruption of oral anticoagulation in patients with prosthetic heart valves:
  - For patients with mechanical heart valves who are undergoing minor procedures (e.g., dental extractions or cataract removal) where bleeding is easily controlled, continuation of VKA anticoagulation with a therapeutic INR is recommended (Class 1, LOE: C-EO)
  - For patients with a bileaflet mechanical AVR and no other risk factors for thromboembolism who are undergoing invasive procedures, temporary interruption of VKA anticoagulation, without bridging agents while the INR is subtherapeutic, is recommended (Class: 1, LOE: C-LD)
  - For patients with a mechanical valve prosthesis receiving VKA therapy who require immediate/emergency noncardiac surgery or an invasive procedure, administration of 4-factor prothrombin complex concentrate (or its activated form) is reasonable. (Class: 2a, LOE: C-LD)
  - For patients with bioprosthetic heart valves or annuloplasty rings who are receiving anticoagulation for AF, it is reasonable to consider the need for bridging anticoagulant therapy around the time of invasive procedures on the basis of the CHA2DS2-VASc score weighed against the risk of bleeding. (Class: 2a, LOE: C-LD)
  - For patients who are undergoing invasive procedures and have 1) a mechanical AVR and any thromboembolic risk factor, 2) an older-generation mechanical AVR, or 3) a mechanical mitral valve replacement, bridging anticoagulation therapy during the preoperative time interval when the INR is subtherapeutic is reasonable on an

individualized basis, with the risks of bleeding weighed against the benefits of thromboembolism prevention. (Class: 2a, LOE: C-LD)

- Recommendations for management of excessive anticoagulation and serious bleeding in patients with prosthetic valves:
    - For patients with mechanical valves and uncontrollable bleeding who require immediate reversal of anticoagulation, administration of 4-factor prothrombin complex (or its activated form) is reasonable (class: 2a, LOE: C-LD)
    - For patients with mechanical valves and uncontrollable bleeding who have received 4-factor prothrombin concentrate complex, adjunctive use of intravenous vitamin K is reasonable if resumption of VKA therapy is not anticipated for 7 days. (Class: 2a, LOE: C-LD)
    - For patients with bioprosthetic valves or annuloplasty rings who are receiving a direct oral anticoagulant and who require immediate reversal of anticoagulation because of uncontrollable bleeding, treatment with idarucizumab (for dabigatran) or andexanet alfa (for anti-Xa agents) is reasonable. (Class: 2a, LOE: B-NR)
    - For patients with a mechanical prosthetic valve and supratherapeutic INR (>5.0) who are not actively bleeding, the benefit of individualized treatment with oral vitamin K, in addition to temporary withdrawal of the VKA, is uncertain (Class: 2b, C-LD)
- Recommendations for management of thromboembolic events with prosthetic valves:
    - In patients with a mechanical AVR who experience a stroke or systemic embolic event while in therapeutic range on VKA anticoagulation, it is reasonable to increase the INR goal from 2.5 (range, 2.0–3.0) to 3.0 (range, 2.5–3.5) or to add daily low-dose aspirin (75– 100 mg), with assessment of bleeding risk. (Class: 2a, LOE: C-EO)
    - In patients with a mechanical mitral valve replacement who experience a stroke or systemic embolic event while in therapeutic range on VKA anticoagulation, it is reasonable to increase the INR goal from 3.0 (range, 2.5–3.5) to 4.0 (range, 3.5–4.0) or to add daily low-dose aspirin (75–100 mg), with assessment of bleeding risk (Class: 2a, LOE: C-EO)
    - In patients with a bioprosthetic surgical or transcatheter aortic valve or bioprosthetic mitral valve who experience a stroke or systemic embolic event while on antiplatelet therapy, VKA anticoagulation, instead of antiplatelet therapy may be considered after assessment of bleeding risk (Class: 2b, LOE: C-EO)

- Recommendation for intervention for mechanical prosthetic valve thrombosis:
    - For patients with a thrombosed left-sided mechanical prosthetic heart valve who present with symptoms of valve obstruction, urgent initial treatment with either slow-infusion, low dose fibrinolytic therapy or emergency surgery is recommended (Class: 1, LOE: B-NR)
- In patients with suspected or confirmed bioprosthetic valve thrombosis who are hemodynamically stable and have no contraindications to anticoagulation, initial treatment with a VKA is reasonable (Class: 2a, LOE: B-NR)
- In patients with IE and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to temporarily discontinue anticoagulation. (Class: 2a, LOE: B-NR)
- In patients receiving VKA anticoagulation at the time of IE diagnosis, temporary discontinuation of VKA anticoagulation may be considered (Class: 2b, LOE: B-NR)
- Women with mechanical heart valves considering pregnancy should be counselled that pregnancy is high risk and that there is no anticoagulation strategy that is consistently safe for the mother and baby (Class: 1, LOE: B-NR)
- Recommendations for anticoagulation for pregnant women with mechanical prosthetic heart valves:
    - Pregnant women with mechanical prostheses should receive therapeutic anticoagulation with frequent monitoring during pregnancy (Class:1, LOE: B-NR)
    - Women with mechanical heart valves who cannot maintain therapeutic anticoagulation with frequent monitoring should be counseled against pregnancy (Class: 1, LOE: B-NR)
    - Women with mechanical heart valves and their providers should use shared decision making to choose an anticoagulation strategy for pregnancy. Women should be informed that VKA during pregnancy is associated with the lowest likelihood of maternal complications but the highest likelihood of miscarriage, fetal death, and congenital abnormalities, particularly if taken during the first trimester and if the warfarin dose exceeds 5 mg/d (Class: 1, LOE: B-NR)
    - Pregnant women with mechanical valve prostheses who are on warfarin should switch to twice-daily LMWH (with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL at 4 to 6 hours after dose) or intravenous UFH

(with an activated partial thromboplastin time [aPTT] 2 times control) at least 1 week before planned delivery (Class: 1, LOE: C-LD)

- Pregnant women with mechanical valve prostheses who are on LMWH should switch to UFH (with an aPTT 2 times control) at least 36 hours before planned delivery 1 C-LD Pregnant women with valve prostheses should stop UFH at least 6 hours before planned vaginal delivery (Class: 1, LOE: C-LD)
- If labor begins or urgent delivery is required in a woman therapeutically anticoagulated with a VKA, cesarean section should be performed after reversal of anticoagulation (Class:1, LOE: C-LD)
- For pregnant women with mechanical prostheses who require a dose of warfarin ≤5 mg/d to maintain a therapeutic INR, continuation of warfarin for all 3 trimesters is reasonable after full discussion with the patient about risks and benefits. (Class: 2a, LOE: B-NR)
- For pregnant women with mechanical prostheses who require >5 mg/d of warfarin to achieve a therapeutic INR, dose-adjusted LMWH (with a target anti-Xa level of 0.8 to 1.2 U/mL at 4 to 6 hours after dose) at least 2 times per day during the first trimester, followed by warfarin during the second and third trimesters, is reasonable (Class: 2a, B-NR)
- For pregnant women with mechanical prostheses who require a dose of warfarin >5 mg/d to achieve a therapeutic INR, and for whom dose-adjusted LMWH is unavailable, dose-adjusted continuous intravenous UFH during the first trimester (with aPTT 2 times control), followed by warfarin for the second and third trimesters, is reasonable (Class: 2a, LOE: B-NR)
- For hemodynamically stable pregnant women with obstructive left-sided mechanical valve thrombosis, it is reasonable to manage with slow-infusion, low-dose fibrinolytic therapy (Class: 2a, LOE: B-NR)
- For pregnant women with mechanical prostheses who require a warfarin dose >5 mg/d to achieve a therapeutic INR, dose adjusted LMWH (with a target anti-Xa level of 0.8 to 1.2 U/mL at 4 to 6 hours after dose) at least 2 times per day for all 3 trimesters may be considered. (Class: 2b, LOE: B-NR)
- For pregnant women with mechanical prostheses who require a dose of warfarin ≤5 mg/d to maintain a therapeutic INR, dose-adjusted LMWH at least 2 times per day during the first trimester, followed by warfarin for the second and third trimesters, may be considered. (Class: 2b, LOE: B-NR)

- For pregnant women with mechanical prostheses, aspirin 75 to 100 mg daily may be considered, in addition to anticoagulation, if needed for other indications (Class: 2b, LOE: B-NR)
- For pregnant women with mechanical prostheses, LMWH should not be administered unless anti-Xa levels are monitored 4 to 6 hours after administration and dose is adjusted according to levels. (Class 3: Harm, LOE: B-NR)
- For patients with mechanical valve prostheses, anticoagulation with the direct thrombin inhibitor, dabigatran, should not be administered (Class 3: Harm, LOE: B-R)
- The use of anti-Xa direct oral anticoagulants with mechanical heart valves in pregnancy has not been assessed and is not recommended (Class 3: Harm, LOE: C-EO)

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI report on Venous Thromboembolism, along with their recommendations.

Table 13. List of Additional Guidelines

Additional Guidelines	
Saudi Critical Care Society Clinical Practice Guidelines on the Prevention of Venous Thromboembolism in Adults with Trauma (**2023**)	
American Society of Hematology (ASH)	Guidelines for Management of Venous Thromboembolism: Thrombophilia Testing (**2023**)
	Guidelines for Management of Venous Thromboembolism: Treatment of Deep Vein Thrombosis and Pulmonary Embolism (**2020**)
	Living Guidelines on the Use of Anticoagulation for Thromboprophylaxis in Patients with COVID-19: Update on Post Discharge Thromboprophylaxis (**2021**)
	Living Guidelines on the Use of Anticoagulation for Thromboprophylaxis for Patients with COVID-19: Update on the Use of Anticoagulation in Critically Ill Patients (**2022**)
	Living Guidelines on the Use of Anticoagulation for Thromboprophylaxis in Patients with COVID-19: Update on the Use of Intermediate-Intensity Anticoagulation in Critically Ill Patients (**2021**)

	Living Guidelines on the Use of Anticoagulation for Thromboprophylaxis in Patients with COVID-19: Update on the Use of Therapeutic-Intensity Anticoagulation in Acutely Ill Patients (**2022**)
National Institute for Health and Care Excellence (NICE) Guideline on Venous Thromboembolism in Adults (**2021**)	
Saudi Consensus for the Management of Cancer-Associated Thromboembolism: A Modified Delphi-Based Study (**2023**)	
American Society of Clinical Oncology (ASCO) Guideline Update on Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer (**2023**)	
American Society of Hematology (ASH) Guidelines for Management of Venous Thromboembolism: Prevention and Treatment in Patients with Cancer (**2021**)	
International Society for Thrombosis and Hemostasis (ISTH) Guidance of the Use of Direct Oral Anticoagulants for Primary Thromboprophylaxis in Ambulatory Cancer Patients (**2019**)	
European Society for Medical Oncology (ESMO) Clinical Practice Guideline on Venous Thromboembolism in Cancer Patients (**2022**)	
European Society for the Study of the Liver (EASL) Clinical Practice Guidelines on Prevention and Management of Bleeding and Thrombosis in Patients with Cirrhosis (**2021**)	
American College of Cardiology (ACC) Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients with Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or with Atherosclerotic Cardiovascular Disease (**2020**)	

1.2.1 Saudi Critical Care Society Clinical Practice Guidelines on the Prevention of Venous Thromboembolism in Adults with Trauma (2023)

The Saudi Critical Care Society (SCCS) sponsored guidelines development and included 22 multidisciplinary panel members who completed conflict-of-interest forms. The panel developed and answered structured guidelines questions. For each question, the literature was searched for relevant studies. To summarize treatment effects, meta-analyses were conducted or updated. The quality of evidence was assessed using the Grading Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the quality of evidence and summarize confidence in the estimate of the effect to support a recommendation. The quality of evidence was rated as high, moderate, low, or very low. The guidelines were reviewed for evidence-based integrity and endorsed by the Scandinavian Society

of Anesthesiology and Intensive Care Medicine. The main recommendations are summarized below[14]:

- In adults with blunt solid organ injuries to liver, spleen, or kidney who are managed nonoperatively and are at low risk of bleeding, the guidelines suggest starting pharmacologic VTE prophylaxis early (i.e., within 24–48 h) over delayed initiation of pharmacologic VTE prophylaxis (> 48 h) (Weak, very low)

  Clinicians should assess the risk of bleeding. This recommendation is inapplicable to patients at high risk of major bleeding (e.g., high grade solid organ injuries and large hemoperitoneum) and those with hemodynamic instability.

- In adults with isolated blunt TBI with a low risk of bleeding progression who had stable repeated brain imaging showing no bleeding progression and stable neurologic examination, the guidelines suggest early pharmacologic VTE prophylaxis (within 24–72 h post-injury) over delayed pharmacologic VTE prophylaxis (> 72 h) (Weak, very low)

  This recommendation is inapplicable to patients with high risk of ICH spontaneous progression demonstrated at baseline or repeated brain imaging or patients with worsening of neurologic examination findings that necessitate upgrading care or emergent neurosurgical intervention.

- In adults with isolated blunt TBI at a high risk of bleeding progression, the guidelines suggest starting early pharmacologic VTE prophylaxis 72 h post-injury with stable brain imaging that shows no bleeding progression and stable neurologic examination over delayed pharmacologic VTE prophylaxis (> 72 h). The decision is usually made in conjunction with multidisciplinary teams' evaluation (Weak, very low)

  Early pharmacologic VTE prophylaxis should be held until follow-up brain imaging (e.g., brain CT) demonstrates no bleeding progression. If progression is demonstrated, mechanical VTE prophylaxis (if no contradictions) should be continued and prophylactic IVCF and/or US screening to be considered.

  This recommendation is inapplicable for patients with known coagulopathy (INR > 1.5, a partial thromboplastin time > 40 s, a platelet counts of < 100×10^9/l)

- There is insufficient evidence to issue a recommendation on the use of early pharmacologic VTE prophylaxis in adults with isolated blunt TBI requiring neurosurgical intervention (including craniectomy, craniotomy, EVD, or ICP monitoring) (No recommendation)

It is agreed that best practice includes withholding early pharmacologic VTE prophylaxis until follow-up brain imaging (e.g., brain CT) demonstrates no bleeding progression.

If progression is demonstrated, we agree that best practice includes continuation of mechanical VTE prophylaxis (if no contradictions) and prophylactic IVCF and/or US screening to be considered (Best Practice Statement)

It is also agreed that best practice includes evaluation of timely initiation of pharmacologic VTE prophylaxis by multidisciplinary teams (trauma, neuro/neurosurgical, critical care, and clinical pharmacist) (Best Practice Statement)

- In adults with isolated spine trauma or fracture and/or SCI who are at low risk of bleeding and are managed non-operatively, the guidelines suggest initiating pharmacologic VTE prophylaxis within 24–48 h post-injury over delayed pharmacologic VTE prophylaxis (> 48 h) (Weak, very low)

  The presence of neurological deficit and presence/or expansion of intraspinal hematoma or epidural hematoma demonstrated on radiologic spine images (CT and/or MRI) should prompt discussion among multidisciplinary teams prior to initiating pharmacologic VTE prophylaxis.

  Mechanical VTE prophylaxis (if no contradictions) should be initiated for all SCI patients. If initiation of pharmacologic VTE prophylaxis is anticipated to be delayed or interrupted, US screening and/or prophylactic IVCF may be considered.

- In adults with isolated spine trauma or fracture and/or SCI and managed operatively, we suggest initiating early pharmacologic VTE prophylaxis within 48 h post-spinal fixation over delayed pharmacologic VTE prophylaxis (> 48 h) (Weak, very low)

  The presence of neurological deficit and presence/or expansion of intraspinal hematoma or epidural hematoma demonstrated on radiologic spine images (CT and/or MRI) should prompt discussion among multidisciplinary teams prior to initiating pharmacologic VTE prophylaxis.

  Mechanical VTE prophylaxis (if no contradictions) should be initiated for all SCI patients. If initiation of pharmacologic VTE prophylaxis is anticipated to be delayed or interrupted, US screening and/or prophylactic IVCF may be considered.

- In adults with trauma who receive pharmacologic VTE prophylaxis, we suggest using LMWH (e.g., enoxaparin, dalteparin) over UFH (Weak, low) UFH

is preferred in patients with end-stage renal disease and in those with low creatinine clearance (< 30 ml/min)

- In adults with trauma and low risk of bleeding who are prescribed LMWH (enoxaparin) for VTE prophylaxis, we suggest using either intermediate–high dose LMWH or conventional dosing LMWH (Weak, very low)

  Most common regimen used was enoxaparin 40 mg subcutaneous every 12 h

  This recommendation is inapplicable to those at a high risk for bleeding (patients older than 65 year, < 50 kg, have low creatinine clearance, and TBI or SCI patients who are high risk for bleeding).

- In adults with trauma who are not candidates for pharmacologic VTE prophylaxis, we recommend using mechanical VTE prophylaxis with IPC over no mechanical VTE prophylaxis when not contraindicated by lower extremity injury (Strong, very low)
- In adults with trauma taking pharmacologic VTE prophylaxis, we suggest either using adjunct mechanical VTE prophylaxis or pharmacologic VTE prophylaxis alone (Weak, very low)
- In adults with trauma who are at an elevated risk of VTE and are not candidates for pharmacologic VTE prophylaxis, we suggest routine bilateral lower extremity US to screen for asymptomatic DVT over no routine screening (Weak, very low)

  This recommendation is inapplicable to trauma patients who are ambulating, those at low VTE risk, and patients with signs or symptoms of DVT in whom diagnostic imaging is indicated.

- In adults with trauma who are not candidates for pharmacologic VTE prophylaxis, we suggest against the routine placement of prophylactic IVCFs (Weak, very low)
- Clinicians may consider using temporary retrievable IVCF in patients who are expected to be off pharmacologic VTE prophylaxis for > 7 days (e.g., severely injured patients with an ongoing bleeding risk).

1.2.2 American Society of Hematology (ASH)

The American Society of Hematology (ASH) published an array of clinical practice guidelines on venous thromboembolism. These include guidelines on anticoagulation therapy, prevention in hospitalized surgical patients, prophylaxis for medical patients, thrombophilia, use of anticoagulation in COVID-19 patients… Some of these guidelines have been discussed in the previous CHI report, while the remaining ones, including updated versions published since, are included in the

section below. The guidelines on the prevention and treatment of VTE in patients with cancer is detailed in section 1.2.6.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess evidence and make recommendations in this guideline.

The strength of a recommendation is expressed as strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests…") and has the following interpretation:

Table 14. Interpretation of Strong and Conditional Recommendations (ASH Guidelines)

Interpretation of Strong Recommendations	
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.
For clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
For policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
For researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.
Interpretation of Conditional Recommendations	
For patients	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
For clinicians	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.

For policy makers	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
For researchers	This recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps

1.2.2.1 Guidelines for Management of Venous Thromboembolism: Thrombophilia Testing (2023)

Hereditary and acquired thrombophilia are risk factors for VTE. Whether testing helps guide management decisions is controversial.

The guidelines recommend the following[21]:

- Recommendation 1: In patients with unprovoked VTE who have completed primary short-term treatment, the ASH guideline panel suggests not to perform thrombophilia testing to guide the duration of anticoagulant treatment (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯).

  Remarks:

  - In the Treatment of VTE ASH guideline indefinite antithrombotic therapy is suggested in most patients with unprovoked VTE (recommendation 19).
  - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment.
  - This recommendation refers to testing for hereditary and acquired types of thrombophilia.

- Recommendation 2: In patients with VTE provoked by surgery who have completed primary short-term treatment, the ASH guideline panel suggests not to perform thrombophilia testing to determine the duration of anticoagulant treatment (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯).

Remarks:

- According to the Treatment of VTE ASH guideline most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment.
- A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment after completion of primary short-term treatment.
- This recommendation refers to testing for hereditary and acquired types of thrombophilia.

- Recommendation 3: In patients with VTE provoked by a non-surgical major transient risk factor who have completed primary short-term treatment, the ASH guideline panel suggests testing for thrombophilia to guide anticoagulant treatment duration. The panel suggests indefinite anticoagulant treatment in patients with thrombophilia and stopping anticoagulant treatment in patients without thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⊕◯◯◯).

  Remarks:

  - According to the Treatment of VTE ASH guideline most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment.
  - Non-surgical major transient risk factors: e.g. confinement to bed in hospital for at least 3 days with an acute illness (“bathroom privileges only”), or a combination of minor transient risk factors such as admission to hospital for less than 3 days with an acute illness, confinement to bed out of hospital for at least 3 days with an acute illness, or leg injury associated with decreased mobility for at least 3 days.
  - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment.
  - This recommendation refers to testing for hereditary and acquired types of thrombophilia.

- Recommendation 4: In women with VTE provoked by pregnancy or postpartum who have completed primary treatment, the ASH guideline panel suggests thrombophilia testing to guide anticoagulant treatment duration.

The panel suggests indefinite anticoagulant treatment in women with thrombophilia and stopping anticoagulant treatment in women without thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯).

Remarks:

- According to the Treatment of VTE ASH guideline most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment.
- A strategy with testing for thrombophilia would mean that women with thrombophilia would receive indefinite anticoagulant treatment, and women without thrombophilia would stop anticoagulant treatment.
- This recommendation refers to testing for hereditary and acquired types of thrombophilia.

- Recommendation 5: In women with VTE associated with combined oral contraceptives who have completed primary short-term treatment, the ASH guideline panel suggests testing for thrombophilia to guide anticoagulant treatment duration. The panel suggests indefinite anticoagulant treatment in women with thrombophilia and stopping anticoagulant treatment in women without thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯).

  Remarks:

  - According to the Treatment of VTE ASH guideline most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment.
  - A strategy with testing for thrombophilia would mean that women with thrombophilia would receive indefinite anticoagulant treatment, and women without thrombophilia would stop anticoagulant treatment.
  - This recommendation refers to testing for hereditary and acquired types of thrombophilia.

- Recommendation 6: In patients with an unspecified type of VTE who have completed primary short-term treatment, the ASH guideline panel suggests not to perform thrombophilia testing to guide anticoagulant treatment duration (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯).

Remarks:

- Whenever anticoagulant treatment decisions are being made without taking into account whether the VTE is provoked or unprovoked, it is advisable not to test for thrombophilia, to start treatment and to refer the patient to an expert for further decision making.
- Thrombosis experts would consider the population "with an unspecified type of VTE" (i.e. without reference to provoked or unprovoked) as theoretical, since determining if a clot is provoked or unprovoked is a standard way to stratify the risk of VTE recurrence and hence, guide treatment decisions. However, in general clinical practice, which is the setting where thrombophilia testing is frequently performed, VTE is often managed regardless of circumstances qualifying the VTE as provoked or unprovoked (an unspecified type of VTE), and for this reason the panel decided to address this question.
- A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment.
- This recommendation refers to testing for hereditary and acquired types of thrombophilia.

- Recommendation 7: In patients with cerebral venous thrombosis who have completed primary treatment in a setting where anticoagulation would be discontinued, the ASH guideline panel suggests thrombophilia testing to guide anticoagulant treatment duration. The panel suggests indefinite anticoagulation in patients with thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯).

  Remarks:

  - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment.
  - This recommendation refers to testing for hereditary and acquired types of thrombophilia.
  - This recommendation addresses settings where the standard of care for cerebral venous thrombosis patients is stopping anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is indefinite anticoagulant treatment (Recommendation 8).

- Recommendation 8: In patients with cerebral venous thrombosis who have completed primary treatment in a setting where anticoagulation would be continued indefinitely, the ASH guideline panel suggests not to perform thrombophilia testing to guide anticoagulant treatment duration (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯).

  Remarks:

  - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment.
  - This recommendation refers to testing for hereditary and acquired types of thrombophilia.
  - This recommendation addresses settings where the standard of care for cerebral venous thrombosis patients is indefinite anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is stopping anticoagulant treatment (Recommendation 7).

- Recommendation 9: In patients with splanchnic venous thrombosis who have completed primary treatment in a setting where anticoagulation would be discontinued, the ASH guideline panel suggests thrombophilia testing to guide anticoagulant treatment duration. The panel suggests indefinite anticoagulation in patients with thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯).

  Remarks:

  - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment.
  - This recommendation refers to testing for hereditary and acquired types of thrombophilia.
  - This recommendation addresses settings where the standard of care for splanchnic venous thrombosis patients is stopping anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is indefinite anticoagulant treatment (Recommendation 10).

- Recommendation 10: In patients with splanchnic venous thrombosis who have completed primary treatment in a setting where anticoagulation would

be continued indefinitely, the ASH guideline panel suggests not to perform thrombophilia testing to guide anticoagulant treatment duration (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯).

Remarks:

- A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment.
- This recommendation refers to testing for hereditary and acquired types of thrombophilia.
- This recommendation addresses settings where the standard of care for splanchnic venous thrombosis patients is indefinite anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is stopping anticoagulant treatment (Recommendation 9).

- Recommendation 11. In individuals with a family history of VTE and known FVL or PGM (low-risk thrombophilia) who have a minor provoking risk factor for VTE (e.g. immobility or minor injury, illness, or infection), the ASH guideline panel suggests not testing for the known familial thrombophilia to guide thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)
  - In individuals with a family history of VTE and known antithrombin, protein C, or protein S deficiency (high-risk thrombophilia) who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests thromboprophylaxis in individuals with thrombophilia and no thromboprophylaxis in individuals without thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

  Remarks:

  - A strategy with selective testing for the known familial thrombophilia type would mean that individuals with thrombophilia would receive thromboprophylaxis for a minor provoking risk factor, and individuals without thrombophilia would receive no thromboprophylaxis.
  - A positive family history is defined as having a first- or second-degree relative with VTE and thrombophilia.

