National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer-Associated Venous Thromboembolic Disease

Version 2.2024 — July 22, 2024

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Cancer-Associated Venous Thromboembolic Disease

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2024 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 1.2024 include:

MS-1

• The discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2024 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 2.2023 include:

Global Updates

• References have been updated throughout the guidelines.

VTE-1

• Initial prophylaxis, header added: Pharmacologic prophylaxis

VTE-B (1 of 5)

• UFH, Standard Dosing
  ▸ 5000 units SC every 8–12 hours, category of evidence changed from category 1 to category 2A.
• UFH, Dosing for actual body weight 25–50 kg
  ▸ Weight <40 kg, dosing modified: ~~5000~~ *2500* units SC every *8*–12 hours
• Footnote d modified: ~~Data is limited in oncology populations with obesity; therefore, dosing recommendations are derived from surgical and medical studies~~. *Limited to no data available to support recommendations. Recommended doses are derived from non-oncology populations.*
• Footnote f modified: ~~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.~~ *Consider laboratory monitoring.* If dose escalation or de-escalation is required twice, consult with Hematology or a Clinical *Anticoagulation* Pharmacy Specialist. Singer GA, et al. J Trauma Acute Care Surg 2016;81:1101-1108. (Also for VTE-B 3 of 5).

VTE-B (2 of 5)

• Apixaban, Renal Dose modified: ~~Avoid~~*Caution* if CrCl <30 mL/min (Also for VTE-B 3 of 5 and VTE-B 4 of 5).
• Footnote j added: Patients with CrCl <30 mL/min were excluded from VTE prophylaxis studies. Due to limited data in this population, use with caution. May consider use in extenuating circumstances such as HIT. (Also for VTE-B 3 of 5 and VTE-B 4 of 5)

SVT-1

• Upper extremity SVT, SVT treatment, bullet 2 modified: If progression symptomatically or on imaging, ~~consider~~ prophylactic dose anticoagulation *is recommended.*

DVT-2

• Footnote modified: ~~Mechanical Thrombectomy Devices (VTE-H 2 of 2).~~ *Providers can consult with interventional radiology or vascular surgery colleagues to determine the appropriate use of mechanical embolectomy, suction embolectomy, and US-facilitated catheter-directed thrombolysis devices at their institutions.*(Also for DVT-3, PE-2, and SVPT-2)

SPVT-1

• Diagnostic Evaluation, Imaging
  ▸ Footnote b applied: Consider local consultation with radiology to optimize imaging techniques/modality.

VTE-D (1 of 6)

• General Guidelines
  ▸ Bullet 1, sub-bullet 1, sub-sub-bullet added: Reconsider the role of anticoagulation therapy near end of life. Elements for Consideration in Decision Not to Treat (VTE-J).
  ▸ Bullet 5 modified: Following initiation of anticoagulant: hemoglobin, hematocrit, and platelet count at least every 2 to 3 days for the first 14 days *while in the inpatient setting* and every 2 weeks thereafter or as clinically indicated.

VTE-D (2 of 6)

• DOACs
  ▸ Apixaban
    ◊ Category 1 replaced with footnote b: Category 1 for DVT/PE
  ▸ Edoxaban
    ◊ Category 1 replaced with footnote b: Category 1 for DVT/PE
  ▸ Rivaroxaban
    ◊ Sub-bullet modified: 15 mg PO every 12 hours for the first 21 days followed by 20 mg daily *with food*
• LMWH
  ▸ Dalteparin
    ◊ Category 1 replaced with footnote b: Category 1 for DVT/PE

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Updates in Version 1.2024 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 2.2023 include:

VTE-E
- Footnote 2 modified: Active bleeding with >2 units *red blood cells (RBC)* transfused, decrease in hemoglobin by ≥2 g/dL, or intracranial or intraspinal bleeding.

VTE-G (2 of 2)
- Table 2, LMWH, Bullet 1: Change to *every-12-hour* dosing.
- Footnote d modified: 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).

VTE-H (2 of 2)
- Page removed

VTE-J
- Bullet 2, sub-bullet 2 modified: High *bleeding* risk
- Bullet 5 added: End-of-life/comfort care

VTE-K (1 of 8)
- LMWH, half-life modified: (Half-life ~~5~~ *4.5*–7 hours)

VTE-K (2 of 8)
- Argatroban half-life modified: half-life ~~45 minutes with normal hepatic function~~ *39–51 minutes*)

VTE-K (3 of 8)
- Dabigatran, half-life modified: (half-life ~~14~~ *12*–17 hours)

VTE-K (4 of 8)
- Rivaroxaban, half-life modified: ~~(Half-life 9–12 hours; upper level for patients >75 years)~~ *(Half-life 5–9 hours for 20–45 years; 11–13 hours for* ~~70~~ *60–76 years)*

VTE-K (7 of 8)
- Footnote removed: Note, the IV infusion dosing recommendations above differ from the package insert prescribing information to round doses to the closest available vial size.

PMA-A
- Footnote a modified: Use of local hemostatic agents such as topical tranexamic acid and aminocaproic acid or thrombin soaked ~~gelfoam~~ *absorbable gelatin powder* is encouraged in the event of bleeding.

PMA-B
- High Thromboembolic Risk, Clinical Conditions
  - Bullet 8 modified: "*High-risk* inherited thrombophilia..."

PMA-C (1 of 3)
- Text modified: "...Some institutions hold anticoagulation for bone marrow biopsy while others continue anticoagulation depending upon the medication (*ie,* DOAC, warfarin, heparin)..."
- Footnote a modified: Some *low-risk* procedures are performed preferably without warfarin discontinuation (eg, pacemaker or AICD). Other low bleeding risk procedures may not require *5-day* interruption (advise discussion with interventionalist).

PMA-C (2 of 3)
- Pre-procedural Bridging Anticoagulation
  - Bullet 1 modified: "For patients taking warfarin, the majority of NCCN *Member Institutions* consider bridging anticoagulation for patients at high risk of thromboembolism..."
- Post-procedural Resumption of Anticoagulation
  - Bullet 2 modified: "...A majority also recommended resumption of *therapeutic-dose* LMWH, DOACs, or fondaparinux on POD1."
  - Bullet 3 modified: "...Since warfarin takes several days to reach therapeutic concentrations, the majority of institutions recommend resumption of warfarin on *POD1*. A minority recommend resumption on POD2–3. The majority of NCCN *Member Institutions* recommend resumption of *therapeutic-dose* LMWH, DOACs, or fondaparinux on POD2 after a moderate bleeding risk procedure..."
  - Bullet 4: "...The majority of institutions recommend resumption of *therapeutic-dose* LMWH, DOACs, or fondaparinux on POD3 after a high bleeding risk procedure, although a minority recommend resumption on either POD2 or on POD4 or later."

HIT-1
- Footnote a added: See HIT-A for HIT Probability Assessment Tools.
- Footnote e modified: For patients without an indication for therapeutic anticoagulation who are judged to be at *high risk* of bleeding and moderate risk of HIT, a prophylactic dose of a non-heparin anticoagulant could be considered while awaiting the results of initial testing (Cuker A, et al. Blood Adv 2018;2:3360-3392).

INPATIENT VENOUS THROMBOEMBOLISM PROPHYLAXIS

POPULATION AT RISK

- Adults admitted for medical or surgical hospitalizations
- Diagnosis of cancer or clinical suspicion of cancer
- Providers are encouraged to assess venous thromboembolism (VTE) risk factors, risks and benefits of VTE prophylaxis, and to stress the importance of adherence to prevention programs[a]

→ **WORKUP**

Initial Workup:
- History and physical (H&P)
- Complete blood count (CBC) with platelet count
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Liver and kidney function tests
- VTE risk assessment

→ Contraindication to anticoagulation[b]

INITIAL PROPHYLAXIS[c]

No →
Pharmacologic prophylaxis
Prophylactic anticoagulation therapy (category 1); see prophylactic anticoagulation options (VTE-B)
Consider preoperative dosing with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) for high-risk surgery (eg, abdominal/pelvic surgery) ± intermittent pneumatic compression (IPC) device[d,e,f]

Yes →
Mechanical prophylaxis[e]
IPC[d,e]

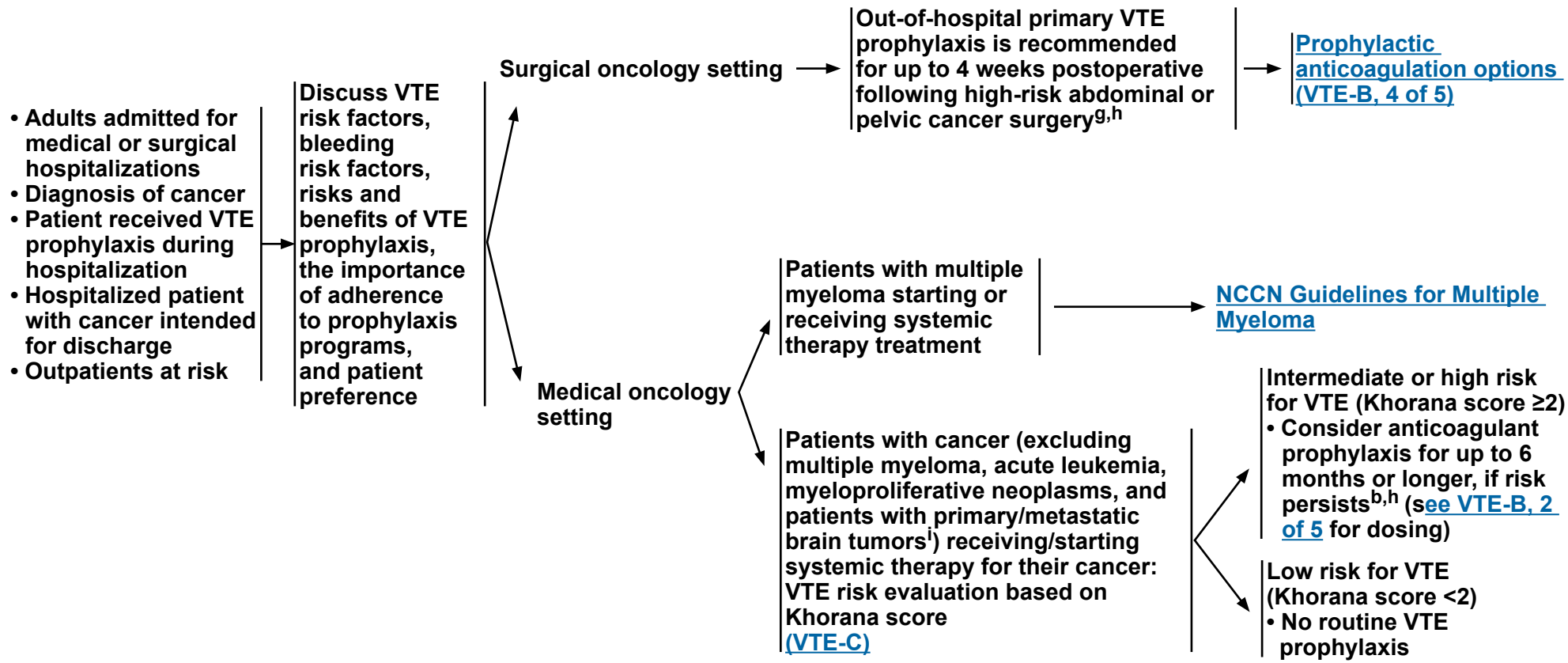
→ VTE Prophylaxis Following Discharge and for At-Risk Ambulatory Patients with Cancer (VTE-2)

[a] 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.
[b] Contraindications to VTE Prophylaxis (VTE-A).
[c] Institutions are strongly encouraged to implement best practice programs to monitor provider and patient adherence to VTE prophylaxis.
[d] In contrast to graduated compression stockings (GCS), IPC significantly reduced deep vein thrombosis (DVT) and was associated with a lower risk of skin complications (CLOTS Trials Collaboration, et al. Lancet 2013;382:516-524; and CLOTS Trials Collaboration, et al. Lancet 2009;373:1958-1965).
[e] Most data come from patients admitted for surgery or stroke; this is an extrapolation to the medical population. See Contraindications to VTE Prophylaxis (VTE-A).
[f] Results from a randomized trial (including a limited number of patients with cancer) suggest that addition of mechanical prophylaxis to pharmacologic prophylaxis in patients who are critically ill may not reduce the incidence of DVT (Arabi YM, et al. N Engl J Med 2019;380:1305-1315).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

VTE PROPHYLAXIS FOLLOWING DISCHARGE AND FOR AT-RISK AMBULATORY PATIENTS WITH CANCER

POPULATION AT RISK



[b] Contraindications to VTE Prophylaxis (VTE-A).
[g] Patients considered at high risk following abdominal/pelvic cancer surgery include patients undergoing surgery for gastrointestinal (GI) malignancies, patients with a previous history of VTE, anesthesia time >2 hours, bed rest ≥4 days, advanced-stage disease, and patient age >60 years.
[h] Patients with gastric and gastroesophageal tumors are at increased risk for hemorrhage with direct oral anticoagulants (DOACs).
[i] Patients receiving hormonal therapy were excluded from the AVERT but not the CASSINI trial.

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CONTRAINDICATIONS TO VTE PROPHYLAXIS[a]

Contraindications to Prophylactic Anticoagulation

- **Active bleeding**
- **Thrombocytopenia (platelet count <50,000/μL or clinical judgment)[b]**
- **Underlying hemorrhagic coagulopathy (eg, abnormal PT or aPTT excluding a lupus inhibitor/anticoagulant) or known bleeding disorder in the absence of replacement therapy (eg, hemophilia, von Willebrand disease)**
- **Indwelling neuraxial catheters (contraindication for apixaban, dabigatran, edoxaban, fondaparinux, rivaroxaban, or enoxaparin dose exceeding 40 mg daily)**
- **Neuraxial anesthesia/lumbar puncture[c,d]**
- **Interventional spine and pain procedures[1]**
- **Current or previous heparin-induced thrombocytopenia (HIT) (contraindication for LMWH and UFH)**

Contraindications to Mechanical Prophylaxis

- **Absolute**
  - **Acute DVT (unless on therapeutic anticoagulation)**
  - **Severe arterial insufficiency (pertains to GCS only)**
- **Relative**
  - **Large hematoma**
  - **Skin ulcerations or wounds[e]**
  - **Mild arterial insufficiency (pertains to GCS only)**
  - **Peripheral neuropathy (pertains to GCS only)**

[1] Narouze S, Benzon HT, Provenzano DA, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med 2015;40:182-212.

[a] For agent-specific contraindications, see Therapeutic Anticoagulation for VTE (VTE-D, 3 of 6).
[b] For patients at high risk, prophylactic anticoagulation may be appropriate even if platelet count is as low as 25,000/μL. See Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-F).
[c] Refer to institutional-specific anesthesia practice guidelines, if available. Twice-daily prophylactic dose UFH (5000 units every 12 h) and once-daily LMWH (eg, enoxaparin 40 mg once daily) may be used with neuraxial anesthesia. Twice-daily prophylactic dose LMWH (eg, enoxaparin 30 mg every 12 h), prophylactic dose fondaparinux (2.5 mg daily), and therapeutic dose anticoagulation should be used with extreme caution with neuraxial anesthesia. The safety of thrice-daily prophylactic dose UFH in conjunction with neuraxial anesthesia has not been established (Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines [Third Edition]. Reg Anesth Pain Med 2010;35:64-101).
[d] Timing of LMWH: For LMWH, placement or removal of a neuraxial catheter should be delayed for at least 12 hours after administration of prophylactic doses such as those used for prevention of DVT. Longer delays (24 h) are appropriate to consider for patients receiving therapeutic doses of LMWH. A post-procedure dose of LMWH should usually be given no sooner than 4 hours after catheter removal (FDA Drug Safety Communications. Updated recommendations to decrease risk of spinal column bleeding and paralysis in patients on LMWH. November 6, 2013: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM373735.pdf). In all cases, a benefit-risk assessment should consider both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors.
[e] Skin ulcerations and wounds are more common with the use of GCS.

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VTE PROPHYLAXIS OPTIONS: MEDICAL ONCOLOGY INPATIENTS (VTE-1)[a]

Agent	Standard Dosing[b,c]	Renal Dose	Dosing for Body Mass Index (BMI) ≥40 kg/m² [d]	Dosing for Actual Body Weight 25–50 kg[e]
Dalteparin[1-7]	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[3-5,8-12]	40 mg SC daily (category 1)	Recommend 30 mg SC daily if CrCl <30 mL/min	BMI >40 kg/m²: Consider 40 mg SC every 12 hours OR 0.5 mg/kg actual body weight SC daily BMI >50 kg/m²: Consider 60 mg SC every 12 hours OR 0.5 mg/kg actual body weight SC daily	Actual body weight 25–40 kg: Consider 20 mg SC daily[f] (avoid if CrCl <30 mL/min) OR Actual body weight 41–50 kg: Consider 30 mg SC daily[f] (avoid if CrCl <30 mL/min)
Fondaparinux[4,13-16]	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[15,17,18]	5000 units SC every 8–12 hours	Same as standard dose	Consider 7500 units SC every 8 hours	Weight <40 kg: 2500 units SC every 8–12 hours[f]

[a] Patients hospitalized for medical oncology care can continue apixaban/rivaroxaban prophylaxis if either option is already being used in the outpatient setting; however, apixaban/rivaroxaban should not be initiated in the hospital. Apixaban/rivaroxaban prophylaxis is also an option for patients with a history of HIT, for whom a heparin-based regimen is not feasible.

[b] Recommendations derived from patients hospitalized with medical illness, including those with cancer.

[c] Thromboprophylaxis for duration of hospital stay or 6 to 14 days or until the patient is fully ambulatory.

[d] Limited to no data available to support recommendations. Recommended doses are derived from non-oncology populations.

[e] 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. Buckheit D, et al. Clin Appl Thromb Hemost 2021;27:1-6; Sebaaly J, et al. Ann Pharmacother 2018;52:898-909.

[f] Consider laboratory monitoring. If dose escalation or de-escalation is required twice, consult with hematology or a clinical anticoagulation pharmacy specialist. Singer GA, et al. J Trauma Acute Care Surg 2016;81:1101-1108.

Note: All recommendations are category 2A unless otherwise indicated.
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VTE PROPHYLAXIS OPTIONS: AMBULATORY MEDICAL ONCOLOGY PATIENTS AND PATIENTS POST-MEDICAL ONCOLOGY DISCHARGE (VTE-2)[g,h]

Agent	Standard Dosing	Renal Dose	Other Dose Modifications
Apixaban[i,19]	2.5 mg PO twice daily	Caution if CrCl <30 mL/min[j]	Avoid if platelet count <50,000/µL Avoid if weight <40 kg
Rivaroxaban[k,20]	10 mg PO once daily	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/µL
Dalteparin[l,21]	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[l,22]	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

[g] 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.
[h] For recommendations for thromboprophylaxis in patients with multiple myeloma, see NCCN Guidelines for Multiple Myeloma.
[i] 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. See VTE-D (4 of 6).
[j] Patients with CrCl <30 mL/min were excluded from VTE prophylaxis studies. Due to limited data in this population, use with caution. May consider use in extenuating circumstances such as HIT.
[k] 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. See VTE-D (4 of 6).
[l] Data support the use of prophylactic dalteparin and enoxaparin for patients with advanced unresectable and metastatic pancreatic cancer (Maraveyas A. Eur J Cancer 2012;48:1283-1292; Pelzer U, et al. J Clin Oncol 2015;33:2028-2034).

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VTE PROPHYLAXIS OPTIONS: SURGICAL ONCOLOGY INPATIENTS (VTE-1)

Agent	Standard Dosing[m,n]	Renal Dose	Dosing for BMI ≥40 kg/m^2 [d]	Dosing for Actual Body Weight 25–50 kg[e]
Dalteparin[1,2,3,4]	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[3,4,8,9]	40 mg SC 2–12 hours prior to surgery, then once daily postoperatively[23,24]	Recommend 30 mg SC daily if CrCl <30 mL/min	Consider 40 mg SC every 12 hours OR 0.5 mg/kg SC daily	Actual body weight 25–40 kg: Consider 20 mg SC daily[f] (avoid if CrCl <30 mL/min) OR Actual body weight 41–50 kg: Consider 30 mg SC daily[f] (avoid if CrCl <30 mL/min)
Fondaparinux[3,4,9,13,14]	2.5 mg SC daily no earlier than 6–8 hours postoperatively Avoid in patients weighing <50 kg	Caution if CrCl 30–49 mL/min Avoid if CrCl <30 mL/min	Consider 5 mg SC daily	No dose adjustment available
UFH[21,22,25]	5000 units SC 2 hours prior to surgery, then 5000 units SC every 8 hours through POD1	Same as standard dose	Consider 7500 units SC every 8 hours postoperatively	Weight <40 kg: 2500 units SC every 8–12 hours[f]
Apixaban[i,o,26]	Apixaban 2.5 mg PO every 12 hours starting POD1–7 depending upon hemostasis. Recommend UFH or LMWH in prophylactic doses starting pre-operation and continuing post-operation until judged safe to switch to apixaban	Caution if CrCl <30 mL/min[j]	No dose adjustment available	No dose adjustment available
Rivaroxaban[p,27]	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

[d] Limited to no data available to support recommendations. Recommended doses are derived from non-oncology populations.
[e] 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. Buckheit D, et al. Clin Appl Thromb Hemost 2021;27:1-6; Sebaaly J, et al. Ann Pharmacother 2018;52:898-909.
[f] Consider laboratory monitoring. If dose escalation or de-escalation is required twice, consult with Hematology or a Clinical Anticoagulation Pharmacy Specialist. Singer GA, et al. J Trauma Acute Care Surg 2016;81:1101-1108.
[i] 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. See VTE-D (4 of 6).
[j] Patients with CrCl <30 mL/min were excluded from VTE prophylaxis studies. Due to limited data in this population, use with caution. May consider use in extenuating circumstances such as HIT.
[m] Recommendations derived from patients undergoing planned, elective, open abdominal, or pelvic surgery for malignancy (operating room [OR] time >45 minutes, age >40 years).
[n] Thromboprophylaxis for 7 to 10 days or until the patient is fully ambulatory.
[o] Only applies to patients with gynecologic cancers. Apixaban was initiated at investigator discretion once epidural anesthesia catheters were removed. Duration of prophylaxis was 28 days.
[p] Only applies to patients after laparoscopic surgery for colorectal cancer.

Note: All recommendations are category 2A unless otherwise indicated.
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VTE PROPHYLAXIS OPTIONS: POST-DISCHARGE PROPHYLAXIS FOR SURGICAL ONCOLOGY PATIENTS (VTE-2)

Agent	Standard Dosing[m]	Renal Dose[1,8]	Other Dose Modifications
Apixaban[i,o,26]	2.5 mg PO every 12 hours x 28 days	Caution if CrCl <30 mL/min[j]	Avoid if platelet count <50,000/µL Avoid if weight <40 kg
Rivaroxaban[p,27]	10 mg daily for 21 days[q]	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/µL
Dalteparin[r,22,28,29]	5000 units SC daily x 28 days	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/µL
Enoxaparin[r,23,28,30,31]	40 mg SC daily x 28 days	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/µL

[i] 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. See VTE-D (4 of 6).
[j] Patients with CrCl <30 mL/min were excluded from VTE prophylaxis studies. Due to limited data in this population, use with caution. May consider use in extenuating circumstances such as HIT.
[m] Recommendations derived from patients undergoing planned, elective, open abdominal, and pelvic surgery for malignancy (OR time >45 minutes, age ≥40 years).
[o] Only applies to patients with gynecologic cancers. Apixaban was initiated at investigator discretion once epidural anesthesia catheters were removed. Duration of prophylaxis was 28 days.
[p] Only applies to patients after laparoscopic surgery for colorectal cancer.
[q] Start rivaroxaban after 1 week of standard-dose LMWH (enoxaparin 40 mg SC daily or dalteparin 5000 units SC daily).
[r] For patients at high risk following abdominal and pelvic surgery (previous VTE, bed rest ≥4 days, OR time >2 hours, advanced-stage disease, or age ≥60 years), 4 weeks of thromboprophylaxis is recommended.[15,17]

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References on VTE-B 5 of 5

VTE PROPHYLAXIS OPTIONS
REFERENCES

[1] Prescribing information for dalteparin sodium injection, for subcutaneous use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020287Orig1s076lbl.pdf.
[2] Kucher N, Leizorovicz A, Vaitkus PT, et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005;165:341-345.
[3] Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: Available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother 2009;43:1064-1083.
[4] Freeman AL, Pendelton RC, Rondina MT. Prevention of venous thromboembolism in obesity. Expert Rev Cardiovasc Ther 2010;8:1711-1721.
[5] Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e737S-e801S.
[6] Simoneau MD, Vachon A, Picard F. Effect of prophylactic dalteparin on anti-factor Xa levels in morbidly obese patients after bariatric surgery. Obes Surg 2010;20:487-91.
[7] Warad D, Rao AN, Mullikin T, et al. A retrospective analysis of outcomes of dalteparin use in pediatric patients: a single institution experience. Thrombosis Research 2015;136:229-233.
[8] Prescribing information for enoxaparin sodium injection, for subcutaneous and intravenous use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020164s129lbl.pdf.
[9] Abildgaard A, Madsen S, Hvas AM. Dosage of anticoagulants in obesity: Recommendations based on a systemic review. Semin Thromb Hemost 2020;46:932-969.
[10] Deremiah E, Franco-Martinez C, Gamboa C, et al. Effectiveness and safety of high-dose thromboprophylaxis in morbidly obese major trauma Patients. Hosp Pharm 2023; 58:92-97
[11] Vaughns JD, Ziesenitz VC, Williams EF, et al. Prophylactic use of enoxaparin in adolescents during bariatric surgery-a prospective clinical study. Obes Surg 2020;30:63-68.
[12] Sebaaly J, Covert K. Enoxaparin dosing at extremes of weight: literature review and dosing recommendations. Ann Pharmacother 2018;52:898-909.
[13] Prescribing information for fondaparinux sodium injection, for subcutaneous use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021345Orig1s043lbl.pdf.
[14] Martinez L, Burnett A, Borrego M, et al. Effect of fondaparinux prophylaxis on anti-factor Xa concentrations in patients with morbid obesity. Am J Health Syst Pharm. 2011;68:1716-1722.
[15] Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141;e195S-e226S.
[16] Steele KE, Canner J, Prokopowicz G, et al. The EFFORT trial: Preoperative enoxaparin versus postoperative fondaparinux for thromboprophylaxis in bariatric surgical patients: a randomized double-blind pilot trial. Surg Obes Relat Dis 2015;13:672-683.
[17] Dentali F, Douketis JD, Gianni M, et al. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med 2007;146:278-288.
[18] Wang TF, Milligan PE, Wong CA, et al. Efficacy and safety of high-dose thromboprophylaxis in morbidly obese inpatients. Thromb Haemost 2014;111:88-93.
[19] Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent VTE in patients with cancer. N Engl J Med 2019;380:711-719.
[20] Khorana AA, Kakkar AK, Vadhan-Raj H, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med 2019;380:720-728.
[21] Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer 2012;48:1283-1292.
[22] Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: Outcomes from the CONKO-004 Trial. J Clin Oncol 2015;33:2028-2034.
[23] ENOXACAN study group. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. Br J Surg 1997;84:1099-1103.
[24] Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002;346:975-80.
[25] Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med 1988;318:1162-1173.
[26] Guntupalli SR, Brennecke A, Behbakht K, et al. Safety and efficacy of apixaban vs enoxaparin for preventing postoperative venous thromboembolism in women undergoing surgery for gynecologic malignant neoplasm: A randomized clinical trial. JAMA Netw Open 2020;3:e207410.
[27] Becattini C, Pace U, Pirozzi F, et al. Rivaroxaban vs placebo for extended antithrombotic prophylaxis after laparoscopic surgery for colorectal cancer. Blood 2022;140:900-908.
[28] Gould MA, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e227S-277S.
[29] Rasmussen MS, Jorgensen LN, Wille-Jorgensen P, et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. J Thromb Haemost 2006;4:2384-2390.
[30] Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev 2019;3:CD004318.
[31] Bergqvist D, Agnelli GC, Cohen AT, et al. Duration of prophylaxis against VTE with enoxaparin after surgery for cancer. N Engl J Med 2002;346:975-980.