- These recommendations do not address homozygous defects or combinations of thrombophilia types.
- This recommendation does not take into account the time it takes to perform the test and is based on the assumption that thrombophilia test results are available at the time the individual is at risk for VTE due to a minor provoking risk factor.
- These recommendations refer to selective testing for the known familial thrombophilia type. A separate question in this guideline addressed testing for all hereditary thrombophilias (using a panel of tests) in this population (Recommendation 12), and the resulting recommendations are the same. It is most sensible to selectively test for the known familial thrombophilia (Recommendation 11), rather than test for the entire panel (Recommendation 12), because of the trivial additional number of VTE episodes prevented and major bleeds caused by a strategy of panel testing for all hereditary thrombophilias.

- Recommendation 12. In individuals with a family history of VTE and known FVL or PGM (low-risk thrombophilia) who have a minor provoking risk factor for VTE (e.g. immobility or minor injury, illness, or infection), the ASH guideline panel suggests not testing for all hereditary thrombophilias to guide thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)
  - In individuals with a family history of VTE and known antithrombin, protein C, or protein S deficiency (high-risk thrombophilia) who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for all hereditary thrombophilias (using a panel of tests).
  - The panel suggests thromboprophylaxis in individuals with thrombophilia and no thromboprophylaxis for a minor provoking risk factor in individuals without thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

  Remarks:

  - A strategy with testing for hereditary thrombophilia (using a panel of tests) would mean that individuals with thrombophilia receive thromboprophylaxis or a minor provoking risk factor, and individuals without thrombophilia would receive no thromboprophylaxis.
  - A positive family history is defined as having a first- or second-degree relative with VTE and thrombophilia.

- These recommendations do not address homozygous defects or combinations of thrombophilia types.
- This recommendation does not take into account the time it takes to perform the test and is based on the assumption that thrombophilia test results are available at the time the individual is at risk for VTE due to a minor provoking risk factor.
- These recommendations refer to testing for all hereditary thrombophilias, using a panel of tests. A separate question in this guideline addressed selective testing only for the known familial thrombophilia type in this population (Recommendation 11), and the resulting recommendations are the same.
- It is most sensible to selectively test for the known familial thrombophilia (Recommendation 11), rather than test for the entire panel (Recommendation 12), because of the trivial additional number of VTE episodes prevented and major bleeds caused by a strategy of panel testing for all hereditary thrombophilias.

- Recommendation 13. In individuals with a family history of VTE and unknown thrombophilia status in the family who have a minor provoking risk factor for VTE (e.g. immobility or minor injury, illness, or infection), the ASH guideline panel suggests not testing for all hereditary thrombophilias (using a panel of tests) to guide thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

  Remarks:

  - Thrombophilia testing may be considered if individuals have multiple family members with VTE, if the family member with VTE was young, with patient preference, and in settings where testing incurs a low cost.
  - A positive family history is defined as having a first- or second-degree relative with VTE.
  - A strategy with testing for hereditary thrombophilia (using a panel of tests) would mean that individuals with thrombophilia receive thromboprophylaxis for a minor provoking risk factor, and individuals without thrombophilia would receive no thromboprophylaxis.
  - These recommendations have not taken into account the possibility of finding homozygous defects or combinations of thrombophilia types in an individual with a positive family history of VTE and unknown thrombophilia status.

- Recommendation 14. In individuals with a family history of FVL or PGM (low-risk thrombophilia) but no family history of VTE who have a minor provoking

risk factor for VTE (e.g. immobility or minor injury, illness, or infection), the ASH guideline panel suggests not testing for the known thrombophilia to guide thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

- In individuals with a first-degree family history of antithrombin, protein C, or protein S deficiency (high-risk thrombophilia) but no family history of VTE who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for the known thrombophilia. The panel suggests thromboprophylaxis in individuals with thrombophilia and no thromboprophylaxis in individuals without thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)
- In individuals with a second-degree family history of antithrombin, protein C, or protein S deficiency (high-risk thrombophilia) but no family history of VTE who have a minor provoking risk factor for VTE, the ASH guideline panel suggests either testing for the known thrombophilia or not testing for thrombophilia to guide the use thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

Remarks:

- A strategy with selective testing for the known familial thrombophilia type would mean that individuals with thrombophilia would receive thromboprophylaxis for a minor provoking risk factor, and individuals without thrombophilia would receive no thromboprophylaxis.
- A positive family history is defined as having a first- or second-degree relative with VTE, unless otherwise specified.
- These recommendations do not address homozygous defects or combinations of thrombophilia types.

- Recommendation 15. In women from the general population who are considering using combined oral contraceptives (COC), the ASH guideline panel recommends not to perform thrombophilia testing to guide the use of COC (strong recommendation based on low certainty in the evidence about effects ⨁⨁◯◯)

  Remarks:

  - Women with risk factors for VTE, such as a family history of VTE and/or a family history of thrombophilia, are at higher risk of VTE. Other recommendations in this guideline address thrombophilia testing in these populations (Recommendations 17 and 19).

- A strategy with testing for thrombophilia (using a panel of tests) would mean that women with thrombophilia would not use COC, and women without thrombophilia would use COC.

- Recommendation 16. In women from the general population who are considering using hormone replacement therapy (HRT), the ASH guideline panel suggests not to perform thrombophilia testing to guide the use of HRT (conditional recommendation based on low certainty in the evidence about effects ⨁⨁◯◯)

  Remarks:

  - Women with risk factors for VTE, such as a family history of VTE and/or thrombophilia, are at higher risk of VTE. Other recommendations in this guideline address thrombophilia testing in these populations (Recommendations 18 and 20).
  - A strategy with testing for thrombophilia (using a panel of tests) would mean that women with thrombophilia would not use HRT, and women without thrombophilia would use HRT.

- Recommendation 17. In women with a family history of VTE and unknown thrombophilia status in the family who are considering using combined oral contraceptives (COC), the ASH guideline panel suggests not testing for hereditary thrombophilia (using a panel of tests) to guide the use of COC (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

  Remarks:

  - Women with a family history of VTE and a known thrombophilia in the family are at higher risk for testing positive for thrombophilia and are therefore at higher risk for VTE. Another recommendation in this guideline addresses thrombophilia testing in this population (Recommendation 19).
  - A strategy with testing for hereditary thrombophilia (using a panel of tests) would mean that women with thrombophilia would not use COC, and women without thrombophilia would use COC.
  - A positive family history is defined as having a first- or second-degree relative with VTE.

- Recommendation 18. In women with a family history of VTE and unknown thrombophilia in the family who are considering using hormone replacement therapy (HRT), the ASH guideline panel suggests not to perform thrombophilia testing for any hereditary thrombophilia to guide the use of

HRT (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

Remarks:

- Women with a family history of VTE and a known thrombophilia in the family are at higher risk for testing positive for thrombophilia and are therefore at higher risk for VTE. Another recommendation in this guideline addresses thrombophilia testing in this population (Recommendation 20).
- A strategy with testing for hereditary thrombophilia (using a panel of tests) would mean that women with thrombophilia would not use HRT, and women without thrombophilia would use HRT.
- A positive family history is defined as having a first- or second-degree relative with VTE.

- Recommendation 19. In women with a family history of VTE and known FVL or PGM in the family (low-risk thrombophilia), the ASH guideline panel suggests not testing for the known familial thrombophilia to guide the use of COC (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯).
    - In women with a family history of VTE and known antithrombin, protein C or protein S deficiency in the family (high-risk thrombophilia), the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests avoidance of COC in women with high-risk thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

  Remarks:

    - A strategy with selective testing for the known familial thrombophilia would mean that women with thrombophilia would avoid COC, and women without thrombophilia would use COC.
    - A positive family history is defined as having a first- or second-degree relative with VTE.
    - These recommendations do not address homozygous defects, or combinations of thrombophilia types.
- Recommendation 20. In women with a family history of VTE and known FVL or PGM in the family (low-risk thrombophilia), the ASH guideline panel suggests not testing for the known familial thrombophilia to guide the use of HRT (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

- In women with a family history of VTE and known antithrombin, protein C or protein S deficiency in the family (high-risk thrombophilia), the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests avoidance of HRT in women with high-risk thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

Remarks:

- A strategy with selective testing for the known familial thrombophilia would mean that women with thrombophilia would avoid HRT, and women without thrombophilia would use HRT.
- A positive family history is defined as having a first- or second-degree relative with VTE.
- These recommendations do not address homozygous defects or combinations of thrombophilia types.

- Recommendation 21. In women with a family history of VTE and known homozygous FVL, combination of FVL and PGM, or antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests antepartum thromboprophylaxis in women with the same familial thrombophilia (i.e. homozygous FVL, combination of FVL and PGM, or antithrombin deficiency) and no antepartum prophylaxis in women without the same familial thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)
  - In women with a family history of VTE and known protein C or protein S deficiency in the family, the ASH guideline panel suggests either testing for the known familial thrombophilia or not testing for thrombophilia to guide antepartum prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

  Remarks:

  - Pharmacological thromboprophylaxis based on antepartum thrombophilia testing is generally continued postpartum.
  - Conditions can include the duration and burden of the treatment, which involves injections with low-molecular-weight heparin, and patient preference.
  - A strategy with selective testing for the known familial thrombophilia type would mean that positive relatives would receive

thromboprophylaxis, and negative relatives would not receive thromboprophylaxis.

- A positive family history is defined as having a first- or second-degree relative with VTE; for homozygous FVL, these recommendations only concern siblings, not children, as these would most often be heterozygous for FVL; management of women with a second-degree family history was not addressed.
- These recommendations do not address heterozygous FVL or PGM alone, as the ASH guidelines on the management of VTE in the context of pregnancy suggest not to use thromboprophylaxis in these women.

- Recommendation 22. In women with a first-degree family history of VTE and known homozygous FVL, a combination of FVL and PGM, antithrombin deficiency, protein C deficiency, or protein S deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests postpartum thromboprophylaxis in women with the same familial thrombophilia (i.e. homozygous FVL, combination of FVL and PGM, or antithrombin deficiency) and no postpartum prophylaxis in women without the same familial thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)
  - In women with a second-degree family history of VTE and a known combination of FVL and PGM, or antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests postpartum thromboprophylaxis in women with thrombophilia and no postpartum prophylaxis in women without thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)
  - In women with a second-degree family history of VTE and known protein C or protein S deficiency in the family, the ASH guideline panel suggests either testing for the known familial thrombophilia or not testing for thrombophilia to guide postpartum thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

  Remarks:

  - Thromboprophylaxis postpartum continues until 6 weeks after delivery.
  - Conditions can include the duration and burden of the treatment, which involves injections, and patient preference.
  - A strategy with selective testing for the known familial thrombophilia type would mean that women with thrombophilia would receive

thromboprophylaxis, and women without thrombophilia would not receive thromboprophylaxis.

- For homozygous FVL, these recommendations only concern siblings, not children, as these would most often be heterozygous for FVL; testing of women with a second-degree family history was not addressed.
- These recommendations do not address heterozygous FVL or PT mutation alone, as the ASH guidelines on the management of VTE in the context of pregnancy suggest not to prescribe thromboprophylaxis in these women.

- Recommendation 23. In ambulatory cancer patients receiving systemic therapy who have a family history of VTE and are otherwise determined to be at low or intermediate risk for VTE, the ASH guideline panel suggests testing for hereditary thrombophilia. The panel suggests ambulatory thromboprophylaxis in patients with thrombophilia and no thromboprophylaxis in patients without thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯)

  Remarks:

  - This question only addresses cancer patients receiving systemic therapy, without a personal history of VTE who are at low or intermediate risk for VTE. The ASH VTE guidelines on prevention and treatment in patients with cancer suggest using direct oral anticoagulant (DOAC) prophylaxis in all ambulatory cancer patients with high VTE risk as assessed by a validated risk assessment tool complemented by clinical judgment and experience.
  - Patient preference is an important factor to consider, as undergoing the thrombophilia test, knowing the positive test result, and receiving additional medication can be an added burden.
  - A strategy with testing for hereditary thrombophilia (using a panel of tests) would mean that ambulatory cancer patients with thrombophilia would receive thromboprophylaxis, and ambulatory cancer patients without thrombophilia would not receive thromboprophylaxis.
  - A positive family history is defined as having a first-degree relative with VTE.
  - This recommendation does not address homozygous defects, or combinations of thrombophilia types.

1.2.2.2 Guidelines for Management of Venous Thromboembolism: Treatment of Deep Vein Thrombosis and Pulmonary Embolism (2020)

These evidence-based guidelines intend to support patients, clinicians, and others in decisions about treatment of VTE.

Results include strong recommendations on the use of thrombolytic therapy for patients with PE and hemodynamic compromise, use of an international normalized ratio (INR) range of 2.0 to 3.0 over a lower INR range for patients with VTE who use a vitamin K antagonist (VKA) for secondary prevention, and use of indefinite anticoagulation for patients with recurrent unprovoked VTE. Conditional recommendations include the preference for home treatment over hospital-based treatment for uncomplicated DVT and PE at low risk for complications and a preference for direct oral anticoagulants over VKA for primary treatment of VTE. Detailed recommendations can be found below[10]:

- For patients with uncomplicated deep vein thrombosis (DVT), the ASH guideline panel suggests offering home treatment over hospital treatment (conditional recommendation based on low certainty in the evidence of effects ⨁⨁◯◯).

  Remarks: This recommendation does not apply to patients who have other conditions that would require hospitalization, have limited or no support at home, and cannot afford medications or have a history of poor compliance. Patients with limb-threatening DVT or a high risk for bleeding and those requiring IV analgesics may benefit from initial treatment in the hospital.

- For patients with DVT and/or PE, the ASH guideline panel suggests using direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) (conditional recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁◯).

  Remarks: This recommendation may not apply to certain subgroups of patients, such as those with renal insufficiency (creatinine clearance <30 mL/min), moderate to severe liver disease, or antiphospholipid syndrome.

- For patients with DVT and/or PE, the ASH guideline panel does not suggest one DOAC over another (conditional recommendation based on very low certainty in the evidence of comparative effects ⨁◯◯◯).

  Remarks: Factors, such as a requirement for lead-in parenteral anticoagulation, once- vs twice-daily dosing, and out-of-pocket cost may drive the selection of specific DOACs. Other factors, such as renal function, concomitant medications (e.g., need for a concomitant drug metabolized

through the CYP3A4 enzyme or P-glycoprotein), and the presence of cancer, may also impact DOAC choice.

- In most patients with proximal DVT, the ASH guideline panel suggests anticoagulation therapy alone over thrombolytic therapy in addition to anticoagulation (conditional recommendation based on low certainty in the evidence of effects ⨁⨁◯◯).

  Remarks: Thrombolysis is reasonable to consider for patients with limb-threatening DVT (phlegmasia cerulea dolens) and for selected younger patients at low risk for bleeding with symptomatic DVT involving the iliac and common femoral veins (higher risk for more severe post thrombotic syndrome [PTS]). Patients in these categories who value rapid resolution of symptoms, are averse to the possibility of PTS, and accept the added risk of major bleeding may prefer thrombolysis. The use of thrombolysis should be rare for patients with DVT limited to veins below the common femoral vein.

- For patients with extensive DVT in whom thrombolysis is considered appropriate, the ASH guideline panel suggests using catheter-directed thrombolysis over systemic thrombolysis (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯).

  Remarks: Given the very-low-certainty evidence (uncertainty regarding the benefits and harms of catheter-directed thrombolysis compared with systemic thrombolysis), the panel followed the GRADE ASH rules and issued a conditional recommendation. However, 4 panel members believed the recommendation should have been graded as strong based on the lack of evidence showing meaningful clinical benefits outweighing the known bleeding risks associated with systemic thrombolysis.

- For patients with proximal DVT and significant preexisting cardiopulmonary disease, the ASH guideline panel suggests anticoagulation alone rather than anticoagulation plus insertion of an inferior vena cava (IVC) filter (conditional recommendations based on low certainty in the evidence of effects ⨁⨁◯◯).

  Remarks: These recommendations apply to patients who are eligible to receive anticoagulation. For patients with a contraindication to anticoagulation, insertion of a retrievable IVC filter may be indicated with retrieval as soon as the patient is able to receive anticoagulation.

- For primary treatment of patients with DVT and/or PE, whether provoked by a transient risk factor or by a chronic risk factor or unprovoked, the ASH guideline panel suggests using a shorter course of anticoagulation for primary treatment (3-6 months) over a longer course of anticoagulation for primary

treatment (6-12 months) (conditional recommendations based on moderate certainty in evidence of effects ⨁⨁⨁◯).

Remarks: These recommendations are intended to address the duration of primary anticoagulant treatment for all patients with DVT and/or PE, defined as the minimal length of time for treatment of the initial VTE. Most patients with DVT and/or PE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment. In contrast, many patients with DVT and/or PE provoked by chronic risk factors, as well as patients with unprovoked DVT and/or PE, may continue anticoagulant therapy indefinitely for secondary prevention after completion of the primary treatment. However, if patients and clinicians decide to stop anticoagulation, the ASH guideline panel suggests against using a longer course of primary anticoagulant therapy (6-12 months). For selected patients with a chronic risk factor for which some improvement is expected over time (e.g., improved mobility with rehabilitation), a longer course of anticoagulation for the primary treatment phase (e.g., 6-12 months) could be justified.

1.2.2.3 Living Guidelines on the Use of Anticoagulation for Thromboprophylaxis in Patients with COVID-19: Update on Post Discharge Thromboprophylaxis (2021)

COVID-19–related acute illness is associated with an increased risk of venous thromboembolism (VTE). The panel agreed on 1 additional recommendation. The panel issued a conditional recommendation against the use of outpatient anticoagulant prophylaxis in patients with COVID-19 who are discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation. This recommendation was based on very low certainty in the evidence, underscoring the need for high-quality randomized controlled trials assessing the role of post discharge thromboprophylaxis[17]:

- The ASH guideline panel suggests that outpatient anticoagulant thromboprophylaxis not be used for patients with COVID-19 who are being discharged from the hospital and do not have suspected or confirmed venous thromboembolism (VTE) or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯).

  Remarks:

  - An individualized assessment of the patient's risk of thrombosis and bleeding and shared decision making are important when deciding on whether to use post discharge thromboprophylaxis. Prospectively

validated risk assessment models to estimate thrombotic and bleeding risk in COVID-19 patients after hospital discharge are not available.

The panel acknowledged that post discharge thromboprophylaxis may be reasonable for patients judged to be at high risk of thrombosis and low risk of bleeding.

1.2.2.4 Living Guidelines on the Use of Anticoagulation for Thromboprophylaxis for Patients with COVID-19: Update on the Use of Anticoagulation in Critically Ill Patients (2022)

The panel made 1 additional recommendation: a conditional recommendation for the use of prophylactic-intensity over therapeutic-intensity anticoagulation for patients with COVID19–related critical illness who do not have suspected or confirmed VTE. The panel emphasized the need for an individualized assessment of thrombotic and bleeding risk[22]:

- The ASH guideline panel suggests using prophylactic-intensity over therapeutic-intensity anticoagulation for patients with COVID-19–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE; conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

1.2.2.5 Living Guidelines on the Use of Anticoagulation for Thromboprophylaxis in Patients with COVID-19: Update on the Use of Intermediate-Intensity Anticoagulation in Critically Ill Patients (2021)

The panel agreed on 1 additional recommendation. The panel issued a conditional recommendation in favor of prophylactic-intensity over intermediate-intensity anticoagulation in patients with COVID-19–related critical illness who do not have confirmed or suspected VTE. This recommendation was based on low certainty in the evidence, which underscores the need for additional high-quality, randomized, controlled trials comparing different intensities of anticoagulation in critically ill patients[18]:

- Patients with COVID-19–related critical illness are defined as those suffering from an immediately life-threatening condition who would typically be admitted to an intensive care unit (ICU). Examples include patients requiring hemodynamic support, ventilatory support, and renal replacement therapy.
- The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity anticoagulation in patients with COVID-19–related critical illness who do not have suspected or confirmed venous

thromboembolism (VTE) (conditional recommendation based on low certainty in the evidence about effects ⨁⨁◯◯).

- At present, there is no direct high-certainty evidence comparing different types of anticoagulants. The selection of a specific agent (e.g., low molecular weight heparin [LMWH], unfractionated heparin [UFH]) may be based on availability, resources required, familiarity, and the aim of minimizing the use of personal protective equipment or exposure of staff to COVID- 19–infected patients as well as patient-specific factors (e.g., renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption).
- This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on extracorporeal membrane oxygenation or continuous renal replacement therapy.

1.2.2.6 Living Guidelines on the Use of Anticoagulation for Thromboprophylaxis in Patients with COVID-19: Update on the Use of Therapeutic-Intensity Anticoagulation in Acutely Ill Patients (2022)

The panel issued a conditional recommendation in favor of therapeutic-intensity over prophylactic-intensity anticoagulation in patients with COVID-19–related acute illness who do not have suspected or confirmed VTE. The panel emphasized the need for an individualized assessment of risk of thrombosis and bleeding. The panel also noted that heparin (unfractionated or low molecular weight) may be preferred because of a preponderance of evidence with this class of anticoagulants. This conditional recommendation was based on very low certainty in the evidence, underscoring the need for additional, high-quality, randomized controlled trials comparing different intensities of anticoagulation in patients with COVID-19–related acute illness[19]:

- The ASH guideline panel suggests using therapeutic-intensity over prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯).

  Remarks:

  - Patients with COVID-19–related acute illness are defined as those with clinical features that would typically result in admission to an inpatient medical ward without requirement for intensive clinical support. Examples include patients with dyspnea or mild-to-moderate hypoxia.

- The panel acknowledges that lower intensity anticoagulation may be preferred for patients judged to be at high risk of bleeding and low risk of thrombosis.
- At present, there is no direct high-certainty evidence comparing different types of anticoagulants in patients with COVID-19. Unfractionated or low molecular weight heparin may be preferred because of a preponderance of evidence with these agents. There are no studies of therapeutic-intensity fondaparinux, argatroban, or bivalirudin in this population.

1.2.3 National Institute for Health and Care Excellence (NICE) Guideline on Venous Thromboembolism in Adults (2021)

The guidelines recommend the following[23]:

- People aged 16 and over who are in hospital and assessed as needing pharmacological VTE prophylaxis start it as soon as possible and within 14 hours of hospital admission. [2010, updated 2021]
- People aged 16 and over who are discharged with lower limb immobilization are assessed to identify their risk of VTE. [new 2021]
- People aged 18 and over with a DVT Wells score of 2 points or more have a proximal leg vein ultrasound scan within 4 hours of it being requested. [2013, updated 2021]
- People aged 18 and over taking anticoagulation treatment after a VTE have a review at 3 months and then at least once a year if they continue to take it long term. [2013, updated 2021]
- People aged 18 and over having outpatient treatment for suspected or confirmed low-risk PE have an agreed plan for monitoring and follow-up. [new 2021]

1.2.4 Saudi Consensus for the Management of Cancer-Associated Thromboembolism: A Modified Delphi-Based Study (2023)

The present modified Delphi-based study combined the best available evidence and clinical experience with the current health care policies and settings in Saudi Arabia to build a consensus statement on the epidemiology, prevention, and management of cancer-associated thrombosis (CAT). The guidelines recommend the following[16]:

Risk assessment

- Primary VTE prophylaxis among cancer patients should be individualized on a case-by-case basis based on risk assessment (level of agreement: 100%)
- VTE risk assessments should be implemented in chemotherapy protocols to adequately prescribe prophylactic treatment and reduce the incidence of thrombosis in cancer patients (level of agreement: 100%)
- In Saudi Arabia, VTE risk assessment is performed in some centers using the Caprini and Khorana risk scores. However, this practice is not standardized (level of agreement: 100%)
- Although many Saudi institutes have protocols and risk assessment tools regards the anticoagulation and prophylaxis of hospitalized patients, there is a need to develop protocols for the prophylactic treatment of ambulatory patients by a multidisciplinary team involving both hematologists and oncologists (level of agreement: 100%)
- There is a need to validate and apply a comprehensive risk assessment score to generate local data and guide prophylaxis use (level of agreement: 100%)

Primary prophylaxis

- For hospitalized medical oncology patients with acute medical illness, primary prophylaxis with LMWH should be offered for patients admitted in the absence of contraindications (Level of agreement: 100%)
- For hospitalized medical oncology patients without additional risk factors, primary pharmacological prophylaxis can be offered in the absence of bleeding or other contraindications (Level of agreement: 83%)
- LMWH is the pharmacological option of choice for the primary prophylaxis of CAT and remained predominately used in an inpatient and outpatient setting in Saudi Arabia unless contraindicated (Level of agreement: 83%)
- Prophylaxis should not be offered for patients admitted for minor procedures or patients with platelets less than 25,000/μL (Level of agreement: 100%)
- Pneumatic compression devices can be offered for patients with contraindications for anticoagulants until the contraindications are resolved (Level of agreement: 100%)
- For ambulatory patients, treatment decisions should be based on the risk of VTE and bleeding, as well as patient preferences/values (Level of agreement: 100%)
- Ambulatory low-risk patients should not be offered primary pharmacological prophylaxis (Level of agreement: 100%)

- High-risk ambulatory patients should be offered thromboprophylaxis. In Saudi Arabia, DOACs and LMWH is commonly used in this setting unless contraindicated (Level of agreement: 75%)
- DOACs can be offered for up to 6 months for primary prophylaxis in high-risk ambulatory cancer patients (KRS ≥ 2) if no contraindications and they cannot take LMWH.

  DOACs are relatively inexpensive and readily available, which allows their use for primary prophylaxis in high-risk patients (Level of agreement: 100%)
- Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered thromboprophylaxis with either aspirin or LMWH (lower-risk patients) or LMWH (higher-risk patients) (Level of agreement: 100%)
- All patients undergoing major surgery should be offered pharmacological, preoperative. Prophylaxis with UFH or LMWH, unless contraindicated, and should be continued for at least 7–10 days (Level of agreement: 100%)
- Extended prophylaxis with LMWH for up to 4 weeks postoperatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic cancer surgery with high-risk features (Level of agreement: 100%)
- Combined pharmacologic/mechanical prophylaxis may improve efficacy, especially in highest-risk patients. However, mechanical prophylaxis should not be used as monotherapy unless pharmacologic prophylaxis is contraindicated (Level of agreement: 100%)
- The choice of anticoagulation regimen should be based on individual risk of thrombosis and bleeding, renal and hepatic function, inpatient/outpatient status, FDA approval status, ease of administration, cost, the burden of laboratory monitoring, agent reversibility, and patient preferences (Level of agreement: 100%)
- DOACs, LMWH, UFH, or fondaparinux, can be used as initial anticoagulants. Among parenteral agents, LMWH is preferred over UFH in the absence of severe renal impairment (Level of agreement: 100%)
- LMWH is preferred for patients with acute VTE at high risk for bleeding or with GI malignancy (Level of agreement: 83.3%)
- For long-term anticoagulation, DOACs or LMWH for at least 6 months is preferred over VKA. VKAs are less effective but may be used if DOACs or LMWH are not accessible (Level of agreement: 100%)

- Catheter-directed pharmaco-mechanical thrombolysis can be considered for DVT in patients at low risk for bleeding but at risk for limb loss or severe persistent symptoms despite anticoagulation (Level of agreement: 100%)
- IVC filters may be offered to patients with absolute contraindications to anticoagulation in the acute setting independent of thrombosis burden (Level of agreement: 100%)
- Incidental VTE should be treated in the same manner as symptomatic VTE (Level of agreement: 100%)
- Treatment of isolated subsegmental PE or splanchnic or visceral vein thrombi should be offered on a case-by-case basis considering the potential benefits and risks (Level of agreement: 100%)
- The use of novel DOACs in patients with other medical conditions such as hemodialysis or valvular atrial fibrillation is still ambiguous and requires further evidence (Level of agreement: 100%)

Secondary prophylaxis

- D-dimer levels can be used to assist during patient follow-up but do not constitute a decision-making tool, as opposed to the presence of active cancer, thrombophilia, and CAT risk factors (Level of agreement: 100%)

1.2.5 American Society of Clinical Oncology (ASCO) Guideline Update on Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer (2023)

ASCO first published a VTE guideline in 2007, with updates in 2013, 2014, and 2019. Pending a full update of the 2019 guideline, the current update adds apixaban as an option for the treatment of VTE in patients with cancer and addresses recent evidence regarding direct factor Xa inhibitors for extended postoperative thromboprophylaxis. The guidelines published the below updated recommendations which are rated as outlined in the table below[24]:

Table 15. Quality of Evidence Definition (ASCO 2023 Guidelines)

Quality of Evidence	
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (e.g., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect

Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available
Strength of Recommendations	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: (a) strong evidence for a true net effect (e.g., benefits exceed harms); (b) consistent results, with no or minor exceptions; (c) minor or no concerns about study quality; and/or (d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: (a) good evidence for a true net effect (e.g., benefits exceed harms); (b) consistent results with minor and/or few exceptions; (c) minor and/or few concerns about study quality; and/or (d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: (a) limited evidence for a true net effect (e.g., benefits exceed harms); (b) consistent results, but with important exceptions; (c) concerns about study quality; and/or (d) the extent of panelists' agreement.

	Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation

- Patients who are candidates for extended pharmacologic thromboprophylaxis after surgery may be offered prophylactic doses of low molecular weight heparin (LMWH) (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong). Alternatively, patients may be offered prophylactic doses of rivaroxaban or apixaban after an initial period of LMWH or unfractionated heparin (UFH) (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak).

  Qualifying statement. Evidence for rivaroxaban and apixaban in this setting remains limited. The two available trials differed with respect to type of cancer, type of surgery, and timing of rivaroxaban or apixaban initiation after surgery.

- Initial anticoagulation may involve LMWH, UFH, fondaparinux, rivaroxaban, or apixaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5-10 days of anticoagulation for the patient with cancer with newly diagnosed VTE without severe renal impairment (defined as creatinine clearance <30 mL/min; Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).
- For long-term anticoagulation, LMWH, edoxaban, rivaroxaban, or apixaban for at least 6 months are preferred over vitamin K antagonists (VKAs) because of improved efficacy. VKAs may be used if LMWH or direct factor Xa inhibitors are not accessible. There is a reduction in recurrent thrombosis but an increase in clinically relevant nonmajor bleeding risk with direct factor Xa inhibitors compared with LMWH. Caution with direct factor Xa inhibitors is warranted in GI and genitourinary malignancies and other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked before using a direct factor Xa inhibitor (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

1.2.6 American Society of Hematology (ASH) Guidelines for Management of Venous Thromboembolism: Prevention and Treatment in Patients with Cancer (2021)

Recommendations address mechanical and pharmacological prophylaxis in hospitalized medical patients with cancer, those undergoing a surgical procedure, and ambulatory patients receiving cancer chemotherapy. The recommendations also address the use of anticoagulation for the initial, short-term, and long-term treatment of VTE in patients with cancer[25]:

- Primary prophylaxis for hospitalized medical patients with cancer:
    - For hospitalized medical patients with cancer without VTE, the American Society of Hematology (ASH) guideline panel suggests using thromboprophylaxis over no thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).
    - For hospitalized medical patients with cancer without VTE, in which pharmacological thromboprophylaxis is used, the ASH guideline panel suggests using LMWH over UFH (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯).
    - For hospitalized medical patients with cancer without VTE, the ASH guideline panel suggests using pharmacological thromboprophylaxis over mechanical thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).
    - For hospitalized medical patients with cancer without VTE, the ASH guideline panel suggests using pharmacological thromboprophylaxis over a combination of pharmacological and mechanical thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).
    - For hospitalized medical patients with cancer, the ASH guideline panel suggests discontinuing thromboprophylaxis at the time of hospital discharge rather than continuing thromboprophylaxis beyond the discharge date (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).
- Primary prophylaxis for patients with cancer undergoing surgery:
    - For patients with cancer without VTE undergoing a surgical procedure at lower bleeding risk, the ASH guideline panel suggests using pharmacological rather than mechanical thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯).
    - For patients with cancer without VTE undergoing a surgical procedure at high bleeding risk, the ASH guideline panel suggests using mechanical rather than pharmacological thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯).
    - For patients with cancer without VTE undergoing a surgical procedure at high risk for thrombosis, except in those at high risk of bleeding, the ASH guideline panel suggests using a combination of mechanical and pharmacologic thromboprophylaxis rather than mechanical

prophylaxis alone (conditional recommendation based on low certainty in the evidence of effects) or pharmacologic thromboprophylaxis alone (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).

- For patients with cancer undergoing a surgical procedure, the ASH guideline panel suggests using LMWH or fondaparinux for thromboprophylaxis rather than UFH (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯).
- For patients with cancer undergoing a surgical procedure, the ASH guideline panel makes no recommendation on the use of VKA or DOAC for thromboprophylaxis, because there were no studies available. (not graded)
- For patients with cancer undergoing a surgical procedure, the ASH guideline panel suggests using postoperative thromboprophylaxis over preoperative thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯).
- For patients with cancer who had undergone a major abdominal/pelvic surgical procedure, the ASH guideline panel suggests continuing pharmacological thromboprophylaxis post discharge rather than discontinuing at the time of hospital discharge (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).

- Primary prophylaxis in ambulatory patients with cancer receiving systemic therapy:
  - For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, we recommend no thromboprophylaxis over parenteral thromboprophylaxis (strong recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯).
  - For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel suggests no prophylaxis over parenteral prophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯).
  - For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel suggests parenteral thromboprophylaxis (LMWH) over no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯).

- For ambulatory patients with cancer receiving systemic therapy, the ASH guideline panel recommends no thromboprophylaxis over oral thromboprophylaxis with VKA (strong recommendation, very low certainty in the evidence of benefits ⨁◯◯◯, but high certainty about the harms ⨁⨁⨁⨁).
- For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, the ASH guideline panel suggests no thromboprophylaxis over oral thromboprophylaxis with a DOAC (apixaban or rivaroxaban) (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯).
- For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel suggests thromboprophylaxis with a DOAC (apixaban or rivaroxaban) or no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯).
- For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel suggests thromboprophylaxis with a DOAC (apixaban or rivaroxaban) over no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯).
- For multiple myeloma patients receiving lenalidomide, thalidomide, or pomalidomide-based regimens, the ASH guideline panel suggests using low-dose acetylsalicylic acid (ASA) or fixed low-dose VKA or LMWH (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯).

- Primary prophylaxis for patients with cancer with central venous catheter:
  - For patients with cancer and a central venous catheter (CVC), the ASH guideline panel suggests not using parenteral thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯).
  - For patients with cancer and a CVC, the ASH guideline panel suggests not using oral thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯).
- Initial treatment (first week) for patients with active cancer and VTE:
  - For patients with cancer and VTE, the ASH guideline panel suggests DOAC (apixaban or rivaroxaban) or LMWH be used for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).

- For patients with cancer and VTE, we recommend LMWH over UFH for initial treatment of VTE for patients with cancer (strong recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯).
- For patients with cancer and VTE, the ASH guideline panel suggests LMWH over fondaparinux for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).

- Short-term treatment for patients with active cancer (initial 3-6 months):
  - For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel suggests DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯).
  - For the short-term treatment of VTE (3-6months) for patients with active cancer, the ASH guideline panel suggests DOAC (apixaban, edoxaban, or rivaroxaban) over VKA (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).
  - For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel suggests LMWH over VKA (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯).
  - For patients with cancer and visceral/ splanchnic vein thrombosis, the ASH guideline panel suggests treating with short-term anticoagulation or observing (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).
  - For patients with cancer with CVC-related VTE receiving anticoagulant treatment, the ASH guideline panel suggests keeping the CVC over removing the CVC (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).
  - For patients with cancer and recurrent VTE despite receiving therapeutic LMWH, the ASH guideline panel suggests increasing the LMWH dose to a supratherapeutic level or continuing with a therapeutic dose (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).
  - For patients with cancer and recurrent VTE despite anticoagulation treatment, the ASH guideline panel suggests not using an inferior vena cava (IVC) filter over using a filter (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).

- Long-term treatment (>6 months) for patients with active cancer and VTE:
    - For patients with active cancer and VTE, the ASH guideline panel suggests long-term anticoagulation for secondary prophylaxis (.6 months) rather than short-term treatment alone (3-6 months) (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).
    - For patients with active cancer and VTE receiving long-term anticoagulation for secondary prophylaxis, the ASH guideline panel suggests continuing indefinite anticoagulation over stopping after completion of a definitive period of anticoagulation (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).
    - For patients with active cancer and VTE requiring long-term anticoagulation (.6 months), the ASH guideline panel suggests using DOACs or LMWH (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

1.2.7 International Society for Thrombosis and Hemostasis (ISTH) Guidance of the Use of Direct Oral Anticoagulants for Primary Thromboprophylaxis in Ambulatory Cancer Patients (2019)

The Scientific and Standardization Committee (SSC) through its subcommittee Hemostasis & Malignancy of the International Society for Thrombosis and Hemostasis (ISTH) aims to review emerging data on primary VTE prophylaxis with direct oral anticoagulants (DOACs) for ambulatory cancer patients and provide guidance to clinicians[26].

- The guidelines suggest the use of DOACs as primary thromboprophylaxis in ambulatory cancer patients starting chemotherapy with Khorana score ≥ 2 in patients with no drug-drug interactions and not at high risk for bleeding (such as patients with gastro-esophageal cancers). Apixaban and rivaroxaban were the only DOACs with evidence from RCTs. A final treatment decision should be made after considering the risk of both VTE and bleeding, as well as patients' preference and values.
- The guidelines suggest that if DOACs were to be used for primary thromboprophylaxis in ambulatory cancer patients, it is administered for up to 6 months after the initiation of chemotherapy. It is recommended to monitor platelet counts and risk of bleeding complications while on anticoagulation.
- In high-risk ambulatory cancer patients where primary thromboprophylaxis is planned but with concerns for safety of DOAC (such as in patients with

concern of drug interaction or high risk of gastrointestinal bleeding), it is suggested to use LWMH.

1.2.8 European Society for Medical Oncology (ESMO) Clinical Practice Guideline on Venous Thromboembolism in Cancer Patients (2022)

The ESMO guidelines recommend the following[27]:

Table 16. Levels of Evidence and Grades of Recommendation Definition (ESMO 2022 Guidelines)

Levels of Evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grades of Recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Primary prevention of VTE

Thromboprophylaxis in the surgical setting

- Unless contraindicated due to a high risk of bleeding, pharmacological VTE prophylaxis with LMWH (preferred) or UFH is recommended in patients

undergoing major cancer surgery [I, A]. Fondaparinux may be used as an alternative [II, C].

- Mechanical methods such as intermittent pneumatic compression (IPC) or graduated compression stockings (GCSs) are suggested as an alternative when pharmacological VTE prophylaxis is contraindicated (e.g. in the presence of active bleeding) [II, B]. Mechanical methods may be used in combination with pharmacological VTE prophylaxis in patients at exceedingly high risk of VTE [II, C].
- Depending on the heparin type and dosage, commencement of pharmacological thromboprophylaxis with LMWH or UFH 2-12 h preoperatively is suggested in cancer surgical patients [II, B].
- Where several prophylactic dosages are approved for a given LMWH, the highest prophylactic LMWH dose o.d. or 5000 IU UFH t.d.s. is recommended [II, A].
- Patients undergoing major cancer surgery should receive pharmacological thromboprophylaxis for at least 10 days post-operatively [I, A]. In patients with cancer undergoing open abdominal or pelvic surgery or laparoscopic colorectal cancer surgery, extended post-operative VTE prophylaxis for 4 weeks with LMWH is recommended [I, A].

<u>Prevention of VTE in non-surgical patients with cancer</u>

- For ambulatory pancreatic cancer patients on first-line systemic anticancer treatment, LMWH given at a higher dose (150 IU/kg dalteparin or 1 mg/kg enoxaparin) for a maximum of 3 months may be considered [II, C].
- In ambulatory cancer patients starting systemic anticancer treatment who have a high thrombosis risk, apixaban, rivaroxaban or LMWH may be considered for primary thromboprophylaxis for a maximum of 6 months [I, B].
- In hospitalized cancer patients confined to bed with an acute medical complication, prophylaxis with LMWH, UFH [I, B] or fondaparinux [II, B] is recommended.
- Where concerns of DOAC safety exist and the patient is perceived as having clinically important risk for VTE, LMWH at conventional primary thromboprophylaxis dosing may be administered [II, C].

<u>Patients with multiple myeloma (MM)</u>

- In ambulatory patients with MM receiving IMiD treatment combined with low-dose dexamethasone and without additional risk factors, aspirin (100 mg/day) is recommended [III, B].

- In ambulatory patients with MM classified as high risk for VTE, pharmacological thromboprophylaxis with LMWH for 3-6 months is recommended [II, B].
- Extension of thromboprophylaxis should be considered on a case-by-case basis [IV, B].
- Apixaban 2.5 mg b.i.d. or rivaroxaban 10 mg o.d. are potential options in patients with CrCl >30 ml/min who present contraindications or intolerance to LMWH [IV, C].

Treatment of cancer-associated thrombosis (CAT)

- In patients with CAT, LMWH, UFH, fondaparinux, apixaban or rivaroxaban are recommended treatments for the acute phase [I, A]. LMWH is preferred over UFH or fondaparinux [V, A]. UFH may be considered in patients with CAT and severe renal impairment (defined as CrCl <30 ml/min) [IV, C].
- Long-term anticoagulation for at least 6 months includes LMWH, apixaban, edoxaban or rivaroxaban which are preferred over VKAs [I, A]. VKAs may be used if LMWH or direct factor Xa inhibitors are not accessible [IV, C].
- In patients with luminal gastrointestinal cancer, LMWH is preferred for treating CAT [II, B]. Similar considerations potentially apply to patients with urothelial cancer [II, B]. The use of oral factor Xa inhibitors should consider patient preferences [IV, C].
- In patients at high risk for gastrointestinal bleeding, such as those with active gastroduodenal ulcers or patients receiving strong inhibitors or inducers of P-glycoprotein and CYP3A4, LMWH is preferred [IV, B]. The author panel acknowledges that only limited evidence is available on drug-drug interactions between direct factor Xa inhibitors and systemic antineoplastic therapy.
- Extended anticoagulation beyond the initial 6 months with LMWH, apixaban, edoxaban, rivaroxaban or VKAs should be considered for patients with active cancer in whom the risk of recurrent thrombosis is higher and may outweigh that of bleeding [III, B]. The risk-benefit profile of anticoagulant therapy should be regularly assessed to ensure a favourable balance [IV, C].
- For incidentally detected VTE, the same treatment as for symptomatic VTE is recommended [II, A].
- In patients with high risk of bleeding or single incidental subsegmental PE without concomitant DVT, provided that there is adequate cardiopulmonary reserve, a watchful approach or a shorter course of anticoagulation may be considered [V, C].

- The insertion of vena cava filters is suggested in patients with acute and life-threatening VTEs who have absolute contraindications to anticoagulant therapy [III, B] or as an adjunct to anticoagulation in patients with recurrent VTE or extension of thrombosis despite optimal anticoagulant therapy [IV, C].

Prevention and management of catheter-related VTE in adults with cancer

- Routine pharmacological prophylaxis of CRT is not recommended [II, D].
- For the treatment of symptomatic CRT in cancer patients, anticoagulant treatment is recommended for a minimum of 3 months [III, A]. LMWH is suggested, although, in the absence of direct comparisons between anticoagulants in this setting, VKAs or DOACs may be considered alternative options [IV, C].
- It is recommended to remove the catheter if it is not needed or is infected, anticoagulant treatment is contraindicated or there is clinical deterioration due to thrombus extension despite treatment [III, B].
- In patients with CRT, who have completed 3 months of anticoagulant treatment, extended anticoagulation until catheter removal is suggested, if the patient's bleeding risk is low [IV, C].

1.2.9 European Society for the Study of the Liver (EASL) Clinical Practice Guidelines on Prevention and Management of Bleeding and Thrombosis in Patients with Cirrhosis (2021)

The prevention and management of bleeding and thrombosis in patients with cirrhosis poses several difficult clinical questions. These Clinical Practice Guidelines have been developed to provide practical guidance on debated topics, including current views on hemostasis in liver disease, controversy regarding the need to correct thrombocytopenia and abnormalities in the coagulation system in patients undergoing invasive procedures, and the need for thromboprophylaxis in hospitalized patients with hemostatic abnormalities. Multiple recommendations in this document are based on interventions that the panel feels are not useful, even though widely applied in clinical practice[28].

The quality of evidence was scored according to the Oxford Centre for Evidence-based Medicine (OCEBM) (adapted from The Oxford 2011 Levels of Evidence, outlined as follows:

Table 17. Level of Evidence Definition (EASL 2021 Guidelines)

Levels of Evidence	
1	Systematic reviews (with homogeneity) of randomized controlled trials
2	Randomized controlled trials or observational studies with dramatic effects; systematic reviews of lower quality studies (i.e. non-randomized, retrospective)
3	Non-randomized controlled cohort/follow-up study/control arm of randomized trial (systematic review is generally better than an individual study)
4	Case series, case-control, or historically controlled studies (systematic review is generally better than an individual study)
5	Expert opinion (mechanism-based reasoning)

- The Delphi panel then examined the CPG. Returning scores were graded as follows:
    - Less than 50% approval: re-write recommendation and resubmit to the Delphi panel;
    - 50%-75% approval: re-write/improve the recommendation, but no resubmission to the Delphi panel;
    - 75-90% approval: no need to re-write the recommendation but the document will take into account the comments;
    - ≥ 90% approval: assumed as consensus, no change needed but small corrections possible.
    - To consider a question approved, an agreement from at least 75% of Delphi panel members was required.
- In patients with cirrhosis at risk of DVT/PE, thromboprophylaxis with LMWH can be recommended as it has a reasonable safety profile, but efficacy is unclear based on available data (LoE 3, weak recommendation); Delphi panel agreement: 93%
- In patients with Child-Pugh class A and B cirrhosis at risk of DVT/PE, thromboprophylaxis with DOACs can be recommended as DOACs have a reasonable safety profile in these patients, but efficacy data are still limited. In patients with Child-Pugh C cirrhosis, DOACs are not recommended (Safety: LoE 2; Efficacy: LoE 4; weak recommendations); Delphi panel agreement: 89%
- For treatment of DVT/PE, vitamin K antagonists should be used with caution in patients with cirrhosis, as these patients can have baseline altered INR and

thus target INR remains unknown. In patients with Child-Pugh A, LMWH, and vitamin K antagonists are reasonable options. Until more data become available, LMWH is recommended for treatment of DVT/PE in patients with Child-Pugh B and Child-Pugh C cirrhosis, whereas UFH is the treatment of choice in case of renal failure (LoE 4, weak recommendation); Delphi panel agreement: 87%

- For the treatment of DVT/PE in patients with cirrhosis, currently available data suggest that there are no major concerns regarding the safety of DOACs in patients with Child-Pugh class A cirrhosis. Due to the possibility of accumulation, DOACs should be used with caution in Child-Pugh class B patients, as well as in patients with creatinine clearance below 30 ml/min. The use of DOACs in Child- Pugh class C patients is not recommended (LoE 4, strong recommendation); Delphi panel agreement: 90%

1.2.10 American College of Cardiology (ACC) Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients with Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or with Atherosclerotic Cardiovascular Disease (2020)

The guidelines recommend the following[29]:

- Recommendations for patients with AF relate specifically to those with nonvalvular AF and should not be extrapolated to those with valvular AF (a controversial term in itself but most commonly defined as AF associated with moderate to severe mitral stenosis, most frequently rheumatic, or with mechanical heart valves)
- The below recommendations are for patients on antiplatelet and developed a new VTE.
- For patients on SAPT for stable ischemic heart disease (SIHD), with no history of ACS and no prior revascularization who develop VTE requiring AC therapy, the appropriate management is nearly always to stop APT and start an AC.
    - For patients on APT for SIHD, with no history of ACS but prior PCI, the time since PCI should be assessed.
    - If it has been ≤ 6 months since PCI, the guidelines' recommendation for most patients would be to stop aspirin, continue clopidogrel, and start an AC (with preference given to a DOAC)
    - If it has been 6 to 12 months since PCI, the guidelines recommend continuing SAPT with either aspirin or clopidogrel until 1-year post-PCI, along with an OAC.

    - If it has been ≥12 months post-PCI, an OAC alone can be used long-term.
    - For patients on APT for SIHD with no history of ACS but who had prior CABG surgery, the time since CABG surgery should be assessed. The guidelines recommend continuing aspirin (<100 mg/day) if < 1 year post-CABG surgery and stopping aspirin if > 1 year post-CABG surgery
- Patients with ACS (unstable angina, non–ST-elevation myocardial infarction, and ST-elevation myocardial infarction) are usually treated with DAPT for 12 months after ACS. If these patients were previously on prasugrel or ticagrelor, the guidelines recommend switching to clopidogrel.
    - If it has been ≤12 months since the ACS, the guidelines' recommendation for most patients would be to stop aspirin, continue the P2Y12i (with preference given to clopidogrel), and start an AC (with preference given to a DOAC)
    - If it has been >12 months since the ACS, APT may be stopped and most patients can be treated with an AC alone.
    - For patients at high bleeding risk and low ischemic risk, shorter durations of APT can be considered.
    - At the clinician's discretion, selected patients felt to be at higher thrombotic risk due to: a) the nature of the coronary lesion; b) the type, location, number, or length of coronary stents; or c) other clinical factors, and low bleeding risk may continue SAPT (aspirin 81 mg daily or clopidogrel 75 mg daily) beyond 12 months while on an AC.
- For patients on APT for prior TIA or cerebrovascular accident who develop VTE requiring AC therapy, the pathway recommends stopping all APT and treating with an AC alone (DOAC preferred) when considered safe from the perspective of hemorrhagic transformation, typically between 2 and 14 days following an acute event. Given that TIA is the diagnosis when no infarct or hemorrhage is noted on imaging, an AC can typically be initiated immediately.
- For patients who have undergone recent carotid endarterectomy, the pathway recommends stopping all APT and treating with an AC alone (DOAC preferred) when considered safe from risk of post-operative bleeding, typically 3 to 14 days after surgery.
- For patients with carotid stenting within the previous 1 to 3 months, our recommendation for most patients would be to stop aspirin, continue the P2Y12i (clopidogrel preferred), and start an AC (DOAC preferred). If the standard duration of DAPT after carotid stenting has ended (usually 1 to 3

months), all APT may be stopped and most patients can be treated with an AC alone.