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VTE RISK ASSESSMENT IN OUTPATIENTS WITH CANCER

Khorana Predictive Model for Chemotherapy-Associated VTE[a,b]

Patient Characteristic	Risk Score
• Site of primary cancer	
▸ Very high risk (stomach, pancreas)	2
▸ High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
• Prechemotherapy platelet count 350 x 10^9/L or higher	1
• Hemoglobin level less than 10 g/dL or use of red cell growth factors	1
• Prechemotherapy leukocyte count higher than 11 x 10^9/L	1
• BMI 35 kg/m^2 or higher	1

Total Score	Risk Category	Risk of Symptomatic VTE[1]
0	Low	0.3–1.5%
1, 2	Intermediate	2.0–4.8%
3 or higher	High	6.7–12.9%

[1] Khorana AA. Cancer and Coagulation. Am J Hematol 2012;87 Supp 1:S82-87.

[a] Reproduced and adapted with permission from Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:4902-4907.

[b] The Khorana Predictive Model is the most validated RAM. Several other RAMs have been published including the Protecht model, the CONKO score, the ONKOTEV score, the TiC-Onco score, and the COMPASS-CAT model. The utility of these models in the oncology population needs to be further evaluated in prospective, randomized trials.

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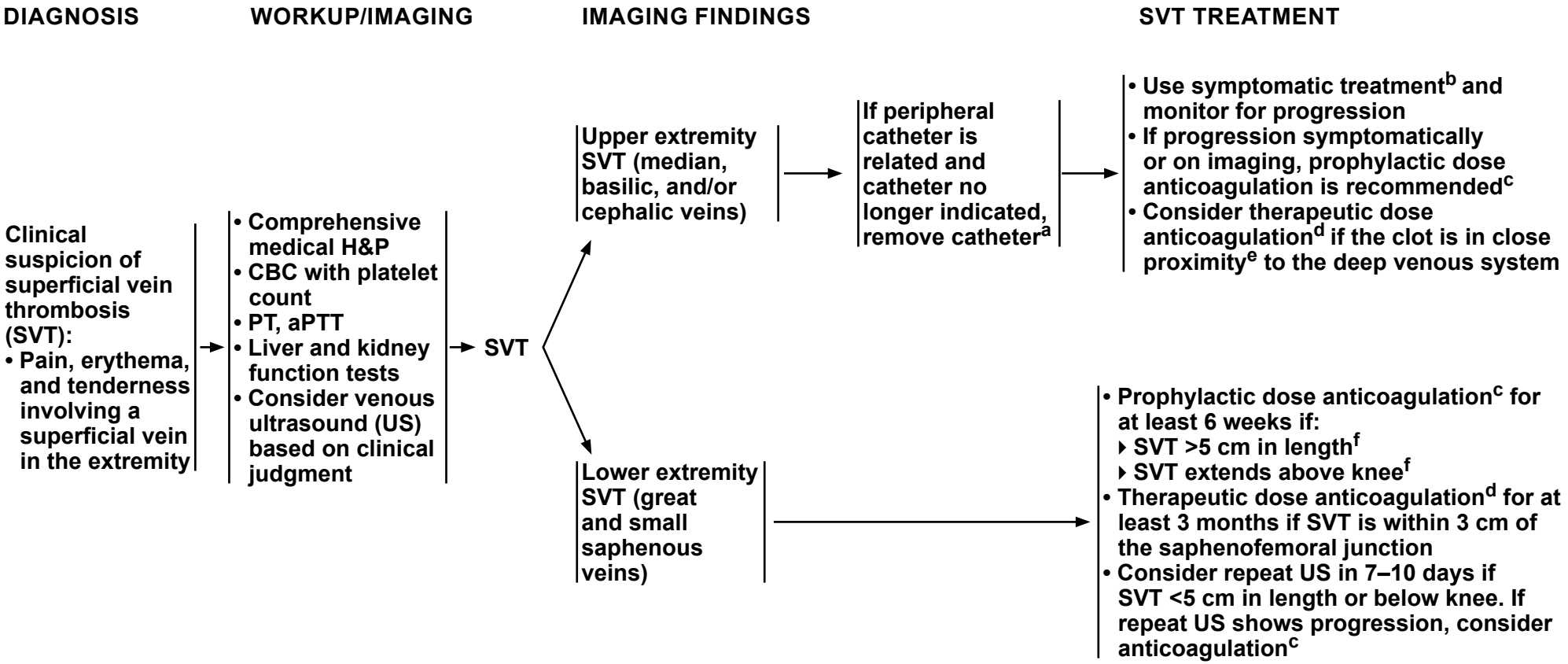

[a] For patients with SVT associated with a peripherally inserted central catheter (PICC) line, catheter removal may not be necessary, especially if the patient is treated with anticoagulation and/or symptoms resolve.
[b] Symptomatic treatment includes warm compresses, nonsteroidal anti-inflammatory drugs (NSAIDs), and elevation.
[c] 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 (Beyer-Westendorf J, et al. Lancet Haematol 2017;4:e105-e113). Therapeutic dosing may be used at the clinician's discretion. See Therapeutic Anticoagulation for VTE (VTE-D).
[d] Therapeutic Anticoagulation for VTE (VTE-D).
[e] Close proximity is defined as within approximately 3 cm.
[f] If SVT is within 3 cm from the saphenofemoral junction, treat with therapeutic dose anticoagulation. See Therapeutic Anticoagulation for VTE (VTE-D).

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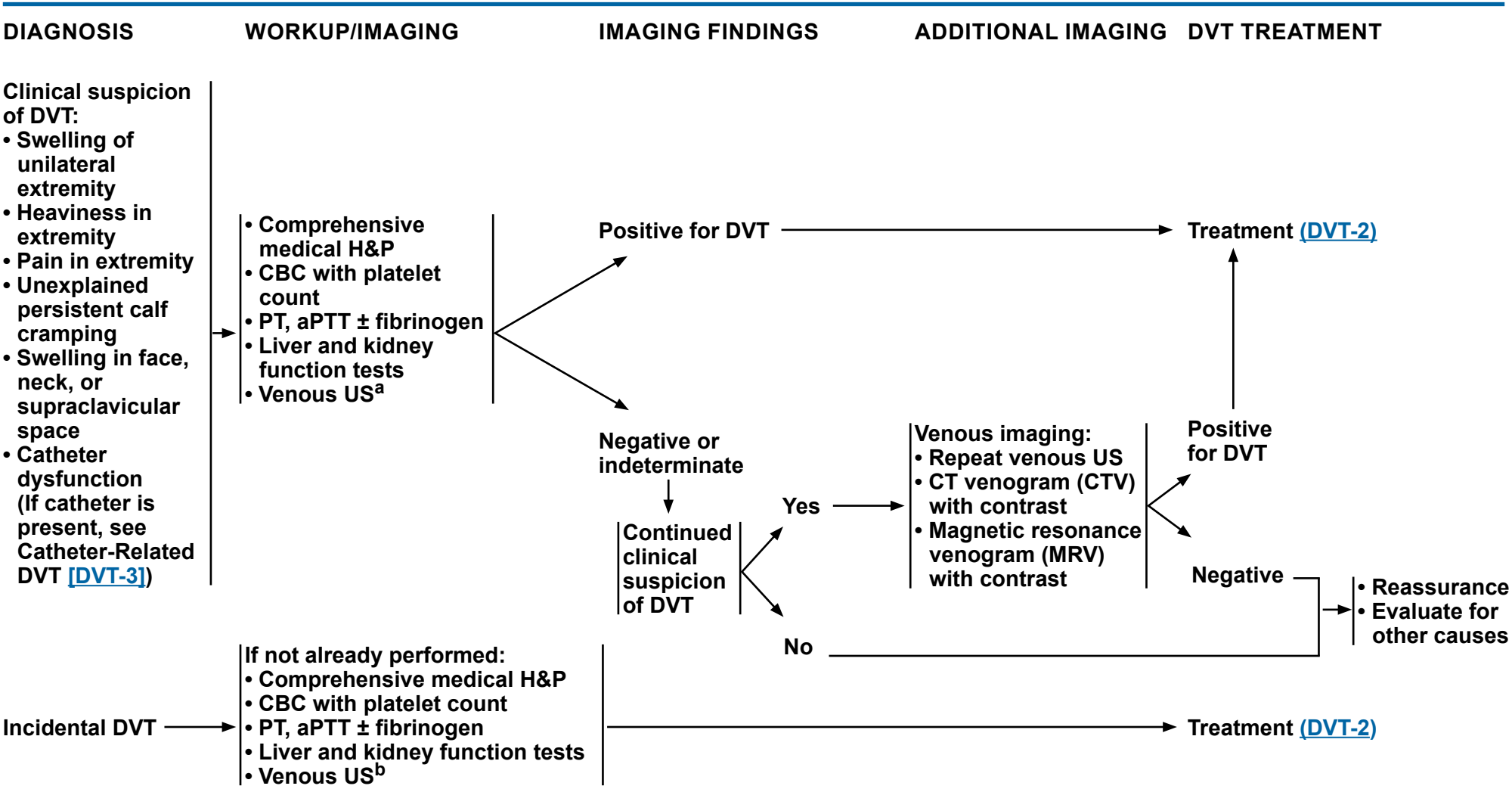

[a] In cases with high suspicion of DVT and no contraindications, consider initiating early anticoagulation while awaiting imaging results.
[b] If initial imaging results are inconclusive, consider venous US to confirm diagnosis.

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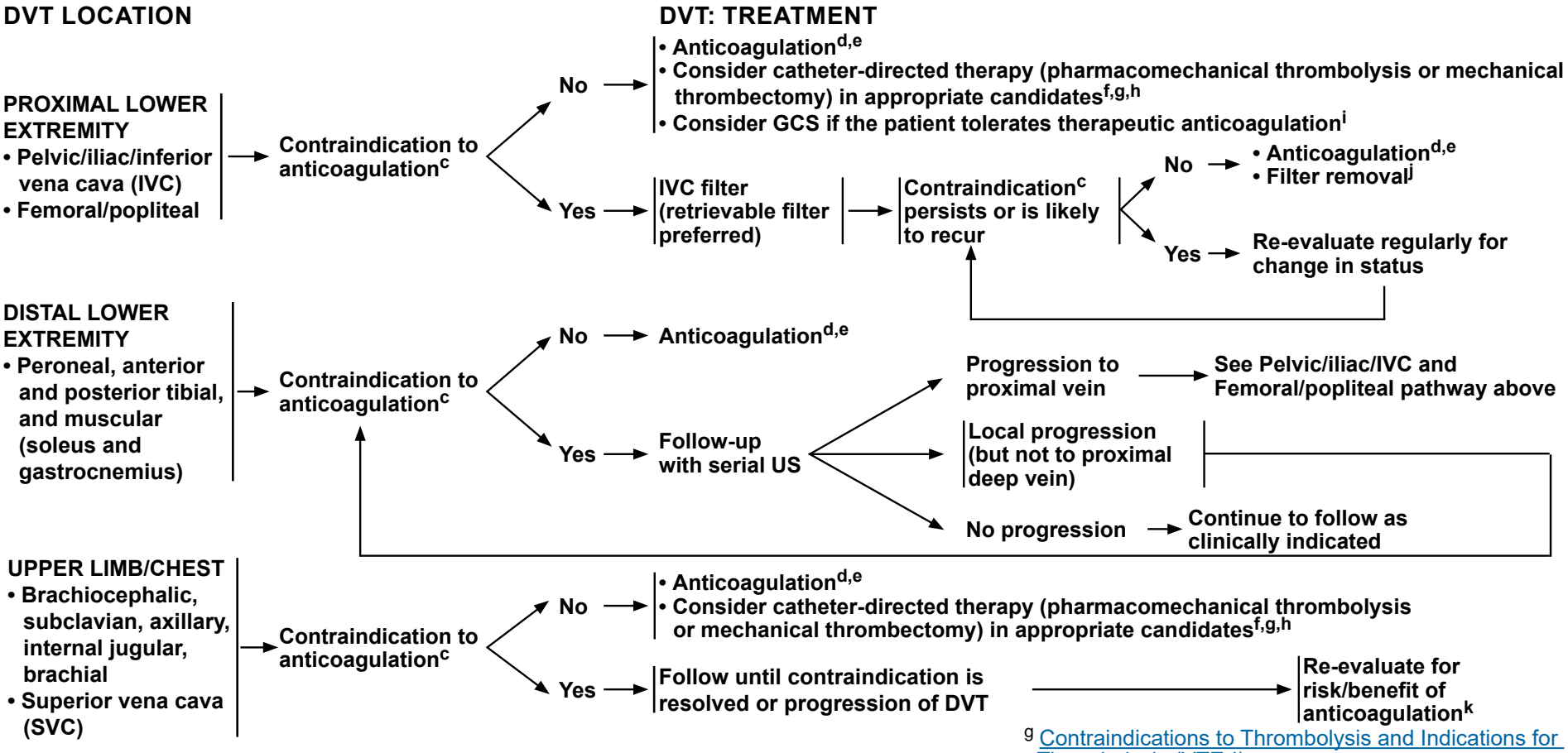
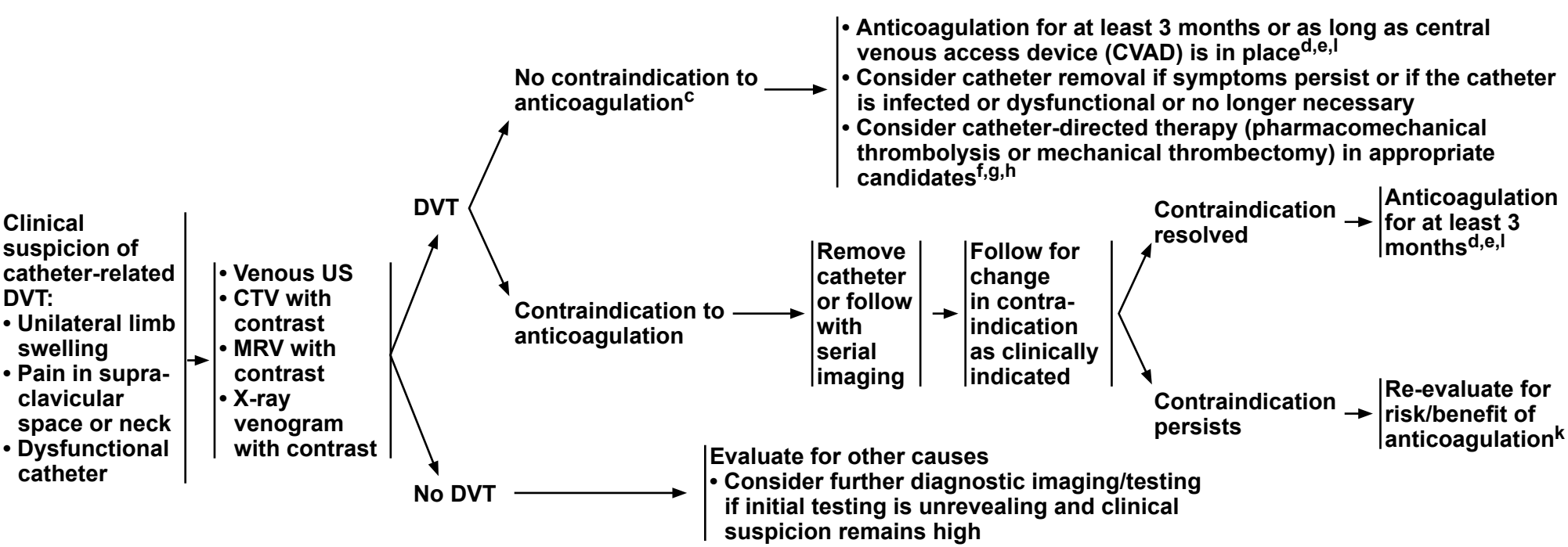


[c] Contraindications to Therapeutic Anticoagulation (VTE-E) and Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-F).
[d] Therapeutic Anticoagulation for VTE (VTE-D).
[e] See Progression or New Thrombosis on Therapeutic Anticoagulation (VTE-G), if extension of VTE or new VTE while on recommended anticoagulation therapy.
[f] Choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues (VTE-H). Appropriate candidates may include: patients at risk of limb loss (eg, phlegmasia cerulea dolens), patients with central thrombus propagation despite anticoagulation, and those with moderate to severely symptomatic proximal DVT. Candidates with high bleeding risk or contraindication to fibrinolytic may be candidates for percutaneous mechanical thrombectomy.
[g] Contraindications to Thrombolysis and Indications for Thrombolysis (VTE-I).
[h] Providers can consult with interventional radiology or vascular surgery colleagues to determine the appropriate use of mechanical embolectomy, suction embolectomy, and US-facilitated catheter-directed thrombolysis devices at their institutions.
[i] GCS did not reduce the incidence of post-thrombotic syndrome (PTS) in a double-blind randomized trial (Kahn SR, et al. Lancet 2014;383:880-888).
[j] Recommend IVC filter removal, if tolerating anticoagulation.
[k] Elements for Consideration in Decision Not to Treat (VTE-J).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CATHETER-RELATED DVT: DIAGNOSIS AND TREATMENT



[c] Contraindications to Therapeutic Anticoagulation (VTE-E) and Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-F).

[d] Therapeutic Anticoagulation for VTE (VTE-D).

[e] See Progression or New Thrombosis on Therapeutic Anticoagulation (VTE-G), if extension of VTE or new VTE while on recommended anticoagulation therapy.

[f] Choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues. (VTE-H). Appropriate candidates may include: patients at risk of limb loss (eg, phlegmasia cerulea dolens), patients with central thrombus propagation despite anticoagulation, and those with moderate to severely symptomatic proximal DVT. Candidates with high bleeding risk or contraindication to fibrinolytic may be candidates for percutaneous mechanical thrombectomy.

[g] Contraindications to Thrombolysis and Indications for Thrombolysis (VTE-I).

[h] Providers can consult with interventional radiology or vascular surgery colleagues to determine the appropriate use of mechanical embolectomy, suction embolectomy, and US-facilitated catheter-directed thrombolysis devices at their institutions.

[k] Elements for Consideration in Decision Not to Treat (VTE-J).

[l] Anticoagulation without catheter removal is the preferred option for initial treatment, even for patients with symptomatic DVT, provided that the catheter is necessary, functional, and free of infection. There is very little clinical evidence regarding the appropriate duration of anticoagulation. The recommended duration of anticoagulation depends on tolerance of anticoagulation, response to anticoagulation, and catheter status. 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.

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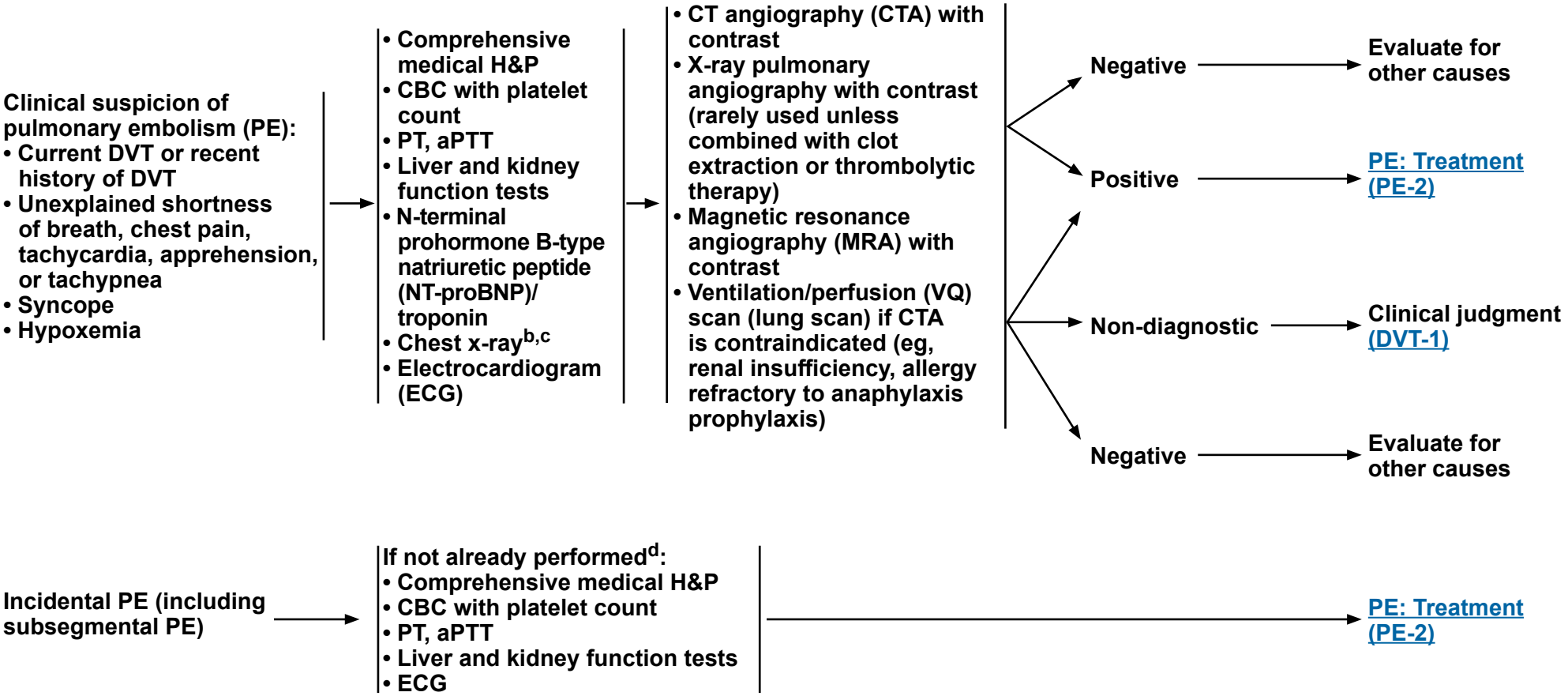
PE: DIAGNOSIS



[a] D-dimer has limited utility in patients with cancer.
[b] In cases with high suspicion of PE and no contraindications, consider initiating early anticoagulation while waiting for imaging results.
[c] Chest x-ray may not be necessary if CTA is planned.
[d] Repeat imaging and diagnostic studies are not routinely needed in patients with incidental PE. Consider outpatient care for these patients.

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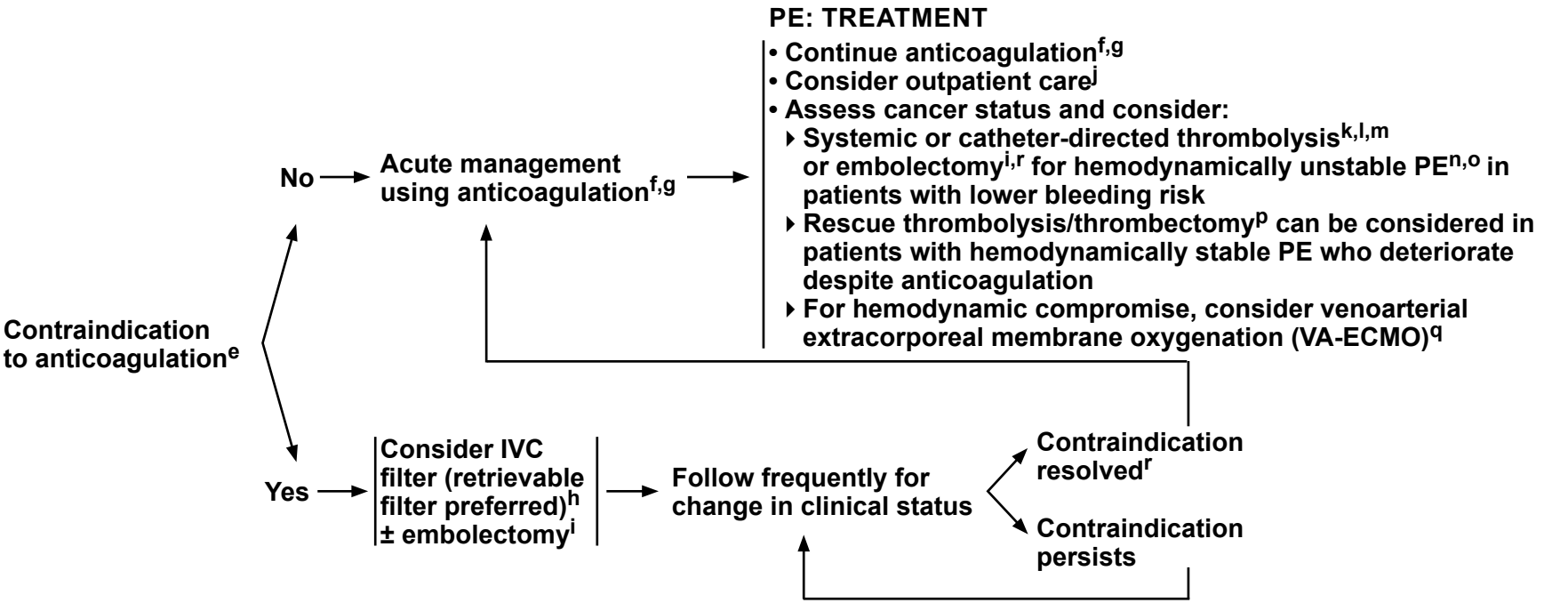

[e] Contraindications to Therapeutic Anticoagulation (VTE-E) and Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-F).

[f] Therapeutic Anticoagulation for VTE (VTE-D).

[g] See Progression or New Thrombosis on Therapeutic Anticoagulation (VTE-G), if extension of VTE or new VTE while on recommended anticoagulation therapy.

[h] Consider filter placement if unable to treat with anticoagulation within 1 month of onset of symptomatic PE (Streiff MB, et al. J Thromb Thrombolysis 2016;41:32-67).

[i] Consider embolectomy for treatment of massive PE (category 2B).

[j] Patients at lower risk as identified by clinical, laboratory, and imaging assessment can be considered for outpatient care. Consider echocardiography or CTA to assess right ventricular overload, NT-proBNP, and troponin. Clinical judgment is recommended for assessing risk in patients with PE based on a variety of clinical parameters. Signs of decompensation or life-threatening PE include: hypoxemia, hypotension, dyspnea, tachycardia, and tachypnea.