- Patients with PAD without prior intervention or with prior surgical repair are usually treated with SAPT (usually aspirin or clopidogrel) for primary or secondary prevention of ischemic events (myocardial infarction, stroke). For such patients presenting with VTE appropriate for an AC, the pathway recommends stopping all APT and treating with an AC alone (DOAC preferred).
- Patients with PAD who have been treated with endovascular intervention/stenting are usually treated with APT for 1 to 3 months. The type and duration of APT is less well-defined and standardized than for coronary interventions. For patients presenting with VTE appropriate for AC therapy, the pathway recommends continuing or switching to SAPT (either clopidogrel or aspirin, clopidogrel preferred) and treating with an AC (DOAC preferred). If the standard duration of DAPT after endovascular intervention/stenting has ended (usually 1 to 3 months), all APT may be stopped and most patients can be treated with an AC alone.
- Table 18 lists the recommended anticoagulation dosing for VTE:

Table 18. Anticoagulation Dosing Table for VTE (ACC 2020 Guidelines)

Agent	VTE Initial Treatment	VTE Secondary Prevention after Initial Therapy	Dosing Adjustments
Apixaban	10 mg orally twice daily for the first 7 days of therapy followed by 5 mg orally twice daily.	After ≥ 6 months of initial therapy, either 5 mg orally twice daily or 2.5 mg orally twice daily can be considered.	Patients with ESKD receiving hemodialysis were not enrolled in clinical trials. However, the prescribing information states that no dose adjustment is necessary for patients with renal impairment, including those with ESKD.
Dabigatran	150 mg orally twice daily when preceded by 5–10 days of parenteral AC.	150 mg orally twice daily.	Patients with severe renal impairment (a CrCl of ≤ 30 mL/min) and with ESKD receiving hemodialysis were not enrolled in clinical trials. The prescribing information makes no recommendations for dosing in this population.
Edoxaban	60 mg orally once daily when preceded by at least 5-10 days of parenteral AC.	60 mg orally once daily.	Dose reduction to 30 mg once daily for patients with a CrCl (estimated using actual body weight) of 15–50 mL/min or body weight ≤ 60 kg.
Rivaroxaban	15 mg orally twice daily with food for the first 21 days followed by 20 mg daily with food.	After ≥ 6 months of initial therapy, either 20 mg orally daily with food or 10 mg orally daily with or without food can be considered.	Patients with a CrCl of < 30 mL/min were excluded from clinical trials. Avoid use in patients with a CrCl of < 15 mL/min.

VKA	When used with APT: INR 2.0–2.5; bridging with parenteral heparin initially.	When used with APT: Consider INR 2.0–2.5.	N/A
Dalteparin	In the setting of cancer: 200 units/kg subcutaneously once daily for 1 month, then 150 IU/kg subcutaneously once daily (months 2–6) for extended treatment.	In the setting of cancer: Not FDA-approved for this indication, but use is consistent with NCCN recommendations.	For patients with a CrCl of < 30 mL/min, the prescribing information recommends monitoring anti–Factor Xa levels with a target peak level (4– 6 hours post-dose) of 0.5–1.5 IU/mL. Patients with ESKD were excluded from clinical trials.
Enoxaparin	In the setting of cancer: 1 mg/kg twice daily or 1.5 mg/kg once daily, subcutaneously.	In the setting of cancer: Not FDA-approved for this indication, but use is consistent with NCCN recommendations.	Patients with a CrCl of < 30 mL/min were excluded from clinical trials. However, the prescribing information recommends a dose reduction to 1 mg/kg subcutaneously once daily for patients with a CrCl (estimated using actual body weight) of < 30 mL/min.

Dosing information in this table does not take drug–drug interactions into consideration. The reader is encouraged to review the specific drug prescribing information.

Reduced-dose rivaroxaban (10 mg daily) and apixaban (2.5 mg twice daily) can be considered for secondary prevention of VTE after 6 months of initial treatment.

Dabigatran, edoxaban: Initial treatment with unfractionated heparin, LMWH, or fondaparinux recommended.

Dabigatran 110 mg twice daily is approved for use in DVT/PE treatment outside of the United States.

Long-term treatment with enoxaparin at this dose has not been tested in cancer patients. Among patients without cancer, enoxaparin is approved for DVT and is also used extensively off-label for treatment of PE.

AC = anticoagulation; APT = antiplatelet therapy; CrCl = creatinine clearance; DVT = deep vein thrombosis; ESKD = end-stage kidney disease; FDA = U.S. Food and Drug Administration; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NA = not applicable; NCCN = National Comprehensive Cancer Network; PE = pulmonary embolism; VKA = vitamin K antagonist.

Section 2.0 Drug Therapy in Venous Thromboembolism

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

No new drugs have been approved by the FDA or EMA for the treatment of Venous Thromboembolism since March 2020.

2.2 Modifications

Below are the modifications made to the list of Venous Thromboembolism drugs since the CHI report in March 2020, reflecting the changes and updates:

Table 19. Prescribing Edits (PE) Modifications of Certain Venous Thromboembolism Drugs

Drugs	PE Modifications
Phytomenadione	**EU:** used in emergency cases to counteract the effect of vitamin K antagonists **MD**: to be prescribed by a specialist in the management of thrombotic events
Protamine Sulfate	**EU:** used in emergency cases to counteract the effect of heparin **MD**: to be prescribed by a specialist in the management of thrombotic events
Alteplase and Tenecteplase	**PA was removed.** **MD was added:** to be prescribed by a specialist in the management of thrombotic events.

2.3 Delisting

After thorough review of the previous CHI drug list for Venous Thromboembolism treatment, it is recommended to delist the below medications from CHI formulary:

- Bivalirudin

Table 20. Delisted Drugs

Delisted Medications	Reason	Medication Status	SFDA-registered Available Alternative
Bivalirudin	Drug is no longer SFDA registered	**Guidelines** recommend the use of direct thrombin inhibitor for the treatment of VTE. Not **FDA** or **EMA** approved for this indication[30,31]	Parenteral direct thrombin inhibitor: Argatroban Oral direct thrombin inhibitor: Dabigatran

Section 3.0 Key Recommendations Synthesis

- For patients with DVT and/or PE, the ASH guideline panel does not suggest one DOAC over another. Factors, such as a requirement for lead-in parenteral anticoagulation, once- vs twice-daily dosing, and out-of-pocket cost may drive the selection of specific DOACs. Other factors, such as renal function, concomitant medications (e.g., need for a concomitant drug metabolized through the CYP3A4 enzyme or P-glycoprotein), and the presence of cancer, may also impact DOAC choice. (conditional recommendation based on very low certainty in the evidence of comparative effects ⨁◯◯◯)[10].
- For patients with extensive DVT in whom thrombolysis is considered appropriate, the ASH guideline panel suggests using catheter-directed thrombolysis over systemic thrombolysis (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯)[10].
- For patients with proximal DVT and significant preexisting cardiopulmonary disease, the ASH guideline panel suggests anticoagulation alone rather than anticoagulation plus insertion of an inferior vena cava (IVC) filter (conditional recommendations based on low certainty in the evidence of effects ⨁⨁◯◯)[10].
- For primary treatment of patients with DVT and/or PE, whether provoked by a transient risk factor or by a chronic risk factor or unprovoked, the ASH guideline panel suggests using a shorter course of anticoagulation for primary treatment (3-6 months) over a longer course of anticoagulation for primary treatment (6-12 months) (conditional recommendations based on moderate certainty in evidence of effects ⨁⨁⨁◯)[10].
- Offer either apixaban or rivaroxaban to people with confirmed proximal DVT or PE. If neither apixaban nor rivaroxaban is suitable offer[11]:
    - LMWH for at least 5 days followed by dabigatran or edoxaban or
    - LMWH concurrently with a vitamin K antagonist (VKA) for at least 5 days, or until the international normalized ratio (INR) is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.
- Offer people with confirmed proximal DVT or PE and renal impairment (estimated creatinine clearance between 15 ml/min and 50 ml/min) one of [11]:
    - apixaban
    - rivaroxaban
    - LMWH for at least 5 days followed by:
        - edoxaban or

        - dabigatran if estimated creatinine clearance is 30 ml/min or above
    - LMWH or UFH, given concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.
- Offer people with confirmed proximal DVT or PE and established renal failure (estimated creatinine clearance less than 15 ml/min) one of[11]:
    - LMWH
    - UFH
    - LMWH or UFH concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.
- Consider using the HAS-BLED score for major bleeding risk to assess the risk of major bleeding in people having anticoagulation treatment for unprovoked proximal DVT or PE. Discuss stopping anticoagulation if the HAS-BLED score is 4 or more and cannot be modified[11].
- If the current treatment is not well tolerated, or the clinical situation or person's preferences have changed, consider switching to apixaban if the current treatment is a direct-acting anticoagulant other than apixaban[11].
- Consider an IVC filter for people with proximal DVT or PE when anticoagulation treatment is contraindicated. Remove the IVC filter when anticoagulation treatment is no longer contraindicated and has been established[11].
- In patients with cerebral vein/venous sinus thrombosis, the guidelines recommend anticoagulation therapy for at least the treatment phase (first 3 months) over no anticoagulant therapy (strong recommendation, low-certainty evidence)[12].
- In patients with VTE diagnosed in the absence of transient risk factor (unprovoked VTE or provoked by a persistent risk factor) who cannot receive a DOAC, the guidelines suggest offering extended-phase anticoagulation with a VKA (weak recommendation, moderate certainty evidence)[12].
- For patients with AF and native valve heart disease (except rheumatic mitral stenosis [MS]) or who received a bioprosthetic valve >3 months ago, a non–vitamin K oral anticoagulant (NOAC) is an effective alternative to VKA anticoagulation and should be administered on the basis of the patient's CHA2DS2-VASc score (COR: 1, LOE: A)[13].

- For patients with AF and rheumatic MS, long-term VKA oral anticoagulation is recommended (COR: 1, LOE: C-EO)[13].
- For patients with new-onset AF ≤3 months after surgical or transcatheter bioprosthetic valve replacement, anticoagulation with a VKA is reasonable (COR: 2a, LOE: B-NR) [13] In adults with trauma who receive pharmacologic VTE prophylaxis, we suggest using LMWH (e.g., enoxaparin, dalteparin) over UFH (Weak, low) UFH is preferred in patients with end-stage renal disease and in those with low creatinine clearance (< 30 ml/min)[14].
- In adults with trauma and low risk of bleeding who are prescribed LMWH (enoxaparin) for VTE prophylaxis, we suggest using either intermediate–high dose LMWH or conventional dosing LMWH (Weak, very low)[14].

  Most common regimen used was enoxaparin 40 mg subcutaneous every 12 h

  This recommendation is inapplicable to those at a high risk for bleeding (patients older than 65 year, < 50 kg, have low creatinine clearance, and TBI or SCI patients who are high risk for bleeding)[14].
- In adults with trauma who are not candidates for pharmacologic VTE prophylaxis, we recommend using mechanical VTE prophylaxis with IPC over no mechanical VTE prophylaxis when not contraindicated by lower extremity injury (Strong, very low)[14].
- The NCCN Guidelines Panel for Cancer-Associated Venous Thromboembolic Disease recommends VTE prophylaxis for all patients hospitalized with cancer, excluding those with basal/squamous cell skin cancer[15].
- Clinical suspicion of superficial vein Thrombosis (SVT) - Upper extremity SVT (median, basilic, and/or cephalic veins)[15]:
    - Use symptomatic treatment and monitor for progression
    - If progression symptomatically or on imaging, consider prophylactic dose anticoagulation
    - Consider initial therapeutic dose anticoagulation if the clot is in close proximity to the deep venous system
- Clinical suspicion of superficial vein Thrombosis (SVT) - Lower extremity SVT (great and small saphenous veins)[15]:
    - Prophylactic dose anticoagulation for at least 6 weeks if:
        - SVT > 5 cm in length
        - SVT extends above knee
    - Therapeutic dose anticoagulation for at least 3 months if SVT is within 3 cm of the saphenofemoral junction

    - Consider repeat US in 7–10 days if SVT <5 cm in length or below knee. If repeat US shows progression, consider anticoagulation.

- Consider longer duration anticoagulation in patients with catheters with poor flow, persistent symptoms, or unresolved thrombus. Consider shorter duration of anticoagulation if clot or symptoms resolve in response to anticoagulation and/or catheter removal[15].

- Progression or new thrombosis on therapeutic anticoagulation – alternative coagulant to UFH[15]:
    - Switch to alternative anticoagulant (DOACs [apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B], LMWH, warfarin, fondaparinux)
    - Increase dose of UFH

- For hospitalized medical oncology patients with acute medical illness, primary prophylaxis with LMWH should be offered for patients admitted in the absence of contraindications (Level of agreement: 100%)[16].
- For hospitalized medical oncology patients without additional risk factors, primary pharmacological prophylaxis can be offered in the absence of bleeding or other contraindications (Level of agreement: 83%)[16].
- LMWH is the pharmacological option of choice for the primary prophylaxis of CT and remained predominately used in an inpatient and outpatient setting in Saudi Arabia unless contraindicated (Level of agreement: 83%)[16].
- Pneumatic compression devices can be offered for patients with contraindications for anticoagulants until the contraindications are resolved (Level of agreement: 100%)[16].
- High-risk ambulatory patients should be offered thromboprophylaxis. In Saudi Arabia, DOACs and LMWH is commonly used in this setting unless contraindicated (Level of agreement: 75%)[16].
- DOACs can be offered for up to 6 months for primary prophylaxis in high-risk ambulatory cancer patients (KRS ≥ 2) if no contraindications and they cannot take LMWH[16].
    - DOACs are relatively inexpensive and readily available, which allows their use for primary prophylaxis in high-risk patients (Level of agreement: 100%)
- Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered thromboprophylaxis with either aspirin or LMWH (lower-risk patients) or LMWH (higher-risk patients) (Level of agreement: 100%)[16].

- All patients undergoing major surgery should be offered pharmacological, preoperative prophylaxis with UFH or LMWH, unless contraindicated, and should be continued for at least 7–10 days (Level of agreement: 100%)[16].
- Extended prophylaxis with LMWH for up to 4 weeks postoperatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic cancer surgery with high-risk features (Level of agreement: 100%)[16].
- Combined pharmacologic/mechanical prophylaxis may improve efficacy, especially in highest-risk patients. However, mechanical prophylaxis should not be used as monotherapy unless pharmacologic prophylaxis is contraindicated (Level of agreement: 100%)[16].
- The choice of anticoagulation regimen should be based on individual risk of thrombosis and bleeding, renal and hepatic function, inpatient/outpatient status, FDA approval status, ease of administration, cost, the burden of laboratory monitoring, agent reversibility, and patient preferences (Level of agreement: 100%)[16].
- DOACs, LMWH, UFH, or fondaparinux, can be used as initial anticoagulants. Among parenteral agents, LMWH is preferred over UFH in the absence of severe renal impairment (Level of agreement: 100%)[16].
- LMWH is preferred for patients with acute VTE at high risk for bleeding or with GI malignancy (Level of agreement: 83.3%)[16].
- For long-term anticoagulation, DOACs or LMWH for at least 6 months is preferred over VKA. VKAs are less effective but may be used if DOACs or LMWH are not accessible (Level of agreement: 100%)[16].
- Catheter-directed pharmaco-mechanical thrombolysis can be considered for DVT in patients at low risk for bleeding but at risk for limb loss or severe persistent symptoms despite anticoagulation (Level of agreement: 100%)[16].
- Incidental VTE should be treated in the same manner as symptomatic VTE (Level of agreement: 100%)[16].
- The ASH guideline panel suggests that outpatient anticoagulant thromboprophylaxis not be used for patients with COVID-19 who are being discharged from the hospital and do not have suspected or confirmed venous thromboembolism (VTE) or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯)[17].
- The American Society of Hematology (ASH) guideline panel suggests using prophylactic-intensity over intermediate-intensity anticoagulation in patients

with COVID-19–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE) (conditional recommendation based on low certainty in the evidence about effects ⨁⨁◯◯)[18].

- The ASH guideline panel suggests using therapeutic-intensity over prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)[19].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Venous Thromboembolism report** and aims to provide recommendations to aid in the management of Venous Thromboembolism. These recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Venous Thromboembolism. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Venous Thromboembolism Scope

Venous Thromboembolism Scope

<table>
<tr><th>Section</th><th>Rationale/Updates</th></tr>
<tr><td>Section 1.1.1
NCCN Clinical Practice Guidelines in Oncology: Cancer-associated venous thromboembolism [2019]</td><td>
NCCN v2.2023 Cancer-Associated Venous Thromboembolic Disease[11]

The NCCN Guidelines Panel for Cancer-Associated Venous Thromboembolic Disease recommends VTE prophylaxis for all patients hospitalized with cancer, excluding those with basal/squamous cell skin cancer. Although multiple risk assessment models (RAMs) have been developed for patients hospitalized for medical or surgical care, none of these RAMs have been validated in prospective management studies conducted in patients hospitalized with cancer.
Contraindications to Prophylactic Anticoagulation:

Current or previous heparin-induced thrombocytopenia (HIT) (contraindication for LMWH and UFH)

VTE prophylaxis options: ambulatory medical oncology patients and patients post-medical oncology discharge:

<table>
<tr><th>Agent</th><th>Standard Dosing</th><th>Renal Dose</th><th>Other Dose Modifications</th></tr>
<tr><td>Apixaban</td><td>2.5 mg PO twice daily</td><td>Avoid if CrCl <30 mL/min</td><td>Avoid if platelet count <50,000/µL

Avoid if weight <40 kg</td></tr>
<tr><td>Rivaroxaban</td><td>10 mg PO once daily</td><td>Avoid if CrCl <30 mL/min</td><td>Avoid if platelet count <50,000/µL</td></tr>
<tr><td>Dalteparin</td><td>200 units/kg SC daily x 1 month, then
150 units/kg SC daily x 2 months</td><td>Avoid if CrCl <30 mL/min</td><td>Avoid if platelet count <50,000/µL</td></tr>
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	Enoxaparin	1 mg/kg SC daily x 3 months, then 40 mg SC daily	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/µL

➔ Recommendations derived from clinical trials of ambulatory patients with cancer with high thrombosis risk (>18 years, Khorana VTE Risk Score of ≥2, initiating new course of chemotherapy) and are not included in product labeling. Prophylaxis duration should be 6 months or longer if risk persists

➔ Apixaban is absorbed in the stomach, proximal small bowel, and colon. Patients who have had significant resections of these portions of the intestinal tract may be at risk for suboptimal absorption

➔ DOACs are absorbed primarily in the stomach and proximal small bowel, so they may not be appropriate for patients who have had significant resections of these portions of the intestinal tract.

➔ Data support the use of prophylactic dalteparin and enoxaparin for patients with advanced unresectable and metastatic pancreatic cancer.

- VTE prophylaxis options: surgical oncology inpatients:
    - Obtain LMWH anti-Xa level 3–5 hours after the third dose to assess dosing. Adjustments may be needed to the dose according to anti-Xa levels, with a recommended target of 0.2 to 0.4 IU/mL for peak levels or 0.1 to 0.2 IU/mL for trough levels. If dose escalation or de-escalation is required twice, consult with Hematology or a Clinical Pharmacy Specialist.
    - Rivaroxaban was added as an option. Only applies to patients after laparoscopic surgery for colorectal cancer.
    - Dosing for actual body weight 25-50 kg:
        - **Dalteparin**: No dose adjustment available
        - **Enoxaparin**:
          Actual body weight 25–40 kg:
          Consider 20 mg SC dailyf (avoid if CrCl <30 mL/min)
          OR
          Actual body weight 41–50 kg:
        - Consider 30 mg SC dailyf (avoid if CrCl <30 mL/min)

	- **Fondaparinux**: No dose adjustment available - **UFH**: Weight <40 kg: 2500 units SC every 8–12 hours - **Apixaban**: No dose adjustment available - **Rivaroxaban**: No dose adjustment available o Dosing recommendations for patients weighing 25–40 kg are included as guidance and based on expert opinion. Available data suggest administration of standard VTE prophylaxis doses to patients in this weight range results in over-exposure and increased bleeding, but there are very limited data available to inform dose reduction strategies. • VTE prophylaxis options: post-discharge prophylaxis for surgical oncology patients o Rivaroxaban was added at 10 mg daily for 21 days: Start rivaroxaban after 1 week of standard dose LMWH (enoxaparin 40 mg SC daily or dalteparin 5000 SC units daily). Avoid if CrCl < 30 ml/min o Oter dose modifications: - Apixaban: Avoid if platelet count <50,000/µL, avoid if weight <40 kg - Rivaroxaban: Avoid if platelet count <50,000/µL - Dalteparin: Avoid if platelet count <50,000/µL - Enoxaparin: Avoid if platelet count <50,000/µL • Clinical suspicion of superficial vein Thrombosis (SVT) - Upper extremity SVT (median, basilic, and/or cephalic veins): o Use symptomatic treatment and monitor for progression o If progression symptomatically or on imaging, consider prophylactic dose anticoagulation o Consider initial therapeutic dose anticoagulation if the clot is in close proximity to the deep venous system • Clinical suspicion of superficial vein Thrombosis (SVT) - Lower extremity SVT (great and small saphenous veins): o Prophylactic dose anticoagulation for at least 6 weeks if: - SVT >5 cm in length - SVT extends above knee o Therapeutic dose anticoagulation for at least 3 months if SVT is within 3 cm of the saphenofemoral

	junction o Consider repeat US in 7–10 days if SVT <5 cm in length or below knee. If repeat US shows progression, consider anticoagulation. ➔ Prophylactic dose anticoagulation with rivaroxaban 10 mg PO daily and fondaparinux 2.5 mg SC daily have been shown to be effective in some studies that included a limited number of patients with cancer ➔ If SVT is within 3 cm from the saphenofemoral junction, treat with therapeutic dose anticoagulation • Consider longer duration anticoagulation in patients with catheters with poor flow, persistent symptoms, or unresolved thrombus. Consider shorter duration of anticoagulation if clot or symptoms resolve in response to anticoagulation and/or catheter removal. • Chronic, portal, mesenteric, and/or splenic vein thrombosis: considering TIPS or surgical shunt was added as an option o Consider TIPS as one of the management options for patients with SPVT and portal hypertension o If thrombectomy expertise is not available, consider consultation with a tertiary medical center. • Enoxaparin 1 mg/kg SC every 12 hours (BMI <40 kg/m2) or 0.8 mg/kg SC every 12 hours (BMI ≥40 kg/m2) (can consider decreasing intensity to 1.5 mg/kg daily after first month) • There are limited data on long-term use of LMWH in patients with CrCl <30 mL/min. • Contraindications – DOACs: o Pregnancy or breast feeding were added o Active/clinically significant liver disease: - Apixaban: Child-Pugh Class B or C or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3x upper limit of normal (ULN); total bilirubin >2x ULN - Rivaroxaban: Child-Pugh class B or C or ALT/AST >3x ULN - Dabigatran: Child-Pugh class C or ALT/AST >2x ULN or active/acute hepatitis or cirrhosis - Edoxaban: Child-Pugh class B or C or AST/ALT >3x ULN and bilirubin >2x ULN, cirrhosis, or active hepatitis - Strong dual inhibitors/inducers of CYP3A4 and P-gp: see prescribing information for rivaroxaban and apixaban

	• DOACs and GI tract surgery considerations:
	  o DOACs are absorbed primarily in the stomach and proximal small bowel (with the exception of apixaban, which is also partially absorbed in the colon), so they may not be appropriate for patients who have had significant resections of these portions of the intestinal tract.
	  o Due to limited data, consider checking a drug-specific anti-Xa level for Xa-inhibitors or a dabigatran level to ensure adequate absorption.
	• Enteral feeding tube administration of DOACs
	  o Apixaban: For nasogastric/gastric feeding tube administration, crushed tablets may be suspended in 60 mL of water or D5W followed by immediate delivery. Crushed tablets are stable in water and D5W for up to 4 hours. Bioavailability is reduced if administered distal to the stomach.
	  o Rivaroxaban: For nasogastric/gastric feeding tube administration, crushed tablets may be suspended in 50 mL of water and administered within 4 hours of preparation. Follow administration of the 15 mg and 20 mg tablets immediately with enteral feeding (2.5 mg and 10 mg tablets may be administered without regard to food). Avoid administration distal to the stomach, which can result in reduced absorption. A commercially prepared oral suspension formulation with an accompanying measuring syringe is also available for pediatric patients.
	  o Edoxaban: Crushed tablets may be suspended in 2 to 3 ounces of water and immediately administered through a gastric tube.
	  o Dabigatran: Should not be administered through an enteral feeding tube.
	• Progression or new thrombosis on therapeutic anticoagulation – alternative coagulant to UFH:
	  o Switch to alternative anticoagulant (DOACs [apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B], LMWH, warfarin, fondaparinux)
	  o Increase dose of UFH
	• LMWH (anti-Xa) levels may be considered in patients with body weight extremes, renal impairment, or for whom adherence is a concern. Obtain LMWH anti-Xa level 3-5 hours after the third dose to assess dosing. Adjustments may be needed to the dose according to anti-Xa levels, with a recommended peak of 0.6-1.0 units/ml (1 mg/kg twice daily dosing) or peak of 1-2 units/mL (1.5 mg/kg once daily dosing).
	• Reversal of anticoagulation
	  o In the event of life-threatening bleeding or the need for urgent/emergent invasive procedures,

anticoagulant effect must be reversed promptly.