[k] Elements for Consideration in Decision Not to Treat (VTE-J).

[l] Thrombolytic Agents (VTE-H).

[m] Contraindications to Thrombolysis and Indications for Thrombolysis (VTE-I).

[n] In randomized controlled trials, systemic or catheter-directed thrombolysis/thrombectomy has not been associated with a favorable risk-versus-benefit profile in patients with hemodynamically stable or submassive PE.

[o] Acute PE with sustained hypotension (systolic blood pressure <90 mmHg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock). See http://emcrit.org/emcrit/aha-pulmonary-embolism-guidelines-2011.

[p] Providers can consult with interventional radiology or vascular surgery colleagues to determine the appropriate use of mechanical embolectomy, suction embolectomy, and US-facilitated catheter-directed thrombolysis devices at their institutions.

[q] Pasrija C, et al. Ann Thorac Surg 2018;105:498-504.

[r] Recommend IVC filter removal, if tolerating anticoagulation therapy.

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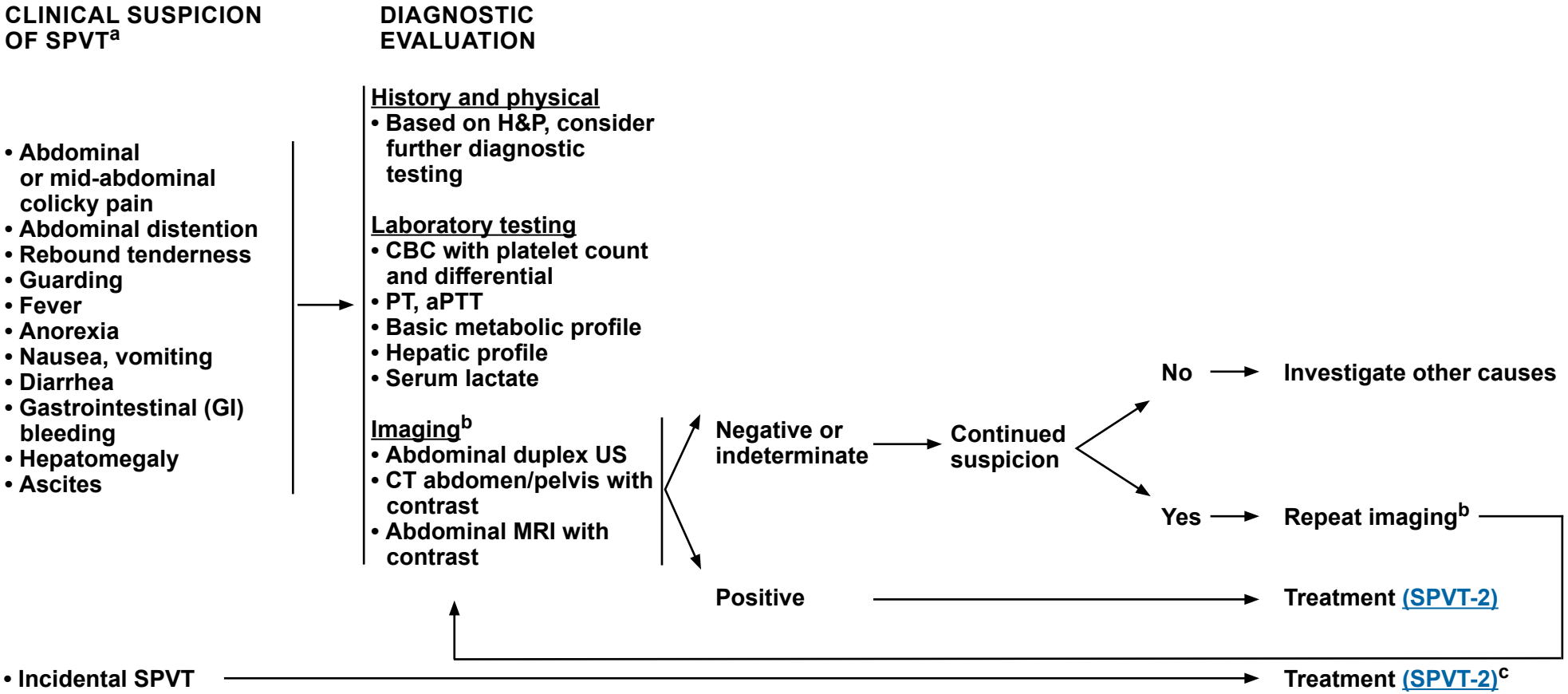
SPLANCHNIC VEIN THROMBOSIS (SPVT): DIAGNOSIS



[a] Risk factors relevant to cancer population for SPVT:
- Recent abdominal surgery (eg, splenectomy)
- Abdominal mass
- Pancreatitis
- Cirrhosis
- Exogenous estrogens
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Myeloproliferative neoplasms associated with the *JAK2* V617F mutation (most common) or *CALR* mutation (rare)

[b] Consider local consultation with radiology to optimize imaging techniques/modality.
[c] For incidental SPVT, weigh the risks and benefits of anticoagulation therapy on an individual basis.

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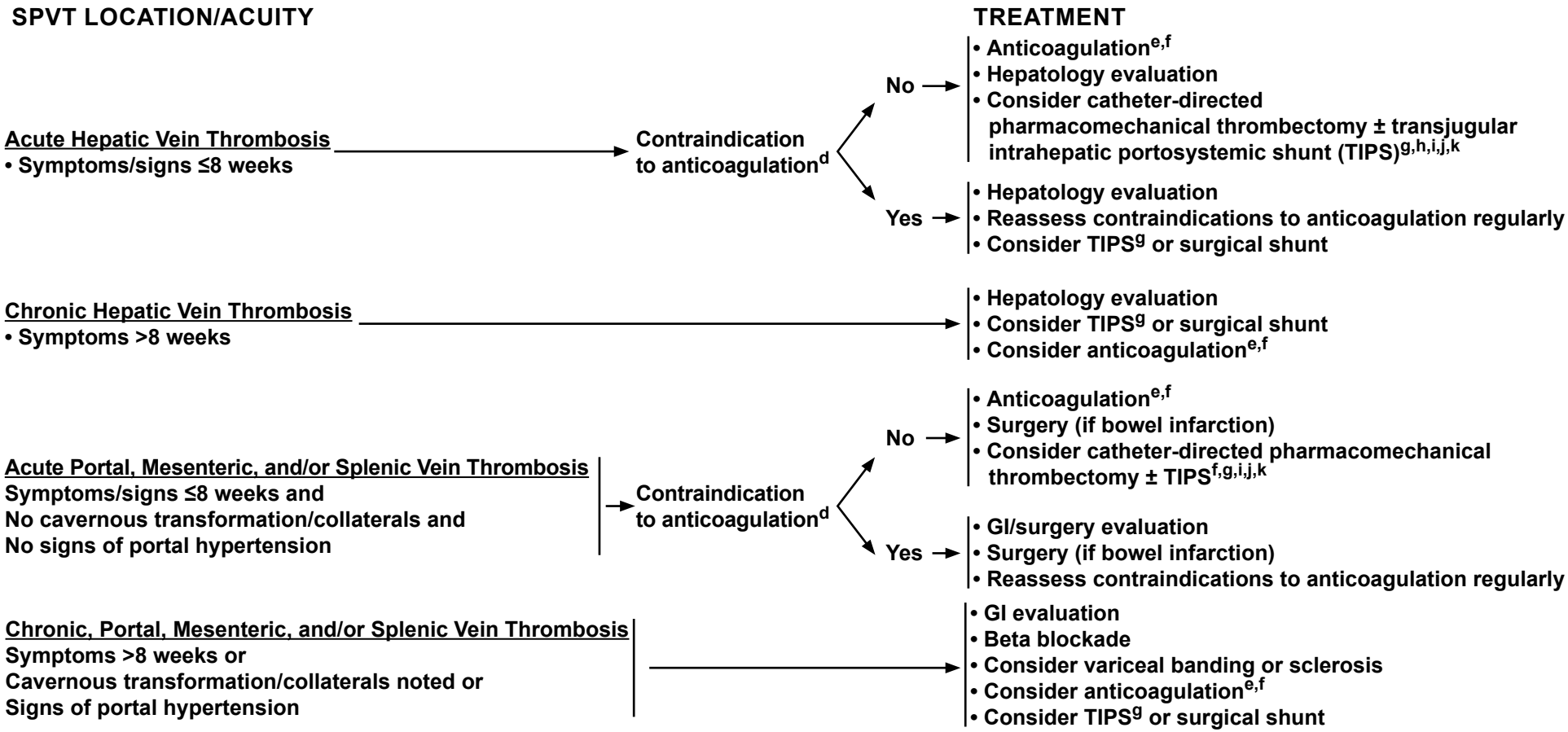
SPVT: TREATMENT



[d] Contraindications to Therapeutic Anticoagulation (VTE-E) and Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-F).
[e] Weigh risks/benefits of anticoagulation, particularly for chronic thromboses. Duration of anticoagulation should be at least 6 months for triggered events (eg, postsurgical) and indefinite if active cancer, persistent thrombophilic state, or unprovoked thrombotic event.
[f] Therapeutic Anticoagulation for VTE (VTE-D).
[g] Consider TIPS as one of the management options for patients with SPVT and portal hypertension.
[h] If thrombectomy expertise is not available, consider consultation with a tertiary medical center.
[i] Providers can consult with interventional radiology or vascular surgery colleagues to determine the appropriate use of mechanical embolectomy, suction embolectomy, and US-facilitated catheter-directed thrombolysis devices at their institutions.
[j] Decision to offer thrombolysis should be based on local availability/expertise, location of thrombus, and risk of bleeding. Choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues. See Thrombolytic Agents (VTE-H).
[k] Contraindications to Thrombolysis and Indications for Thrombolysis (VTE-I).

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THERAPEUTIC ANTICOAGULATION FOR VTE

General Guidelines

- **Anticoagulation options recommended for management of VTE in patients with cancer include regimens involving only one agent (monotherapy) as well as regimens that use more than one type of agent (combination therapy). This section lists the recommended regimens, including dosing and duration, as well as a list of contraindications and warnings to help guide treatment selection.[1]**
  - **Duration of Anticoagulation as Recommended by Guideline:**
    - **Duration should be at least 3 months or as long as active cancer or cancer therapy.**
    - **For non–catheter-associated DVT or PE recommend indefinite anticoagulation while cancer is active, under treatment, or if risk factors for recurrence persist.**
    - **For symptomatic catheter-associated DVT, consider anticoagulation treatment for at least 3 months or as long as the catheter is in place.**
    - **Providers should continue to discuss with patients the risks/benefits of anticoagulation to determine the appropriate duration of therapy. See Elements for Consideration in Decision Not to Treat (VTE-J).**
    - **Reconsider the role of anticoagulation therapy near the end of life. See Elements for Consideration in Decision Not to Treat (VTE-J).**
- **Select regimen based on these factors (not in order of importance): Renal failure (CrCl <30 mL/min), hepatic disease (elevated transaminases or bilirubin, Child-Pugh B and C liver impairment, or cirrhosis), inpatient/outpatient status, U.S. FDA approval, cost, patient preference, ease of administration, monitoring, bleeding risk assessment, and ability to reverse anticoagulation. See Contraindications and Warnings on VTE-D, 3 of 6.**
- **Baseline laboratory testing: CBC with platelet count, renal and hepatic function panel, aPTT, and PT/international normalized ratio (INR).**
- **Follow institutional standard operating procedures (SOPs) for dosing schedules. If there are no SOPs, then use the American College of Chest Physicians (ACCP) recommendations.[2]**
- **Following initiation of anticoagulant: hemoglobin, hematocrit, and platelet count at least every 2 to 3 days for the first 14 days while in the inpatient setting and every 2 weeks thereafter or as clinically indicated.**
- **Direct oral anticoagulants (DOACs), LMWH, and warfarin have all been used to treat patients with SPVT. Although published experience in the treatment of SPVT with DOACs is limited, results appear to be comparable to LMWH and warfarin. Therefore, we suggest that DOACs can be used for long-term treatment of SPVT in appropriate candidates in the recommended doses. In the absence of contraindications, NCCN suggests that DOACs, LMWH, and warfarin can be considered for treatment of SPVT. In patients with cancer, DOACs and LMWH are preferable to warfarin.**

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THERAPEUTIC ANTICOAGULATION FOR VTE (CONTINUED)

DOACs (preferred for patients without gastric or gastroesophageal lesions)[a]

- **Apixaban[b,c]**
  - **10 mg PO every 12 hours for 7 days followed by 5 mg PO every 12 hours[3-8]**
- **Edoxaban[b]**
  - **Initial therapy with LMWH[d,9,10] or UFH[e,11] for at least 5 days followed by edoxaban 60 mg PO daily (or 30 mg PO daily in patients with Cockcroft-Gault estimated CrCl 30–50 mL/min or weight <60 kg or concomitant potent P-glycoprotein (P-gp) inhibitors)[f,12,13,14]**
- **Rivaroxaban**
  - **15 mg PO every 12 hours for the first 21 days followed by 20 mg daily with food[15-18]**

LMWH (preferred for patients with gastric or gastroesophageal lesions)

- **Dalteparin[b]**
  - **200 units/kg SC daily for 30 days, then switch to 150 units/kg once daily[d,g,10,19,20]**
- **Enoxaparin**
  - **1 mg/kg SC every 12 hours (BMI <40 kg/m^2) or 0.8 mg/kg SC every 12 hours (BMI ≥40 kg/m^2) (can consider decreasing intensity to 1.5 mg/kg daily after first month)[h,9,21,22-24]**

DOACs (if above regimens not appropriate or unavailable)[a]

- **Dabigatran**
  - **Initial therapy with LMWH[d,9,10] or UFH[e,11] for at least 5 days followed by dabigatran 150 mg PO every 12 hours[f,25,26]**

Fondaparinux[27,28]

- **5 mg SC daily (<50 kg)**
- **7.5 mg SC daily (50–100 kg)**
- **10 mg SC daily (>100 kg)**

UFH (category 2B)[11]

- **IV 80 units/kg bolus, followed by 18 units/kg/h adjusted to target aPTT of 2–2.5 X control or per hospital SOPs, followed by SC 250 units/kg every 12 hours (category 2B)**
- **SC 333 units/kg load, followed by 250 units/kg every 12 hours[29]**

Warfarin[i,30-32]

- **Start warfarin concurrently with LMWH, fondaparinux, or UFH (see dosing below)**
- **Warfarin 5 mg daily adjusted to INR 2–3 (2.5 mg daily initial dose for liver disease or use with interacting medications)**
  - **LMWH[9,10] + warfarin[i] options:**
    - ◊ **Dalteparin 200 units/kg SC daily[10] or 100 units/kg SC every 12 hours**
    - ◊ **Enoxaparin 1 mg/kg SC every 12 hours[9]**
  - **Fondaparinux + warfarin[i,27,28]**
    - ◊ **5 mg SC daily (<50 kg)**
    - ◊ **7.5 mg SC daily (50–100 kg)**
    - ◊ **10 mg SC daily (>100 kg)**
  - **UFH[11] + warfarin[i] options:**
    - ◊ **IV 80 units/kg bolus, followed by 18 units/kg/h adjusted to target aPTT of 2–2.5 X control or per hospital SOPs**
    - ◊ **SC 333 units/kg load, followed by 250 units/kg every 12 hours**

[a] Patients with gastric and gastroesophageal tumors are at increased risk for hemorrhage with DOACs.
[b] Category 1 for DVT/PE.
[c] Apixaban may be safer than edoxaban or rivaroxaban for patients with gastric or gastric esophageal lesions (category 2B).
[d] LMWH dosing options: Dalteparin 200 units/kg SC daily; Enoxaparin 1 mg/kg SC every 12 hours.
[e] UFH dosing options: IV 80 units/kg bolus, followed by 18 units/kg/h, adjusted to a target aPTT of 2–2.5x control or per hospital SOPs; SC 333 units/kg load, followed by 250 units/kg every 12 hours.
[f] Unlike warfarin, concurrent administration with parenteral anticoagulants is not recommended when transitioning to edoxaban or dabigatran. See prescribing information for protocols for transitioning between agents.
[g] Although each of the LMWH agents has been studied in randomized controlled trials in patients with cancer, the efficacy of dalteparin in this population is supported by the highest quality evidence and is the only LMWH approved by the FDA for this indication.
[h] Long-term management with enoxaparin dosing of 1 mg/kg SC every 12 hours has not been tested in patients with cancer.
[i] If warfarin is selected for chronic anticoagulation, initiate warfarin concurrently with the parenteral agent used for acute therapy and continue both therapies for at least 5 days and until INR is ≥2. During the transition to warfarin monotherapy, the INR should be measured at least twice weekly. Once the patient is on warfarin alone, the INR should be measured initially at least once weekly. Once the patient is on a stable dose of warfarin with an INR of 2–3, INR testing can be gradually decreased to a frequency of no less than once a month.

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References on VTE-D 5 of 6

THERAPEUTIC ANTICOAGULATION FOR VTE (CONTINUED)

Agent(s)	Contraindications and Warnings
LMWH	• Use with caution in patients with renal dysfunction. Consider dose adjustments or alternative therapy for patients with severe renal dysfunction (CrCl <30 mL/min).[j] • Follow package insert for renal dysfunction dosing. • Anti-Xa monitoring (peak and trough) of LMWH has been recommended for patients with severe renal dysfunction, although limited data are available to support the clinical relevance of anti-Xa levels. • Absolute contraindication: recent/acute HIT • Relative contraindication: past history of HIT
Fondaparinux	• Contraindicated in patients with CrCl <30 mL/min • Use with caution in patients with moderate renal insufficiency (CrCl 30–50 mL/min), weight <50 kg, or age >75 y
UFH	• Absolute contraindication: recent/acute HIT • Relative contraindication: past history of HIT
Warfarin	Relative contraindications: • Concomitant inhibitors and inducers of CYP2C9, 1A2, or 3A4
DOACs: Apixaban, dabigatran, edoxaban, and rivaroxaban	Contraindications: • Pregnancy or breastfeeding • Stage IV/V chronic kidney disease: ▸ Apixaban[k]: CrCl <30 mL/min[4] ▸ Dabigatran,[25] edoxaban,[33] rivaroxaban[18]: CrCl <30 mL/min • Active/clinically significant liver disease: ▸ Apixaban[7]: Child-Pugh Class B or C or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3x upper limit of normal (ULN); total bilirubin >2x ULN ▸ Rivaroxaban[15,18]: Child-Pugh class B or C or ALT/AST >3x ULN ▸ Dabigatran[25,26,34-36]: Child-Pugh class C or ALT/AST >2x ULN or active/acute hepatitis or cirrhosis ▸ Edoxaban[12,13]: 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[15] and apixaban[3] • Inducers/inhibitors of P-gp: see prescribing information for dabigatran[25] and edoxaban[12] Relative contraindications, use with caution: • DOACs have been associated with an increased risk of GI and possibly genitourinary tract bleeding, and should be used with caution in patients with genitourinary or GI tract lesions, pathology, or instrumentation. • Use with caution in patients with compromised renal or liver function. • For patients receiving nephrotoxic or hepatotoxic chemotherapy, consider monitoring patients more closely with laboratory testing. • Consider drug-drug interactions.

[j] There are limited data on long-term use of LMWH in patients with CrCl <30 mL/min.
[k] Although stage IV chronic kidney disease is not listed as a contraindication in the FDA-approved label for apixaban, the NCCN Panel acknowledges that there are insufficient data to support safe apixaban dosing in these patients, especially those who are on hemodialysis.

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References on VTE-D 5 of 6

THERAPEUTIC ANTICOAGULATION FOR VTE (CONTINUED)
DOACs: GI CONSIDERATIONS AND ALTERNATIVE ROUTES OF ADMINISTRATION

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. The table below provides absorption guidance following GI surgical interventions based on available data.[37-39]
- 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.[40]
- 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.[40]
- Edoxaban: Crushed tablets may be suspended in 2 to 3 ounces of water and immediately administered through a gastric tube.[12,41]
- Dabigatran: Should not be administered through an enteral feeding tube.[40]

Surgical Procedure	Anticoagulant Systemic Absorption			
	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Total or partial gastrectomy	Possibly reduced[38,39] or not impacted[42]	Possibly reduced[38,39]	Possibly reduced[38,47]	Possibly reduced[39,15] or not impacted[48,49]
Roux-en-Y gastric bypass (RYGB)	Possibly reduced[38,39] or not impacted[42]	Possibly reduced[38,39,44,45]	Possibly reduced[38]	Possibly reduced[38,39,15] or not impacted[48,49]
Distal resection and short bowel syndrome	Possibly reduced[38,43]	Possibly reduced[38,46]	Unlikely to be affected[38]	Unlikely to be affected[38,50]
Colectomy	Possibly reduced[38,43]	Unlikely to be affected[38]	Unlikely to be affected[38]	Unlikely to be affected[38]

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References on VTE-D 5 of 6

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REFERENCES

[1] Hakoum M, Kahale L, Tsolakian I, et al. Anticoagulation for the initial treatment of venous thromboembolism in people with cancer. Cochrane Database Syst Rev 2018;1:CD006649.
[2] Garcia D, Baglin T, Weitz J, Samama M. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e24S-43S.
[3] Prescribing information for apixaban tablets, for oral use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202155s034lbl.pdf.
[4] Agnelli G, Buller H, Cohen A, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. J Thromb Haemost 2015;13:2187-2191.
[5] McBane RD, 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost 2020;18:411-421.
[6] Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 2019;380:711-719.
[7] Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020;382:1599-1607.
[8] Ageno W, Vedovati MC, Cohen A, et al. Bleeding with apixaban and dalteparin in patients with cancer-associated venous thromboembolism: Results from the Caravaggio Study. Thromb Haemost 2021;121:616-624.
[9] Prescribing information for enoxaparin sodium injection, for subcutaneous and intravenous use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020164s129lbl.pdf.
[10] Prescribing information: Dalteparin sodium injection, for subcutaneous use; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020287Orig1s076lbl.pdf.
[11] Prescribing information for heparin sodium injection, for intravenous or subcutaneous use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/017029s159lbl.pdf.
[12] Prescribing information for edoxaban tablets, for oral use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206316s017lbl.pdf.
[13] Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-624.
[14] Kraaijpoel N, Di Nisio M, Mulder FI, et al. Clinical impact of bleeding in cancer-associated venous thromboembolism: Results from the Hokusai VTE Cancer Study. Thromb Haemost 2018;118:1439-1449.
[15] Prescribing information for rivaroxaban tablets, for oral use and for oral suspension 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022406s041lbl.pdf.
[16] Prins M, Lensing AW, Brighton TA, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. Lancet Haematol 2014;1:e37-46.
[17] Mantha S, Laube E, Miao Y, et al. Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease: a prospective cohort study. J Thromb Thrombolysis 2017;43:166-171.
[18] Young A, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial (SELECT-D). J Clin Oncol 2018;36:2017-2023.
[19] Lee A, Levine M, Baker R, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-153.
[20] Francis C, Kessler C, Goldhaber S, et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. J Thromb Haemost 2015;13:1028-1035.
[21] Curry MA, LaFollette JA, Kempton CL, et al. Evaluation of treatment-dose enoxaparin in acutely ill morbidly obese patients at an academic medical center: a randomized clinical trial Ann Pharmacother 2019;53:567-573.
[22] Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med 2002;162:1729-1735.
[23] Deitcher S, Kessler C, Merli G, et al. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed
by warfarin for a 180-day period. Clin Appl Thromb Hemost 2006;12:389-396.
[24] Merli G, Spiro TE, Olsson C, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med 2001;134:191-202.
[25] Prescribing information for dabigatran etexilate capsules, for oral use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022512s041lbl.pdf.

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Continued

THERAPEUTIC ANTICOAGULATION FOR VTE
REFERENCES

[26] Schulman S, Goldhaber S, Kearon C, et al. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. Thromb Haemost 2015;114:150-157.
[27] Prescribing information: Fondaparinux sodium solution for subcutaneous injection; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021345Orig1s043lbl.pdf.
[28] van Doormaal F, Raskob G, Davidson B, et al. Treatment of venous thromboembolism in patients with cancer: subgroup analysis of the Matisse clinical trials. Thromb Haemost 2009;101:762-769.
[29] Kearon C, Ginsberg J, Julian J, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. JAMA 2006;296:935-942.
[30] Palareti G, Legnani C, Lee A, et al. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignancy. Thromb Haemost 2000;84:805-810.
[31] Hutten B, Prins M, Gent M, et al. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol 2000;18:3078-3083.
[32] Prandoni P, Lensing A, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484-3488.
[33] Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-624.
[34] Potze W, Arshad F, Adelmeijer J, et al. Differential in vitro inhibition of thrombin generation by anticoagulant drugs in plasma from patients with cirrhosis. PLOS ONE 2014;9:e88390.
[35] Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-2352.
[36] Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709-718.
[37] Martin KA, Lee CR, Farrell TM, et al. Oral anticoagulant use after bariatric surgery: a literature review and clinical guidance. Am J Med 2017;130:517-524.
[38] Hakeam HA, Al-Sanea N. Effect of major gastrointestinal tract surgery on the absorption and efficacy of direct acting oral anticoagulants (DOACs). J Thromb Thrombolysis 2017;43:343-351.
[39] Rottenstreich A, Barkai A, Arad A, et al. The effect of bariatric surgery on direct-acting oral anticoagulant drug levels. Thrombosis Research 2018;163:190-195.
[40] Peterson JJ, Hoehns JD. Administration of direct oral anticoagulants through enteral feeding tubes. J Pharmacy Tech 2016;32:196-200.
[41] Duchin K, Duggal A, Atiee GJ, et al. An open-label crossover study of the pharmacokinetics of the 60-mg edoxaban tablet crushed and administered either by a nasogastric tube or in apple puree in healthy adults. Clin Pharmacokinet 2018;57:221-228.
[42] Steele KE, Prokopowicz GP, Canner JP, et al. The APB Study: apixaban pharmacokinetics in bariatric patients before to 1 year after vertical sleeve gastrectomy or Roux-en-Y gastric bypass. Surg Obes Relat Dis 2022;18:594-603.
[43] Byon W, Nepal S, Schuster AE, et al. Regional gastrointestinal absorption of apixaban in healthy subjects. J Clin Pharmacol 2018;58:965-971.
[44] Lee D, Defilipp Z, Judson K, et al. Subtherapeutic anticoagulation with dabigatran following Roux-en-Y gastric bypass surgery. J Cardiol Cases 2013;8:e49-e50.
[45] Grainger B, Holloway R, Merriman E, et al. Evidence of impaired dabigatran absorption following laparoscopic Roux-en-Y gastric bypass surgery: the Auckland regional experience (2011–2018). Br J Haemat 2020;191:e41-e61.
[46] Douros A, Schlemm L, Bolbrinker J, et al. Insufficient anticoagulation with dabigatran in a patient with short bowel syndrome. Thromb Haemost 2014;112:419-420.
[47] Puhr HC, Ilhan-Mutlu A, Preusser M, et al. Absorption of direct oral anticoagulants in cancer patients after gastrectomy. Pharmaceutics 2022;14:662.
[48] Mahlmann A, Gehrisch S, Beyer-Westendorf J. Pharmacokinetics of rivaroxaban after bariatric surgery: a case report. J Thromb Thrombolysis 2013;36:533-535.
[49] Kröll D, Nett PC, Borbély YM, et al. The effect of bariatric surgery on the direct oral anticoagulant rivaroxaban: the extension study. Surg Obes Relat Dis 2018;14:1890-1896.
[50] Christensen LD, Vinter-Jensen L, Rasmussen HH, et al. Rivaroxaban as anticoagulant therapy in short bowel syndrome. Report of three cases. Thromb Res 2015;135:568-570.