- UFH: Follow aPTT or anti-Xa levels in accordance with institutional SOP closely, was added
- In the event of ongoing bleeding and persistent drug levels, consider a second dose of protamine for both UFH and LWMH.
- DOACs: Drug-specific anti-Xa assays should not be used to assess reversal of direct factor Xa inhibitors after administration of andexanet alfa, as they are not interpretable, was added
- Andexanet alfa dosing and administration:

Medication	Last Dose	Dosing Strategy Based on Time Since Last Dose	
		Last Dose <8 Hours Prior or Unknown	Last Dose ≥8 Hours Prior
Rivaroxaban	≤10 mg	Low-dose	Low-dose
	>10 mg or unknown	High-dose	Low-dose
Apixaban	≤5 mg	Low-dose	Low-dose
	>5 mg or unknown	High-dose	Low-dose
Edoxaban	≤30 mg	Low-dose	Low-dose
	>30 mg	High-dose	Low-dose

Dose	Initial IV Bolus (administered at a rate of 30 mg/min)	IV Infusion
Low-dose	400 mg	480 mg administered over 120 minutes (4 mg/min)
High-dose	800 mg	960 mg administered over 120 minutes (8 mg/min)

➔ All patients should receive an initial IV bolus followed immediately by IV infusion as outlined above. The safety and efficacy of repeat dosing or extension of infusion beyond this time frame have not been evaluated.

➔ Note, the IV infusion dosing recommendations above differ from the package insert prescribing

	information to round doses to the closest available vial size. • Workup and management for suspected hit: A "low" pre-test probability score combined with a negative antibody test is useful in ruling out a diagnosis of HIT; a positive test increases the suspicion for HIT. In patients without cancer with 4T scores of 1–3, the risk of HIT is small but not zero, but this has not been validated in patients with cancer. Based on clinical judgment, HIT antibody testing and initiation of argatroban/ bivalirudin or fondaparinux in place of UFH/LMWH may be warranted in select patients.
Section 1.1.2 **NICE guidelines for Venous thromboembolic diseases: diagnosis, management and thrombophilia testing [2012]**	**NICE Venous thromboembolic diseases: diagnosis, management and thrombophilia testing 2023**[11] **DVT likely (Wells score 2 points or more)** • If a proximal leg vein ultrasound scan result cannot be obtained within 4 hours, offer people with a DVT Wells score of 2 points or more: o a D-dimer test, **then** o interim therapeutic anticoagulation **and** o proximal leg vein ultrasound scan with the result available within 24 hours • For people with a negative proximal leg vein ultrasound scan and a positive D-dimer test result: o stop interim therapeutic anticoagulation, but do not stop: - long-term anticoagulation when used for secondary prevention, or - short-term anticoagulation when used for primary venous thromboembolism (VTE) prevention in people with COVID-19 o offer a repeat proximal leg vein ultrasound scan 6 to 8 days later and - if the repeat scan result is positive, follow the actions in below sections - if the repeat scan result is negative, follow the actions in below sections • For people with a negative proximal leg vein ultrasound scan and a negative D-dimer test result: o Stop interim therapeutic anticoagulation, but do not stop: - long-term anticoagulation when used for secondary prevention, or - short-term anticoagulation when used for primary VTE prevention in people with COVID-19 o Think about alternative diagnoses o Tell the person that it is not likely they have DVT. Discuss with them the signs and symptoms of DVT and when and where to seek further medical help.

	DVT unlikely (Wells score 1 point or less)
	• Offer people with an **unlikely** DVT Wells score (1 point or less):
	  o A D-dimer test with the result available within 4 hours or
	  o If the D-dimer test result cannot be obtained within 4 hours, offer interim therapeutic anticoagulation while awaiting the result
	• If the D-dimer test result is positive, offer:
	  o A proximal leg vein ultrasound scan, with the result available within 4 hours if possible or
	  o Interim therapeutic anticoagulation and a proximal leg vein ultrasound scan with the result available within 24 hours.
	• If the proximal leg vein ultrasound scan is negative:
	  o Stop interim therapeutic anticoagulation, but do not stop:
	  - long-term anticoagulation when used for secondary prevention, or
	  o short-term anticoagulation when used for primary VTE prevention in people with COVID-19
	  o think about alternative diagnoses
	  o tell the person that it is not likely they have DVT. Discuss with them the signs and symptoms of DVT and when and where to seek further medical help.
	• If possible, choose an interim anticoagulant that can be continued if DVT or PE is confirmed
	• When using interim therapeutic anticoagulation for suspected proximal DVT or PE:
	  o Carry out baseline blood tests including full blood count, renal and hepatic function, prothrombin time (PT) and activated partial thromboplastin time (APTT)
	  o Do not wait for the results of baseline blood tests before starting anticoagulation treatment
	  o Review, and if necessary act on, the results of baseline blood tests within 24 hours of starting interim therapeutic anticoagulation.
	• Offer anticoagulation treatment for at least 3 months to people with confirmed proximal DVT or PE.
	• When offering anticoagulation treatment, take into account comorbidities, contraindications and the person's preferences.
	• Offer either apixaban or rivaroxaban to people with confirmed proximal DVT or PE. If neither apixaban nor rivaroxaban is suitable offer:

	○ LMWH for at least 5 days followed by dabigatran or edoxaban or ○ LMWH concurrently with a vitamin K antagonist (VKA) for at least 5 days, or until the international normalized ratio (INR) is at least 2.0 in 2 consecutive readings, followed by a VKA on its own. • Do not routinely offer unfractionated heparin (UFH) with a VKA to treat confirmed proximal DVT or PE unless the person has renal impairment or established renal failure or an increased risk of bleeding. • Consider anticoagulation treatment with regular monitoring of therapeutic levels for people with confirmed proximal DVT or PE who weigh less than 50 kg or more than 120 kg, to ensure effective anticoagulation. Note the cautions and requirements for dose adjustment and monitoring in the medicine's summary of product characteristics (SPC), and follow locally agreed protocols or advice from a specialist or multidisciplinary team. • For people with confirmed PE and hemodynamic instability, offer continuous UFH infusion and consider thrombolytic therapy. • Offer people with confirmed proximal DVT or PE and renal impairment (estimated creatinine clearance between 15 ml/min and 50 ml/min) one of: ○ apixaban ○ rivaroxaban ○ LMWH for at least 5 days followed by: - edoxaban or - dabigatran if estimated creatinine clearance is 30 ml/min or above ○ LMWH or UFH, given concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own. Note the cautions and requirements for dose adjustment and monitoring in the medicine's SPC, and follow locally agreed protocols or advice from a specialist or multidisciplinary team. • Offer people with confirmed proximal DVT or PE and established renal failure (estimated creatinine clearance less than 15 ml/min) one of: ○ LMWH ○ UFH ○ LMWH or UFH concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2

	consecutive readings, followed by a VKA on its own. Note the cautions and requirements for dose adjustment and monitoring in the medicine's SPC, and follow locally agreed protocols or advice from a specialist or multidisciplinary team. • Offer people with active cancer and confirmed proximal DVT or PE anticoagulation treatment for 3 to 6 months. Review at 3 to 6 months according to clinical need.. • When choosing anticoagulation treatment for people with active cancer and confirmed proximal DVT or PE, take into account the tumor site, interactions with other drugs including those used to treat cancer, and the person's bleeding risk. • Consider a direct-acting oral anticoagulant (DOAC) for people with active cancer and confirmed proximal DVT or PE. • If a DOAC is unsuitable consider LMWH alone or LMWH concurrently with a VKA for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own. • Offer people with confirmed proximal DVT or PE and an established diagnosis of triple positive antiphospholipid syndrome LMWH concurrently with a VKA for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own. • If anticoagulation treatment fails: o Check adherence to anticoagulation treatment o Address other sources of hypercoagulability o Increase the dose of anticoagulant or change to an anticoagulant with a different mode of action. • Assess and discuss the benefits and risks of continuing, stopping or changing the anticoagulant with people who have had anticoagulation treatment for 3 months (3 to 6 months for people with active cancer) after a proximal DVT or PE. • Consider stopping anticoagulation treatment 3 months (3 to 6 months for people with active cancer) after a provoked DVT or PE if the provoking factor is no longer present and the clinical course has been uncomplicated. If anticoagulation treatment is stopped, give advice about the risk of recurrence and provide: o Written information on symptoms and signs to look out for o Direct contact details of a healthcare professional or team with expertise in thrombosis who can discuss any new symptoms or signs, or other concerns

	○ information about out-of-hours services they can contact when their healthcare team is not available. [2020] • Consider continuing anticoagulation beyond 3 months (6 months for people with active cancer) after an unprovoked DVT or PE. Base the decision on the balance between the person's risk of VTE recurrence and their risk of bleeding. Discuss the risks and benefits of long-term anticoagulation with the person, and take their preferences into account. • Explain to people with unprovoked DVT or PE and a low bleeding risk that the benefits of continuing anticoagulation treatment are likely to outweigh the risks. • Do not rely solely on predictive risk tools to assess the need for long-term anticoagulation treatment • Consider using the HAS-BLED score for major bleeding risk to assess the risk of major bleeding in people having anticoagulation treatment for unprovoked proximal DVT or PE. Discuss stopping anticoagulation if the HAS-BLED score is 4 or more and cannot be modified. • Take into account the person's preferences and their clinical situation when selecting an anticoagulant for long-term treatment. • For people who do not have renal impairment, active cancer, established triple positive antiphospholipid syndrome or extreme body weight (less than 50 kg or more than 120 kg): ○ Offer continued treatment with the current anticoagulant if it is well tolerated or ○ If the current treatment is not well tolerated, or the clinical situation or person's preferences have changed, consider switching to apixaban if the current treatment is a direct-acting anticoagulant other than apixaban. • For people with renal impairment, active cancer, established triple positive antiphospholipid syndrome or extreme body weight (less than 50 kg or more than 120 kg), consider carrying on with the current treatment if it is well tolerated • For people who decline continued anticoagulation treatment, consider aspirin 75 mg or 150 mg daily. In March 2020, the use of aspirin for secondary prevention of DVT or PE was off label. • Review general health, risk of VTE recurrence, bleeding risk and treatment preferences at least once a year for people taking long-term anticoagulation treatment or aspirin. • Be aware that heparins are of animal origin and that apixaban and rivaroxaban contain lactose from cow's milk. For people who have concerns about using animal products because of a religious or ethical

	belief, or a food intolerance
	• Do not offer an inferior vena caval (IVC) filter to people with proximal DVT or PE unless:
	  o It is part of a prospective clinical study or
	  o Anticoagulation is contraindicated or a PE has occurred during anticoagulation treatment
	• Consider an IVC filter for people with proximal DVT or PE when anticoagulation treatment is contraindicated. Remove the IVC filter when anticoagulation treatment is no longer contraindicated and has been established.
	• Consider an IVC filter for people with proximal DVT or PE who have a PE while taking anticoagulation treatment only after taking the steps outlined in the recommendation on treatment failure.
	• Before fitting an IVC filter, ensure that there is a strategy in place for it to be removed at the earliest possible opportunity. Document the strategy and review it if the clinical situation changes.
	• For people with unprovoked DVT or PE who are not known to have cancer, review the medical history and baseline blood test results including full blood count, renal and hepatic function, PT and APTT, and offer a physical examination.
	• Do not offer further investigations for cancer to people with unprovoked DVT or PE unless they have relevant clinical symptoms or signs.
	• Do not offer testing for hereditary thrombophilia to people who are continuing anticoagulation treatment.
	• Consider testing for antiphospholipid antibodies in people who have had unprovoked DVT or PE if it is planned to stop anticoagulation treatment, but be aware that these tests can be affected by anticoagulants and specialist advice may be needed.
	• Consider testing for hereditary thrombophilia in people who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment, but be aware that these tests can be affected by anticoagulants and specialist advice may be needed.

Section 1.1.3 **Antithrombotic Therapy and Prevention of Thrombosis, 9th ed:**	**Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report 2021**[12] Certainty of evidence was based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach and categorized as high, moderate, low, or very low. • In patients with acute isolated distal DVT of the leg and (i) without severe symptoms or risk factors for

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [2012]	extension, the guidelines suggest serial imaging of the deep veins for 2 weeks over anticoagulation (weak recommendation, moderate-certainty evidence); or (ii) with severe symptoms or risk factors for extension, the guidelines suggest anticoagulation over serial imaging of the deep veins (weak recommendation, low-certainty evidence). • In patients with acute isolated distal DVT of the leg who are treated with serial imaging, the guidelines (i) recommend no anticoagulation if the thrombus does not extend (strong recommendation, moderate-certainty evidence), (ii) suggest anticoagulation if the thrombus extends but remains confined to the distal veins (weak recommendation, very low-certainty evidence), and (iii) recommend anticoagulation if the thrombus extends into the proximal veins (strong recommendation, moderate-certainty evidence). • In patients with subsegmental pulmonary embolism (PE) (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE, the guidelines suggest clinical surveillance over anticoagulation (weak recommendation, low-certainty evidence) or (ii) high risk for recurrent VTE, the guidelines suggest anticoagulation over clinical surveillance (weak recommendation, low-certainty evidence). • In patients with cerebral vein/venous sinus thrombosis, the guidelines recommend anticoagulation therapy for at least the treatment phase (first 3 months) over no anticoagulant therapy (strong recommendation, low-certainty evidence). • In patients with acute DVT of the leg the guidelines suggest anticoagulant therapy alone over interventional (thrombolytic, mechanical, or pharmacomechanical) therapy (weak recommendation, moderate-certainty evidence). • In patients with acute DVT of the leg, the guidelines recommend against the use of an inferior vena cava (IVC) filter in addition to anticoagulants (strong recommendation, moderate-certainty evidence). • In patients with acute proximal DVT of the leg and a contraindication to anticoagulation, the guidelines recommend the use of an IVC filter (strong recommendation, moderate-certainty evidence). • In patients with VTE (DVT of the leg or PE) the guidelines recommend apixaban, dabigatran, edoxaban, or rivaroxaban over VKA as treatment-phase (first 3 months) anticoagulant therapy (strong recommendation, moderate-certainty evidence). • In patients with acute VTE in the setting of cancer (cancer-associated thrombosis) the guidelines recommend an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and

	treatment phases of therapy (strong recommendation, moderate-certainty evidence). • In patients with confirmed antiphospholipid syndrome being treated with anticoagulant therapy, the guidelines suggest adjusted-dose VKA (target international normalized ratio [INR] 2.5) over DOAC therapy during the treatment phase (weak recommendation, low-certainty evidence). • In patients with superficial venous thrombosis (SVT) of the lower limb at increased risk of clot progression to DVT or PE, the guidelines suggest the use of anticoagulation for 45 days over no anticoagulation (weak recommendation, moderate certainty evidence). • In patients with SVT who are treated with anticoagulation, the guidelines suggest fondaparinux 2.5 mg daily over other anticoagulant treatment regimens such as (prophylactic- or therapeutic-dose) LMWH (weak recommendation, low-certainty evidence). • In patients with SVT who refuse or are unable to use parenteral anticoagulation, the guidelines suggest rivaroxaban 10 mg daily as a reasonable alternative for fondaparinux 2.5 mg daily (weak recommendation, low-certainty evidence). • In patients with acute VTE who do not have a contraindication the guidelines recommend a 3-month treatment phase of anticoagulation (strong recommendation, moderate-certainty evidence). • In patients with VTE diagnosed in the setting of a major transient risk factor, the guidelines recommend against offering extended-phase anticoagulation (strong recommendation, moderate-certainty evidence). • In patients with VTE diagnosed in the setting of a minor transient risk factor, the guidelines suggest against offering extended-phase anticoagulation (weak recommendation, moderate-certainty evidence). • In patients with VTE diagnosed in the absence of transient provocation (unprovoked VTE or provoked by persistent risk factor), the guidelines recommend offering extended-phase anticoagulation with a DOAC (strong recommendation, moderate-certainty evidence). • In patients with VTE diagnosed in the absence of transient risk factor (unprovoked VTE or provoked by a persistent risk factor) who cannot receive a DOAC, the guidelines suggest offering extended-phase anticoagulation with a VKA (weak recommendation, moderate certainty evidence). • In patients offered extended-phase anticoagulation, the guidelines suggest the use of reduced-dose apixaban or rivaroxaban over full-dose apixaban or rivaroxaban (weak recommendation, very low certainty evidence).

	• In patients offered extended-phase anticoagulation, the guidelines recommend reduced-dose DOAC over aspirin or no therapy (strong recommendation, low-certainty evidence) and suggest rivaroxaban over aspirin (weak recommendation, moderate-certainty evidence). • In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, the guidelines suggest aspirin over no aspirin to prevent recurrent VTE (weak recommendation, low-certainty evidence). • In patients with acute DVT of the leg, the guidelines suggest against using compression stockings routinely to prevent PTS (weak recommendation, low-certainty evidence).
Section 1.1.4 **2017 ESC/EACTS Guidelines for the management of valvular heart disease: The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)**	**2021 ESC/EACTS Guidelines for the management of valvular heart disease Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio – Thoracic Surgery (EACTS)**[20] • Management of atrial fibrillation in patients with native VHD: For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs in patients with aortic stenosis, aortic and mitral regurgitation (Class I) • Recommendations for prosthetic valve selection: o A bioprosthesis may be considered in patients already on long-term NOACs due to the high risk for thromboembolism. (Class: IIb) o A bioprosthesis is recommended when good-quality anticoagulation is unlikely (adherence problems, not readily available), contraindicated because of high bleeding risk (previous major bleed, comorbidities, unwillingness, adherence problems, lifestyle, occupation) and in those patients whose life expectancy is lower than the presumed durability of the bioprosthesis. • Management of antithrombotic therapy in the perioperative period: o Bridging of OAC, when interruption is needed, is recommended in patients with any of the following indication (Class I): - Mechanical prosthetic heart valve. - AF with significant mitral stenosis. - AF with a CHA2DS2-VASc score >_3 for women or 2 for men. - Acute thrombotic event within the previous 4 weeks. - High acute thromboembolic risk.

	○ It is recommended that VKAs are timely discontinued prior to elective surgery to aim for an INR <1.5. (Class: I) ○ In patients undergoing surgery, it is recommended that aspirin therapy, if indicated, is maintained during the periprocedural period. (Class: I) ○ In patients who have undergone valve surgery with an indication for postoperative therapeutic bridging, it is recommended to start either UFH or LMWH 12-24 hours after surgery. (Class: I) ○ In patients with MHVs, it is recommended to (re)- initiate VKAs on the first postoperative day. (Class: I) ○ In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery, in the absence of an indication for OAC, it is recommended to resume the P2Y12 inhibitor postoperatively, as soon as there is no concern over bleeding. (Class: I) ○ In patients treated with DAPT after recent PCI (within 1 month) who need to undergo heart valve surgery, in the absence of an indication for OAC, bridging P2Y12 inhibitors with glycoprotein IIb/IIIa inhibitors or cangrelor may be considered. (Class: IIb) • Patients with an indication to concomitant antiplatelet therapy: ○ After uncomplicated PCI or ACS in patients requiring long -term OAC, early cessation (≤1 week) of aspirin and continuation of dual therapy with OAC and a P2Y12 inhibitor (preferably clopidogrel) for up to 6 months (or up to 12 months in ACS) is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used. (Class: I) ○ Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months. (Class: I) ○ In patients treated with a VKA (e.g. MHVs), clopidogrel alone should be considered in selected patients (e.g. HAS-BLED >_3 or ARC-HBR met and low risk of stent thrombosis) for up to 12 months. (Class: IIa) ○ In patients requiring aspirin and/or clopidogrel in addition to VKA, the dose intensity of VKA should be considered and carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65-70%. (Class: IIa) ○ After uncomplicated PCI or ACS in patients requiring both OAC and antiplatelet therapy, triple

	therapy with aspirin, clopidogrel and OAC for longer than 1 week should be considered when the risk of stent thrombosis outweighs the risk of bleeding, with a total duration (≤1 month) decided according to assessment of these risks and clearly specified at hospital discharge. (Class: IIa) • Surgical valve replacement o NOACs should be considered over VKA after 3 months following surgical implantation of a BHV, in patients with AF. (Class: IIa) o In patients with no baseline indications for OAC, low-dose aspirin (75-100 mg/day) or OAC using a VKA should be considered for the first 3 months after surgical implantation of an aortic BHV. (Class: IIa) o NOACs may be considered over VKA within 3 months following surgical implantation of a BHV in mitral position in patients with AF. (Class: IIb) • Transcatheter Aortic Valve Implantation o OAC is recommended lifelong for TAVI patients who have other indications for OAC. (Class: I) o Revised SAPT may be considered after TAVI in the case of high bleeding risk. (Class: IIb) o Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC. (Class: I) o Routine use of OAC is not recommended after TAVI in patients with no baseline indication for OAC. (Class: III) • Bioprosthetic thrombosis: o Anticoagulation should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients, at least until resolution. (Class: IIa)
Section 1.1.5 **2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease- A Report of**	**2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines**[13] • Recommendations for Anticoagulation for AF in Patients With VHD: o For patients with AF and native valve heart disease (except rheumatic mitral stenosis [MS]) or who received a bioprosthetic valve >3 months ago, a non–vitamin K oral anticoagulant (NOAC) is an effective alternative to VKA anticoagulation and should be administered on the basis of the patient's CHA2DS2-VASc score (COR: 1, LOE: A). o For patients with AF and rheumatic MS, long-term VKA oral anticoagulation is recommended

the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guideline	(COR: 1, LOE: C-EO). o For patients with new-onset AF ≤3 months after surgical or transcatheter bioprosthetic valve replacement, anticoagulation with a VKA is reasonable (COR: 2a, LOE: B-NR) o In patients with mechanical heart valves with or without AF who require long-term anticoagulation with VKA to prevent valve thrombosis, NOACs are not recommended (COR: 3 Harm, LOE: B-R). • Recommendations for Choice of Mechanical Versus Bioprosthetic AVR: o For patients of any age requiring AVR for whom VKA anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired, a bioprosthetic AVR is recommended (Class: 1, LOE: C-EO). o For patients <50 years of age who do not have a contraindication to anticoagulation and require AVR, it is reasonable to choose a mechanical aortic prosthesis over a bioprosthetic valve (Class: 2a, LOE: B-R). o For patients 50 to 65 years of age who require AVR and who do not have a contraindication to anticoagulation, it is reasonable to individualize the choice of either a mechanical or bioprosthetic AVR with consideration of individual patient factors and after informed shared decision-making (Class: 2a, LOE: B-NR). • Recommendations for Medical Therapy in Patients with Rheumatic MS o In patients with rheumatic MS and 1) AF, 2) a prior embolic event, or 3) an LA thrombus, anticoagulation with a VKA is indicated (Class: 1, LOE: C-LD) • Recommendations for Diagnosis and Follow-Up of Prosthetic Valves: o For patients of any age requiring valve replacement for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired, a bioprosthetic valve is recommended (Class: 1, LOE: C-EO) o For patients <50 years of age who do not have a contraindication to anticoagulation and require AVR, it is reasonable to choose a mechanical aortic prosthesis over a bioprosthetic valve (Class 2a, LOE: B-NR). o For patients 50 to 65 years of age who require AVR and who do not have a contraindication to anticoagulation, it is reasonable to individualize the choice of either a mechanical or bioprosthetic

	AVR, with consideration of individual patient factors and after informed shared decision-making (Class 2a, LOE: B-NR) o For patients <65 years of age who have an indication for mitral valve replacement, do not have a contraindication to anticoagulation, and are unable to undergo mitral valve repair, it is reasonable to choose a mechanical mitral prosthesis over a bioprosthetic valve (Class 2a, LOE: B-NR) • Recommendations for Antithrombotic Therapy for Prosthetic Valves: o In patients with a mechanical prosthetic valve, anticoagulation with a VKA is recommended (Class: 1, LOE: A) o For patients with a mechanical bileaflet or current-generation single-tilting disk AVR and no risk factors for thromboembolism, anticoagulation with a VKA to achieve an INR of 2.5 is recommended (Class 1, LOE: B-NR) o For patients with a mechanical AVR and additional risk factors for thromboembolism (eg, AF, previous thromboembolism, LV dysfunction, hypercoagulable state) or an older-generation prosthesis (eg, ball-in-cage), anticoagulation with a VKA is indicated to achieve an INR of 3.0. (Class 1, LOE: B-NR) o For patients with a mechanical mitral valve replacement, anticoagulation with a VKA is indicated to achieve an INR of 3.0 (Class 1, LOE B-NR) o For patients with a bioprosthetic TAVI, aspirin 75 to 100 mg daily is reasonable in the absence of other indications for oral anticoagulants (Class 2a, LOE B-R) o For all patients with a bioprosthetic SAVR or mitral valve replacement, aspirin 75 to 100 mg daily is reasonable in the absence of other indications for oral anticoagulants (Class 2a, LOE B-NR) o For patients with a bioprosthetic SAVR or mitral valve replacement who are at low risk of bleeding, anticoagulation with a VKA to achieve an INR of 2.5 is reasonable for at least 3 months and for as long as 6 months after surgical replacement (Class 2a, LOE B-NR) o For patients with a mechanical SAVR or mitral valve replacement who are managed with a VKA and have an indication for antiplatelet therapy, addition of aspirin 75 to 100 mg daily may be considered when the risk of bleeding is low (Class 2B, LOE B-R) o For patients with a mechanical On-X AVR and no thromboembolic risk factors, use of a VKA targeted to a lower INR (1.5–2.0) may be reasonable starting ≥3 months after surgery, with

	continuation of aspirin 75 to 100 mg daily. (Class: 2b, LOE: B-R) o For patients with a bioprosthetic TAVI who are at low risk of bleeding, dual antiplatelet therapy with aspirin 75 to 100 mg and clopidogrel 75 mg may be reasonable for 3 to 6 months after valve implantation (Class: 2b, LOE: B-NR) o For patients with a bioprosthetic TAVI who are at low risk of bleeding, anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after valve implantation (Class: 2b, LOE: B-NR) o For patients with bioprosthetic TAVI, treatment with low-dose rivaroxaban (10 mg daily) plus aspirin (75–100 mg) is contraindicated in the absence of other indications for oral anticoagulants (Class: 3 Harm, LOE: B-R) o For patients with a mechanical valve prosthesis, anticoagulation with the direct thrombin inhibitor, dabigatran, is contraindicated (Class: 3 Harm, LOE: B-R) o For patients with a mechanical valve prosthesis, the use of anti-Xa direct oral anticoagulants has not been assessed and is not recommended. (Class: 3 Harm, LOE: C-EO) • Recommendations for Bridging Therapy During Interruption of Oral Anticoagulation in Patients With Prosthetic Heart Valves: o For patients with mechanical heart valves who are undergoing minor procedures (eg, dental extractions or cataract removal) where bleeding is easily controlled, continuation of VKA anticoagulation with a therapeutic INR is recommended (Class 1, LOE: C-EO) o For patients with a bileaflet mechanical AVR and no other risk factors for thromboembolism who are undergoing invasive procedures, temporary interruption of VKA anticoagulation, without bridging agents while the INR is subtherapeutic, is recommended (Class: 1, LOE: C-LD) o For patients with a mechanical valve prosthesis receiving VKA therapy who require immediate/emergency noncardiac surgery or an invasive procedure, administration of 4-factor prothrombin complex concentrate (or its activated form) is reasonable. (Class: 2a, LOE: C-LD) o For patients with bioprosthetic heart valves or annuloplasty rings who are receiving anticoagulation for AF, it is reasonable to consider the need for bridging anticoagulant therapy around the time of invasive procedures on the basis of the CHA2DS2-VASc score weighed against the risk of bleeding. (Class: 2a, LOE: C-LD)

	○ For patients who are undergoing invasive procedures and have 1) a mechanical AVR and any thromboembolic risk factor, 2) an older-generation mechanical AVR, or 3) a mechanical mitral valve replacement, bridging anticoagulation therapy during the preoperative time interval when the INR is subtherapeutic is reasonable on an individualized basis, with the risks of bleeding weighed against the benefits of thromboembolism prevention. (Class: 2a, LOE: C-LD) • Recommendations for Management of Excessive Anticoagulation and Serious Bleeding in Patients With Prosthetic Valves: ○ For patients with mechanical valves and uncontrollable bleeding who require immediate reversal of anticoagulation, administration of 4-factor prothrombin complex (or its activated form) is reasonable 2a C-LD ○ For patients with mechanical valves and uncontrollable bleeding who have received 4-factor prothrombin concentrate complex, adjunctive use of intravenous vitamin K is reasonable if resumption of VKA therapy is not anticipated for 7 days. (Class: 2a, LOE: C-LD) ○ For patients with bioprosthetic valves or annuloplasty rings who are receiving a direct oral anticoagulant and who require immediate reversal of anticoagulation because of uncontrollable bleeding, treatment with idarucizumab (for dabigatran) or andexanet alfa (for anti-Xa agents) is reasonable. (Class: 2a, LOE: B-NR) ○ For patients with a mechanical prosthetic valve and supratherapeutic INR (>5.0) who are not actively bleeding, the benefit of individualized treatment with oral vitamin K, in addition to temporary withdrawal of the VKA, is uncertain (Class: 2b, C-LD) • Recommendations for Management of Thromboembolic Events With Prosthetic Valves: ○ In patients with a mechanical AVR who experience a stroke or systemic embolic event while in therapeutic range on VKA anticoagulation, it is reasonable to increase the INR goal from 2.5 (range, 2.0–3.0) to 3.0 (range, 2.5–3.5) or to add daily low-dose aspirin (75– 100 mg), with assessment of bleeding risk. (Class: 2a, LOE: C-EO) ○ In patients with a mechanical mitral valve replacement who experience a stroke or systemic embolic event while in therapeutic range on VKA anticoagulation, it is reasonable to increase the INR goal from 3.0 (range, 2.5–3.5) to 4.0 (range, 3.5–4.0) or to add daily low-dose aspirin (75–100 mg), with assessment of bleeding risk (Class: 2a, LOE: C-EO)

	○ In patients with a bioprosthetic surgical or transcatheter aortic valve or bioprosthetic mitral valve who experience a stroke or systemic embolic event while on antiplatelet therapy, VKA anticoagulation, instead of antiplatelet therapy may be considered after assessment of bleeding risk (Class: 2b, LOE: C-EO) • Recommendation for Intervention for Mechanical Prosthetic Valve Thrombosis: ○ For patients with a thrombosed left-sided mechanical prosthetic heart valve who present with symptoms of valve obstruction, urgent initial treatment with either slow-infusion, low dose fibrinolytic therapy or emergency surgery is recommended (Class: 1, LOE: B-NR) • In patients with suspected or confirmed bioprosthetic valve thrombosis who are hemodynamically stable and have no contraindications to anticoagulation, initial treatment with a VKA is reasonable (Class: 2a, LOE: B-NR) • In patients with IE and with evidence of cerebral embolism or stroke, regardless of the other indications for anticoagulation, it is reasonable to temporarily discontinue anticoagulation. (Class: 2a, LOE: B-NR) • In patients receiving VKA anticoagulation at the time of IE diagnosis, temporary discontinuation of VKA anticoagulation may be considered (Class: 2b, LOE: B-NR) • Women with mechanical heart valves considering pregnancy should be counselled that pregnancy is high risk and that there is no anticoagulation strategy that is consistently safe for the mother and baby (Class: 1, LOE: B-NR) • Recommendations for Anticoagulation for Pregnant Women with Mechanical Prosthetic Heart Valves: ○ Pregnant women with mechanical prostheses should receive therapeutic anticoagulation with frequent monitoring during pregnancy (Class:1, LOE: B-NR) ○ Women with mechanical heart valves who cannot maintain therapeutic anticoagulation with frequent monitoring should be counseled against pregnancy (Class: 1, LOE: B-NR) ○ Women with mechanical heart valves and their providers should use shared decision making to choose an anticoagulation strategy for pregnancy. Women should be informed that VKA during pregnancy is associated with the lowest likelihood of maternal complications but the highest likelihood of miscarriage, fetal death, and congenital abnormalities, particularly if taken during the first trimester and if the warfarin dose exceeds 5 mg/d (Class: 1, LOE: B-NR) ○ Pregnant women with mechanical valve prostheses who are on warfarin should switch to twice-

	daily LMWH (with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL at 4 to 6 hours after dose) or intravenous UFH (with an activated partial thromboplastin time [aPTT] 2 times control) at least 1 week before planned delivery (Class: 1, LOE: C-LD) o Pregnant women with mechanical valve prostheses who are on LMWH should switch to UFH (with an aPTT 2 times control) at least 36 hours before planned delivery 1 C-LD Pregnant women with valve prostheses should stop UFH at least 6 hours before planned vaginal delivery (Class: 1, LOE: C-LD) o If labor begins or urgent delivery is required in a woman therapeutically anticoagulated with a VKA, cesarean section should be performed after reversal of anticoagulation (Class:1, LOE: C-LD) o For pregnant women with mechanical prostheses who require a dose of warfarin ≤5 mg/d to maintain a therapeutic INR, continuation of warfarin for all 3 trimesters is reasonable after full discussion with the patient about risks and benefits. (Class: 2a, LOE: B-NR) o For pregnant women with mechanical prostheses who require >5 mg/d of warfarin to achieve a therapeutic INR, dose-adjusted LMWH (with a target anti-Xa level of 0.8 to 1.2 U/mL at 4 to 6 hours after dose) at least 2 times per day during the first trimester, followed by warfarin during the second and third trimesters, is reasonable (Class: 2a, B-NR) o For pregnant women with mechanical prostheses who require a dose of warfarin >5 mg/d to achieve a therapeutic INR, and for whom dose-adjusted LMWH is unavailable, dose-adjusted continuous intravenous UFH during the first trimester (with aPTT 2 times control), followed by warfarin for the second and third trimesters, is reasonable (Class: 2a, LOE: B-NR) o For hemodynamically stable pregnant women with obstructive left-sided mechanical valve thrombosis, it is reasonable to manage with slow-infusion, low-dose fibrinolytic therapy (Class: 2a, LOE: B-NR) o For pregnant women with mechanical prostheses who require a warfarin dose >5 mg/d to achieve a therapeutic INR, dose adjusted LMWH (with a target anti-Xa level of 0.8 to 1.2 U/mL at 4 to 6 hours after dose) at least 2 times per day for all 3 trimesters may be considered. (Class: 2b, LOE: B-NR) o For pregnant women with mechanical prostheses who require a dose of warfarin ≤5 mg/d to maintain a therapeutic INR, dose-adjusted LMWH at least 2 times per day during the first

	trimester, followed by warfarin for the second and third trimesters, may be considered. (Class: 2b, LOE: B-NR) o For pregnant women with mechanical prostheses, aspirin 75 to 100 mg daily may be considered, in addition to anticoagulation, if needed for other indications (Class: 2b, LOE: B-NR) o For pregnant women with mechanical prostheses, LMWH should not be administered unless anti-Xa levels are monitored 4 to 6 hours after administration and dose is adjusted according to levels. (Class 3: Harm, LOE: B-NR) o For patients with mechanical valve prostheses, anticoagulation with the direct thrombin inhibitor, dabigatran, should not be administered (Class 3: Harm, LOE: B-R) o The use of anti-Xa direct oral anticoagulants with mechanical heart valves in pregnancy has not been assessed and is not recommended (Class 3: Harm, LOE: C-EO)
Section 1.1.6 **American Society of Hematology 2023 Guidelines for Management of Venous Thromboembolism: Thrombophilia Testing**[21]	• The recommendations are labeled as either “strong” or “conditional” according to the GRADE approach. The words “the guideline panel recommends” are used for strong recommendations and “the guideline panel suggests” for conditional recommendations. • Recommendation 1. In patients with unprovoked VTE who have completed primary short term treatment, the ASH guideline panel suggests not to perform thrombophilia testing to guide the duration of anticoagulant treatment (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯). Remarks: - In the Treatment of VTE ASH guideline indefinite antithrombotic therapy is suggested in most patients with unprovoked VTE (recommendation 19). - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment. - This recommendation refers to testing for hereditary and acquired types of thrombophilia • Recommendation 2. In patients with VTE provoked by surgery who have completed primary short-term treatment, the ASH guideline panel suggests not to perform thrombophilia testing to determine the duration of anticoagulant treatment (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯).

	Remarks: - According to the Treatment of VTE ASH guideline most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment. - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment after completion of primary short-term treatment. - This recommendation refers to testing for hereditary and acquired types of thrombophilia. • Recommendation 3. In patients with VTE provoked by a non-surgical major transient risk factor who have completed primary short-term treatment, the ASH guideline panel suggests testing for thrombophilia to guide anticoagulant treatment duration. The panel suggests indefinite anticoagulant treatment in patients with thrombophilia and stopping anticoagulant treatment in patients without thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯). Remarks: - According to the Treatment of VTE ASH guideline most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment. - Non-surgical major transient risk factors: e.g. confinement to bed in hospital for at least 3 days with an acute illness (“bathroom privileges only”), or a combination of minor transient risk factors such as admission to hospital for less than 3 days with an acute illness, confinement to bed out of hospital for at least 3 days with an acute illness, or leg injury associated with decreased mobility for at least 3 days. - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment. - This recommendation refers to testing for hereditary and acquired types of thrombophilia • Recommendation 4. In women with VTE provoked by pregnancy or postpartum who have completed primary treatment, the ASH guideline panel suggests thrombophilia testing to guide anticoagulant

	treatment duration. The panel suggests indefinite anticoagulant treatment in women with thrombophilia and stopping anticoagulant treatment in women without thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯). Remarks: - According to the Treatment of VTE ASH guideline most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment. - A strategy with testing for thrombophilia would mean that women with thrombophilia would receive indefinite anticoagulant treatment, and women without thrombophilia would stop anticoagulant treatment. - This recommendation refers to testing for hereditary and acquired types of thrombophilia. • Recommendation 5. In women with VTE associated with combined oral contraceptives who have completed primary short-term treatment, the ASH guideline panel suggests testing for thrombophilia to guide anticoagulant treatment duration. The panel suggests indefinite anticoagulant treatment in women with thrombophilia and stopping anticoagulant treatment in women without thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯). Remarks: - According to the Treatment of VTE ASH guideline most patients with VTE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment. - A strategy with testing for thrombophilia would mean that women with thrombophilia would receive indefinite anticoagulant treatment, and women without thrombophilia would stop anticoagulant treatment. - This recommendation refers to testing for hereditary and acquired types of thrombophilia • Recommendation 6. In patients with an unspecified type of VTE who have completed primary short-term treatment, the ASH guideline panel suggests not to perform thrombophilia testing to guide anticoagulant treatment duration (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯). Remarks:

	- Whenever anticoagulant treatment decisions are being made without taking into account whether the VTE is provoked or unprovoked, it is advisable not to test for thrombophilia, to start treatment and to refer the patient to an expert for further decision making. - Thrombosis experts would consider the population "with an unspecified type of VTE" (i.e. without reference to provoked or unprovoked) as theoretical, since determining if a clot is provoked or unprovoked is a standard way to stratify the risk of VTE recurrence and hence, guide treatment decisions. However, in general clinical practice, which is the setting where thrombophilia testing is frequently performed, VTE is often managed regardless of circumstances qualifying the VTE as provoked or unprovoked (an unspecified type of VTE), and for this reason the panel decided to address this question. - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment. - This recommendation refers to testing for hereditary and acquired types of thrombophilia • Recommendation 7. In patients with cerebral venous thrombosis who have completed primary treatment in a setting where anticoagulation would be discontinued, the ASH guideline panel suggests thrombophilia testing to guide anticoagulant treatment duration. The panel suggests indefinite anticoagulation in patients with thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯). Remarks: - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment. - This recommendation refers to testing for hereditary and acquired types of thrombophilia. - This recommendation addresses settings where the standard of care for cerebral venous thrombosis patients is stopping anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is indefinite anticoagulant treatment (Recommendation 8). • Recommendation 8. In patients with cerebral venous thrombosis who have completed primary

	treatment in a setting where anticoagulation would be continued indefinitely, the ASH guideline panel suggests not to perform thrombophilia testing to guide anticoagulant treatment duration (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯). Remarks: - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment. - This recommendation refers to testing for hereditary and acquired types of thrombophilia. - This recommendation addresses settings where the standard of care for cerebral venous thrombosis patients is indefinite anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is stopping anticoagulant treatment (Recommendation 7). • Recommendation 9. In patients with splanchnic venous thrombosis who have completed primary treatment in a setting where anticoagulation would be discontinued, the ASH guideline panel suggests thrombophilia testing to guide anticoagulant treatment duration. The panel suggests indefinite anticoagulation in patients with thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯). Remarks: - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment. - This recommendation refers to testing for hereditary and acquired types of thrombophilia. - This recommendation addresses settings where the standard of care for splanchnic venous thrombosis patients is stopping anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is indefinite anticoagulant treatment (Recommendation 10). • Recommendation 10. In patients with splanchnic venous thrombosis who have completed primary treatment in a setting where anticoagulation would be continued indefinitely, the ASH guideline panel suggests not to perform thrombophilia testing to guide anticoagulant treatment duration (conditional

	recommendation based on very low certainty of the evidence about effects ⨁◯◯◯). Remarks: - A strategy with testing for thrombophilia would mean that patients with thrombophilia would receive indefinite anticoagulant treatment, and patients without thrombophilia would stop anticoagulant treatment. - This recommendation refers to testing for hereditary and acquired types of thrombophilia. - This recommendation addresses settings where the standard of care for splanchnic venous thrombosis patients is indefinite anticoagulant treatment; the ASH guideline panel provides a separate recommendation for settings where the standard of care is stopping anticoagulant treatment (Recommendation 9). • Recommendation 11. In individuals with a family history of VTE and known FVL or PGM (low-risk thrombophilia) who have a minor provoking risk factor for VTE (e.g. immobility or minor injury, illness, or infection), the ASH guideline panel suggests not testing for the known familial thrombophilia to guide thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯) o In individuals with a family history of VTE and known antithrombin, protein C, or protein S deficiency (high-risk thrombophilia) who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests thromboprophylaxis in individuals with thrombophilia and no thromboprophylaxis in individuals without thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯) Remarks: - A strategy with selective testing for the known familial thrombophilia type would mean that individuals with thrombophilia would receive thromboprophylaxis for a minor provoking risk factor, and individuals without thrombophilia would receive no thromboprophylaxis. - A positive family history is defined as having a first- or second-degree relative with VTE and thrombophilia. - These recommendations do not address homozygous defects or combinations of thrombophilia types.

	- This recommendation does not take into account the time it takes to perform the test and is based on the assumption that thrombophilia test results are available at the time the individual is at risk for VTE due to a minor provoking risk factor. - These recommendations refer to selective testing for the known familial thrombophilia type. A separate question in this guideline addressed testing for all hereditary thrombophilias (using a panel of tests) in this population (Recommendation 12), and the resulting recommendations are the same. It is most sensible to selectively test for the known familial thrombophilia (Recommendation 11), rather than test for the entire panel (Recommendation 12), because of the trivial additional number of VTE episodes prevented and major bleeds caused by a strategy of panel testing for all hereditary thrombophilias • Recommendation 12. In individuals with a family history of VTE and known FVL or PGM (low-risk thrombophilia) who have a minor provoking risk factor for VTE (e.g. immobility or minor injury, illness, or infection), the ASH guideline panel suggests not testing for all hereditary thrombophilias to guide thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯) o In individuals with a family history of VTE and known antithrombin, protein C, or protein S deficiency (high-risk thrombophilia) who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for all hereditary thrombophilias (using a panel of tests). o The panel suggests thromboprophylaxis in individuals with thrombophilia and no thromboprophylaxis for a minor provoking risk factor in individuals without thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯) Remarks: - A strategy with testing for hereditary thrombophilia (using a panel of tests) would mean that individuals with thrombophilia receive thromboprophylaxis or a minor provoking risk factor, and individuals without thrombophilia would receive no thromboprophylaxis. - A positive family history is defined as having a first- or second-degree relative with VTE and thrombophilia. - These recommendations do not address homozygous defects or combinations of thrombophilia types.

	- This recommendation does not take into account the time it takes to perform the test and is based on the assumption that thrombophilia test results are available at the time the individual is at risk for VTE due to a minor provoking risk factor. - These recommendations refer to testing for all hereditary thrombophilias, using a panel of tests. A separate question in this guideline addressed selective testing only for the known familial thrombophilia type in this population (Recommendation 11), and the resulting recommendations are the same. - It is most sensible to selectively test for the known familial thrombophilia (Recommendation 11), rather than test for the entire panel (Recommendation 12), because of the trivial additional number of VTE episodes prevented and major bleeds caused by a strategy of panel testing for all hereditary thrombophilias. • Recommendation 13. In individuals with a family history of VTE and unknown thrombophilia status in the family who have a minor provoking risk factor for VTE (e.g. immobility or minor injury, illness, or infection), the ASH guideline panel suggests not testing for all hereditary thrombophilias (using a panel of tests) to guide thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯) Remarks: - Thrombophilia testing may be considered if individuals have multiple family members with VTE, if the family member with VTE was young, with patient preference, and in settings where testing incurs a low cost. - A positive family history is defined as having a first- or second-degree relative with VTE. - A strategy with testing for hereditary thrombophilia (using a panel of tests) would mean that individuals with thrombophilia receive thromboprophylaxis for a minor provoking risk factor, and individuals without thrombophilia would receive no thromboprophylaxis. - These recommendations have not taken into account the possibility of finding homozygous defects or combinations of thrombophilia types in an individual with a positive family history of VTE and unknown thrombophilia status. • Recommendation 14. In individuals with a family history of FVL or PGM (low-risk thrombophilia) but no family history of VTE who have a minor provoking risk factor for VTE (e.g. immobility or minor injury,

illness, or infection), the ASH guideline panel suggests not testing for the known thrombophilia to guide thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯)

- In individuals with a first-degree family history of antithrombin, protein C, or protein S deficiency (high-risk thrombophilia) but no family history of VTE who have a minor provoking risk factor for VTE, the ASH guideline panel suggests testing for the known thrombophilia. The panel suggests thromboprophylaxis in individuals with thrombophilia and no thromboprophylaxis in individuals without thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯)
- In individuals with a second-degree family history of antithrombin, protein C, or protein S deficiency (high-risk thrombophilia) but no family history of VTE who have a minor provoking risk factor for VTE, the ASH guideline panel suggests either testing for the known thrombophilia or not testing for thrombophilia to guide the use thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯)

Remarks:

- A strategy with selective testing for the known familial thrombophilia type would mean that individuals with thrombophilia would receive thromboprophylaxis for a minor provoking risk factor, and individuals without thrombophilia would receive no thromboprophylaxis.
- A positive family history is defined as having a first- or second-degree relative with VTE, unless otherwise specified.
- These recommendations do not address homozygous defects or combinations of thrombophilia types

- Recommendation 15. In women from the general population who are considering using combined oral contraceptives (COC), the ASH guideline panel recommends not to perform thrombophilia testing to guide the use of COC (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯)

  Remarks:

  - Women with risk factors for VTE, such as a family history of VTE and/or a family history of thrombophilia, are at higher risk of VTE. Other recommendations in this guideline address

	thrombophilia testing in these populations (Recommendations 17 and 19). - A strategy with testing for thrombophilia (using a panel of tests) would mean that women with thrombophilia would not use COC, and women without thrombophilia would use COC. • Recommendation 16. In women from the general population who are considering using hormone replacement therapy (HRT), the ASH guideline panel suggests not to perform thrombophilia testing to guide the use of HRT (conditional recommendation based on low certainty in the evidence about effects ⨁⨁◯◯) Remarks: - Women with risk factors for VTE, such as a family history of VTE and/or thrombophilia, are at higher risk of VTE. Other recommendations in this guideline address thrombophilia testing in these populations (Recommendations 18 and 20). - A strategy with testing for thrombophilia (using a panel of tests) would mean that women with thrombophilia would not use HRT, and women without thrombophilia would use HRT • Recommendation 17. In women with a family history of VTE and unknown thrombophilia status in the family who are considering using combined oral contraceptives (COC), the ASH guideline panel suggests not testing for hereditary thrombophilia (using a panel of tests) to guide the use of COC (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯) Remarks: - Women with a family history of VTE and a known thrombophilia in the family are at higher risk for testing positive for thrombophilia and are therefore at higher risk for VTE. Another recommendation in this guideline addresses thrombophilia testing in this population (Recommendation 19). - A strategy with testing for hereditary thrombophilia (using a panel of tests) would mean that women with thrombophilia would not use COC, and women without thrombophilia would use COC. - A positive family history is defined as having a first- or second-degree relative with VTE. • Recommendation 18. In women with a family history of VTE and unknown thrombophilia in the family who are considering using hormone replacement therapy (HRT), the ASH guideline panel suggests not to perform thrombophilia testing for any hereditary thrombophilia to guide the use of HRT (conditional

recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

Remarks:

- Women with a family history of VTE and a known thrombophilia in the family are at higher risk for testing positive for thrombophilia and are therefore at higher risk for VTE. Another recommendation in this guideline addresses thrombophilia testing in this population (Recommendation 20).
- A strategy with testing for hereditary thrombophilia (using a panel of tests) would mean that women with thrombophilia would not use HRT, and women without thrombophilia would use HRT.
- A positive family history is defined as having a first- or second-degree relative with VTE

- Recommendation 19. In women with a family history of VTE and known FVL or PGM in the family (low-risk thrombophilia), the ASH guideline panel suggests not testing for the known familial thrombophilia to guide the use of COC (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯).
    - In women with a family history of VTE and known antithrombin, protein C or protein S deficiency in the family (high-risk thrombophilia), the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests avoidance of COC in women with high-risk thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

  Remarks:

  - A strategy with selective testing for the known familial thrombophilia would mean that women with thrombophilia would avoid COC, and women without thrombophilia would use COC.
  - A positive family history is defined as having a first- or second-degree relative with VTE.
  - These recommendations do not address homozygous defects, or combinations of thrombophilia types.
- Recommendation 20. In women with a family history of VTE and known FVL or PGM in the family (low-risk thrombophilia), the ASH guideline panel suggests not testing for the known familial thrombophilia to guide the use of HRT (conditional recommendation based on very low certainty in the evidence about

effects ⨁◯◯◯)

- In women with a family history of VTE and known antithrombin, protein C or protein S deficiency in the family (high-risk thrombophilia), the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests avoidance of HRT in women with high-risk thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

Remarks:

- A strategy with selective testing for the known familial thrombophilia would mean that women with thrombophilia would avoid HRT, and women without thrombophilia would use HRT.
- A positive family history is defined as having a first- or second-degree relative with VTE.
- These recommendations do not address homozygous defects or combinations of thrombophilia types.