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CONTRAINDICATIONS TO THERAPEUTIC ANTICOAGULATION[a]

- **Absolute contraindications**
  - **Active bleeding (major)[b]**
  - **Indwelling neuraxial catheters**
  - **Neuraxial anesthesia/lumbar puncture[c,d]**
  - **Interventional spine and pain procedures[1]**

- **Relative contraindications**
  - **Chronic, clinically significant measurable bleeding >48 hours**
  - **Thrombocytopenia (platelet count <30,000–50,000/μL or clinical judgment)[e]**
  - **Underlying hemorrhagic coagulopathy (eg, abnormal PT or aPTT excluding a lupus inhibitor/anticoagulant) or known bleeding disorder in the absence of replacement therapy (eg, hemophilia, von Willebrand disease)**
  - **Severe platelet dysfunction**
  - **Recent major operation at high risk for bleeding**
  - **High risk for falls (head trauma)**
  - **Primary and metastatic brain tumors[f]**
  - **Long-term antiplatelet therapy[g]**

[1] Narouze S, Benzon HT, Provenzano D, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med 2015;40:182-212.

[a] For agent-specific contraindications, see VTE-D, 3 of 6.
[b] Active bleeding with >2 units red blood cells (RBCs) transfused, decrease in hemoglobin by ≥2 g/dL, or intracranial or intraspinal bleeding.
[c] Refer to institutional-specific anesthesia practice guidelines, if available. Twice-daily prophylactic dose UFH (5000 units every 12 h) and once-daily LMWH (eg, enoxaparin 40 mg once daily) may be used with neuraxial anesthesia. Twice-daily prophylactic dose LMWH (eg, enoxaparin 30 mg every 12 h), prophylactic dose fondaparinux (2.5 mg daily), and therapeutic dose anticoagulation should be used with extreme caution with neuraxial anesthesia. The safety of thrice-daily prophylactic dose UFH in conjunction with neuraxial anesthesia has not been established (Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines [Third Edition]. Reg Anesth Pain Med 2010;35:64-101).
[d] Timing of LMWH: For LMWH, placement or removal of a neuraxial catheter should be delayed for at least 12 hours after administration of prophylactic doses such as those used for prevention of DVT. Longer delays (24 h) are appropriate to consider for patients receiving therapeutic doses of LMWH. A post-procedure dose of LMWH should usually be given no sooner than 4 hours after catheter removal (FDA Drug Safety Communications. Updated recommendations to decrease risk of spinal column bleeding and paralysis in patients on LMWH. November 6, 2013: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM373735.pdf). In all cases, a benefit-risk assessment should consider both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors.
[e] Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-F).
[f] In general, brain metastases are a relative contraindication to anticoagulation except in cases where more caution is warranted due to the location of the metastases, tumor type (eg, thyroid, melanoma, renal, choriocarcinoma), or presence of other comorbidities.
[g] For patients on long-term antiplatelet therapy, reassess the need for antiplatelet therapy and discontinue/reduce dose of antiplatelet treatment if possible.

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MANAGEMENT OF ANTICOAGULATION FOR VTE IN PATIENTS WITH CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA

- **Thrombocytopenia is a common occurrence in patients with cancer who are receiving therapeutic anticoagulation for cancer-associated thrombosis. Generally, anticoagulation is considered safe with platelet counts ≥50,000/μL. The risk of bleeding is thought to increase as platelet counts decline below this threshold. Traditionally, physicians have transfused platelet concentrations to maintain platelet counts above 50,000/μL in patients with thrombocytopenia on therapeutic anticoagulation, but this is not always feasible depending upon the duration and severity of thrombocytopenia and availability of blood products.**

- **When managing cancer-associated thrombosis with thrombocytopenia the provider should consider:**
  - **The patient's risk for recurrent thromboembolism, and**
  - **The patient's risk of bleeding including the anticipated depth and duration of thrombocytopenia**

- **For patients at high risk of recurrent thromboembolism (includes recent proximal DVT or PE [within 1 month of anticoagulation treatment], 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 (includes DVT/PE occurring after more than 1 month of anticoagulation treatment, central venous catheter-associated DVT, upper extremity DVT, acute distal DVT) management options include:**
  - **Use of lower dose anticoagulation as outlined below in the table**
  - **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)**

Enoxaparin Dose Modification in the Setting of Thrombocytopenia

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 daily
25,000–50,000/μL	Half-dose enoxaparin	0.5 mg/kg twice daily	—
<25,000/μL	Temporarily hold enoxaparin		

- **Note: NCCN currently does not recommend use of DOACs below a platelet count of 50,000/μL as there is limited published experience using DOACs in this situation.**

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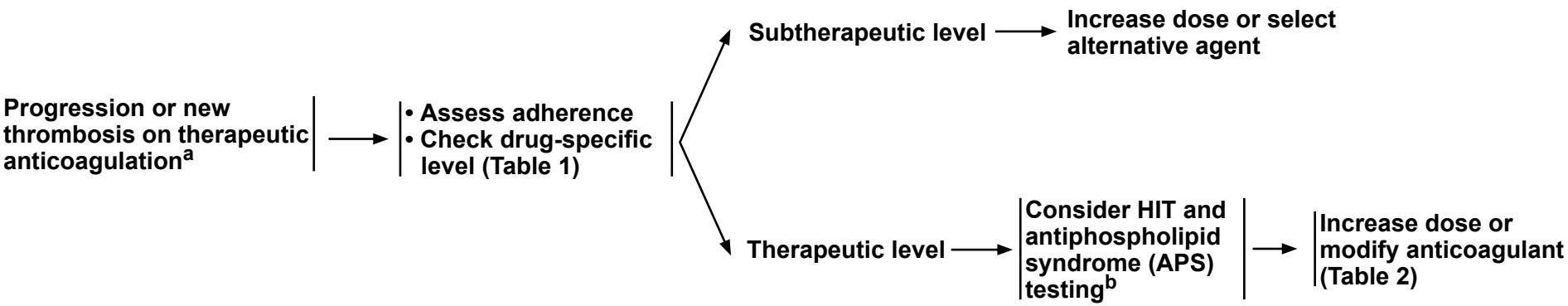
PROGRESSION OR NEW THROMBOSIS ON THERAPEUTIC ANTICOAGULATION



[a] Progression or new thrombosis on therapeutic anticoagulation is defined as an extension of DVT or new DVT or PE while on therapeutic levels of recommended anticoagulation therapy. An early embolism event might not indicate progression or new thrombosis on therapeutic anticoagulation. See Therapeutic Anticoagulation for VTE (VTE-D).

[b] Conditions associated with venous stasis such as vascular compression by tumors or lymphatic masses or stasis associated with IVC filters.

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PROGRESSION OR NEW THROMBOSIS ON THERAPEUTIC ANTICOAGULATION

Table 1: Therapeutic Range of Anticoagulants

Anticoagulation Agent	Drug-level	Adjustment
UFH	UFH anti-Xa or aPTT	• Calibrated to UFH
LMWH	LMWH anti-Xa	• Calibrated to LMWH
Fondaparinux	Fondaparinux anti-Xa	• Calibrated to fondaparinux
Warfarin	INR	• Goal 2–3
Apixaban	Apixaban anti-Xa	• No established "therapeutic range." Peak/trough levels observed in the clinical trials for apixaban may serve as point of reference but should not be used to make dose adjustments/titrations
Dabigatran	Ecarin clotting time or diluted thrombin time (dTT)	• No established "therapeutic range." Peak/trough levels observed in the clinical trials for dabigatran may serve as point of reference but should not be used to make dose adjustments/titrations
Edoxaban	Edoxaban anti-Xa	• No established "therapeutic range." Peak/trough levels observed in the clinical trials for edoxaban may serve as point of reference but should not be used to make dose adjustments/titrations
Rivaroxaban	Rivaroxaban anti-Xa	• No established "therapeutic range." Peak/trough levels observed in the clinical trials for rivaroxaban may serve as point of reference but should not be used to make dose adjustments/titrations

Table 2: Alternative Anticoagulant Options in Case of Progression or New Thrombosis on Therapeutic Anticoagulation

Failed Anticoagulant	Alternative Anticoagulant(s)[c]
UFH	• Switch to alternative anticoagulant (DOACs [apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B], LMWH, warfarin, fondaparinux) • Increase dose of UFH
LMWH	• Change to every-12-hour dosing • Switch to DOAC (apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B) or fondaparinux • Increase dose of LMWH[d,e]
Fondaparinux	• Switch to LMWH, DOAC (apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B), UFH
Warfarin	• Switch to LMWH, DOAC (apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B), UFH, fondaparinux
Apixaban	• Switch to LMWH, fondaparinux
Dabigatran	• Switch to LMWH, fondaparinux
Edoxaban	• Switch to LMWH, fondaparinux
Rivaroxaban	• Switch to LMWH, fondaparinux

[c] As renal function allows.

[d] 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).

[e] Although data are limited, doses are generally increased to 120%–125% of full dose for LMWH and fondaparinux (Ihaddadene R, Le Gal G, Delluc A, Carrier M. Dose escalation of low molecular weight heparin in patients with recurrent cancer-associated thrombosis. Thromb Res 2014;134:93-95; Carrier M, Le Gal G, Cho R, et al. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. J Thromb Haemost 2009;7:760-765).

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THROMBOLYTIC AGENTS

- **DVT[a,b]:**
  - **Pharmacomechanical devices[b,1]**
    - ◊ **Alteplase 10 mg to 25 mg per session**
  - **Infusion catheters[b,1]**
    - ◊ **Alteplase 0.5 mg to 1 mg per hour for 12–24 hours**
    - ◊ **Reteplase 0.5 unit to 1 unit per hour for 12–24 hours**

- **SPVT**
  - **Thrombolysis with catheter-directed therapies is limited to case reports and small studies. Follow local institutional protocols.**

- **PE**
  - **Systemic thrombolysis**
    - ◊ **Alteplase 100 mg IV over 2 hours[c]**
    - ◊ **Alteplase 50 mg as a 10 mg bolus followed by 20 mg per hour for 2 hours[c,2]**
    - ◊ **Reteplase 10 unit IV bolus followed 30 minutes later by a second 10 unit IV bolus injection, both doses administered over 2 minutes[3]**
    - ◊ **Tenecteplase (category 2B)[4]**

Weight	Tenecteplase Dose
<60 kg	30 mg
≥60 to <70 kg	35 mg
≥70 to <80 kg	40 mg
≥80 to <90 kg	45 mg
≥90 kg	50 mg

  - **US-assisted, catheter-directed thrombolysis[5]**
    - ◊ **Alteplase 1 mg per hour per lung for 12–24 hours[d]**

[1] Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med 2017;377:2240-2252.
[2] Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" trial). Am J Cardiol 2013;111:273-277.
[3] Tebbe U, Graf A, Kamke W, et al. Hemodynamic effects of double bolus reteplase versus alteplase infusion in massive pulmonary embolism. Am Heart J 1999;138:39-44; Liu Z, Wang J. The use of reteplase in patients with pulmonary embolism reteplase after haemodynamic changes. Heart 2012;98(Suppl 2):E281-282.
[4] Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402-1411.
[5] Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE Trial. JACC Cardiovasc Interv 2018;11:1401-1410.

[a] A post-procedural imaging study is recommended to confirm the results of thrombolysis.
[b] Different FDA-approved catheters and devices exist to deliver thrombolytic agents into the thrombus in conjunction with mechanical thrombectomy. No single catheter or device has been proven to be superior to another. The extent of thrombus may be an important factor in device and agent selection as well as the likelihood of success.
[c] Altepase 50 mg may be appropriate for patients aged >75 years, with recent surgery (within 1 mo), or with high risk of bleed.
[d] US-assisted, catheter-directed thrombolysis has been used for PE patients with ≥50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥25 mmHg) or echocardiographic evaluation. Alteplase is administered at a rate of 1 mg/h per drug delivery catheter (2 mg/h for bilateral PE). Alteplase is infused for 24 hours with one catheter and 12 hours for two catheters.

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CONTRAINDICATIONS TO THROMBOLYSIS AND INDICATIONS FOR THROMBOLYSIS

Contraindications to Thrombolysis[a,b]

- **Absolute**
  - **History of hemorrhagic stroke or stroke of unknown origin**
  - **Intracranial tumor**
  - **Ischemic stroke in previous 3 months**
  - **History of major trauma, surgery, or head injury in previous 3 weeks**
  - **Active bleeding**
  - **Bleeding diathesis**

- **Relative**
  - **Age >75 years**
  - **Pregnancy or first postpartum week**
  - **Non-compressible puncture sites**
  - **Traumatic resuscitation**
  - **Platelet count <100,000/μL**
  - **Refractory hypertension (systolic pressure >180 mmHg; diastolic blood pressure >100 mmHg)**
  - **Advanced liver disease**
  - **Infective endocarditis**
  - **Recent GI bleed (last 3 months)**
  - **Life expectancy ≤1 year**

Indications for Thrombolysis

- **Limb-threatening/life-threatening acute proximal DVT**
- **Symptomatic iliofemoral thrombosis**
- **Massive/life-threatening PE**
- **Intestinal SPVT with high risk of ischemia**

[a] Reproduced and adapted with permission from Kearon C, Akl E, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic therapy prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e419S-e494S.

[b] The risks and benefits of thrombolysis should be assessed on a case-by-case basis by the clinician caring for the patient. Use of a thrombolytic agent may be considered in pregnant and lactating individuals with life-threatening thrombosis. Studies examining the safety of thrombolytic therapy during pregnancy or lactation are not available, but thrombolytic agents are unlikely to cross the placenta or transfer to breast milk due to their large molecular weight.

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ELEMENTS FOR CONSIDERATION IN DECISION NOT TO TREAT

- **Patient non-acceptance**
- **No therapeutic advantage**
  - **Limited survival**
  - **High bleeding risk**
  - **No planned oncologic intervention**
- **No palliative benefit (eg, alleviate dyspnea, prevent leg swelling)**
- **Unreasonable burden of anticoagulation treatment**
  - **Painful injections**
  - **Frequent monitoring with phlebotomy**
- **End-of-life/comfort care**

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REVERSAL OF ANTICOAGULATION

- **In the event of life-threatening bleeding or the need for urgent/emergent invasive procedures, anticoagulant effect must be reversed promptly.**
- **All anticoagulation reversal protocols are associated with a risk of thromboembolism.**
- **It is recommended that institutions have treatment pathways or guidelines for the reversal of anticoagulation, which might make use of the agents listed below:**
  - **4-factor prothrombin complex concentrate (PCC)**
  - **Andexanet alfa**
  - **Desmopressin (DDAVP)**
  - **Fresh frozen plasma (FFP)**
  - **Idarucizumab**
  - **Oral charcoal**
  - **Protamine**
  - **Recombinant human coagulation Factor VIIa (rhFVIIa)**
  - **Activated prothrombin complex concentrates (aPCC) (anti-inhibitor coagulant complex, vapor heated)**
  - **Vitamin K_1 oral (phytonadione) and IV solution**

- **The reversal guidelines for different anticoagulants are displayed in the following tables:**

Heparin	Reversal of Anticoagulation	Precautions/Additional Considerations
• UFH (Half-life 1 hour)	• Protamine 1 mg/100 units of UFH (taking into account UFH ~1-hour half-life) by slow IV infusion (no faster than 5 mg per min) • Follow aPTT or anti-Xa levels in accordance with institutional SOP closely • Maximum dose: 50 mg Examples: ▸ Bleeding immediately after 5000 units bolus and patient is given 50 mg of protamine ▸ Patient on 1250 units per hour bleeds and is given 24 mg of protamine to reverse the UFH remaining from the last 4 hours of the infusion	• Protamine can cause anaphylaxis if administered too rapidly. • Patients with fish allergies, previous exposure to protamine (eg, NPH insulin), or individuals who have had a vasectomy or individuals assigned male at birth who are infertile are at increased risk. • Excessive protamine (protamine: heparin ratios >1.3:1 mg/U) are associated with platelet dysfunction and decreased thrombin activity, resulting in bleeding. • Protamine reverses a variable amount of LMWH anti-Xa activity. • In the event of ongoing bleeding and persistent drug levels, consider a second dose of protamine.
• LMWH (Half-life 4.5–7 hours)	• Protamine 1 mg/mg of enoxaparin or 1 mg/100 units of dalteparin within 8 hours of dose • Protamine 0.5 mg/mg of enoxaparin or 0.5 mg/100 units of dalteparin if dose administered >8 hours prior • If >12 hours since dose, consider clinical scenario (eg, LMWH dose, renal function, bleeding severity) when deciding whether protamine is indicated • Administer protamine by slow IV infusion (no faster than 5 mg per min) • Maximum dose: 50 mg	

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REVERSAL OF ANTICOAGULATION

DTI	Reversal of Anticoagulation	Precautions/Additional Considerations
• Bivalirudin[a] (half-life 25 minutes with normal renal function)	• Discontinue drug. • No specific antidote exists, but beneficial effects have been ascribed to the following: ‣ Hemofiltration and hemodialysis are effective in removal of bivalirudin. ‣ Animal models and ex-vivo experiments suggest aPCCs (50–100 units/kg IV at 2 units per kg body weight per minute) or rhFVIIa (90 mcg/kg IV over 2–5 minutes) may be effective. ‣ DDAVP 0.3 mcg/kg reduced bleeding in animal and ex-vivo models, and if used should be administered over 15–30 minutes.	• Limited data exist to support all reversal strategies. • Repeated doses (more than 3 or 4) of DDAVP are associated with tachyphylaxis and hyponatremia.
• Argatroban[b] (half-life 39–51 minutes)	• Discontinue drug. • No specific antidote exists, but beneficial effects have been ascribed to the following: ‣ Animal models and case reports suggest PCCs and aPCCs (50–100 units/kg IV) may be effective. ‣ Ex-vivo studies suggest rhFVIIa (90 mcg/kg IV) also may be effective. ‣ DDAVP (0.3 mcg/kg) reduced bleeding in animal and ex-vivo models. ‣ Monitor reversal with aPTT.	

[a] Limited information is available on the clinical efficacy of all these proposed reversal strategies. For life-threatening bleeding, the NCCN Guidelines Panel currently favors use of rhFVIIa as the first-line agent. Hemofiltration or hemodiafiltration can accelerate the clearance of bivalirudin.
[b] Limited information is available on the clinical efficacy of all these proposed reversal strategies. For life-threatening bleeding, the NCCN Guidelines Panel currently favors use of aPCC or rhFVIIa as the first-line agent.

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REVERSAL OF ANTICOAGULATION

DTI	Reversal of Anticoagulation	Precautions/Additional Considerations
• Dabigatran[b] (half-life 12–17 hours)	• Discontinue drug. • Administer idarucizumab, 2.5 g in 2 consecutive boluses. • Oral charcoal if dose within 2 hours of ingestion ▸ Standard initial adult dose 50–100 g followed by doses every 1, 2, or 4 hours equivalent to 12.5 g/h • For special situations with slow or incomplete clearance (eg, renal dysfunction or failure), consider adding to idarucizumab: ▸ Hemodialysis ▸ Hemodialysis with a charcoal filter • Monitor reversal with aPTT or dTT or Hemoclot thrombin inhibitor test to ensure complete reversal.	• Limited data exist to support all reversal strategies. • In patients with renal failure/severe renal insufficiency, dialysis may be helpful in addition to idarucizumab. • Idarucizumab is associated with thromboembolism within 30 days.

Factor Xa Inhibitor	Reversal of Anticoagulation	Precautions/Additional Considerations
• Fondaparinux (half-life 17–21 hours)	• Discontinue drug. No specific antidote exists; however, limited data suggest rhFVIIa (90 mcg/kg IV) may be beneficial.	• rhFVIIa has been associated with thromboembolic events.

[b] Limited information is available on the clinical efficacy of all these proposed reversal strategies. For life-threatening bleeding, the NCCN Guidelines Panel currently favors use of aPCC or rhFVIIa as the first-line agent.

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REVERSAL OF ANTICOAGULATION

Direct Factor Xa Inhibitor	Reversal of Anticoagulation	Precautions/Additional Considerations
• Rivaroxaban (Half-life 5–9 hours for patients 20–45 years; 11–13 hours for patients 60–76 years) OR • Apixaban (Half-life 12 hours) OR • Edoxaban (Half-life 10–14 hours)	Discontinue drug. Beneficial effects have been ascribed to the following: • Consider oral charcoal if dose within 2 hours of ingestion and repeat within 6 hours ‣ Standard initial adult dose 50–100 g followed by doses every 1, 2, or 4 hours equivalent to 12.5 g/h • Administer: ‣ Andexanet alfa (consider for patients with intracranial hemorrhage) ‣ Alternative options may include: ◊ aPCC 25–50 units/kg IV ◊ 4-factor PCC 25–50 units per kg (based on units of Factor IX per kg of actual body weight) or fixed dose of 2000 units ◊ If 4-factor PCC is unavailable or patient is allergic to heparin and/or has a history of HIT in the last 12 months, then administer 3-factor PCC 50 units/kg (based on units of Factor IX per kg of actual body weight)	• See andexanet alfa dosing and administration tables (VTE-K 7 of 8). • Andexanet alfa is associated with thromboembolism within 30 days of administration. • aPCC and 4-factor PCC have been associated with a risk of thromboembolism when used for reversal of direct factor Xa inhibitors. • 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.

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REVERSAL OF ANTICOAGULATION

Warfarin (effective half-life 20–60 hours)	Reversal of Anticoagulation	Precautions/Additional Considerations
• INR 4.5–10, no bleeding	• Hold warfarin dose. • Look for drug or dietary interactions and eliminate them if possible. • Look for evidence of acute hepatic dysfunction/injury. • Follow INR closely[c] (at least daily as an inpatient, every 1–2 days as outpatient). • When INR approaches therapeutic range (INR <4) restart warfarin at reduced dose (10%–20% dose reduction) if causal factor not present or cannot be eliminated. • Recheck INR within 4–7 days. • Adjust warfarin dose based on weekly INR until stable.	• N/A
• INR >10, no bleeding	• Hold warfarin dose. • Consider small dose of oral vitamin K_1 1–2.5 mg in patients at high risk of bleeding (may repeat dose in 24 hours if INR remains elevated). • Look for drug or dietary interactions and eliminate them if possible. • Look for evidence of acute hepatic dysfunction/injury. • Follow INR closely[c] (at least daily as an inpatient, every 1–2 days as outpatient). • When INR approaches therapeutic range (INR <4) restart warfarin at reduced dose (at least 20% dose reduction) if causal factor not present or cannot be eliminated. • Recheck INR within 4–7 days. • Adjust warfarin dose based on weekly INR until stable.	• Avoid vitamin K_1 SC administration due to erratic absorption, and delayed onset compared with oral administration. • Vitamin K_1 IV administration can be used for more rapid absorption than tablets.

[c] The impact of warfarin dose changes can take at least 5 to 7 days to be fully manifested in the INR.

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REVERSAL OF ANTICOAGULATION

Warfarin (effective half-life 20–60 hours)	Reversal of Anticoagulation	Precautions/Additional Considerations
• Management of urgent surgery (within 24–48 hours)	Within 24 hours: • Hold warfarin dose • Administer vitamin K_1 1–2.5 mg IV slowly (no faster than 1 mg/min) • Repeat INR preoperative to determine need for supplemental FFP Within 48 hours: • Hold warfarin dose • Administer vitamin K_1 2.5 mg orally • Repeat INR at 24 and 48 hours to assess need for supplemental vitamin K_1 or FFP	• Infection due to pathogen transmission (all plasma-derived agents; greater risk with FFP compared with solvent/detergent-treated products [3- or 4-factor PCC, aPCC]) • Immune reactions, including allergic/anaphylactic, alloimmunization (vitamin K_1 and all plasma-derived agents; greater risk with FFP compared with solvent/detergent-treated products [3- or 4-factor PCC, aPCC]) • Excessive intravascular volume (FFP) • Transfusion-related acute lung injury (FFP) • Pulmonary edema (FFP) • Agglutination reactions/hemolysis due to blood-type incompatibility (FFP) • Transfusion-associated graft-versus-host disease (if not irradiated FFP) • Febrile nonhemolytic transfusion reactions (FFP)
• Life-threatening bleeding	• Hold warfarin dose • Administer vitamin K_1 10 mg IV slowly (no faster than 1 mg/min) • Administer 4-factor PCC ▸ 4-factor PCC dosing (based on units of Factor IX per kg of actual body weight) ◊ INR 2 to <4: 25 units/kg (maximum 2500 units) ◊ INR 4–6: 35 units/kg (maximum 3500 units) ◊ INR >6: 50 units/kg (maximum 5000 units) ▸ If 4-factor PCC unavailable or patient is allergic to heparin and/or a history of HIT in the last 12 months: ◊ INR <4: 3-factor PCC 25 units/kg + FFP 2–3 units ◊ INR >4: 3-factor PCC 50 units/kg + FFP 2–3 units ▸ FFP 15 mL/kg (consider if PCC unavailable) ▸ rhFVIIa 25 mcg/kg (consider if PCC is unavailable or bleeding is unresponsive to PCC) • Monitor INR closely • Consider repeating administration depending on clinical or laboratory parameters	• Three hours or longer may be required for phytonadione to halt or slow active bleeding. Rapid administration of IV vitamin K_1 is associated with a higher risk of anaphylaxis (risk ~1 in 3000 doses). • Monitor vital signs closely. • Administer 4-factor PCC (contains heparin) IV push at a rate not exceeding 5 mL/min. • PCCs are associated with a risk of thromboembolism within 30 days of administration. • Administer 3-factor PCC IV push at a rate not exceeding 10 mL/min. • FFP is associated with thromboembolism within 30 days of administration. • Administer rhFVIIa IV push over 2–5 minutes. • rhFVIIa has been associated with thromboembolic events. • For patients with a history of HIT use 3-factor PCC without heparin[d] (Factor IX complex).

[d] Prescribing information for factor IX complex. 2010. Available at: https://www.fda.gov/media/80956/download.

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ANDEXANET ALFA DOSING AND ADMINISTRATION

Table 1: Andexanet Alfa Dosing Strategy§

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 2: 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)

§ Prescribing information for coagulation factor Xa (recombinant), inactivated-zhzo. Lyophilized powder for solution for intravenous injection 2022. Available at: https://www.fda.gov/media/113279/download.

* 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.

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REVERSAL OF ANTICOAGULATION
REFERENCES

The preceding tables are comprised of data from the following references:

- Benz AP, Xu L, Eikelboom JW, et al. Andexanet Alfa for specific anticoagulation reversal in patients with acute bleeding during treatment with edoxaban. Thromb Haemost 2022;122:998-1005.
- Prescribing information for edoxaban tablets, for oral use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206316s017lbl.pdf.
- Bhagirath VC, O'Malley L, Crowther MA. Management of bleeding complications in the anticoagulated patient. Semin Hematol 2011;48:285-294.
- Bucklin MH, Acquisto NM, Nelson C. The effects of recombinant activated factor VII dose on the incidence of thromboembolic events in patients with coagulopathic bleeding. Thromb Res 2014;133:768-771.
- Burbury KL, Milner A, Snooks B, et al. Short-term warfarin reversal for elective surgery--using low-dose intravenous vitamin K: safe, reliable and convenient. Br J Haematol 2011;154:626-634.
- Connolly SJ, Crowther MA, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med 2019;380:1326-1335.
- Crowther MA, Warkentin TE. Bleeding risk and management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood 2008;111:4871-4879.
- Dager WE, Roberts AJ, Nishijima DK. Effect of low and moderate dose FEIBA to reverse major bleeding in patients on direct oral coagulants. Thromb Res 2019;173:71-76.
- Elmer J, Wittels KA. Emergency reversal of pentasaccharide anticoagulants: a systematic review of the literature. Transfus Med 2012;22:108-115.
- Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e24S-43S.
- Goldstein JN, Refaai MA, Milling TJ, Jr, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet 2015;385:2077-2087.
- Ghanny S, Warkentin TE, Crowther MA. Reversing anticoagulant therapy. Curr Drug Discovery Technologies 2012;9:143-149.
- Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. American College of Chest Physicians. Chest 2012;141(2 Suppl):e152S-184S.
- Holland L, Warkentin TE, Refaai M, et al. Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supratherapeutic international normalized ratio due to warfarin overdose. Transfusion 2009;49:1171-1177.
- Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am J Hematol 2012;87 Suppl 1:S141-145.
- Koster A, Buz S, Krabatsch T, et al. Effect of modified ultrafiltration on bivalirudin elimination and postoperative blood loss after on-pump coronary artery bypass grafting: assessment of different filtration strategies. J Card Surg 2008;23:655-658.
- Lubetsky A, Yonath H, Olchovsky D, et al. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med 2003;163:2469-2473.
- Marlu R, Enkelejda H, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. A randomised crossover ex vivo study in healthy volunteers. Thromb Haemost 2012;108:217-224.
- Nutescu EA, Dager WE, Kalus JS, et al. Management of bleeding and reversal strategies for oral anticoagulants: Clinical practice considerations. Am J Health-Syst Pharm 2013;70:1914-1929.
- Pernod G, Albaladejo P, Godier A, et al. Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors: proposals of the working group on perioperative haemostasis (GIHP) - March 2013. Arch Cardiovasc Dis 2013;106:382-393.
- Pollack CV Jr., Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med 2017;377:431-441.
- Sarode R, Milling TJ, Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234-1243.
- Schulman S, Bjisterveld NR. Anticoagulants and their reversal. Transfus Med Rev 2007;21:37-48.
- Schulman S, Gross PL, Richie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: A prospective cohort study. Thromb Haemost 2018;118:842-851.
- Tanaka KA, Mazzeffi M, Durila M. Role of prothrombin complex concentrate in perioperative coagulation therapy. J Intensive Care 2014;2:60.
- Zatta A, McQuilten Z, Kandane-Rathnayake R, et al. The Australian and New Zealand Haemostasis Registry: ten years of data on off-licence use of recombinant activated factor VII. Blood Transfus 2015;13:86-99.

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NCCN Guidelines Version 2.2024
Perioperative Management of Anticoagulation and Antithrombotic Therapy

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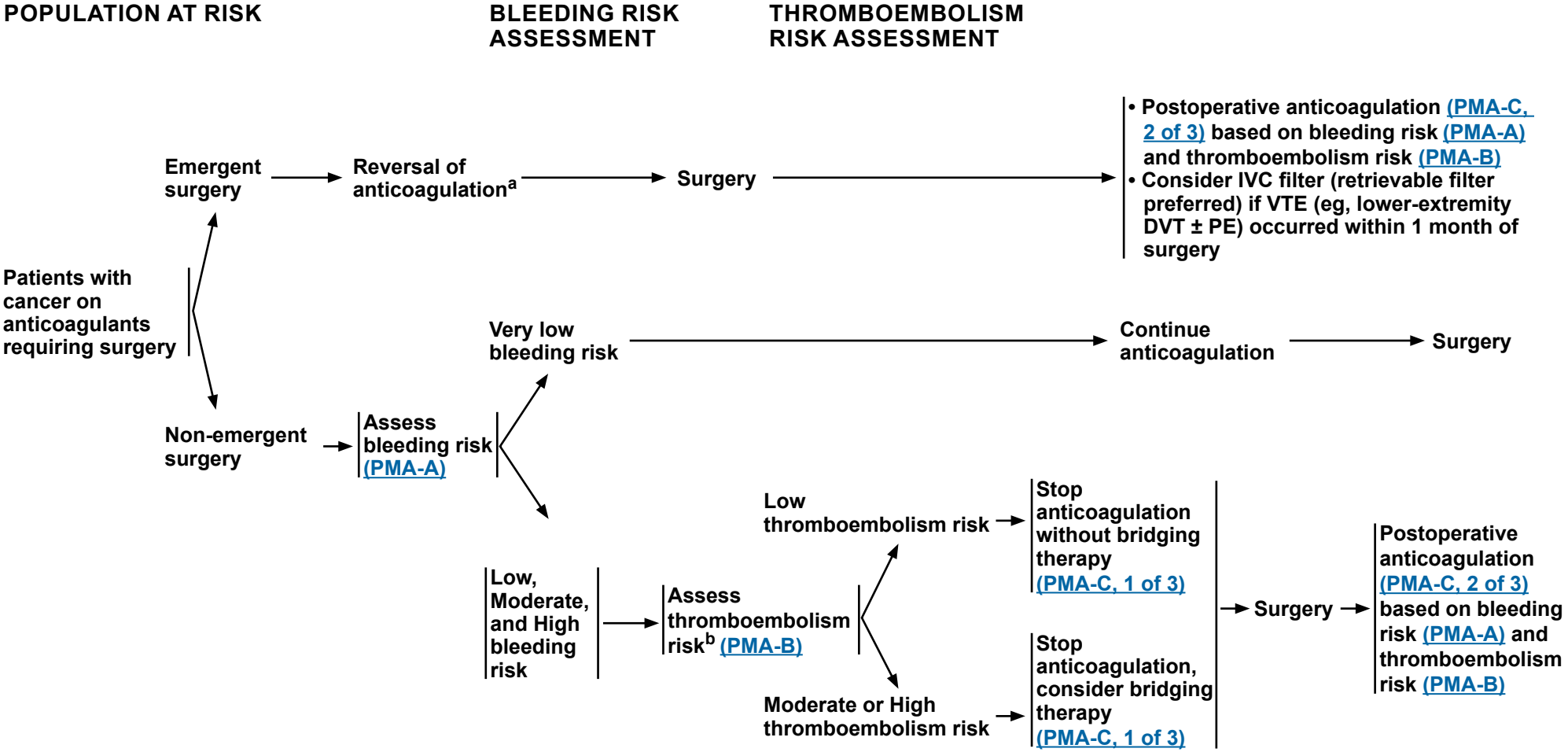

[a] Reversal of Anticoagulation (VTE-K 1 of 8).

[b] Consider IVC filter (retrievable filter preferred) if VTE (eg, lower-extremity DVT ± PE) occurred within 1 month of surgery. Patient should be assessed periodically for filter retrieval once anticoagulation is safely resumed.

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BLEEDING RISK ASSESSMENT

Patients with cancer frequently undergo invasive procedures as part of their treatment. Many patients with cancer are on anticoagulation. Patients with cancer are at increased risk for bleeding and thrombotic complications. The purpose of this section is to provide guidance to clinicians caring for patients with cancer on anticoagulation who are scheduled for an invasive procedure.

- **Step 1: Assess the bleeding risk of the procedure (Table 1) and the patient's risk for thromboembolism (Table 2, PMA-B).**
- **Step 2: Determine whether anticoagulation needs to be held and the duration of anticoagulation interruption (PMA-C 1 of 3).**
- **Step 3: Determine if bridging anticoagulation is appropriate (PMA-C 2 of 3).**
- **Step 4: Determine when therapeutic anticoagulation can be resumed post-procedure (PMA-C 2 of 3).**

Table 1: Bleeding Risk Associated with Different Invasive Procedures

Bleeding Risk Category	Type of Surgery or Procedure		
High	• Neurosurgical procedure (intracranial or spinal) • Cardiac surgery • Urologic surgery		
Moderate	• Major vascular surgery (abdominal aortic aneurysm [AAA] repair, peripheral artery bypass) • Reconstructive plastic surgery • Major orthopedic surgery • Head and neck surgery • Bronchoscopy with biopsy • Biopsy (prostate, bladder, kidney, liver, thyroid, lymph node)	• Major intra-abdominal surgery • Major intra-thoracic surgery • GI endoscopy (esophagogastroduodenoscopy [EGD], enteroscopy, flexible sigmoidoscopy, colonoscopy) with polypectomy • GI laser ablation and coagulation • Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy • Pneumatic or bougie dilation of benign or malignant strictures	• Endoscopic US (EUS) fine-needle aspiration (FNA) • Endoscopy with esophageal variceal band ligation/gastric variceal ligation • Laparoscopic cholecystectomy or hernia repair • Percutaneous endoscopic gastrostomy (PEG) tube placement
Low	• Core needle breast biopsy • Coronary angiography and right heart catheterization (including biopsy) • Arthroscopy	• Central venous catheter placement • Bone marrow biopsy • Pacemaker or automatic implantable cardioverter defibrillator (AICD) placement • Arteriovenous (AV) fistula placement	• Spinal injections • Lumbar puncture • GI endoscopy (EGD, enteroscopy, flexible sigmoidoscopy, colonoscopy) with biopsy
Very low	• Minor dermatologic procedures (skin biopsy, excisions of basal and squamous cell carcinomas, actinic keratoses, and malignant or premalignant nevi) • Cataract removal • Electroconvulsive therapy (ECT) • IVC filter placement or removal • Arthrocentesis	• Joint or soft tissue injections • Endovascular ablation for varicose veins • GI endoscopy (EGD, push enteroscopy, flexible sigmoidoscopy, colonoscopy) without biopsy or polypectomy • ERCP without sphincterotomy • Biliary/pancreatic stent insertion without endoscopic sphincterotomy • EUS without FNA • Push enteroscopy	• Minor dental procedures[a] ▸ Subgingival scaling ▸ Restorations with subgingival preparations ▸ Standard root canal therapy ▸ Simple extractions of one or more teeth • Regional injection of local anesthetics • Standard dental cleanings or cavity fillings

[a] Use of local hemostatic agents such as topical tranexamic acid and aminocaproic acid or thrombin-soaked absorbable gelatin powder is encouraged in the event of bleeding.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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THROMBOEMBOLIC RISK ASSESSMENT FOR ARTERIAL THROMBOEMBOLISM AND VTE

Table 2: Thromboembolic Risk Categories

Risk Category	Clinical Conditions
High Thromboembolic Risk	• Mitral mechanical valve (bileaflet) • Single-leaflet or caged-ball mechanical valve • Mechanical valve with recent stroke (<3 months) • Atrial fibrillation (CHADSVasc ≥7) • Atrial fibrillation with recent stroke (<3 months) • Recent embolic stroke (<3 months) • VTE within 3 months • High-risk inherited thrombophilia (antithrombin deficiency, protein C deficiency, protein S deficiency, homozygous Factor V Leiden or prothrombin gene mutation, compound heterozygous Factor V Leiden/prothrombin gene mutation or other combined thrombophilic defects [eg, Factor V Leiden + protein C deficiency]) • APS • Active high thrombotic risk cancer[a] with previous thromboembolism
Moderate Thromboembolic Risk	• Aortic mechanical valve (bileaflet) with atrial fibrillation or prior stroke (>3 months) • Atrial fibrillation (CHADSVasc 5–6) • VTE in last 3–12 months • Factor V Leiden or prothrombin gene mutation heterozygosity • Active non-high thrombotic risk cancer[a] with previous thromboembolism
Low Thromboembolic Risk	• Aortic mechanical valve (bileaflet) without atrial fibrillation or prior stroke • Atrial fibrillation (CHADSVasc <5) • VTE >12 months

[a] High thrombotic risk cancers include pancreatic, liver, biliary, lung, stomach, brain, and esophageal cancers. Non-high thrombotic risk cancers include all other cancers, excluding non-melanoma skin cancer. Mulder FI, et al. Blood 2021;137:1959-1969.

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PERIOPERATIVE MANAGEMENT OF ANTICOAGULATION IN PATIENTS WITH CANCER

For high and moderate bleeding risk procedures, the panel recommends holding anticoagulation as outlined in Tables 3–4.

For low bleeding risk procedures, anticoagulation is often held according to the schedule in Tables 3–4, although practice varies with the procedure, anticoagulant, and institution. Some institutions hold anticoagulation for bone marrow biopsy while others continue anticoagulation depending upon the medication (ie, DOAC, warfarin, heparin). Pacemaker or AICD placement is routinely done on warfarin without interruption, but practice varies with DOACs. Anticoagulation is held for spinal injections and lumbar puncture.

For very low bleeding risk procedures, the panel recommends continuation of anticoagulation in most instances. Follow institutional SOPs, if available.

Table 3: Periprocedural Management of Oral Anticoagulants: Hold Times

Medication	Renal Function	Low Bleeding Risk Procedure	High/Moderate Bleeding Risk Procedure
Apixaban	CrCl ≥30 mL/min	2 days (4 doses)	3 days (6 doses)
	CrCl <30 mL/min	3 days (6 doses)	3–4 days (6–8 doses)
Dabigatran	CrCl ≥50 mL/min	2 days (4 doses)	3 days (6 doses)
	CrCl 30–49 mL/min	3 days (6 doses)	4 days (8 doses)
Edoxaban	CrCl ≥30 mL/min	2 days (2 doses)	3 days (3 doses)
Rivaroxaban	CrCl ≥30 mL/min	2 days (2 doses)	3 days (3 doses)
Warfarin	Not relevant	5 days[a]	5 days (INR 2–3)
			>5 days (INR >3)[b]

Table 4: Periprocedural Management of Parenteral Anticoagulants: Hold Times

Medication	Dosage	Renal Function	Low Bleeding Risk Procedure	High/Moderate Bleeding Risk Procedure
Enoxaparin (Half-life 4.5–7 hours)	1 mg/kg every 12 hrs	CrCl >50 mL/min	12–24 hours (1–2 doses)	24 hours (2 doses)
	0.8 mg/kg every 12 hrs	CrCl 30–50 mL/min	24 hours (2 doses)	24–36 hours (2–3 doses)
	1 mg/kg every 24 hrs	CrCl <30 mL/min	24 hours (1 dose)	24–48 hours (1–2 doses)
Fondaparinux (Half-life 17–21 hours)	5 mg every 24 hours for body weight <50 kg	CrCl ≥50 mL/min	84 hours (4 doses)	105–126 hours (5–6 doses)
	7.5 mg every 24 hours for body weight 50–100 kg			
	10 mg every 24 hours for body weight >100 kg			

[a] Some low-risk procedures are performed preferably without warfarin discontinuation (eg, pacemaker or AICD). Other low bleeding risk procedures may not require 5-day interruption (advise discussion with interventionalist).

[b] Patients with a target goal or pre-procedure INR >3 may require more than 5 days of interruption for normal hemostasis. Suggest pre-procedure INR assessment to determine hold time if feasible.

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PERIOPERATIVE MANAGEMENT OF ANTICOAGULATION IN PATIENTS WITH CANCER

Pre-procedural Bridging Anticoagulation

- For patients taking warfarin, the majority of NCCN Member Institutions consider bridging anticoagulation for patients at high risk of thromboembolism. A minority consider bridging anticoagulation for patients at moderate or high thromboembolic risk. A smaller minority consider bridging anticoagulation for patients only at exceptionally high risk (eg, recent VTE or stroke <1 month, previous episode of thromboembolism in a perioperative period without bridging). The panel does not recommend bridging anticoagulation for patients at low thromboembolic risk.
- For most patients taking DOACs, bridging anticoagulation is not necessary since the duration of interruption is shorter than warfarin. The majority of institutions reported considering bridging anticoagulation only for select DOAC recipients at exceptionally high risk of thromboembolism (eg, recent VTE or stroke <1 month, previous episode of thromboembolism in the perioperative period without bridging). A minority reported that they do not consider bridging anticoagulation for any patients taking DOACs. Smaller minorities of institutions consider bridging anticoagulation for patients at high thromboembolic risk or for patients at moderate or high risk of thromboembolism.

Post-procedural Resumption of Anticoagulation

- All patients should receive standard VTE thromboprophylaxis once hemostasis is adequate (generally within 12–24 hours postoperatively). VTE prophylaxis can be continued until therapeutic dose anticoagulation is resumed.
- For low bleeding risk procedures, therapeutic anticoagulation can generally be resumed ≥24 hours post-operation if hemostasis is adequate. Since warfarin takes several days to reach therapeutic concentrations, the majority of institutions recommend resumption of warfarin on the night of surgery after a low bleeding risk procedure. A majority also recommended resumption of therapeutic-dose LMWH, DOACs, or fondaparinux on POD1.
- For moderate bleeding risk procedures, resumption of therapeutic anticoagulation may be considered 48–72 hours post-procedure if hemostasis is adequate. Since warfarin takes several days to reach therapeutic concentrations, the majority of institutions recommend resumption of warfarin on POD1. A minority recommend resumption on POD2–3. The majority of NCCN Member Institutions recommend resumption of therapeutic-dose LMWH, DOACs, or fondaparinux on POD2 after a moderate bleeding risk procedure. A minority recommend resumption on POD3.
- For high bleeding risk procedures, resumption of therapeutic anticoagulation may be considered ≥72 hours post-procedure depending upon hemostasis. Warfarin may be resumed in the first 24–48 hours since it takes several days to reach therapeutic concentrations and the majority of institutions recommend resumption of warfarin on POD2. The majority of institutions recommend resumption of therapeutic-dose LMWH, DOACs, or fondaparinux on POD3 after a high bleeding risk procedure, although a minority recommend resumption on either POD2 or on POD4 or later.

Limitations and Important Considerations

- This section is based upon the panel's assessment of the current literature on perioperative anticoagulation management in patients with cancer. There were considerable differences of opinions on management in many areas, which reflects the limited information on perioperative outcomes in patients with cancer on anticoagulation, who are likely to be at higher bleeding and thrombotic risk compared to patients without cancer. Since the risk of perioperative bleeding or thrombosis can be influenced by a large number of variables, including but not limited to the patient's cancer site and stage, proposed invasive procedure, antithrombotic medications, and concurrent medical conditions, periprocedural anticoagulation management should be determined on a case-by-case basis. For optimal outcomes, it is essential to develop a perioperative anticoagulation plan in advance in conjunction with the patient's proceduralist.

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PERIOPERATIVE MANAGEMENT OF ANTICOAGULATION IN PATIENTS WITH CANCER
REFERENCES

The preceding pages are comprised of data from the following references:

- ASGE Standards of Practice Committee; Acosta RD, Abraham NS, Chandrasekhara V, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc 2016;83:3-16.
- Benzon HT, Asher Y, Kendall MC, et al. Clotting-factor concentrations 5 days after discontinuation of warfarin. Reg Anesth Pain Med 2018;43:616-620.
- Chang M, Yu Z, Shenker A, et al. Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban. J Clin Pharmacol 2016;56:637-645.
- Clark NP, Witt DM, Davies LE, et al. Bleeding, recurrent venous thromboembolism, and mortality risks during warfarin interruption for invasive procedures. JAMA Intern Med 2015;175:1163-1168.
- Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: A report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol 2017;69:871-898.
- Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy: An American College of Chest Physicians Clinical Practice Guideline. Chest 2022;162:e207-e243.
- Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. JAMA Intern Med 2019;179:1469-1478.
- Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med 2015;373:823-33.
- Frost C, Nepal S, Wang J, et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. Br J Clin Pharmacol 2013;76:776-786.
- Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J 2013;34:2094-2106.
- Hulot JS, Montalescot G, Lechat P, et al. Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. Clin Pharmacol Ther 2005;77:542-552.
- January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1-76.
- Jørgensen ME, Torp-Pedersen C, Gislason GH, et al. Time elapsed after ischemic stroke and risk of adverse cardiovascular events and mortality following elective noncardiac surgery. JAMA 2014;312:269-277.
- Kovacs MJ, Wells PS, Anderson DR, et al; PERIOP2 Investigators. Postoperative low molecular weight heparin bridging treatment for patients at high risk of arterial thromboembolism (PERIOP2): double blind randomised controlled trial. BMJ 2021;373:n1205.
- Kubitza D, Becka M, Roth A, et al. The influence of age and gender on the pharmacokinetics and pharmacodynamics of rivaroxaban--an oral, direct Factor Xa inhibitor. J Clin Pharmacol 2013;53:249-255.
- Kubitza D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol 2010;70:703-712.
- Lee J, Kong X, Haymart B, et al. Outcomes in patients undergoing periprocedural interruption of warfarin or direct oral anticoagulants. J Thromb Haemost 2022;20:2571-2578.
- Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood 2021;137:1959-1969.
- Parasrampuria DA, Truitt KE. Pharmacokinetics and Pharmacodynamics of Edoxaban, a Non-Vitamin K Antagonist Oral Anticoagulant that Inhibits Clotting Factor Xa. Clin Pharmacokinet 2016;55:641-655.
- Pon TK, Dager WE, Roberts AJ, et al. Subcutaneous enoxaparin for therapeutic anticoagulation in hemodialysis patients. Thromb Res 2014;133:1023-1028.
- Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab Dispos 2009;37:74-81.
- Shaw JR, Douketis J, Le Gal G, et al. Periprocedural interruption of anticoagulation in patients with cancer-associated venous thromboembolism: An analysis of thrombotic and bleeding outcomes. J Thromb Haemost 2019;17:1171-1178.
- van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010;103:1116-1127.
- Veitch AM, Vanbiervliet G, Gershlick AH, et al. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. Endoscopy 2016;48:385-402.
- White RH, McKittrick T, Hutchinson R, Twitchell J. Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. Ann Intern Med 1995;122:40-42.

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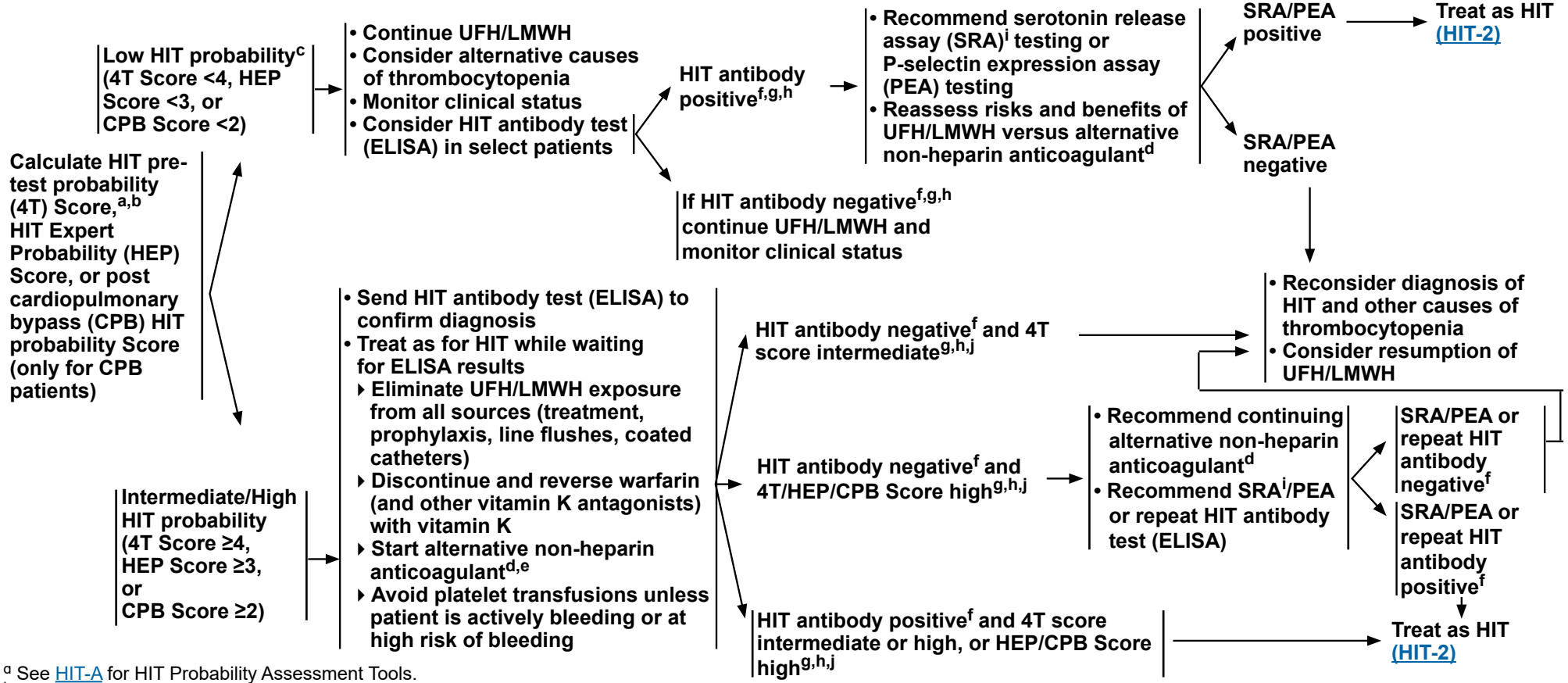
WORKUP AND MANAGEMENT FOR SUSPECTED HIT



[a] See HIT-A for HIT Probability Assessment Tools.
[b] The 4T score has not been validated in patients with cancer, so it may have less utility, particularly in patients receiving chemotherapy who have alternative causes for thrombocytopenia.
[c] 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.
[d] Initial Treatment for Suspected or Confirmed HIT (HIT-2).
[e] For patients without an indication for therapeutic anticoagulation who are judged to be at high risk of bleeding and moderate risk of HIT, a prophylactic dose of a non-heparin anticoagulant could be considered while awaiting the results of initial testing (Cuker A, et al. Blood Adv 2018;2:3360-3392).
[f] Cutoff for ELISA HIT antibody test may vary depending on the specific assay used.
[g] Cuker A. Blood 2016;127:522-524.
[h] Nagler M, et al. Blood 2016;127:546-557.
[i] Consider institution-specific ELISA optical density (OD) value thresholds when determining whether to send SRA/PEA.
[j] 4T score: 0–3 low probability of HIT, 4–5 intermediate probability of HIT, 6–8 high probability of HIT; HEP score: 1st cutoff: ≥2 positive for HIT, <2 negative for HIT (sensitivity 1.00 [0.56–1.00], specificity 0.60 [0.45–0.75]); 2nd cutoff: ≥5 positive for HIT, <5 negative for HIT (sensitivity 0.86 [0.42–0.99], specificity 0.88 [0.74–0.96]); CPB score: <2 low probability of HIT, ≥2 high probability of HIT.