- Recommendation 21. In women with a family history of VTE and known homozygous FVL, combination of FVL and PGM, or antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests antepartum thromboprophylaxis in women with the same familial thrombophilia (i.e. homozygous FVL, combination of FVL and PGM, or antithrombin deficiency) and no antepartum prophylaxis in women without the same familial thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)
  - In women with a family history of VTE and known protein C or protein S deficiency in the family, the ASH guideline panel suggests either testing for the known familial thrombophilia or not testing for thrombophilia to guide antepartum prophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯)

  Remarks:

  - Pharmacological thromboprophylaxis based on antepartum thrombophilia testing is generally continued postpartum.
  - Conditions can include the duration and burden of the treatment, which involves injections with low-molecular-weight heparin, and patient preference.
  - A strategy with selective testing for the known familial thrombophilia type would mean that

	positive relatives would receive thromboprophylaxis, and negative relatives would not receive thromboprophylaxis. - A positive family history is defined as having a first- or second-degree relative with VTE; for homozygous FVL, these recommendations only concern siblings, not children, as these would most often be heterozygous for FVL; management of women with a second-degree family history was not addressed. - These recommendations do not address heterozygous FVL or PGM alone, as the ASH guidelines on the management of VTE in the context of pregnancy suggest not to use thromboprophylaxis in these women. • Recommendation 22. In women with a first-degree family history of VTE and known homozygous FVL, a combination of FVL and PGM, antithrombin deficiency, protein C deficiency, or protein S deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests postpartum thromboprophylaxis in women with the same familial thrombophilia (i.e. homozygous FVL, combination of FVL and PGM, or antithrombin deficiency) and no postpartum prophylaxis in women without the same familial thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯) o In women with a second-degree family history of VTE and a known combination of FVL and PGM, or antithrombin deficiency in the family, the ASH guideline panel suggests testing for the known familial thrombophilia. The panel suggests postpartum thromboprophylaxis in women with thrombophilia and no postpartum prophylaxis in women without thrombophilia (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯) o In women with a second-degree family history of VTE and known protein C or protein S deficiency in the family, the ASH guideline panel suggests either testing for the known familial thrombophilia or not testing for thrombophilia to guide postpartum thromboprophylaxis (conditional recommendation based on very low certainty in the evidence about effects ⨁◯◯◯) Remarks: - Thromboprophylaxis postpartum continues until 6 weeks after delivery. - Conditions can include the duration and burden of the treatment, which involves injections, and patient preference.

	- A strategy with selective testing for the known familial thrombophilia type would mean that women with thrombophilia would receive thromboprophylaxis, and women without thrombophilia would not receive thromboprophylaxis. - For homozygous FVL, these recommendations only concern siblings, not children, as these would most often be heterozygous for FVL; testing of women with a second-degree family history was not addressed. - These recommendations do not address heterozygous FVL or PT mutation alone, as the ASH guidelines on the management of VTE in the context of pregnancy suggest not to prescribe thromboprophylaxis in these women. • Recommendation 23. In ambulatory cancer patients receiving systemic therapy who have a family history of VTE and are otherwise determined to be at low or intermediate risk for VTE, the ASH guideline panel suggests testing for hereditary thrombophilia. The panel suggests ambulatory thromboprophylaxis in patients with thrombophilia and no thromboprophylaxis in patients without thrombophilia (conditional recommendation based on very low certainty of the evidence about effects ⨁◯◯◯) Remarks: - This question only addresses cancer patients receiving systemic therapy, without a personal history of VTE who are at low or intermediate risk for VTE. The ASH VTE guidelines on prevention and treatment in patients with cancer suggest using direct oral anticoagulant (DOAC) prophylaxis in all ambulatory cancer patients with high VTE risk as assessed by a validated risk assessment tool complemented by clinical judgment and experience. - Patient preference is an important factor to consider, as undergoing the thrombophilia test, knowing the positive test result, and receiving additional medication can be an added burden. - A strategy with testing for hereditary thrombophilia (using a panel of tests) would mean that ambulatory cancer patients with thrombophilia would receive thromboprophylaxis, and ambulatory cancer patients without thrombophilia would not receive thromboprophylaxis. - A positive family history is defined as having a first-degree relative with VTE. - This recommendation does not address homozygous defects, or combinations of thrombophilia types.

Section 1.1.7 **American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism**[10]	The recommendations are labeled as “strong” or “conditional” according to the GRADE approach. The words “the guideline panel recommends” are used for strong recommendations and “the guideline panel suggests” are used for conditional recommendations. Table below provides GRADE’s interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers (insert table) • For patients with uncomplicated deep vein thrombosis (DVT), the ASH guideline panel suggests offering home treatment over hospital treatment (conditional recommendation based on low certainty in the evidence of effects ⨁⨁◯◯). **Remarks**: This recommendation does not apply to patients who have other conditions that would require hospitalization, have limited or no support at home, and cannot afford medications or have a history of poor compliance. Patients with limb-threatening DVT or a high risk for bleeding and those requiring IV analgesics may benefit from initial treatment in the hospital. • For patients with DVT and/or PE, the ASH guideline panel suggests using direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) (conditional recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁◯). **Remarks**: This recommendation may not apply to certain subgroups of patients, such as those with renal insufficiency (creatinine clearance <30 mL/min), moderate to severe liver disease, or antiphospholipid syndrome. • For patients with DVT and/or PE, the ASH guideline panel does not suggest one DOAC over another (conditional recommendation based on very low certainty in the evidence of comparative effects ⨁◯◯◯). **Remarks**: Factors, such as a requirement for lead-in parenteral anticoagulation, once- vs twice-daily dosing, and out-of-pocket cost may drive the selection of specific DOACs. Other factors, such as renal function, concomitant medications (eg, need for a concomitant drug metabolized through the CYP3A4 enzyme or P-glycoprotein), and the presence of cancer, may also impact DOAC choice. • In most patients with proximal DVT, the ASH guideline panel suggests anticoagulation therapy alone over thrombolytic therapy in addition to anticoagulation (conditional recommendation based on low certainty in the evidence of effects ⨁⨁◯◯). **Remarks**: Thrombolysis is reasonable to consider for patients with limb-threatening DVT (phlegmasia cerulea dolens) and for selected younger patients at low risk for bleeding with symptomatic DVT

	involving the iliac and common femoral veins (higher risk for more severe post thrombotic syndrome [PTS]). Patients in these categories who value rapid resolution of symptoms, are averse to the possibility of PTS, and accept the added risk of major bleeding may prefer thrombolysis. The use of thrombolysis should be rare for patients with DVT limited to veins below the common femoral vein. • For patients with extensive DVT in whom thrombolysis is considered appropriate, the ASH guideline panel suggests using catheter-directed thrombolysis over systemic thrombolysis (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯). **Remarks**: Given the very-low-certainty evidence (uncertainty regarding the benefits and harms of catheter-directed thrombolysis compared with systemic thrombolysis), the panel followed the GRADE ASH rules and issued a conditional recommendation. However, 4 panel members believed the recommendation should have been graded as strong based on the lack of evidence showing meaningful clinical benefits outweighing the known bleeding risks associated with systemic thrombolysis. • For patients with proximal DVT and significant preexisting cardiopulmonary disease, as well as for patients with PE and hemodynamic compromise, the ASH guideline panel suggests anticoagulation alone rather than anticoagulation plus insertion of an inferior vena cava (IVC) filter (conditional recommendations based on low certainty in the evidence of effects ⨁⨁◯◯). **Remarks**: These recommendations apply to patients who are eligible to receive anticoagulation. For patients with a contraindication to anticoagulation, insertion of a retrievable IVC filter may be indicated with retrieval as soon as the patient is able to receive anticoagulation. • For primary treatment of patients with DVT and/or PE, whether provoked by a transient risk factor or by a chronic risk factor or unprovoked, the ASH guideline panel suggests using a shorter course of anticoagulation for primary treatment (3-6 months) over a longer course of anticoagulation for primary treatment (6-12 months) (conditional recommendations based on moderate certainty in evidence of effects ⨁⨁⨁◯). **Remarks**: These recommendations are intended to address the duration of primary anticoagulant treatment for all patients with DVT and/or PE, defined as the minimal length of time for treatment of the initial VTE. Most patients with DVT and/or PE provoked by temporary risk factors will discontinue anticoagulant therapy after completion of the primary treatment. In contrast, many patients with DVT and/or PE provoked by chronic risk factors, as well as patients with unprovoked DVT and/or PE, may

	continue anticoagulant therapy indefinitely for secondary prevention after completion of the primary treatment. However, if patients and clinicians decide to stop anticoagulation, the ASH guideline panel suggests against using a longer course of primary anticoagulant therapy (6-12 months). For selected patients with a chronic risk factor for which some improvement is expected over time (eg, improved mobility with rehabilitation), a longer course of anticoagulation for the primary treatment phase (eg, 6-12 months) could be justified. • For patients with unprovoked DVT and/or PE, the ASH guideline panel suggests against routine use of prognostic scores, D-dimer testing, or ultrasound to detect residual vein thrombosis to guide the duration of anticoagulation (conditional recommendations based on very low certainty in the evidence of effects ⨁○○○). **Remarks**: Indefinite anticoagulation is probably appropriate for the majority of patients with unprovoked VTE. However, in certain circumstances, such as when patients are undecided or the balance between risks and benefits is uncertain, clinicians and patients may use prognostic scores, D-dimer testing, or ultrasound assessment for residual thrombosis from an initial DVT to aid in reaching a final decision. • After completion of primary treatment for patients with DVT and/or PE provoked by a chronic risk factor, the ASH guideline panel suggests indefinite antithrombotic therapy over stopping anticoagulation (conditional recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁○). **Remarks**: Patients with DVT and/or PE provoked by a transient risk factor typically do not require antithrombotic therapy after completion of primary treatment. This recommendation refers to patients with DVT and/or PE provoked by a chronic persistent risk factor. However, this recommendation does not apply to patients who have a high risk for bleeding complications. • After completion of primary treatment for patients with unprovoked DVT and/or PE, the ASH guideline panel suggests indefinite antithrombotic therapy over stopping anticoagulation (conditional recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁○). **Remarks**: This recommendation does not apply to patients who have a high risk for bleeding complications. • For patients with DVT and/or PE who have completed primary treatment and will continue to receive secondary prevention, the ASH guideline panel suggests using anticoagulation over aspirin (conditional recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁○).

	• For patients with DVT and/or PE who have completed primary treatment and will continue VKA therapy as secondary prevention, the ASH guideline panel recommends using an international normalized ratio (INR) range of 2.0 to 3.0 over a lower INR range (eg, 1.5-1.9) (strong recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁◯). • For patients with DVT and/or PE who have completed primary treatment and will continue with a DOAC for secondary prevention, the ASH guideline panel suggests using a standard-dose DOAC or a lower-dose DOAC (conditional recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁◯). **Remarks**: Lower-dose DOAC regimens that may be considered for patients who have completed primary treatment and will continue with a DOAC include rivaroxaban, 10 mg daily, or apixaban, 2.5 mg twice daily. • For patients with breakthrough DVT and/or PE during therapeutic VKA treatment, the ASH guideline panel suggests using low-molecular-weight heparin (LMWH) over DOAC therapy (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯). **Remarks**: Patients who present with a new VTE event during therapeutic VKA treatment should be further investigated to identify potential underlying causes. This recommendation does not apply to patients who develop breakthrough VTE in the setting of poor INR control, in whom a DOAC may be a reasonable option. • For patients who develop DVT and/or PE provoked by a transient risk factor and have a history of previous unprovoked VTE or VTE provoked by a chronic risk factor, the ASH guideline panel suggests indefinite antithrombotic therapy over stopping anticoagulation after completing primary treatment (conditional recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁◯). • For patients who develop DVT and/or PE provoked by a transient risk factor and have a history of a previous VTE also provoked by a transient risk factor, the ASH guideline panel suggests stopping anticoagulation after completion of primary treatment over indefinite antithrombotic therapy (conditional recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁◯). • For patients with a recurrent unprovoked DVT and/or PE, the ASH guideline panel recommends indefinite antithrombotic therapy over stopping anticoagulation after completion of primary treatment (strong recommendation based on moderate certainty in the evidence of effects ⨁⨁⨁◯).

	• For patients with DVT and/or PE with stable cardiovascular disease (CVD) who initiate anticoagulation and were previously taking aspirin for cardiovascular risk modification, the ASH guideline panel suggests suspending aspirin over continuing it for the duration of anticoagulation therapy (conditional recommendation based on very low certainty in the evidence of effects ⨁○○○). **Remarks**: A critical review of the indication for aspirin therapy is needed at the time anticoagulant therapy is initiated, considering the increased risk of bleeding vs the potential benefit in terms of cardiovascular prevention. This recommendation does not apply to patients with a recent acute coronary event or coronary intervention. • For patients with DVT, with or without an increased risk for PTS, the ASH guideline panel suggests against the routine use of compression stockings (conditional recommendations based on very low certainty in the evidence of effects ⨁○○○). **Remarks**: Although the majority of patients may not benefit from the use of stockings to reduce the risk of PTS, stockings may help to reduce edema and pain associated with acute DVT in selected patients.
Section 1.1.8 **Saudi Critical Care Society clinical practice guidelines on the prevention of venous thromboembolism in adults with trauma: reviewed for evidence-based integrity and endorsed by the Scandinavian Society of Anesthesiology and Intensive Care Medicine 2023**[14]	The guidelines methodologists used the GRADE approach to assess the quality of evidence and summarize confidence in the estimate of the effect to support a recommendation. The quality of evidence was rated as high, moderate, low, or very low. • In adults with blunt solid organ injuries to liver, spleen, or kidney who are managed nonoperatively and are at low risk of bleeding, the guidelines suggest starting pharmacologic VTE prophylaxis early (i.e., within 24–48 h) over delayed initiation of pharmacologic VTE prophylaxis (> 48 h) (Weak, very low) Clinicians should assess risk of bleeding. This recommendation is inapplicable to patients at high risk of major bleeding (e.g., high grade solid organ injuries and large hemoperitoneum) and those with hemodynamic instability • In adults with isolated blunt TBI with a low risk of bleeding progression who had stable repeated brain imaging showing no bleeding progression and stable neurologic examination, the guidelines suggest early pharmacologic VTE prophylaxis (within 24–72 h post-injury) over delayed pharmacologic VTE prophylaxis (> 72 h) (Weak, very low) This recommendation is inapplicable to patients with high risk of ICH spontaneous progression demonstrated at baseline or repeated brain imaging or patients with worsening of neurologic examination findings that necessitate upgrading care or emergent neurosurgical intervention

	• In adults with isolated blunt TBI at a high risk of bleeding progression, the guidelines suggest starting early pharmacologic VTE prophylaxis 72 h post-injury with stable brain imaging that shows no bleeding progression and stable neurologic examination over delayed pharmacologic VTE prophylaxis (> 72 h). The decision is usually made in conjunction with multidisciplinary teams' evaluation (Weak, very low) Early pharmacologic VTE prophylaxis should be held until follow-up brain imaging (e.g., brain CT) demonstrates no bleeding progression. If progression is demonstrated, mechanical VTE prophylaxis (if no contradictions) should be continued and prophylactic IVCF and/or US screening to be considered This recommendation is inapplicable for patients with known coagulopathy (INR > 1.5, a partial thromboplastin time > 40 s, a platelet counts of < 100 × 10^9/l) • There is insufficient evidence to issue a recommendation on the use of early pharmacologic VTE prophylaxis in adults with isolated blunt TBI requiring neurosurgical intervention (including craniectomy, craniotomy, EVD, or ICP monitoring) (No recommendation) It is agreed that best practice includes withholding early pharmacologic VTE prophylaxis until follow-up brain imaging (e.g., brain CT) demonstrates no bleeding progression. If progression is demonstrated, we agree that best practice includes continuation of mechanical VTE prophylaxis (if no contradictions) and prophylactic IVCF and/or US screening to be considered (Best Practice Statement) It is also agreed that best practice includes evaluation of timely initiation of pharmacologic VTE prophylaxis by multidisciplinary teams (trauma, neuro/neurosurgical, critical care, and clinical pharmacist) (Best Practice Statement) • In adults with isolated spine trauma or fracture and/or SCI who are at low risk of bleeding and are managed non-operatively, the guidelines suggest initiating pharmacologic VTE prophylaxis within 24–48 h post-injury over delayed pharmacologic VTE prophylaxis (> 48 h) (Weak, very low) The presence of neurological deficit and presence/or expansion of intraspinal hematoma or epidural hematoma demonstrated on radiologic spine images (CT and/or MRI) should prompt discussion among multidisciplinary teams prior to initiating pharmacologic VTE prophylaxis Mechanical VTE prophylaxis (if no contradictions) should be initiated for all SCI patients. If initiation of pharmacologic VTE prophylaxis is anticipated to be delayed or interrupted, US screening and/or prophylactic IVCF may be considered

	• In adults with isolated spine trauma or fracture and/or SCI and managed operatively, we suggest initiating early pharmacologic VTE prophylaxis within 48 h post-spinal fixation over delayed pharmacologic VTE prophylaxis (> 48 h) (Weak, very low) The presence of neurological deficit and presence/or expansion of intraspinal hematoma or epidural hematoma demonstrated on radiologic spine images (CT and/or MRI) should prompt discussion among multidisciplinary teams prior to initiating pharmacologic VTE prophylaxis Mechanical VTE prophylaxis (if no contradictions) should be initiated for all SCI patients. If initiation of pharmacologic VTE prophylaxis is anticipated to be delayed or interrupted, US screening and/or prophylactic IVCF may be considered • In adults with trauma who receive pharmacologic VTE prophylaxis, we suggest using LMWH (e.g., enoxaparin, dalteparin) over UFH (Weak, low) UFH is preferred in patients with end-stage renal disease and in those with low creatinine clearance (< 30 ml/min) • In adults with trauma and low risk of bleeding who are prescribed LMWH (enoxaparin) for VTE prophylaxis, we suggest using either intermediate–high dose LMWH or conventional dosing LMWH (Weak, very low) Most common regimen used was enoxaparin 40 mg subcutaneous every 12 h This recommendation is inapplicable to those at a high risk for bleeding (patients older than 65 year, < 50 kg, have low creatinine clearance, and TBI or SCI patients who are high risk for bleeding) • In adults with trauma who are not candidates for pharmacologic VTE prophylaxis, we recommend using mechanical VTE prophylaxis with IPC over no mechanical VTE prophylaxis when not contraindicated by lower extremity injury (Strong, very low) • In adults with trauma taking pharmacologic VTE prophylaxis, we suggest either using adjunct mechanical VTE prophylaxis or pharmacologic VTE prophylaxis alone (Weak, very low) • In adults with trauma who are at an elevated risk of VTE and are not candidates for pharmacologic VTE prophylaxis, we suggest routine bilateral lower extremity US to screen for asymptomatic DVT over no routine screening (Weak, very low) This recommendation is inapplicable to trauma patients who are ambulating, those at low VTE risk, and patients with signs or symptoms of DVT in whom diagnostic imaging is indicated • In adults with trauma who are not candidates for pharmacologic VTE prophylaxis, we suggest against

	the routine placement of prophylactic IVCFs (Weak, very low) Clinicians may consider using temporary retrievable IVCF in patients who are expected to be off pharmacologic VTE prophylaxis for > 7 days (e.g., severely injured patients with an ongoing bleeding risk)
Section 1.1.9 **NICE Venous thromboembolism in adults guidelines 2021**[23]	• People aged 16 and over who are in hospital and assessed as needing pharmacological venous thromboembolism (VTE) prophylaxis start it as soon as possible and within 14 hours of hospital admission. • People aged 18 and over taking anticoagulation treatment after a venous thromboembolism (VTE) have a review at 3 months and then at least once a year if they continue to take it long term.
Section 1.1.10 **The Saudi Consensus for the Management of Cancer-Associated Thromboembolism: A Modified Delphi-Based Study 2023**[16]	• For hospitalized medical oncology patients with acute medical illness, primary prophylaxis with LMWH should be offered for patients admitted in the absence of contraindications (Level of agreement: 100%) • For hospitalized medical oncology patients without additional risk factors, primary pharmacological prophylaxis can be offered in the absence of bleeding or other contraindications (Level of agreement: 83%) • LMWH is the pharmacological option of choice for the primary prophylaxis of CT and remained predominately used in an inpatient and outpatient setting in Saudi Arabia unless contraindicated (Level of agreement: 83%) • Prophylaxis should not be offered for patients admitted for minor procedures or patients with platelets less than 25,000/uL (Level of agreement: 100%) • Pneumatic compression devices can be offered for patients with contraindications for anticoagulants until the contraindications are resolved (Level of agreement: 100%) • For ambulatory patients, treatment decisions should be based on the risk of VTE and bleeding, as well as patient preferences/values (Level of agreement: 100%) • Ambulatory low-risk patients should not be offered primary pharmacological prophylaxis (Level of agreement: 100%) • High-risk ambulatory patients should be offered thromboprophylaxis. In Saudi Arabia, DOACs and LMWH is commonly used in this setting unless contraindicated (Level of agreement: 75%) • DOACs can be offered for up to 6 months for primary prophylaxis in high-risk ambulatory cancer patients (KRS ≥ 2) if no contraindications and they cannot take LMWH

	○ DOACs are relatively inexpensive and readily available, which allows their use for primary prophylaxis in high-risk patients (Level of agreement: 100%) • Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered thromboprophylaxis with either aspirin or LMWH (lower-risk patients) or LMWH (higher-risk patients) (Level of agreement: 100%) • All patients undergoing major surgery should be offered pharmacological, preoperative. Prophylaxis with UFH or LMWH, unless contraindicated, and should be continued for at least 7–10 days (Level of agreement: 100%) • Extended prophylaxis with LMWH for up to 4 weeks postoperatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic cancer surgery with high-risk features (Level of agreement: 100%) • Combined pharmacologic/mechanical prophylaxis may improve efficacy, especially in highest-risk patients. However, mechanical prophylaxis should not be used as monotherapy unless pharmacologic prophylaxis is contraindicated (Level of agreement: 100%) • The choice of anticoagulation regimen should be based on individual risk of thrombosis and bleeding, renal and hepatic function, inpatient/outpatient status, FDA approval status, ease of administration, cost, the burden of laboratory monitoring, agent reversibility, and patient preferences (Level of agreement: 100%) • DOACs, LMWH, UFH, or fondaparinux, can be used as initial anticoagulants. Among parenteral agents, LMWH is preferred over UFH in the absence of severe renal impairment (Level of agreement: 100%) • LMWH is preferred for patients with acute VTE at high risk for bleeding or with GI malignancy (Level of agreement: 83.3%) • For long-term anticoagulation, DOACs or LMWH for at least 6 months is preferred over VKA. VKAs are less effective but may be used if DOACs or LMWH are not accessible (Level of agreement: 100%) • For hospitalized medical oncology patients with acute medical illness, primary prophylaxis with LMWH should be offered for patients admitted in the absence of contraindications (Level of agreement: 100%) • Catheter-directed pharmaco-mechanical thrombolysis can be considered for DVT in patients at low risk for bleeding but at risk for limb loss or severe persistent symptoms despite anticoagulation (Level of agreement: 100%)

	• IVC filters may be offered to patients with absolute contraindications to anticoagulation in the acute setting independent of thrombosis burden (Level of agreement: 100%) • Incidental VTE should be treated in the same manner as symptomatic VTE (Level of agreement: 100%) • Treatment of isolated subsegmental PE or splanchnic or visceral vein thrombi should be offered on a case-by-case basis considering the potential benefits and risks (Level of agreement: 100%) • The use of novel DOACs in patients with other medical conditions such as hemodialysis or valvular atrial fibrillation is still ambiguous and requires further evidence (Level of agreement: 100%)
Section 1.1.11 **Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: ASCO Guideline Update 2023**[24]	• Patients who are candidates for extended pharmacologic thromboprophylaxis after surgery may be offered prophylactic doses of low molecular weight heparin (LMWH) (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong). Alternatively, patients may be offered prophylactic doses of rivaroxaban or apixaban after an initial period of LMWH or unfractionated heparin (UFH) (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak). **Qualifying statement**. Evidence for rivaroxaban and apixaban in this setting remains limited. The two available trials differed with respect to type of cancer, type of surgery, and timing of rivaroxaban or apixaban initiation after surgery • Initial anticoagulation may involve LMWH, UFH, fondaparinux, rivaroxaban, or apixaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5-10 days of anticoagulation for the patient with cancer with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance <30 mL/min; Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong). • For long-term anticoagulation, LMWH, edoxaban, rivaroxaban, or apixaban for at least 6 months are preferred over vitamin K antagonists (VKAs) because of improved efficacy. VKAs may be used if LMWH or direct factor Xa inhibitors are not accessible. There is reduction in recurrent thrombosis but an increase in clinically relevant nonmajor bleeding risk with direct factor Xa inhibitors compared with LMWH. Caution with direct factor Xa inhibitors is warranted in GI and genitourinary malignancies and other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked before using a direct factor Xa inhibitor (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).
Section 1.1.12	• The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was

American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer[25]	used to assess evidence and make recommendations in this guidelines. • Primary prophylaxis for hospitalized medical patients with cancer: o For hospitalized medical patients with cancer without VTE, the American Society of Hematology (ASH) guideline panel suggests using thromboprophylaxis over no thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯). o For hospitalized medical patients with cancer without VTE, in which pharmacological thromboprophylaxis is used, the ASH guideline panel suggests using LMWH over UFH (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯). o For hospitalized medical patients with cancer without VTE, the ASH guideline panel suggests using pharmacological thromboprophylaxis over mechanical thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯). o For hospitalized medical patients with cancer without VTE, the ASH guideline panel suggests using pharmacological thromboprophylaxis over a combination of pharmacological and mechanical thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯). o For hospitalized medical patients with cancer, the ASH guideline panel suggests discontinuing thromboprophylaxis at the time of hospital discharge rather than continuing thromboprophylaxis beyond the discharge date (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯). • Primary prophylaxis for patients with cancer undergoing surgery o For patients with cancer without VTE undergoing a surgical procedure at lower bleeding risk, the ASH guideline panel suggests using pharmacological rather than mechanical thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯). o For patients with cancer without VTE undergoing a surgical procedure at high bleeding risk, the ASH guideline panel suggests using mechanical rather than pharmacological thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯). o For patients with cancer without VTE undergoing a surgical procedure at high risk for thrombosis, except in those at high risk of bleeding, the ASH guideline panel suggests using a combination of mechanical and pharmacologic thromboprophylaxis rather than mechanical prophylaxis alone

	(conditional recommendation based on low certainty in the evidence of effects) or pharmacologic thromboprophylaxis alone (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯). ○ For patients with cancer undergoing a surgical procedure, the ASH guideline panel suggests using LMWH or fondaparinux for thromboprophylaxis rather than UFH (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯). ○ For patients with cancer undergoing a surgical procedure, the ASH guideline panel makes no recommendation on the use of VKA or DOAC for thromboprophylaxis, because there were no studies available. (not graded) ○ For patients with cancer undergoing a surgical procedure, the ASH guideline panel suggests using postoperative thromboprophylaxis over preoperative thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯). ○ For patients with cancer who had undergone a major abdominal/pelvic surgical procedure, the ASH guideline panel suggests continuing pharmacological thromboprophylaxis post discharge rather than discontinuing at the time of hospital discharge (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯). • Primary prophylaxis in ambulatory patients with cancer receiving systemic therapy ○ For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, we recommend no thromboprophylaxis over parenteral thromboprophylaxis (strong recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯). ○ For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel suggests no prophylaxis over parenteral prophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯). ○ For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel suggests parenteral thromboprophylaxis (LMWH) over no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯). ○ For ambulatory patients with cancer receiving systemic therapy, the ASH guideline panel recommends no thromboprophylaxis over oral thromboprophylaxis with VKA (strong

	recommendation, very low certainty in the evidence of benefits ⨁◯◯◯, but high certainty about the harms ⨁⨁⨁⨁). ○ For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, the ASH guideline panel suggests no thromboprophylaxis over oral thromboprophylaxis with a DOAC (apixaban or rivaroxaban) (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯). ○ For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel suggests thromboprophylaxis with a DOAC (apixaban or rivaroxaban) or no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯). ○ For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel suggests thromboprophylaxis with a DOAC (apixaban or rivaroxaban) over no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯). ○ For multiple myeloma patients receiving lenalidomide, thalidomide, or pomalidomide-based regimens, the ASH guideline panel suggests using low-dose acetylsalicylic acid (ASA) or fixed low-dose VKA or LMWH (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯). • Primary prophylaxis for patients with cancer with central venous catheter ○ For patients with cancer and a central venous catheter (CVC), the ASH guideline panel suggests not using parenteral thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯). ○ For patients with cancer and a CVC, the ASH guideline panel suggests not using oral thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯). • Initial treatment (first week) for patients with active cancer and VTE ○ For patients with cancer and VTE, the ASH guideline panel suggests DOAC (apixaban or rivaroxaban) or LMWH be used for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯).