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TREATMENT FOR HIT

- **Global assessment of bleeding and clotting should be performed prior to treatment.**

Initial Treatment for Patients with Suspected or Confirmed HIT

- **Start/continue alternative non-heparin anticoagulant**
  - **There are no data from randomized controlled trials comparing different non-heparin anticoagulants to inform anticoagulant selection for treatment of HIT (with or without thrombosis). Therefore, an IV direct thrombin inhibitor (DTI) is preferred for initial treatment of hospitalized patients with suspected HIT (ie, patients awaiting test results) or confirmed HIT, as many of these patients are critically ill and have contraindications to fondaparinux or DOACs.[k]**
  - **DOACs or fondaparinux are considered reasonable options for the initial treatment of clinically stable patients without hemodynamically unstable PE or limb-threatening thrombosis or planned invasive procedures who do not have contraindications to the use of these agents as listed on VTE-D, 3 of 6.[l]**
  - **Full-dose anticoagulation is generally preferred, depending on assessment of bleed and clot risks.**
  - **For more information on agent selection and dosing, see Therapeutic Options for HIT (HIT-B).**

Additional Recommendations for Patients with Confirmed HIT

- **Lower-extremity US is recommended to identify asymptomatic DVT; consider upper-extremity US based on clinical situation.**
- **For patients who are stabilized on initial HIT treatment and have no procedures planned, consider transitioning to an alternative agent:**
  - **DOACs (preferred): For patients with adequate renal and hepatic function and no other contraindications (listed on VTE-D, 2 of 6)**
  - **Fondaparinux**
  - **Warfarin**
  - **For more information on agent selection and administration, see Therapeutic Options for HIT (HIT-B).**
- **Duration of therapy:**
  - **HIT without thrombosis: At least 4 weeks (in the absence of serious bleeding risk)**
  - **HIT with thrombosis: At least 3 months as indicated for thrombotic event**

[k] Opinions vary among panel members regarding the quality of data supporting treatment options for the management of HIT in patients with cancer.
[l] Among the DOAC options listed for the management of HIT, rivaroxaban is supported by the most data, but there is no evidence to suggest that other DOAC options are not equally effective. Due to the lack of data, caution is recommended when using DOACs for management of HIT in patients with cancer.

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NCCN Guidelines Version 2.2024
Heparin-Induced Thrombocytopenia

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Discussion

HIT PRE-TEST PROBABILITY SCORE ASSESSMENT TOOL[a]

Suspicion of HIT based on the "4 T's"	Score	HIT Pre-test Probability Score Criteria: 2	1	0
Thrombocytopenia	☐	Nadir 20,000–100,000/μL or >50% platelet fall	Nadir 10,000–19,000/μL or 30%–50% platelet fall	Nadir <10,000/μL or <30% platelet fall
Timing of onset platelet fall (days of heparin therapy)	☐	Days 5–10 or ≤ day 1 with recent heparin[b]	> day 10 or timing unclear (but fits with HIT)	≤ day 1 (no recent heparin)
Thrombosis or other sequelae	☐	Proven thrombosis, skin necrosis, or ASR[c]	Progressive, recurrent, or silent thrombosis; erythematous skin lesions	None
OTher cause of platelet fall	☐	None evident	Possible	Definite
Total Pre-test Probability Score	☐	Periodic reassessment as new information can change pre-test probability (eg, positive blood cultures)		

Total HIT Pre-test Probability Score

High			Moderate		Low			
8	7	6	5	4	3	2	1	0

[a] Modified with permission from Warkentin TE, Aird WC, Rand JH. Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program 2003;497-519.
[b] Recent heparin indicates exposure within the past 30 days (2 points) or past 30–100 days (1 point).
[c] Acute systemic reaction (ASR) following IV heparin bolus.

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HIT EXPERT PROBABILITY (HEP) SCORE[d,e]

Clinical Features	Points
1. Magnitude of fall in platelet count (measured from peak platelet count to nadir platelet count since heparin exposure)	
<30%	-1
30%–50%	1
>50%	3
2. Timing of fall in platelet count	
For patients in whom typical onset HIT is suspected	
Fall begins <4 days after heparin exposure	-2
Fall begins 4 days after heparin exposure	2
Fall begins 5–10 days after heparin exposure	3
Fall begins 11–14 days after heparin exposure	2
Fall begins >14 days after heparin exposure	-1
For patients with heparin exposure in past 100 days in whom rapid onset HIT is suspected	
Fall begins ≤48 hours after heparin re-exposure	2
Fall beings >48 hours after heparin re-exposure	-1
3. Nadir platelet count	
≤ 20 x 10^9/L	-2
> 20 x 10^9/L	2

NOTE: <3 is negative; ≥3 is positive

[d] Reproduced with permission from Cuker A. Clinical and laboratory diagnosis of heparin-Induced thrombocytopenia: An integrated approach. Semin Thromb Hemost 2014;40:106-114. © Georg Thieme Verlag KG.
[e] See HEP calculator accessible at https://www.mdcalc.com/hit-expert-probability-hep-score-heparin-induced-thrombocytopenia

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SCORE FOR PATIENTS WITH PRIOR CPB[f]

Variables	Score
Platelet count time course	
Pattern A[g]	2
Pattern B[h]	1
Time from CPB to index date	
≥5 days	2
<5 days	0
CPB duration	
≤118 min	1
>118 min	0
Total Score	
Classification	
High probability of HIT	≥2
Low probability of HIT	<2

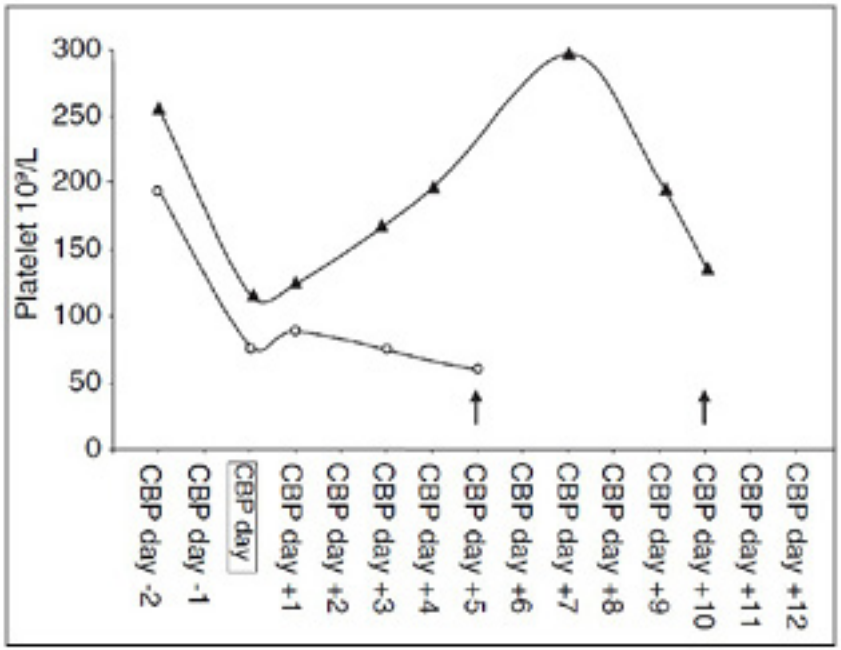

Figure 1 - Example of platelet time courses from 2 distinct patients. Representation of one pattern A (biphasic pattern, solid triangles), characterized by a fall in the platelet count more than 4 days after CPB (the initial fall immediately after CPB is followed by a rise within 5 days and then by a further fall) and one pattern B (open circles), characterized by post-CPB thrombocytopenia persisting beyond day 4. Platelet counts are reported until the index date (first day of suspected HIT, arrows).

[f] Reproduced with permission from Lillo-Le Louët A, Boutouyrie P, Alhenc-Gelas M, et al. Diagnostic score for heparin-induced thrombocytopenia after cardiopulmonary bypass. J Thromb Haemost 2004;2:1882-1888.
[g] Pattern A: platelet count fall >4 days after CPB; usually biphasic, with an initial fall immediately after CPB, followed by a rise of ≥30% within 5 days and then by a further fall.
[h] Pattern B: thrombocytopenia occurring immediately after CPB and persisting or worsening for >4 days (or before in case of previous heparin treatment).

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THERAPEUTIC OPTIONS FOR HIT[a]

DOACs

- Options: apixaban, rivaroxaban, dabigatran (category 2B), edoxaban (category 2B)
- Rarely used for initial treatment of HIT; may be a reasonable option for patients who have stabilized on initial treatment for HIT (DTI or fondaparinux), have no procedures planned, and have no contraindications (listed on VTE-D, 3 of 6). There are limited data to support the use of DOACs in patients with HIT.
  - For patients transitioning from DTI to DOAC: If DTI is in the therapeutic range, stop DTI and give the first dose of DOAC at the same time.
  - For patients transitioning from fondaparinux to DOAC: Give the first dose of DOAC instead of fondaparinux at the next scheduled administration time for fondaparinux.

Indirect Factor Xa Inhibitor[b]

- Fondaparinux (half-life 17–21 h with normal renal function)
  - For patients with CrCl 30–50 mL/min (clearance reduced by 40%): Consider using a DTI[c]
  - For patients with CrCl <30 mL/min: Avoid fondaparinux
  - Dosing
    - ◊ Body weight <50 kg: 5 mg SC daily
    - ◊ Body weight 50–100 kg: 7.5 mg SC daily
    - ◊ Body weight >100 kg: 10 mg SC daily

DTIs

- Argatroban (half-life 45 min with normal liver function; aPTT 1.5–3x initial baseline value not to exceed 100 sec)[d]
  - Normal liver function, non-intensive care unit (ICU) status: 2 mcg/kg/min adjusted to aPTT ratio (first check in 4 h)
  - Abnormal liver function (total bilirubin 1.8–3.6 mg/dL; AST/ALT 150–600 IU/L) or ICU status, patient with cardiac conditions, or patient with multi-organ failure: 0.5 mcg/kg/min
  - Severe liver dysfunction (total bilirubin >3.6 mg/dL or AST/ALT >600 IU/L): Use bivalirudin or fondaparinux
- Bivalirudin (half-life 25 minutes with normal renal function; aPTT 1.5–2.5x initial baseline value)[e,1]
  - Strongly consider for patients with combined hepatic and renal dysfunction
  - Dosing
    - ◊ Estimated CrCl >60 mL/min: 0.15 mg/kg/h – adjust to aPTT (first check 2 h)
    - ◊ Estimated CrCl 45–60 mL/min: 0.1 mg/kg/h
    - ◊ Estimated CrCl 31–44 mL/min: 0.075 mg/kg/h
    - ◊ Estimated CrCl <30 mL/min (no renal replacement therapy): 0.05 mg/kg/h
    - ◊ Renal replacement therapy or combined hepatic/renal failure: Consider argatroban for isolated renal failure or use 0.04 mg/kg/h

Platelet Transfusions

- Avoid unless active bleeding or invasive procedure necessary and platelet count <50,000/µL

Warfarin

- Initiate once platelet count ≥150,000/µL or return to baseline
- Initial dose 5 mg (consider lower dose for patients: age >75 years, CYP2C9 inhibitors, poor oral intake, liver disease)
- DTIs, particularly argatroban, can increase the INR substantially during warfarin co-therapy; therefore, a higher target INR (approximately 4.0) should be achieved before DTI therapy is discontinued. Bivalirudin slightly prolongs the INR during co-therapy.
- Discontinue DTI or fondaparinux after at least 5 to 7 days overlap and when the INR reaches intended target range (≥2).
- INR and aPTT should be repeated within 2 to 6 hours after DTI has been discontinued to ensure the INR is still therapeutic when the effects of DTI are no longer present.
- If available, chromogenic factor X activity, which is not affected by DTIs, can be used to monitor warfarin during co-therapy.

[1] Joseph L, Casanegra AI, Dhariwal M, et al. Bivalirudin for the treatment of patients with confirmed or suspected heparin-induced thrombocytopenia. J Thromb Haemost 2014;12:1044-1053.

[a] The NCCN Guidelines Panel encourages the development of protocols or order sets for HIT treatment that includes DTI dosing, adjustment in renal or hepatic dysfunction, nursing instructions, and monitoring parameters.

[b] Used as a second-line agent. Fondaparinux has been rarely associated with HIT.

[c] Prescribing information for fondaparinux sodium injection, for subcutaneous use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021345Orig1s043lbl.pdf.

[d] Prescribing information for argatroban injection, for intravenous infusion only. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020883s019lbl.pdf.; Lewis BE, Wallis DE, Leya F, et al. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med 2003;163:1849-1856.

[e] Anaphylaxis has occurred with bivalirudin.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ABBREVIATIONS

AAA	abdominal aortic aneurysm
AICD	automatic implantable cardioverter defibrillator
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
APS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AV	arteriovenous
BMI	body mass index
CBC	complete blood count
CPB	cardiopulmonary bypass
CrCl	creatinine clearance
CTA	computed tomography angiography
CTV	CT venogram
CVAD	central venous access device
DDAVP	desmopressin
DOAC	direct oral anticoagulant
DTI	direct thrombin inhibitor
dTT	diluted thrombin time
DVT	deep vein thrombosis
ECG	electrocardiogram
ECT	electroconvulsive therapy
EGD	esophagogastroduodenoscopy
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
FFP	fresh frozen plasma
FNA	fine-needle aspiration
GCS	graduated compression stockings
GI	gastrointestinal
H&P	history and physical
HEP	HIT expert probability
HIT	heparin-induced thrombocytopenia
ICU	intensive care unit
INR	international normalized ratio
IPC	intermittent pneumatic compression
IVC	inferior vena cava
LMWH	low-molecular-weight heparin
LV	left ventricular
MRA	magnetic resonance angiography
MRV	magnetic resonance venogram
NSAID	nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
OD	optical density
OR	operating room
PCC	prothrombin complex concentrate
PE	pulmonary embolism
PEA	P-selectin expression assay
PEG	percutaneous endoscopic gastrostomy
P-gp	P-glycoprotein
PICC	peripherally inserted central catheter
PNH	paroxysmal nocturnal hemoglobinuria
POD	postoperative day
PT	prothrombin time
PTS	post-thrombotic syndrome
RAM	risk assessment model
RBC	red blood cell
RYGB	Roux-en-Y gastric bypass
rhFVIIa	recombinant human coagulation Factor VIIa
SOP	standard operating procedure
SPVT	splanchnic vein thrombosis
SRA	serotonin release assay
SVC	superior vena cava
SVT	superficial vein thrombosis
TIPS	transjugular intrahepatic portosystemic shunt
UFH	unfractionated heparin
ULN	upper limit of normal
VA-ECMO	venoarterial extracorporeal membrane oxygenation
VTE	venous thromboembolism
VQ	ventilation/perfusion

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Guidelines Version 2.2024
Cancer-Associated Venous Thromboembolic Disease

Discussion

This discussion corresponds to the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease. Last updated: July 22, 2024.

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Overview

Venous thromboembolism (VTE) is a common and life-threatening condition in patients with cancer.[1] Results from a 2021 population-based cohort study showed that the presence of cancer increased the risk of VTE by 9-fold.[2] In a health claims database analysis of patients with cancer undergoing chemotherapy, VTE occurred in 12.6% of patients during the 12-month period from initiation of chemotherapy, compared with a rate of 1.4% among an age- and gender-matched control cohort without cancer.[3] Chemotherapy, anti-angiogenic therapy, protein kinase inhibitors, and immunotherapy have all been shown to increase the risk of VTE.[2] More importantly, thrombosis is a leading cause of death in patients with cancer, found to be second only to cancer itself in a large prospective observational study.[4] Multiple studies have reported significantly higher mortality and reduced overall survival among patients with cancer who developed VTE compared to those who did not.[5-10] Specifically, the occurrence of VTE has been reported to increase the likelihood of death for patients with cancer by 2- to 6-fold.[8-12] VTE has been reported to be the most common cause of death at 30-day follow-up among patients with cancer undergoing surgery.[13]

The underlying etiology of cancer-associated VTE is multifaceted and attributable to patient-related, cancer-related, and treatment-related factors. Stratification of these factors and accurate identification of patients with cancer at risk of developing VTE are important to prevent potentially deadly complications. It has also been acknowledged that patients with medical and surgical oncology needs, both hospitalized and ambulatory, are at increased risk of developing VTE.[1,3,5,14,15] Therefore, appropriate use of VTE prophylaxis can bring about substantial benefits in patients at risk.[16,17] The different subtypes of VTE, despite sharing similarities, can have vastly different symptoms and prognoses, requiring customized management plans with suitable diagnostic tools and therapeutics.[18-22] There are many treatment options for VTE, encompassing anticoagulants, thrombolytics, mechanical devices, and surgical procedures, each with their own pros and cons.[16,23] Careful selection of treatment methods with the optimal efficacy to safety consideration is instrumental in achieving the best outcomes. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cancer-Associated Venous Thromboembolic Disease outline iterative implementations of therapeutic measures based on risk assessment, diagnoses of VTE subtypes, contraindications to therapeutic interventions, and cancer and treatment status of the patient.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Guidelines® for Cancer-Associated Venous Thromboembolic Disease, an electronic search of the PubMed database was performed to obtain key literature in Cancer-Associated Venous Thromboembolic Disease since the previous Guidelines update, using the following search terms: cancer-associated venous thromboembolism and cancer thrombosis. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[24]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; Multicenter Studies; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel have been included in this version of the Discussion section.

Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

VTE Risk Assessment in Patients with Cancer

VTE risk factors in patients with cancer can be grouped into three general categories: patient-related factors, cancer-related factors, and treatment-related factors. For an individual patient with cancer, VTE risk factors in all three categories are likely to be present, and the VTE risk conferred by a single risk factor cannot be evaluated in isolation from the others.

Patient-Related Factors

Advanced age, a common characteristic of many patients with cancer, was shown to be associated with an increased risk for VTE in some clinical settings.[6,13] Obesity has also been identified as a risk factor for VTE.[25-28] Other modifiable risk factors for VTE are smoking/tobacco use and level of physical activity.[29-34] There might be confounding factors, such as other smoking-attributable diseases and higher body mass index (BMI), in the association between smoking and VTE.[30,31] Moreover, the relationship between level of physical activity and VTE is not straightforward, with multiple studies reporting a U-shaped association between the two entities.[29,33,34] A number of other patient-related VTE risk factors, although not exclusive to patients with cancer, are commonly found. These risk factors include familial and/or acquired hypercoagulability[35,36] (eg, strong thrombophilia such as antiphospholipid syndrome [APS],[37,38] pregnancy[39-41]) and other medical comorbidities, such as infection.[42,43] Although factor V Leiden and prothrombin gene 20210 mutations were identified in 3.7% and 2.6% of patients, respectively, with breast or colon cancer receiving adjuvant chemotherapy in a prospective observation study, these inherited risk factors were not associated with an increased risk for VTE among patients with cancer.[44]

With regard to medical comorbidities, a population-based study reported an estimated VTE incidence rate increase of 3-fold within the first 3 months after infection.[43] Other noteworthy independent risk factors for VTE development include renal disease,[45-47] pulmonary disease,[48-51] congestive heart failure (CHF),[52,53] and arterial thromboembolism.[54-56] A history of prior VTE has also been identified as an independent risk factor for developing a subsequent VTE.[13,44,57-59] Moreover, recurrent VTE was found to be more common among patients with cancer; for example, in a prospective follow-up study, 12-month cumulative incidences of recurrent VTE of 20.7% and 6.8% were reported for patients with and without cancer, respectively, receiving anticoagulant treatment.[60]

Other patient-related characteristics that are considered major risk factors for VTE include hospitalization, prolonged immobilization, and poor performance status.[61-63] These factors can also be considered to be treatment-related if they result from cancer-related treatments. According to the U.S. Centers for Disease Control and Prevention (CDC), between 2007 and 2009, VTE was reported in more than 547,000 patients who were hospitalized annually, with more than 28,700 deaths.[64] Moreover, the risk for VTE increased with age in patients that were hospitalized. This report confirms that hospitalization is an important risk factor for VTE and emphasizes the need for greater awareness of VTE risks and appropriate implementation of preventive measures in this setting.

Cancer-Related Factors

Several VTE risk factors are exclusive to patients with cancer, including the presence of malignancy and type and stage of cancer. As established in the *Overview*, cancer is a significant risk factor for VTE, and causes approximately 20% of VTE cases seen in the community.[61] Several studies have evaluated the association between types of cancer and the risk of developing VTE.[1,3,6,8,65-67] Pancreatic cancer[3,6,8,65-68] and brain tumors[6,67,69] are consistently associated with a high risk for VTE. It has been postulated that the tissue factor expression that occurs early in malignant transformation of the pancreas in association with angiogenesis may be predictive of VTE in pancreatic cancer.[70,71] Although differences in study designs make it difficult to compare VTE rates in a specific type of malignancy, other cancers that have been associated with an increased risk for VTE include cancers of the stomach, kidney, uterus, lung, ovary, bladder, and testes.[1,3,6] In contrast, breast cancer was associated with a relatively low VTE risk in some studies.[9,72] Nevertheless, due to the relatively high prevalence of breast cancer, VTE in patients with breast cancer is not uncommon.[9,72]

An increased risk for VTE has also been observed in certain hematologic malignancies, such as lymphoma, acute leukemia, and multiple myeloma (for guidance on management of VTE in patients receiving treatment for multiple myeloma, refer to the NCCN Guidelines for Multiple Myeloma).[6,73] Notably, patients with high-grade lymphoma and acute promyelocytic leukemia appear to be at higher risk of VTE than patients with other forms of lymphoma or leukemia.[74,75] Furthermore, in a study of patients with high-grade non-Hodgkin lymphoma, disease-related venous compression was shown to be the most common cause of VTE.[76] Thus, the mechanisms for VTE development in hematologic malignancies can differ from those in solid tumors and are worth further investigation.

In addition, advanced disease stages and distant metastases increase VTE risk.[1,67,68,77-79] For example, Blom et al reported an adjusted odds ratio (OR) of 19.8 for VTE risk in patients with solid tumors with distant metastases compared to patients without distant metastases.[1] The strength of associations can differ substantially between cancer types, with the highest incidence rate difference for VTE according to stages reported for pancreatic cancer, and the lowest incidence rate difference reported for prostate cancer.[79]

Treatment-Related Factors

Treatment-related VTE risk factors include major surgery, the presence of a central venous access device (CVAD), also known as a central venous catheter, and administration of systemic therapies. Heit et al reported a nearly 22-fold increase in the risk for VTE development in patients hospitalized for recent surgery compared with those who had not been hospitalized or who had not undergone recent surgery.[61] The overall 30-day VTE rate in patients with cancer after major surgeries ranges from 1.8% to 13.2%, with patients undergoing esophageal resection having the highest rate of 13.2% (95% CI, 8.8%–18.9%).[80] Importantly, a significant proportion of VTE episodes (34%) among patients admitted for surgical

oncology care are diagnosed after hospital discharge, highlighting the importance of extended VTE prophylaxis in this patient population.[81]

CVADs have been identified as risk factors for the development of upper-extremity acute deep vein thrombosis (DVT).[82-85] Hematopoietic cell transplantation (HCT) is a common procedure among individuals with hematologic malignancies and has been associated with increased VTE risk, principally due to catheter usage.[86] The association between CVADs and VTE may be the result of venous stasis and vessel injury after insertion of the CVAD[87,88] or related to infections as a result of catheter placement.[89,90] One study identified more than one insertion attempt and previous CVAD insertion as significant risk factors for CVAD-related thrombosis, supporting the hypothesis that vessel wall trauma or endothelial damage may contribute to this phenomenon.[85]

Many agents used in cancer treatment are also associated with an increased risk of developing VTE, notably systemic therapy (eg, chemotherapy, protein kinase inhibitors, immunotherapy), hormone therapy with estrogenic compounds, and antiangiogenic agents. The association of systemic therapy with VTE in patients with cancer has been shown in several studies.[2,27,83,91,92] In one population-based case-control study, the ORs for development of VTE were 6.5 and 4.1 for patients with cancer receiving chemotherapy and those not receiving chemotherapy, respectively.[83] It was estimated that the annual incidence of VTE could be as high as 15% in patients with colorectal cancer treated with chemotherapeutic regimens.[92] There is also evidence that pre-chemotherapy thrombocytosis,[27,44,91] leukocytosis,[27] and hemoglobin level less than 10 g/dL[27,91] are predictive of VTE in patients receiving chemotherapy, although the association of anemia with VTE may be complicated by the use of erythropoiesis-stimulating agents (ESAs).

Exogenous hormonal compounds, such as selective estrogen receptor modulators (eg, tamoxifen, raloxifene for breast cancer) can lead to increased VTE risk.[93-97] Diethylstilbestrol phosphate used in combination with doxorubicin for the treatment of hormone-refractory prostate cancer was reported to increase VTE risk compared with doxorubicin alone.[98] Use of hormonal compounds, such as hormone replacement therapy[99,100] or hormonal contraceptive agents,[101-103] have also been associated with increased risk of developing VTE. VTE risks may vary between different formulations of combined oral contraceptives, depending on the type of progestogen used.[102,104,105] Additionally, progestin-only contraceptives do not definitively increase the risk of VTE in the general population, but may contribute to VTE risk in patients with multiple risk factors.[106]

Finally, the association between immunomodulating agents with antiangiogenic properties (eg, thalidomide in combination with doxorubicin and/or dexamethasone; lenalidomide in combination with dexamethasone) and increased incidence of VTE has been supported by multiple studies, most often in the context of treatment for multiple myeloma. For guidance on management of VTE in patients receiving treatment for multiple myeloma, refer to the NCCN Guidelines for Multiple Myeloma.[107-109] ESAs, which are used to treat anemia in patients with cancer, have also been associated with the development of VTE, and though they remain a reasonable option for supportive care, attention to the safety and risks/benefits must be considered.[3,91,110,111]

Risk Assessment in Outpatients with Cancer

A predictive model for chemotherapy-associated VTE was published by Khorana et al and has been reproduced and adapted in the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease as a risk assessment tool for outpatients with cancer (see *VTE Risk Assessment in Outpatients with Cancer* in the algorithm).[27] The association of VTE with five readily available clinical and laboratory variables (very high risk and high risk cancers associated with an increased risk of VTE, pre-chemotherapy platelet count ≥350 × 10^9/L,

hemoglobin <10 g/dL or use of red cell growth factors, pre-chemotherapy white blood cell count ≥11 × 10^9/L, and BMI ≥35 kg/m^2) was characterized in a derivation cohort of 2701 outpatients with cancer from a prospective observational study. A risk model was derived and validated in an independent cohort of 1365 patients from the same study. This risk assessment model (RAM) was externally validated by several retrospective and prospective studies; however, reported rates for developing VTE based on the three risk categories vary widely because of differences in patient populations and follow-up periods.[112-116] In the original study, the rate of symptomatic VTE in the derivation cohort was 0.8%, 1.8%, and 7.1% for the low-, intermediate-, and high-risk categories, respectively. In the validation cohort, the rates were 0.3%, 2%, and 6.7%, respectively.[27] An analysis of 1412 patients from phase I studies with a comparable duration of follow-up reported rates of 1.5%, 4.8%, and 12.9%, respectively, for each of the risk categories. This study also identified the risk assessment score to be the only predictor of VTE.[113] These rates are thus summarized and reported as part of the risk assessment tool for outpatients with cancer (see *VTE Risk Assessment in Outpatients with Cancer* in the algorithm).

The RAM by Khorana et al was also validated and extended by Ay and colleagues,[112] who identified D-dimer and P-selectin as additional discriminatory risk factors for VTE in ambulatory patients with cancer. However, these laboratory tests are not routinely measured in patients with cancer, so their inclusion in routine thrombotic risk assessment should be predicated upon their validation in future studies. In addition to the Vienna CATS RAM,[117] several other RAMs have been published, including the Protecht model,[118] CONKO score,[119] ONKOTEV score,[120] TiC-Onco score,[121] and COMPASS-CAT model.[122] A prospective multicenter study of the Khorana score, the Vienna CATS score, the Protecht score, and the CONKO score found that the discriminatory performance of these models was modest (C-statistics from 0.50–0.57).[123] This study has been criticized because only 25% (230 of 876) of participants were enrolled at the start of chemotherapy, the highest risk period for VTE. Thus far, only the Khorana risk score has been successfully used in prospective randomized trials of thromboprophylaxis to identify patients at risk.[124,125]

VTE Prophylaxis in Patients with Cancer

Clinical practice guidelines and data from numerous clinical trials have confirmed that the appropriate use of VTE prophylaxis is safe and effective.[126-130] Despite this, practice survey results indicate that VTE prophylaxis is perhaps still underutilized. The Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey noted that only 50% of surgical oncologists and 5% of medical oncologists routinely used VTE prophylaxis in patients with cancer.[131] Similar results were documented in the multinational IMPROVE and ENDORSE registries of patients hospitalized with medical illness, in which only 45% of patients with cancer received any form of VTE prophylaxis.[132,133] The NCCN Panel recommends identification of patients at risk for developing VTE and subsequent initiation of VTE prophylaxis based on inpatient/outpatient and medical/surgical oncology status.

The Panel does not recommend VTE prophylaxis to prevent CVAD-associated thrombosis in patients with cancer, as in several studies thromboprophylaxis has not been demonstrated to be effective.[134-137] However, a recent systematic review and meta-analysis of 12 randomized controlled trials evaluated the efficacy and safety of thromboprophylaxis in patients with cancer and a CVAD and found that VTE rates were significantly lower in patients receiving thromboprophylaxis compared to those not receiving thromboprophylaxis (7.6% vs. 13%; $P < .01$).[138] Additionally, rates of major bleeding were similar between the two arms (0.9% vs. 0.6%; $P = .87$).[138] In a recent subgroup analysis of the AVERT trial, the safety and efficacy of apixaban versus placebo as

thromboprophylaxis in 217 patients with cancer and a CVAD was assessed.[139] Rates of VTE were significantly lower in the apixaban arm (4.8% vs. 18.7%; *P* < .0001) and rates of major bleeding events were similar between the two groups, at 1.6% in the apixaban group versus 2.2% in the placebo group (*P* = .556).[139] These data suggest that thromboprophylaxis in patients with cancer and a CVAD may be safe and effective, though future studies are needed to corroborate these findings.

Inpatient VTE Prophylaxis

Population At Risk

Patients with cancer who are hospitalized are at high risk for VTE.[6] The NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease recommend VTE prophylaxis for all adult medical and surgical inpatients with a diagnosis of cancer, excluding those with basal/squamous cell skin cancer. Although multiple RAMs have been developed for patients hospitalized for medical and surgical care,[140-143] none have been validated in prospective management studies for patients with cancer who are hospitalized. Therefore, providers are encouraged to assess VTE risk factors, risks, and benefits of VTE prophylaxis, and to stress the importance of adherence to prevention programs prior to the initiation of VTE prophylaxis.

Adult patients with cancer who are hospitalized should undergo the following evaluation prior to the initiation of thromboprophylaxis: comprehensive medical history and physical examination (H&P), complete blood count (CBC) with platelet count and differential, prothrombin time (PT), activated partial thromboplastin time (aPTT), and comprehensive metabolic panel (CMP) including liver and kidney function tests. In addition to these components, initial workup for inpatient VTE prophylaxis should also include a VTE and bleeding risk assessment.

Initial Prophylaxis

If there is no contraindication to anticoagulation (see *Contraindications to VTE Prophylaxis* in the algorithm), prophylactic anticoagulation therapy is recommended (category 1). The recommendation assumes that ambulation in patients with cancer who are hospitalized is inadequate to reduce VTE risk. Preoperative dosing with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) for high-risk surgery (eg, abdominal/pelvic surgery) can be considered with or without an intermittent pneumatic compression (IPC) device.

Medical Oncology Inpatients

Anticoagulant options for VTE prophylaxis for patients hospitalized for medical oncology care are LMWHs (dalteparin[144-146] and enoxaparin[147-150]), fondaparinux,[151-153] (all category 1 for standard dosing) and UFH[152,154] category 2a for standard dosing. Recommendations are derived from patients with and without cancer hospitalized with a medical illness, most commonly CHF and acute or chronic respiratory disease, who undergo hospitalization for more than 6 days, have immobility or are on bed rest for 3 or more days, are ≥40 years of age, and have additional risk factors for VTE.[155] The Panel recommends that thromboprophylaxis is carried out for the duration of the hospital stay, for 6 to 14 days, or until the patient is fully ambulatory. A meta-analysis of nine randomized trials concluded that during anticoagulant prophylaxis with LMWHs, fondaparinux, or UFH, patients had significant reductions in any pulmonary embolism (PE) (relative risk [RR], 0.43; 95% CI, 0.26–0.71; absolute risk reduction, 0.29%) and fatal PE (RR, 0.38; 95% CI, 0.21–0.69; absolute risk reduction, 0.25%) compared with no treatment.[155]

Patients hospitalized for medical oncology care can continue apixaban/rivaroxaban prophylaxis if either option is already being used in the outpatient setting; however, apixaban/rivaroxaban should not be initiated in the hospital. Apixaban/rivaroxaban prophylaxis is also an option

for patients with a history of heparin-induced thrombocytopenia (HIT), for whom a heparin-based regimen is not feasible.

The PREVENT trial demonstrated that fixed-dose dalteparin (5000 units daily) reduced the incidence of VTE in patients with acute medical illness from 4.96% in the placebo group to 2.77% in the dalteparin group (RR, 0.55; 95% CI, 0.38–0.80; *P* = .0015).[146] A subgroup analysis of the PREVENT trial found that dalteparin reduced the incidence of symptomatic VTE, fatal PE, sudden death, or asymptomatic proximal DVT in both patients with obesity (2.8% vs. 4.3% with placebo; RR, 0.64; 95% CI, 0.32–1.28) and patients ≥75 years of age (4.2% vs. 8.0% with placebo; RR, 0.52; 95% CI, 0.31–0.87).[145] In the MEDENOX trial, enoxaparin 40 mg daily led to a significantly lower rate of VTE than placebo (5.5% vs. 14.9%; RR, 0.37; 97.6% CI, 0.22–0.63; *P* < .001) in patients with acute medical illness. In this study, a lower dose of enoxaparin (20 mg daily) did not have the same benefits.[148] Enoxaparin 40 mg daily was explored in two other studies among patients hospitalized with general medical illness and among patients with acute medical illness, respectively, and did not result in a reduction in death rate over placebo.[149,150]

The ARTEMIS trial demonstrated that fondaparinux 2.5 mg daily led to a significantly lower VTE rate compared with placebo among inpatients ≥60 years of age with acute medical illness (5.6% vs. 10.5%; RR reduction, 46.7%; 95% CI, 7.7%–69.3%).[153] In a randomized trial among patients with heart failure and/or chest infection, UFH 5000 units every 8 hours significantly lowered the frequency of DVT in the legs (26% vs. 4% with placebo; *P* < .01).[154] Multiple studies have shown that dosing UFH 3 times per day is more effective than twice daily in preventing DVT in general surgery and medical inpatients.[126,156,157]

Surgical Oncology Inpatients

It is well-established that low-dose heparin offers an effective way of preventing VTE and VTE-related deaths in the general population undergoing surgery, which also applies to patients with cancer.[126,128,158,159] Anticoagulant options for VTE prophylaxis for patients hospitalized for surgical oncology care are LMWHs (dalteparin,[144,160] enoxaparin[147,161]), fondaparinux,[130,151,162] UFH,[163-166] apixaban,[167] (only for patients with gynecologic cancers), and rivaroxaban[168] (only for patients following laparoscopic surgery for colorectal cancer). Recommended doses are derived from studies of patients undergoing planned, elective, open abdominal, or pelvic surgery for malignancy (operating room [OR] time >45 minutes, patients aged >40 years). Thromboprophylaxis should be carried out for at least 7 to 10 days or until the patient is fully ambulatory. It must be noted that UFH led to higher rates of HIT in patients hospitalized for surgical care as much as 10-fold compared to LMWHs like enoxaparin.[169]

The recommended prophylactic options are presumed to be equivalent, as studies have not clearly identified a particular anticoagulant regimen to have superior efficacy for the prevention of VTE in patients with cancer.[129,130,166,167,170,171] These comparisons have been made in patients undergoing major abdominal surgery receiving postoperative fondaparinux versus perioperative dalteparin,[130] first-generation LMWH versus UFH,[163,164] enoxaparin versus UFH,[165,166] dalteparin versus UFH,[171] and enoxaparin versus apixaban.[167] In particular, some of these studies focused exclusively on patients undergoing major surgeries for various malignancies, including gynecologic neoplasms and colorectal cancer.[166-168,171] In particular, apixaban prophylaxis should only apply to patients with gynecologic cancers, as data for safety and efficacy are currently only available for this specific population. In the supportive study, apixaban was initiated at investigator discretion once epidural anesthesia catheters were removed and continued for 28 days.[167] Similarly, rivaroxaban prophylaxis should only be applied to patients following laparoscopic surgery for colorectal cancer, as data for safety and efficacy are currently only available for this specific population.[168] In the supportive study, patients

who had undergone laparoscopic surgery for colorectal cancer received LMWH prophylaxis prior to a switch to rivaroxaban 10 mg daily starting 5 to 9 days following surgery and continued for a total of 3 weeks.

Renal Dosing

The doses for some anticoagulants might need to be adjusted in both patients hospitalized for medical oncology and surgical oncology care with renal disease. LMWHs are excreted via the kidney; due to pharmacologic and pharmacokinetic differences, there might be variation in the degree of accumulation of various LMWHs in patients with renal impairment.[172] In the TIMI-11A trial in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS), patients with renal impairment showed a reduction in enoxaparin clearance compared to those with normal renal function.[173] Other studies have supported this observation, noting that the inverse relationship between creatinine clearance (CrCl) and anti-Xa concentrations might be enoxaparin dose-dependent.[174,175] In contrast, dalteparin might not accumulate in patients with severe renal function.[176,177] LMWH accumulation can increase the risk of major bleeding; thus, its benefits must be carefully weighed against potential complications in this subset of patients.[178]

It has been suggested that a reduced dose of enoxaparin in patients with severe renal impairment led to fewer major bleeding events compared with standard doses.[178] Some studies, primarily in the setting of NSTE-ACS, comparing the efficacy and safety of enoxaparin versus UFH or enoxaparin versus fondaparinux have found no clinically meaningful difference between these options in patients with renal impairment.[179-182] The Panel recommends that in patients with severe renal disease (estimated CrCl <30 mL/min), dalteparin and fondaparinux should be avoided, apixaban should be cautioned as limited data exists for its use in this population, and UFH should be used instead.[172] If enoxaparin is used, it should be dosed at 30 mg subcutaneously (SC) once daily.[172] In those with moderate renal disease (CrCl 30–49 mL/min), fondaparinux should be used with caution.[151,152]

Dosing for Body Mass Index ≥40 kg/m^2

It has been suggested that fixed doses of anticoagulants might not be sufficient in patients with obesity.[183-185] Due to an inverse correlation between anti-Xa levels and body weight, patients with body weight extremes may not achieve adequate anti-Xa levels for maximal anticoagulant effectiveness.[186,187] Although there are limited to no data available to support dosing recommendations for patients with cancer and a BMI ≥40 kg/m^2, the NCCN Panel suggests consideration of increased prophylactic anticoagulation doses in patients hospitalized for medical and surgical oncology care in this weight range. The studies supporting these recommended dosing regimens have been carried out in non-oncology populations, primarily in patients undergoing gastric bypass surgery receiving prophylactic dalteparin (7500 units daily,[188,189] 5000 units every 12 hours,[190] or 40–75 units/kg daily[191]), enoxaparin (40 mg every 12 hours[183-185,192-199] or 0.5 mg/kg daily[200-204] for those weighing ≥40 kg/m^2 and 60 mg every 12 hours[203,204] for those weighing ≥50 kg/m^2), fondaparinux (5 mg daily[205]), and UFH (7500 units every 8 hours[196]). Prospective investigations of these dosing regimens are warranted to further ascertain their efficacy for patients with obesity and cancer.

Dosing for Actual Body Weight 25–50 kg

Available data suggest administration of standard VTE prophylaxis doses to patients weighing 25 to 50 kg may result in over-exposure and increased bleeding, but there are very limited data available to inform dose reduction strategies.[206, 207] Although there are limited data to support dosing recommendations for patients weighing 25 to 50 kg, the NCCN Panel suggests consideration of lower prophylactic doses in patients in this weight range hospitalized for medical or surgical oncology care. For dalteparin, the NCCN Panel suggests lowering prophylactic dose to 2500

units daily or 100 units/kg daily.[208,209] For enoxaparin, the NCCN Panel suggests lowering prophylactic dose to 30 mg daily for patients with an actual body weight of 41 to 50 kg and considering further reduction to 20 mg daily for patients weighing 25 to 40 kg.[207,208] For either weight range, use of enoxaparin should be avoided if CrCl is <30 mL/min. For prophylactic use of enoxaparin in patients weighing 25 to 50 kg, the NCCN Panel recommends the consideration of laboratory monitoring.[210] If dose escalation or de-escalation is required twice, consultation with hematology or a clinical anticoagulation pharmacy specialist is recommended.[210] Use of fondaparinux is contraindicated in those weighing <50 kg.[151] For UFH, the NCCN Panel suggests a prophylactic dose of 2500 units every 8 to 12 hours for those weighing <40 kg.[206]

Mechanical Prophylaxis

In case of contraindication to anticoagulation, mechanical prophylaxis is recommended (for contraindications to mechanical prophylaxis, see *Contraindications to VTE Prophylaxis* in the algorithm*).* Most data regarding the use of mechanical prophylaxis come from studies of patients hospitalized with surgical needs or stroke and have been extrapolated to the medical population.[211-213] According to one study, no difference was seen in the VTE rate in patients undergoing gynecologic oncology surgery receiving either low-dose heparin or IPC of the calf, even though the former was more frequently associated with postoperative bleeding complications.[211] Additionally, in contrast to graduated compression stockings (GCS), IPC significantly reduced DVT and was associated with a lower risk of skin complications.[213,214] However, IPC might not be an equivalent substitute for anticoagulants in all scenarios. Results from a retrospective study of patients who had undergone abdominal surgery for gynecologic cancers and received IPC showed that the incidence of PE in patients with cancer (4.1%) exceeded by 14-fold that in patients with benign disease (0.3%).[215] Additionally, results from a randomized trial (including a limited number of patients with cancer) suggest that addition of mechanical prophylaxis to pharmacologic prophylaxis in patients with critical illness may not reduce the incidence of DVT.[216] Other disadvantages of IPC include the potential for interference with ambulation and the need to keep the devices in place nearly continuously until patients are fully ambulatory.

GCS is an alternative mechanical prophylactic method that might provide benefit in VTE reduction, especially when combined with other therapies.[217] However, similar to IPC, it should not be relied upon as the sole method of VTE prophylaxis. First, many studies demonstrating its efficacy were conducted more than a decade ago and used fibrinogen uptake scans as a primary outcome measure—a now antiquated diagnostic method.[218] Additionally, a randomized controlled trial in patients undergoing hip surgery found that GCS did not provide significant additive protection against VTE in patients receiving fondaparinux.[219] Similarly, results from the CLOTS1 trial in patients with stroke found that GCS did not reduce the incidence of DVT and was associated with a 4-fold increase in the frequency of skin ulcers and necrosis.[214] In addition, the GAPS study noted that pharmacologic VTE prophylaxis was non-inferior to pharmacologic prophylaxis combined with GCS; therefore, GCS may be unnecessary in patients undergoing surgery who are receiving pharmacologic thromboprophylaxis.[220] Most of these trials either did not include patients with cancer or only included a small number of patients with cancer. Thus, IPC or GCS should only be used when prophylactic anticoagulants are contraindicated.

Overall, clinicians should discuss VTE prevention and the risks/benefits of pharmacologic and mechanical VTE prophylaxis with patients. Institutions are strongly encouraged to implement best practice programs to monitor provider and patient adherence to VTE prophylaxis.

VTE Prophylaxis Following Discharge and for At-Risk Ambulatory Patients with Cancer

Population At Risk

Certain groups of patients with cancer are known to remain at risk for VTE after discharge from the hospital. In a systematic review of VTE, 74% of patients were diagnosed in the outpatient setting, with a substantial portion having undergone surgery (23%) or hospitalization (37%) in the preceding 3 months.[221] Furthermore, in the @RISTOS observational cohort study of patients undergoing general, urologic, and gynecologic cancer surgeries, 40% of VTE events occurred later than 21 days postoperatively and greatly exceeded hemorrhagic complications as a cause of death.[13] The NCCN Panel identifies patients at risk for VTE to be adults with a diagnosis of cancer hospitalized for medical or surgical care, patients who received VTE prophylaxis during hospitalization, inpatients with cancer intended for discharge, and any outpatients at risk based on VTE risk assessment. Providers are encouraged to assess VTE risk factors, bleeding risk factors, and risks and benefits of VTE prophylaxis, and to stress the importance of adherence to prevention programs and patient preference prior to the initiation of VTE prophylaxis.

Prophylaxis

Medical Oncology Inpatients

Although there is a lack of consistent evidence to support extended outpatient prophylaxis in most populations of ambulatory patients with cancer, it is recommended for patients with multiple myeloma receiving highly thrombogenic regimens. For guidance on management of VTE in patients receiving treatment for multiple myeloma, refer to the NCCN Guidelines for Multiple Myeloma.

The Khorana risk score can be used to assess VTE risk in other patients receiving medical oncology care in the outpatient setting (excluding those with multiple myeloma, acute leukemia, myeloproliferative neoplasms, and primary/metastatic brain tumors) receiving/starting systemic therapy for their cancer (See *VTE Risk Assessment in Outpatients with Cancer* in the algorithm). Patients receiving hormonal therapy were excluded from the AVERT trial, but not the CASSINI trial; therefore, they should still be evaluated for VTE risk. Those with low risk for VTE (Khorana score <2) do not need routine VTE prophylaxis. Those with an intermediate or high risk of VTE (Khorana score ≥2) should consider anticoagulant prophylaxis for up to 6 months or longer, if risk persists. Anticoagulant options for VTE prophylaxis for ambulatory patients with cancer include direct oral anticoagulants (DOACs) (apixaban,[125] rivaroxaban[124]) and LMWHs (dalteparin[222] and enoxaparin[223]). The recommended dosing is derived from clinical trials of ambulatory patients with cancer at high thrombotic risk (>18 years of age, Khorana risk score for VTE >2, initiating a new course of chemotherapy) and are not included in product labeling. DOACs are primarily absorbed in the stomach, proximal small bowel (apixaban and rivaroxaban), and colon (apixaban only). Therefore, patients who have had significant resections of these portions of the intestinal tracts may be at risk for suboptimal absorption. See *Therapeutic Anticoagulation for VTE: DOACS: GI Considerations and Alternative Routes of Administration* in the algorithm. Importantly, patients with gastric and gastroesophageal tumors are at increased risk for hemorrhage with DOACs.

DOACs have demonstrated efficacy in preventing VTE in ambulatory patients with cancer.[124,125] Specifically, the rate of VTE significantly decreased with apixaban prophylaxis versus placebo (4.2% vs. 10.2%; hazard ratio [HR], 0.41; 95% CI, 0.26–0.65; $P < .001$).[125] Furthermore, rivaroxaban prophylaxis yielded a lower incidence of VTE compared to placebo (6.0% vs. 8.8%; HR, 0.66; 95% CI, 0.40–1.09; $P = .10$).[124] It is recommended that LMWHs be considered in patients with advanced unresectable or metastatic pancreatic cancer. In particular, dalteparin has been shown in this group of patients to significantly reduce the incidence of VTE from 23% to 3.4% ($P = .002$).[222] The CONKO-004 trial also

reported a significantly decreased rate of symptomatic VTEs in patients with pancreatic cancer in the enoxaparin group versus the observation group (6.4% vs. 15.1%; HR, 0.40; 95% CI, 0.19–0.83; *P* = .01).[223]

Other Dose Modifications for Medical Oncology Inpatients

In order to balance bleeding risk and VTE likelihood, the NCCN Panel recommends that prophylactic anticoagulation therapy be avoided in patients hospitalized for medical oncology care whose platelet counts are less than 50,000/µL. The NCCN Panel also recommends avoiding the use of prophylactic apixaban in patients hospitalized for medical oncology care weighing <40 kg (see *Contraindications to VTE Prophylaxis* in the algorithm).

Surgical Oncology Inpatients

The Panel recommends prophylaxis for up to 4 weeks postoperatively for patients who have undergone high-risk abdominal or pelvic cancer surgery.[13,215] These include patients undergoing surgery for gastrointestinal (GI) malignancies, those with a previous episode of VTE, anesthesia time greater than 2 hours, perioperative bed rest for 4 or more days, advanced-stage disease, and age >60 years.[13] Extended anticoagulant options for patients hospitalized for surgical oncology care are listed within *VTE Prophylaxis* in the algorithm. DOACs (apixaban[167] and rivaroxaban[168]) and LMWHs (dalteparin[160,223,224] and enoxaparin[161,167,224]) are recommended options for this group of patients. The recommended dosing is derived from studies of patients undergoing planned, elective, open abdominal, and pelvic surgery for malignancy (OR time >45 minutes, patients aged ≥40 years).

Multiple studies have demonstrated the clinical benefit of extended VTE prophylaxis for patients undergoing major surgeries.[160,161] In a study evaluating the optimal duration of dalteparin in patients after major abdominal surgery, the cumulative incidence of VTE was reduced from 16.3% with short-term thromboprophylaxis (7-day) to 7.3% with prolonged thromboprophylaxis (28-day) (RR reduction, 55%; 95% CI, 15–76; *P* = .012).[160] Another study in patients after abdominal or pelvic surgery for cancer showed that the rates of VTE were 12.0% in the placebo group and 4.8% in the enoxaparin group (*P* = .02) at 4 weeks, a significant difference that persisted at 3 months (13.8% vs. 5.5%; *P* = .01).[161] Data from a meta-analysis comparing prolonged thromboprophylaxis with LMWH versus control showed that the incidence of overall VTE after major abdominal or pelvic surgery was reduced from 13.2% in the control group to 5.3% in patients receiving out-of-hospital LMWH (Mantel-Haentzel [M-H] OR, 0.38; 95% CI, 0.26–0.54).[225]

As previously discussed, apixaban[167] and rivaroxaban[168] prophylaxis should only be applied to patients with gynecologic cancers and patients following laparoscopic surgery for colorectal cancer, respectively, as data for safety and efficacy are currently only available for these specific populations.

Renal Dosing

The rationale and guidance for anticoagulant usage in patients with renal disease is the same for patients with cancer who are receiving treatment while hospitalized or in an outpatient setting. Apixaban should be cautioned in patients with CrCl lower than 30 mL/min due to limited data in this population, but may be considered in extenuating circumstances, such as HIT. Rivaroxaban should be avoided in patients with a CrCl lower than 30 mL/min.[124,125]

Other Dose Modifications for Surgical Oncology Inpatients

The rationale and guidance for other dose modifications for patients hospitalized for surgical oncology care is the same for patients hospitalized for medical oncology care. Prophylactic anticoagulation therapy should be avoided in patients hospitalized for surgical oncology

care whose platelet counts are less than 50,000/µL and prophylactic apixaban should be avoided in patients hospitalized for surgical oncology care weighing <40 kg.

Contraindications to VTE Prophylaxis

Contraindications to Prophylactic Anticoagulation

Contraindications to anticoagulation can be relative or absolute, and temporary or permanent. Consideration of the degree of contraindication to anticoagulation and its duration are essential when evaluating the risks and benefits of anticoagulation (see *Contraindications to VTE Prophylaxis* in the algorithm).

It must be noted that patients with a recent history of bleeding associated with the central nervous system or a spinal lesion are at increased risk of anticoagulant-associated bleeding. Package inserts for LMWHs and fondaparinux include boxed warnings specifying that the risk for spinal or epidural hematoma resulting in long-term paralysis is increased when these anticoagulants are administered to patients receiving epidural or spinal anesthesia or those undergoing spinal puncture.[144,147,151] UFH should also be used with extreme caution in patients receiving spinal anesthesia or undergoing spinal puncture.[144,147,151] Anticoagulant prophylaxis is usually considered unsafe for platelet counts less than 50,000/µL.[226] Data on withholding or lowering doses of anticoagulants in the case of significant thrombocytopenia have been reported mostly for the treatment of VTE in retrospective cohort studies and case series of patients with hematologic malignancies.[227-229]

Of note, a prolonged aPTT is not considered a contraindication to anticoagulation therapy in patients with a lupus inhibitor or lupus anticoagulant, such as those diagnosed with APS. Antiphospholipid antibodies prolong the aPTT by interfering with the interaction between coagulation factors in the patient plasma sample and the phospholipids provided in the aPTT test reagent. Antiphospholipid antibodies have been associated with an increased risk for venous and arterial thromboembolism and adverse pregnancy outcomes.[230,231] Any patient who has experienced a thrombotic event and fulfills diagnostic criteria for APS should be considered for indefinite anticoagulation therapy.[231]

Specific use of LMWH or UFH for prophylactic anticoagulation is contraindicated in patients with current or previous HIT (see *Heparin-Induced Thrombocytopenia* in the algorithm).