	○ For patients with cancer and VTE, we recommend LMWH over UFH for initial treatment of VTE for patients with cancer (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). ○ For patients with cancer and VTE, the ASH guideline panel suggests LMWH over fondaparinux for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). • Short-term treatment for patients with active cancer (initial 3-6 months) ○ For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel suggests DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯). ○ For the short-term treatment of VTE (3-6months) for patients with active cancer, the ASH guideline panel suggests DOAC (apixaban, edoxaban, or rivaroxaban) over VKA (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). ○ For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel suggests LMWH over VKA (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). ○ For patients with cancer and visceral/ splanchnic vein thrombosis, the ASH guideline panel suggests treating with short-term anticoagulation or observing (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). ○ For patients with cancer with CVC-related VTE receiving anticoagulant treatment, the ASH guideline panel suggests keeping the CVC over removing the CVC (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). ○ For patients with cancer and recurrent VTE despite receiving therapeutic LMWH, the ASH guideline panel suggests increasing the LMWH dose to a supratherapeutic level or continuing with a therapeutic dose (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯). ○ For patients with cancer and recurrent VTE despite anticoagulation treatment, the ASH guideline panel suggests not using an inferior vena cava (IVC) filter over using a filter (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

	• Long-term treatment (>6 months) for patients with active cancer and VTE
	  o For patients with active cancer and VTE, the ASH guideline panel suggests long-term anticoagulation for secondary prophylaxis (.6 months) rather than short-term treatment alone (3-6 months) (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).
	  o For patients with active cancer and VTE receiving long-term anticoagulation for secondary prophylaxis, the ASH guideline panel suggests continuing indefinite anticoagulation over stopping after completion of a definitive period of anticoagulation (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).
	  o For patients with active cancer and VTE requiring long-term anticoagulation (.6 months), the ASH guideline panel suggests using DOACs or LMWH (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Section 1.1.13
2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients with Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or with Atherosclerotic Cardiovascular Disease A Report of the American
	• Recommendations for patients with AF relate specifically to those with nonvalvular AF and should not be extrapolated to those with valvular AF (a controversial term in itself but most commonly defined as AF associated with moderate to severe mitral stenosis, most frequently rheumatic, or with mechanical heart valves)
	• The below recommendations are for patients on antiplatelet and developed a new VTE.
	• For patients on SAPT for SIHD, with no history of ACS and no prior revascularization who develop VTE requiring AC therapy, the appropriate management is nearly always to stop APT and start an AC.
	  o For patients on APT for SIHD, with no history of ACS but prior PCI, the time since PCI should be assessed.
	  o If it has been ≤6 months since PCI, the guidelines' recommendation for most patients would be to stop aspirin, continue clopidogrel, and start an AC (with preference given to a DOAC)
	  o If it has been 6 to 12 months since PCI, the guidelines recommend continuing SAPT with either aspirin or clopidogrel until 1-year post-PCI, along with an OAC.
	  o If it has been ≥12 months post-PCI, an OAC alone can be used long-term.
	  o For patients on APT for SIHD with no history of ACS but who had prior CABG surgery, the time since CABG surgery should be assessed. The guidelines recommend continuing aspirin (<100 mg/day) if <1 year post- CABG surgery and stopping aspirin if >1 year post-CABG surgery
	• Patients with ACS (unstable angina, non–ST-elevation myocardial infarction, and ST-elevation myocardial

College of Cardiology Solution Set Oversight Committee[29]	infarction) are usually treated with DAPT for 12 months after ACS. If these patients were previously on prasugrel or ticagrelor, the guidelines recommend switching to clopidogrel o If it has been ≤12 months since the ACS, the guidelines' recommendation for most patients would be to stop aspirin, continue the P2Y12i (with preference given to clopidogrel), and start an AC (with preference given to a DOAC) o If it has been >12 months since the ACS, APT may be stopped and most patients can be treated with an AC alone. o For patients at high bleeding risk and low ischemic risk, shorter durations of APT can be considered. o At the clinician's discretion, selected patients felt to be at higher thrombotic risk due to: a) the nature of the coronary lesion; b) the type, location, number, or length of coronary stents; or c) other clinical factors, and low bleeding risk may continue SAPT (aspirin 81 mg daily or clopidogrel 75 mg daily) beyond 12 months while on an AC. • For patients on APT for prior TIA or cerebrovascular accident who develop VTE requiring AC therapy, the pathway recommends stopping all APT and treating with an AC alone (DOAC preferred) when considered safe from the perspective of hemorrhagic transformation, typically between 2 and 14 days following an acute event. Given that TIA is the diagnosis when no infarct or hemorrhage is noted on imaging, an AC can typically be initiated immediately. • For patients who have undergone recent carotid endarterectomy, the pathway recommends stopping all APT and treating with an AC alone (DOAC preferred) when considered safe from risk of post-operative bleeding, typically 3 to 14 days after surgery. • For patients with carotid stenting within the previous 1 to 3 months, our recommendation for most patients would be to stop aspirin, continue the P2Y12i (clopidogrel preferred), and start an AC (DOAC preferred). If the standard duration of DAPT after carotid stenting has ended (usually 1 to 3 months), all APT may be stopped and most patients can be treated with an AC alone. • Patients with PAD without prior intervention or with prior surgical repair are usually treated with SAPT (usually aspirin or clopidogrel) for primary or secondary prevention of ischemic events (myocardial infarction, stroke). For such patients presenting with VTE appropriate for an AC, the pathway recommends stopping all APT and treating with an AC alone (DOAC preferred).

	• Patients with PAD who have been treated with endovascular intervention/stenting are usually treated with APT for 1 to 3 months. The type and duration of APT is less well-defined and standardized than for coronary interventions. For patients presenting with VTE appropriate for AC therapy, the pathway recommends continuing or switching to SAPT (either clopidogrel or aspirin, clopidogrel preferred) and treating with an AC (DOAC preferred). If the standard duration of DAPT after endovascular intervention/stenting has ended (usually 1 to 3 months), all APT may be stopped and most patients can be treated with an AC alone. • The below figure showcases the recommended anticoagulation dosing for VTE:

Agent	VTE Initial Treatment	VTE Secondary Prevention after Initial Therapy	Dosing Adjustments*
Apixaban	10 mg orally twice daily for the first 7 days of therapy followed by 5 mg orally twice daily.	After ≥6 months of initial therapy, either 5 mg orally twice daily or 2.5 mg orally twice daily can be considered.†	Patients with ESKD receiving hemodialysis were not enrolled in clinical trials. However, the prescribing information states that no dose adjustment is necessary for patients with renal impairment, including those with ESKD.
Dabigatran	150 mg orally twice daily when preceded by 5-10 days of parenteral AC.‡	150 mg orally twice daily.§	Patients with severe renal impairment (a CrCl of ≤30 mL/min) and with ESKD receiving hemodialysis were not enrolled in clinical trials. The prescribing information makes no recommendations for dosing in this population.
Edoxaban	60 mg orally once daily when preceded by at least 5-10 days of parenteral AC.‡	60 mg orally once daily.	Dose reduction to 30 mg once daily for patients with a CrCl (estimated using actual body weight) of 15-50 mL/min or body weight ≤60 kg.
Rivaroxaban	15 mg orally twice daily with food for the first 21 days followed by 20 mg daily with food.	After ≥6 months of initial therapy, either 20 mg orally daily with food or 10 mg orally daily with or without food can be considered.†	Patients with a CrCl of <30 mL/min were excluded from clinical trials. Avoid use in patients with a CrCl of <15 mL/min.
VKA	When used with APT: INR 2.0-2.5‖; bridging with parenteral heparin initially.	When used with APT: Consider INR 2.0-2.5.‖	NA
Dalteparin	In the setting of cancer: 200 units/kg subcutaneously once daily for 1 month, then 150 IU/kg subcutaneously once daily (months 2-6) for extended treatment.	In the setting of cancer: Not FDA-approved for this indication, but use is consistent with NCCN recommendations.	For patients with a CrCl of <30 mL/min, the prescribing information recommends monitoring anti-Factor Xa levels with a target peak level (4-6 hours post-dose) of 0.5-1.5 IU/mL. Patients with ESKD were excluded from clinical trials.
Enoxaparin	In the setting of cancer: 1 mg/kg twice daily or 1.5 mg/kg once daily, subcutaneously.¶#**	In the setting of cancer: Not FDA-approved for this indication, but use is consistent with NCCN recommendations¶#**	Patients with a CrCl of <30 mL/min were excluded from clinical trials. However, the prescribing information recommends a dose reduction to 1 mg/kg subcutaneously once daily for patients with a CrCl (estimated using actual body weight) of <30 mL/min).

*Dosing information in this table does not take drug–drug interactions into consideration. The reader is encouraged to review the specific drug prescribing information.
†Reduced-dose rivaroxaban (10 mg daily) and apixaban (2.5 mg twice daily) can be considered for secondary prevention of VTE after 6 months of initial treatment.
‡Initial treatment with unfractionated heparin, LMWH, or fondaparinux recommended.
§Dabigatran 110 mg twice daily is approved for use in DVT/PE treatment outside of the United States.
‖Monitor INR more frequently.
¶Long-term treatment with enoxaparin at this dose has not been tested in cancer patients.
#Agent and dosing supported by the NCCN Clinical Practice Guidelines in Oncology for Cancer-Associated Venous Thromboembolic Disease (Version 1.2019).
**Among patients without cancer, enoxaparin is approved for DVT and is also used extensively off-label for treatment of PE

Section 1.1.14

EASL Clinical Practice Guidelines on prevention and

- The quality of evidence was scored according to the Oxford Centre for Evidence-based Medicine (OCEBM)
- The Delphi panel then examined the CPG. Returning scores were graded as follows:
  - Less than 50% approval: re-write recommendation and resubmit to the Delphi panel;

management of bleeding and thrombosis in patients with cirrhosis 2022[28]	○ 50%-75% approval: re-write/improve the recommendation, but no resubmission to the Delphi panel; ○ 75-90% approval: no need to re-write the recommendation but the document will take into account the comments; ○ ≥ 90% approval: assumed as consensus, no change needed but small corrections possible. ○ To consider a question approved, an agreement from at least 75% of Delphi panel members was required. • In patients with cirrhosis at risk of DVT/PE, thromboprophylaxis with LMWH can be recommended as it has a reasonable safety profile, but efficacy is unclear based on available data (LoE 3, weak recommendation); Delphi panel agreement: 93% • In patients with Child-Pugh class A and B cirrhosis at risk of DVT/PE, thromboprophylaxis with DOACs can be recommended as DOACs have a reasonable safety profile in these patients, but efficacy data are still limited. In patients with Child-Pugh C cirrhosis, DOACs are not recommended (Safety: LoE 2; Efficacy: LoE 4; weak recommendations); Delphi panel agreement: 89% • For treatment of DVT/PE, vitamin K antagonists should be used with caution in patients with cirrhosis, as these patients can have baseline altered INR and thus target INR remains unknown. In patients with Child-Pugh A, LMWH, and vitamin K antagonists are reasonable options. Until more data become available, LMWH is recommended for treatment of DVT/PE in patients with Child-Pugh B and Child-Pugh C cirrhosis, whereas UFH is the treatment of choice in case of renal failure (LoE 4, weak recommendation); Delphi panel agreement: 87% • For the treatment of DVT/PE in patients with cirrhosis, currently available data suggest that there are no major concerns regarding the safety of DOACs in patients with Child-Pugh class A cirrhosis. Due to the possibility of accumulation, DOACs should be used with caution in Child-Pugh class B patients, as well as in patients with creatinine clearance below 30 ml/min. The use of DOACs in Child- Pugh class C patients is not recommended (LoE 4, strong recommendation); Delphi panel agreement: 90%
Section 1.1.15 **American Society of Hematology living guidelines on the use**	• The American Society of Hematology released updated recommendations in accordance with the grading outlined as previously mentioned in the report. • The ASH guideline panel suggests that outpatient anticoagulant thromboprophylaxis not be used for patients with COVID-19 who are being discharged from the hospital and do not have suspected or

of anticoagulation for thromboprophylaxis in patients with COVID-19: July 2021 update on post discharge thromboprophylaxis[17]	confirmed venous thromboembolism (VTE) or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remarks**: o An individualized assessment of the patient's risk of thrombosis and bleeding and shared decision making are important when deciding on whether to use post discharge thromboprophylaxis. Prospectively validated risk assessment models to estimate thrombotic and bleeding risk in COVID-19 patients after hospital discharge are not available. o The panel acknowledged that post discharge thromboprophylaxis may be reasonable for patients judged to be at high risk of thrombosis and low risk of bleeding.
Section 1.1.16 **American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis for patients with COVID-19: March 2022 update on the use of anticoagulation in critically ill patients**[22]	• The American Society of Hematology released updated recommendations in accordance with the grading outlined as previously mentioned in the report. • The ASH guideline panel suggests using prophylactic-intensity over therapeutic-intensity anticoagulation for patients with COVID-19–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE; conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).
Section 1.1.17 **American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis**	• The American Society of Hematology released updated recommendations in accordance with the grading outlined as previously mentioned in the report. • Patients with COVID-19–related critical illness are defined as those suffering from an immediately life-threatening condition who would typically be admitted to an intensive care unit (ICU). Examples include patients requiring hemodynamic support, ventilatory support, and renal replacement therapy. • The American Society of Hematology (ASH) guideline panel suggests using prophylactic-intensity over intermediate-intensity anticoagulation in patients with COVID-19–related critical illness who do not have

in patients with COVID-19: May 2021 update on the use of intermediate-intensity anticoagulation in critically ill patients[18]	suspected or confirmed venous thromboembolism (VTE) (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯). • At present, there is no direct high-certainty evidence comparing different types of anticoagulants. The selection of a specific agent (eg, low molecular weight heparin [LMWH], unfractionated heparin [UFH]) may be based on availability, resources required, familiarity, and the aim of minimizing the use of personal protective equipment or exposure of staff to COVID- 19–infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption). • This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on extracorporeal membrane oxygenation or continuous renal replacement therapy.
Section 1.1.18 **American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: January 2022 update on the use of therapeutic-intensity anticoagulation in acutely ill patients** [19]	• The American Society of Hematology released updated recommendations in accordance with the grading outlined as previously mentioned in the report. • The ASH guideline panel suggests using therapeutic-intensity over prophylactic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯). **Remarks**: o Patients with COVID-19–related acute illness are defined as those with clinical features that would typically result in admission to an inpatient medical ward without requirement for intensive clinical support. Examples include patients with dyspnea or mild-to-moderate hypoxia. o The panel acknowledges that lower intensity anticoagulation may be preferred for patients judged to be at high risk of bleeding and low risk of thrombosis. o At present, there is no direct high-certainty evidence comparing different types of anticoagulants in patients with COVID-19. Unfractionated or low molecular weight heparin may be preferred because of a preponderance of evidence with these agents. There are no studies of therapeutic-intensity fondaparinux, argatroban, or bivalirudin in this population.
Section 1.1.19 **The use of direct oral**	The Scientific and Standardization Committee (SSC) through its subcommittee Hemostasis & Malignancy of the International Society for Thrombosis and Hemostasis (ISTH) aims to review emerging data on primary VTE

anticoagulants for primary thromboprophylaxis in ambulatory cancer patients: guidance from the SSC of the ISTH[26]	prophylaxis with direct oral anticoagulants (DOACs) for ambulatory cancer patients and provide guidance to clinicians. • The guidelines suggest the use of DOACs as primary thromboprophylaxis in ambulatory cancer patients starting chemotherapy with Khorana score ≥ 2 in patients with no drug-drug interactions and not at high risk for bleeding (such as patients with gastro-esophageal cancers). Apixaban and rivaroxaban were the only DOACs with evidence from RCTs. A final treatment decision should be made after considering the risk of both VTE and bleeding, as well as patients' preference and values. • The guidelines suggest that if DOACs were to be used for primary thromboprophylaxis in ambulatory cancer patients, it is administered for up to 6 months after the initiation of chemotherapy. It is recommended to monitor platelet counts and risk of bleeding complications while on anticoagulation. • In high-risk ambulatory cancer patients where primary thromboprophylaxis is planned but with concerns for safety of DOAC (such as in patients with concern of drug interaction or high risk of gastrointestinal bleeding), it is suggested to use LWMH.
Section 1.1.20 **Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline 2022**[27]	Thromboprophylaxis in the surgical setting • Unless contraindicated due to a high risk of bleeding, pharmacological VTE prophylaxis with LMWH (preferred) or UFH is recommended in patients undergoing major cancer surgery [I, A]. Fondaparinux may be used as an alternative [II, C]. • Mechanical methods such as intermittent pneumatic compression (IPC) or graduated compression stockings (GCSs) are suggested as an alternative when pharmacological VTE prophylaxis is contraindicated (e.g. in the presence of active bleeding) [II, B]. Mechanical methods may be used in combination with pharmacological VTE prophylaxis in patients at exceedingly high risk of VTE [II, C]. • Depending on the heparin type and dosage, commencement of pharmacological thromboprophylaxis with LMWH or UFH 2-12 h preoperatively is suggested in cancer surgical patients [II, B]. • Where several prophylactic dosages are approved for a given LMWH, the highest prophylactic LMWH dose o.d. or 5000 IU UFH t.d.s. is recommended [II, A]. • Patients undergoing major cancer surgery should receive pharmacological thromboprophylaxis for at least 10 days post-operatively [I, A]. In patients with cancer undergoing open abdominal or pelvic surgery or laparoscopic colorectal cancer surgery, extended post-operative VTE prophylaxis for 4 weeks with LMWH is recommended [I, A].

	Prevention of VTE in non-surgical patients with cancer • For ambulatory pancreatic cancer patients on first-line systemic anticancer treatment, LMWH given at a higher dose (150 IU/kg dalteparin or 1 mg/kg enoxaparin) for a maximum of 3 months may be considered [II, C]. • In ambulatory cancer patients starting systemic anticancer treatment who have a high thrombosis risk, apixaban, rivaroxaban or LMWH may be considered for primary thromboprophylaxis for a maximum of 6 months [I, B]. • In hospitalized cancer patients confined to bed with an acute medical complication, prophylaxis with LMWH, UFH [I, B] or fondaparinux [II, B] is recommended. • Where concerns of DOAC safety exist and the patient is perceived as having clinically important risk for VTE, LMWH at conventional primary thromboprophylaxis dosing may be administered [II, C]. Patients with MM • In ambulatory patients with MM receiving IMiD treatment combined with low-dose dexamethasone and without additional risk factors, aspirin (100 mg/day) is recommended [III, B]. • In ambulatory patients with MM classified as high risk for VTE, pharmacological thromboprophylaxis with LMWH for 3-6 months is recommended [II, B]. • Extension of thromboprophylaxis should be considered on a case-by-case basis [IV, B]. • Apixaban 2.5 mg b.i.d. or rivaroxaban 10 mg o.d. are potential options in patients with CrCl >30 ml/min who present contraindications or intolerance to LMWH [IV, C]. TREATMENT OF CAT • In patients with CAT, LMWH, UFH, fondaparinux, apixaban or rivaroxaban are recommended treatments for the acute phase [I, A]. LMWH is preferred over UFH or fondaparinux [V, A]. UFH may be considered in patients with CAT and severe renal impairment (defined as CrCl <30 ml/min) [IV, C]. • Long-term anticoagulation for at least 6 months includes LMWH, apixaban, edoxaban or rivaroxaban which are preferred over VKAs [I, A]. VKAs may be used if LMWH or direct factor Xa inhibitors are not accessible [IV, C]. • In patients with luminal gastrointestinal cancer, LMWH is preferred for treating CAT [II, B]. Similar considerations potentially apply to patients with urothelial cancer [II, B]. The use of oral factor Xa

	inhibitors should consider patient preferences [IV, C]. • In patients at high risk for gastrointestinal bleeding, such as those with active gastroduodenal ulcers or patients receiving strong inhibitors or inducers of P-glycoprotein and CYP3A4, LMWH is preferred [IV, B]. The author panel acknowledges that only limited evidence is available on drug-drug interactions between direct factor Xa inhibitors and systemic antineoplastic therapy. • Extended anticoagulation beyond the initial 6 months with LMWH, apixaban, edoxaban, rivaroxaban or VKAs should be considered for patients with active cancer in whom the risk of recurrent thrombosis is higher and may outweigh that of bleeding [III, B]. The risk-benefit profile of anticoagulant therapy should be regularly assessed to ensure a favourable balance [IV, C]. • For incidentally detected VTE, the same treatment as for symptomatic VTE is recommended [II, A]. • In patients with high risk of bleeding or single incidental subsegmental PE without concomitant DVT, provided that there is adequate cardiopulmonary reserve, a watchful approach or a shorter course of anticoagulation may be considered [V, C]. • The insertion of vena cava filters is suggested in patients with acute and life-threatening VTEs who have absolute contraindications to anticoagulant therapy [III, B] or as an adjunct to anticoagulation in patients with recurrent VTE or extension of thrombosis despite optimal anticoagulant therapy [IV, C]. PREVENTION AND MANAGEMENT OF CATHETER-RELATED VTE IN ADULTS WITH CANCER • Routine pharmacological prophylaxis of CRT is not recommended [II, D]. • For the treatment of symptomatic CRT in cancer patients, anticoagulant treatment is recommended for a minimum of 3 months [III, A]. LMWH is suggested, although, in the absence of direct comparisons between anticoagulants in this setting, VKAs or DOACs may be considered alternative options [IV, C]. • It is recommended to remove the catheter if it is not needed or is infected, anticoagulant treatment is contraindicated or there is clinical deterioration due to thrombus extension despite treatment [III, B]. • In patients with CRT, who have completed 3 months of anticoagulant treatment, extended anticoagulation until catheter removal is suggested, if the patient's bleeding risk is low [IV, C].
HTA Pharmacoeconomics Analysis	Recommendations from HTA bodies should be added under each drug therapy section as they are missing from the previous/initial document.

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Venous Thromboembolism:

Query	Filters	Search Details	Results
(Thromboembolism[MeSH Terms]) OR (Thromboembolisms[Title/Abstract])	Guideline, in the last 5 years	("thromboembolism"[MeSH Terms] OR "Thromboembolisms"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	65

Appendix D. Treatment Algorithm of Venous Thromboembolism