Contraindications to Mechanical Prophylaxis

Whenever mechanical prophylaxis is employed, steps should be taken to ensure its proper use and continuous application (see *Contraindications to VTE Prophylaxis* in the algorithm). Mechanical prophylaxis should not be used in patients with an acute DVT. In addition, consideration of risks and benefits should be weighed in the presence of large hematomas. It has been established earlier that skin ulceration or wounds might be a particular concern for GCS, as opposed to IPC.[213,214] Other contraindications for GCS include arterial insufficiency and peripheral neuropathy (due to potential skin damage). In particular, it has been shown that the use of GCS on legs with impaired arterial flow can worsen ischemia.[232]

Evaluation and Treatment of VTE in Patients with Cancer

Evaluation and Treatment of Acute Superficial Vein Thrombosis

Even though few data are available on the incidence of acute superficial vein thrombosis (SVT) in patients with cancer, it has been estimated that the majority of SVT occur in the lower extremities (most often in the great saphenous vein) and external jugular veins.[233,234] SVT is more likely than DVT to be symptomatic, especially if occurring in the lower extremities. Intravenous (IV) catheter or peripherally inserted central catheter (PICC)-related SVT, sometimes referred to as infusion thrombophlebitis, is

often associated with a palpable tender cord along the course of the affected vein. PICC-related SVT has been estimated to occur in 29% of patients who are hospitalized requiring IV therapy for more than 5 days.[235]

Although SVT does not generally have the same implications for morbidity and mortality as DVT, the OPTIMEV study in patients with cancer reported that patients with isolated SVT had similar risks of death and DVT/PE recurrence to patients with DVT. These risks were higher than those in patients with SVT without cancer.[236] Furthermore, SVT and DVT can occur simultaneously and each predisposes the patient to the other condition.[233,236,237] In a retrospective cohort study to determine the risk of arterial and venous complications after a spontaneous SVT in the leg, DVT was reported as the only primary outcome to show a significant relationship with SVT (OR, 10.2; 95% CI, 2.0–51.6).[238] An extensive SVT in the saphenous vein can progress to involve the deep venous system at the saphenofemoral junction.[239-241] Such clots can precipitate PE.[240] An observational study of patients with symptomatic SVT reported that approximately 10% of patients developed thromboembolic complications at 3-month follow-up (DVT, PE, extension or recurrence of SVT) despite anticoagulation use in about 90% of individuals.[233] In particular, male sex, active solid cancer, personal history of VTE, and saphenofemoral involvement have been reported among the factors significantly associated with concurrent or future DVT/PE in patients with SVT.[237,242,243] In one study, the prevalence of malignancy was reported to be 18.8% among patients with SVT and concurrent DVT/PE, compared with 4.2% among those with isolated SVT ($P < .001$).[237]

Evaluation

Diagnosis of SVT is made primarily on the basis of clinical symptoms, which consist of pain, erythema, and tenderness involving a superficial vein in the extremity. Workup consists of comprehensive H&P, CBC with platelet count, PT, aPTT, liver and kidney function tests, as well as venous ultrasound (US) based on clinical judgment, especially if the possibility of proximal deep vein involvement exists. Progression of symptoms should be accompanied by follow-up imaging.

Treatment

For SVT involving the upper extremity (median, basilic, and/or cephalic veins), if a peripheral catheter is involved and is no longer indicated, the first step is to remove the catheter. For patients with SVT associated with a PICC line, catheter removal may not be necessary, especially if the patient is treated with anticoagulation and/or if symptoms resolve. Whether or not a catheter is involved, symptomatic treatment involving warm compresses, nonsteroidal anti-inflammatory drugs (NSAIDs), and elevation of the affected limb should be used as clinically indicated. Aspirin and NSAIDs should be avoided in patients with platelet counts less than 20,000 to 50,000/mcL or with severe platelet dysfunction. If there is symptomatic progression or progression on imaging, prophylactic dose anticoagulation is recommended. Anticoagulation at prophylactic doses, such as rivaroxaban 10 mg PO daily and fondaparinux 2.5 mg SC daily for 45 days, has been shown to be effective in some studies that included a limited number of patients with cancer.[244-246] Specifically, in a small randomized trial, rivaroxaban was determined to be effective and safe in the treatment of SVT in the legs when compared with placebo based on parameters such as treatment “failure” (defined in the study as requirement for an alternative, non-study anticoagulant); development of proximal DVT or PE; or requirement for surgery for SVT (1 vs. 5 patients; absolute risk reduction 9.0%; 95% CI, -22% to 5.9%) and leg pain improvement ($P = .011$) by 90 days.[245] In the much larger CALISTO trial, fondaparinux resulted in significantly reduced composite of death from any cause, symptomatic DVT/PE, symptomatic extension to the saphenofemoral junction, or symptomatic recurrence of SVT over placebo (0.9% vs. 5.9%; RR reduction 85%; 95% CI, 74–92; $P < .001$).[246] In the randomized, phase 3b SURPRISE trial, rivaroxaban was non-inferior to

fondaparinux for the treatment of SVT in terms of symptomatic DVT/PE, progression or recurrence of SVT, and all-cause mortality (3% vs. 2%; HR, 1.9; 95% CI, 0.6–6.4; *P* = .0025).[244]

Therapeutic dose anticoagulation should be considered if the clot is in close proximity (defined as within approximately 3 cm) to the deep venous system (see *Therapeutic Anticoagulation for VTE* in the algorithm).

For SVT involving the lower extremity (great and small saphenous veins), prophylactic dose anticoagulation is recommended for at least 6 weeks if SVT is greater than 5 cm in length or if SVT extends above the knee. Therapeutic dose anticoagulation is recommended for at least 3 months if the SVT is within 3 cm of the saphenofemoral junction (see *Therapeutic Anticoagulation for VTE* in the algorithm). Additionally, repeat US should be considered in 7 to 10 days if the SVT is less than 5 cm in length or below the knee. If progression is indicated on US, prophylactic dose anticoagulation should be considered.

Evaluation and Treatment of Acute Deep Vein Thrombosis

There have been a limited number of investigations on the long-term sequelae of DVT, especially in patients with cancer. A prospective study in patients with symptomatic DVT showed that the cumulative incidence of recurrent VTE was 17.5% after 2 years of follow-up, 24.6% after 5 years, and 30.3% after 8 years. The cumulative incidence of the post-thrombotic syndrome (PTS), a frequent complication of DVT, was 22.8%, 28.0%, and 29.1% after 2, 5, and 8 years, respectively.[247] Some other studies have examined the prognostic significance of different subtypes of DVT. Data from OPTIMEV and the Cleveland Clinic examining isolated cancer-associated distal DVT and isolated proximal DVT individually came to the conclusion that the two conditions had similar prognoses; however, cancer-associated isolated distal DVT had dramatically poorer prognosis compared to those without cancer.[248,249] The risk of VTE recurrence for patients with isolated distal DVT was reported in another study to be as high as 15.3% despite anticoagulant therapy in 99% of patients.[250] A prospective, multicenter cohort study of 3032 patients who had venous ports implanted reported the incidence of catheter-related thrombosis with or without PE at 12 months to be 3.8%.[251] Recurrent VTE, bleeding complications, and mortality rates among patients with upper-extremity DVT were reported in a systematic review to average 5.1%, 3.1%, and 24% in prospective studies and 9.8%, 6.7%, and 35% in retrospective studies, respectively.[252] According to data from the RIETE Registry, at presentation, patients with arm DVT often have less clinically overt PE than those with lower-limb DVT (9.0% vs. 29%; OR, 0.24; 95% CI, 0.18–0.33), but their 3-month outcome is similar. Among patients with arm DVT, those with cancer had an increased incidence of major bleeding, recurrent VTE, and death compared to those with catheter-related DVT.[253]

Evaluation

Classic clinical symptoms are not present in all cases of acute DVT; however, clinical suspicion is warranted in case of swelling of the unilateral extremity; heaviness in the extremity distal to the site of the venous thrombosis; pain in the extremity; unexplained persistent calf cramping; swelling in the face, neck, or supraclavicular space; and catheter dysfunction (if a catheter is present). DVT may also be an incidental finding. The most common presenting symptoms of DVT presented in the MASTER registry were extremity edema, pain, and erythema, which were observed in 80%, 75%, and 26% of patients with DVT, respectively.[254] Diagnosis of DVT in adults with cancer should be tempered by an increased level of clinical suspicion on presentation of any clinically overt signs/symptoms that could represent an acute DVT. For patients for whom there is a high suspicion of DVT that do not have contraindications to anticoagulation, early initiation of anticoagulation should be considered while awaiting results from imaging studies.

Workup consists of comprehensive medical H&P, CBC with platelet count, PT, aPTT ± fibrinogen, and liver and kidney function tests. Venous US is the preferred imaging method for the initial diagnosis of DVT and has been shown to detect asymptomatic DVT of the lower extremities in 34% of patients who are non-ambulatory with advanced cancer in a small prospective study.[255] It has been reported that two normal US examinations obtained 1 week apart can be used to exclude progressive lower-extremity DVT.[256]

In cases of negative or indeterminate US results following repeat venous imaging and a continued high clinical suspicion of DVT, other venous imaging modalities are recommended and include repeat venous US, contrast-enhanced CT venography (CTV), and magnetic resonance venogram (MRV) with contrast. CTV has been reported to be as accurate as US, particularly in diagnosing femoropopliteal DVT.[257,258] This method might be superior to US in detecting thrombus in large pelvis veins and the inferior vena cava (IVC).[258] However, this method requires relatively high concentrations of contrast agent. Conversely, MRV with contrast allows enhanced venous signal and was reported in a meta-analysis to have higher sensitivity for proximal DVT than distal DVT, with equivalent sensitivity and specificity to US for diagnosing DVT.[259] Some prospective studies suggested that MRV was more sensitive than US in the detection of lower-extremity DVT,[260] and extension of DVT,[261] and might be a valuable technique for assessing iliofemorocaval venous thrombosis.[262] Drawbacks to this method include higher cost, longer imaging times, and limited availability in some practice settings.[263] Standard invasive venography, once considered the gold standard for DVT diagnosis, has largely been replaced by less invasive methods such as US and MRV, which provide equivalent accuracies.[262-264] Venography remains an important imaging modality when performed in conjunction with pharmacomechanical thrombectomy/thrombolysis. If all imaging tests are negative for DVT, reassurance should be provided and symptoms should be further evaluated for other causes.

The risk factors for upper-extremity DVT differ from those for lower-extremity DVT, as upper-extremity DVT is frequently related to the presence of a CVAD[82,84,265] and associated with insertion attempts, previous insertion, or catheter placement.[85,266] It must be noted that neither a clot within a catheter nor a simple fibrin sheath around a catheter represents a DVT. Clinical suspicion of catheter-related DVT is warranted when a patient presents with unilateral limb swelling, pain in the supraclavicular space or neck, or with catheter dysfunction. Workup for catheter-related DVT consists of venous US, CTV with contrast, MRV with contrast, and x-ray venogram with contrast. Venous US has been reported to accurately detect DVT in the peripheral upper extremity, in the brachial, distal subclavian, and axillary veins. In patients with catheters with isolated flow abnormalities, contrast venography may be preferred.[84,267] Invasive venography for the detection of upper-extremity DVT should be performed through a peripheral vessel in the extremity, although venous access may be limited by edema. If no DVT is identified, symptoms should be evaluated for other causes and further diagnostic imaging/testing should be considered if initial testing is unrevealing or clinical suspicion remains high.

Treatment

DVT Involving the Proximal Lower Extremity

For patients with thrombosis in the pelvic and iliac veins, the IVC, and the femoral/popliteal veins, anticoagulation is recommended if no contraindication is present. Catheter-directed therapy (pharmacomechanical thrombolysis or mechanical thrombectomy) can be considered in appropriate candidates. Appropriate candidates for catheter-directed therapies include: patients at risk for limb loss (eg, phlegmasia cerulea dolens), patients with central thrombus propagation in

spite of anticoagulation, and those with severely symptomatic proximal DVT. If deemed appropriate for thrombolysis, the choice of regimen for thrombolysis should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues (see *Thrombolytic Agents* and *Contraindications to Thrombolysis and Indications for Thrombolysis* in the algorithm). GCS can be considered for symptom management if therapeutic anticoagulation is tolerated. Since the SOX trial reported that GCS did not reduce the incidence of PTS after a first proximal DVT, routine prescription of GCS after DVT for the purpose of reducing PTS is not recommended.[268] If a contraindication to anticoagulation is present, an IVC filter, preferably retrievable, is recommended, as long as contraindication persists or is likely to recur. Patients should be re-evaluated regularly for change in the status of contraindication to anticoagulation until the contraindication is resolved, at which point anticoagulation should be initiated and IVC filter removed.

DVT Involving the Distal Lower Extremity

For patients with thrombosis in the peroneal, anterior and posterior tibial, and muscular (soleus and gastrocnemius) veins, anticoagulation is recommended unless contraindication is present. If a contraindication is present, follow-up with serial US is recommended. If US indicates progression of DVT to the popliteal vein, treatment should be initiated as outlined previously. Otherwise, local progression (but not to proximal deep vein) can be closely monitored for any change in status, in terms of both progression and contraindication to coagulation. If there is no progression of DVT, the patient should be followed as clinically indicated.

DVT Involving the Upper Limb/Chest

For patients with thrombosis in the brachiocephalic, subclavian, axillary, internal jugular, and brachial veins, and the SVC, anticoagulation and catheter-directed therapy in appropriate candidates should be prescribed with the same caveats as DVT involving the proximal lower extremity. GCS are rarely considered in this setting. In the case of a contraindication to anticoagulation, patients should be followed until contraindication resolves or DVT progression occurs, at which point re-evaluation of the risk/benefit of anticoagulation is recommended (see *Elements for Consideration in Decision Not to Treat* in the algorithm).

Catheter-Related DVT

For patients with catheter-related DVT, in the absence of contraindication, anticoagulation is recommended. Anticoagulation without catheter removal is the preferred option for initial treatment, even for patients with asymptomatic DVT, provided that the catheter is necessary, functional, and free of infection. Catheter removal should be considered otherwise. Anticoagulation is continued for at least 3 months. If the catheter remains in place, then anticoagulation should continue as long as the catheter is present. However, it is important to recognize that there is very little clinical evidence regarding the appropriate duration of anticoagulation for catheter-associated DVT. The recommended duration of therapy also depends on tolerance of anticoagulation, response to anticoagulation, and catheter status. Longer duration of anticoagulation can be considered in patients with catheters with poor flow, persistent symptoms, or unresolved thrombus. Shorter duration of anticoagulation can be considered if the clot or symptoms resolve in response to anticoagulation and/or catheter removal. Catheter-directed thrombolysis (CDT) is rarely considered with the same caveats as DVT involving the proximal lower extremity. In the case of contraindication to anticoagulation, catheter removal is recommended, or the patient should be followed with serial imaging until contraindication is resolved, at which point anticoagulation is recommended for at least 3 months. Otherwise, the patient should be re-evaluated for risk/benefit of anticoagulation.

Anticoagulation for DVT

Several studies have supported the use of anticoagulation specifically for the treatment of DVT in the non-cancer population. A meta-analysis comparing UFH and LMWHs found that LMWHs reduced mortality rates over 3 to 6 months of patient follow-up (OR, 0.71; 95% CI, 0.53–0.94; *P* = .02), as well as major bleeding complications (OR, 0.57; 95% CI, 0.33–0.99; *P* = .047), even though the absolute risk reduction was small and not statistically significant (0.61%; 95% CI, -0.04% to 1.26%; *P* = .07).[269] This comparison was also made in a systematic review that compiled five studies enrolling a total of 1636 patients with proximal (above the knee) DVT. A sub-analysis of these trials showed statistically significant reductions favoring LMWH in three areas: thrombotic complications; major hemorrhages; and overall mortality.[270] Data from the Cancer-DACUS study suggest that LMWH for up to 6 months is just as effective as a 12-month course in preventing recurrence for patients with cancer-associated DVT of the lower limbs and subsequent residual vein thrombosis.[271] The NCCN Panel recommends a minimum anticoagulation duration of 3 months. The presence of active cancer, ongoing cancer treatment, an unprovoked DVT, or persistent thrombosis are reasons to consider continuation of anticoagulation. In a systematic review of 11 studies involving 3019 patients with cancer-associated VTE, both rates of VTE recurrence and major bleeding were assessed to investigate the risk/benefit of continuing anticoagulation beyond 6 months.[272] It was noted that VTE recurrence remains common between 6 to 12 months after a cancer-associated VTE, though the risk is lower in this time frame compared to the first 6 months following the event. For example, this study highlights the Hokusai-VTE Cancer study, which revealed a VTE recurrence rate of 7.6% in the first 6 months compared to 2.1% between 6 to 12 months in patients with cancer receiving extended anticoagulant therapy.[272,273] This systematic review also noted an acceptable safety profile of extended anticoagulation between 6 to 12 months following a cancer-associated VTE, with major bleeding rates between 1% to 4% in patients receiving anticoagulation compared to 0% to 1% in those not receiving anticoagulation.[272]

No randomized controlled trials have reported the effects of particular therapeutic strategies on outcomes of catheter-related DVT. In one prospective study, patients with catheter-related thrombosis received anticoagulants alone, anticoagulants and catheter removal, or no treatment; none had recurrent thrombosis or symptomatic PE.[85] Another study demonstrated that anticoagulation with dalteparin followed by warfarin was not associated with recurrent VTE or line removal due to infusion failure or recurrence/extension of DVT.[157] In the Catheter 2 study, treatment with rivaroxaban for 12 weeks showed preservation of line function at 100% by study endpoint. The risk of recurrent VTE was 1.43%, with one episode of fatal PE.[274] It must be noted that these studies enrolled a small number of patients and thus, their results should be interpreted with care.

The NCCN Panel recommends that the effectiveness of anticoagulation in patients with established DVT be monitored clinically during and after treatment. Follow-up examinations and imaging evaluations allow physicians to detect clot progression in patients undergoing anticoagulation, detect DVT recurrence after successful treatment, and identify chronic injury to the venous system. These studies should be performed in response to symptoms.

Evaluation and Treatment of Pulmonary Embolism

Evaluation

Clinical suspicion of PE depends on the presence of current DVT or a recent history of DVT, or presentation of any clinically overt signs or symptoms of PE, including unexplained shortness of breath, chest pain—particularly pleuritic chest or back pain—tachycardia, apprehension or tachypnea, syncope, and hypoxemia. In the prospective multicenter

MASTER registry, the most common presenting symptoms of PE were dyspnea, pain, and tachypnea, which were present in 85%, 40%, and 29% of patients with PE, respectively.[254] In the International Cooperative Pulmonary Embolism Registry, the most common symptoms at PE diagnosis were dyspnea (82%), chest pain (49%), cough (20%), syncope (14%), and hemoptysis (7%).[275] PE may also be an incidental finding.

Workup consists of a comprehensive medical H&P, CBC with platelet count, PT, aPTT, liver and kidney function tests, N-terminal prohormone B-type natriuretic peptide (NT-proBNP) evaluation, chest x-ray, and electrocardiogram (ECG). In cases with a high suspicion of PE and no contraindications, early initiation of anticoagulation should be considered while waiting for imaging results. Chest x-rays may not be necessary if a CT angiography (CTA) is planned.

The preferred imaging technique for the initial diagnosis of PE is CTA, which allows for indirect evaluation of pulmonary vessels. Advantages of this method include accurate imaging of mediastinal and parenchymal structures; accurate visualization of emboli in many regions of the pulmonary vasculature; ability to be performed in conjunction with indirect CTV, which can detect DVT[276,277]; and ability to detect signs of right ventricular (RV) enlargement, which can be used in assessing risk for adverse clinical outcomes.[278,279] Disadvantages of CTA include the associated radiation exposure and the need for large amounts of IV contrast, particularly when CTA is followed by indirect CTV.[276]

Alternative imaging modalities used for the diagnosis of PE include: 1) X-ray pulmonary angiography with contrast, which is infrequently used today because of its invasive nature. When used, this method is often combined with clot extraction or thrombolytic therapy; 2) Magnetic resonance angiography (MRA) with contrast; and 3) Ventilation-perfusion (VQ) scan if CTA is contraindicated (eg, renal insufficiency, contrast allergy refractory to anaphylaxis prophylaxis, and pregnancy, since a VQ scan is associated with less fetal radiation exposure than CTA). In a randomized, single-blind, noninferiority study, VQ scans identified significantly fewer PE than CTA (14.2% vs. 19.2%; 95% CI, 1.1%–8.9%). However, there was no difference in the number of symptomatic VTE that occurred within 3 months in patients in whom PE was considered to be excluded (CTA 0.4% vs. VQ scan 1.0%; 95% CI, 1.6%–0.3%).[280] Patients >70 years of age are more likely than younger patients to be diagnosed with an intermediate-probability VQ scan result.[281] Both intermediate- and low-probability VQ scan results lack diagnostic utility and should be considered indeterminate. In the setting of high clinical suspicion for PE, a high-probability VQ scan is diagnostic.

Clinical Prediction Tools for PE

Even though Wells criteria and D-dimer testing have been shown to be useful in the diagnosis of DVT/PE, with comparable results to conventional radiologic imaging strategies, patients with cancer made up a small number of patients in these studies.[282,283] One study using the Wells criteria and D-dimer testing in the diagnosis of PE noted the performance of this strategy was comparable in patients with and without cancer; however, the number of patients with symptomatic VTE during follow-up was 4-fold higher than that in the total study population (2% vs. 0.5%). In addition, the number needed to test in order to rule out PE in one patient was 3-fold higher in patients with cancer compared to patients without cancer.[284] Results of a large prospective study of patients with suspected DVT in whom DVT had been excluded on radiologic testing showed that high D-dimer levels were present in a large percentage of patients with cancer.[285] Other studies have supported that Wells criteria and D-dimer testing were less predictive of PE in patients with cancer.[286-289] Therefore, most patients with cancer undergo imaging to exclude a diagnosis of PE.

The Panel recommends risk stratification for patients with PE.[290,291] Cardiac biomarkers such as troponin, which is released due to

endomyocardial damage, and NT-proBNP, as well as cardiac imaging results (ie, RV enlargement on echocardiography, CTA) and the presence of residual DVT on lower-extremity duplex imaging have demonstrated high predictive values for overall mortality in patients with PE.[275,278,292-299] NCCN recommends the use of these tools, together with clinical judgment, in assessing risks in patients with PE. It has been demonstrated that combining the results from at least two of the above tests improved the specificity and positive predictive value compared with the use of individual tests alone in identifying patients at high risk for PE-related mortality.[290] Since the 3-month mortality rate of patients with PE has been reported to be 15%,[275] outpatient care of PE should be limited to individuals at low risk as identified by clinical, laboratory, and imaging assessment.

Clinical risk assessment tools have been developed to assess the advisability of outpatient treatment and intensity of initial follow-up and treatment. Generic scoring systems such as the Pulmonary Embolism Severity Index (PESI),[300,301] the Hestia criteria,[302] and the Geneva Prognostic Score (GPS)[303] are validated tools that can be used to determine risk for an adverse outcome associated with PE. However, it has been suggested that the PESI score might not be useful in patients with cancer.[304] On the other hand, scoring systems such as the Computerized Registry of Patients with Venous Thromboembolism (RIETE), POMPE-C, as well as the EPIPHANY index, predict PE-related mortality risk and have been specifically developed for and externally validated in patients with cancer.[305-309] One study postulated that cancer-specific prognostic scores performed better than generic scales in estimating PE mortality in patients with cancer.[310] Other comparative studies, however, have not found such an association.[311,312] Therefore, these scores can be included as an adjunct risk assessment tool, but should not be substituted for the above risk-stratification procedures until data from large, prospective trials in patients with cancer are available.

Treatment

Once a diagnosis of PE is made, anticoagulation therapy is recommended for all patients with acute PE who do not have a contraindication to such therapy,[313] including patients with incidental or subsegmental PEs. Anticoagulation should be continued after acute management of PE unless there is extension of VTE or new VTE while on recommended therapy (see *Progression or New Thrombosis on Therapeutic Anticoagulation* in the algorithm). Outpatient care should be considered for PE in patients at low risk. After assessment of the cancer status, the physician should consider the use of systemic thrombolysis or CDT or embolectomy for hemodynamically unstable PE in patients with lower bleeding risk.[313,314] Hemodynamically unstable PE is defined as acute PE with sustained hypotension (systolic blood pressure <90 mmHg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock).[315] Rescue thrombolysis or thrombectomy can be considered in patients with hemodynamically stable PE who deteriorate despite anticoagulation.[313,314] For patients with hemodynamic compromise, venoarterial extracorporeal membrane oxygenation (VA-ECMO) can be considered to optimize end-organ function as a bridge to recovery or intervention.[316]

In patients with a contraindication to anticoagulation, an IVC filter, preferably retrievable, should be strongly considered with or without embolectomy. The patient should be closely followed for a change in clinical status that would allow anticoagulation to be instituted. Permanent filters should only be considered for rare patients with chronic comorbidities or with permanent contraindication to anticoagulation. Filter placement should be considered if anticoagulation treatment is not possible within 1 month of symptomatic VTE onset.[317]

Embolectomy may be considered in patients with hemodynamic instability who have contraindications to thrombolytic therapy or those who remain unstable following thrombolysis (category 2B).[313,314] Selection of thrombolytic agents and thrombectomy devices should be made based on local expertise and experience.

Thrombolytic Therapies/Thrombectomy for PE

Overall, favorable risk-versus-benefit profiles have not been clearly identified for systemic or CDT/catheter-directed thrombectomy for patients who are hemodynamically stable. In the MAPPET-3 trial, the addition of thrombolysis with alteplase to standard heparin treatment was associated with significantly decreased incidence of in-hospital mortality and clinical deterioration requiring treatment escalation (11% vs. 25%; *P* = .006). However, this difference was due to a higher incidence of clinical instability in the placebo group, as in-hospital mortality rates were similar between treatment groups.[318] The clinical endpoints and other aspects of the design of this trial have also been criticized.[319,320] The PEITHO study, which included patients with cancer, reported significantly less death or hemodynamic decompensation (composite outcome) in patients receiving tenecteplase plus heparin versus placebo plus heparin (2.6% vs. 5.6%; OR, 0.44; 95% CI, 0.23–0.87; *P* = .02). There was no difference in death between the two groups (1.2% vs. 1.8%; *P* = .42), but there was significantly more frequent extracranial bleeding and stroke in the tenecteplase group (6.3% vs. 1.2%; *P* < .001 and 2.4% vs. 0.2%; *P* = .003, respectively).[321] This benefit-to-risk profile is corroborated by results from a meta-analysis whereby the use of thrombolytic therapy was associated with lower all-cause mortality (OR, 0.53; 95% CI, 0.32–0.88) but higher risk of major bleeding (OR, 2.73; 95% CI, 1.91–3.91).[322] Other meta-analyses reported no significant benefit with thrombolytic therapy compared with heparin alone in terms of recurrent PE or death, particularly for patients with hemodynamically stable PE.[323-327] In the case of CDT, grade II clot lysis was achieved in a similar proportion of patients with cancer and those without cancer with no significant difference in bleeding risk in a retrospective consecutive case series.[328] Reports from several studies evaluating the use of pulmonary embolectomy provide support for the use of this procedure in patients with hemodynamically stable or unstable acute PE characterized by RV dysfunction.[329-331] It must be noted, however, that none of these studies specifically address patients with cancer. In a small, randomized trial, US-assisted CDT was shown to reverse RV dilatation in patients with hemodynamic stability. For PE, however, there was no difference in mortality or recurrent VTE.[332] Larger randomized studies with clinical outcomes are needed to confirm the benefits of this approach.

IVC Filters for DVT/PE

IVC filter usage has increased substantially in the last few decades; however, due to the lack of randomized controlled trials evaluating their safety and efficacy, no particular filter should be considered superior.[333-335] Moreover, IVC filters have been associated with an increased risk for recurrent DVT.[336-338] The pivotal PREPIC trial, which compared permanent IVC filters in conjunction with anticoagulation with anticoagulant therapy alone, did not test the efficacy of IVC filters in the usual clinical scenario in which they are used, which is in patients without concomitant anticoagulation.[336,337] In the PREPIC II study of retrievable IVC filters, there was no difference in recurrent PE between patients treated with anticoagulation and filters compared with anticoagulation alone (3% vs. 1.5%; RR, 2.0; 95% CI, 0.51–7.89).[339] In a multicenter trial of IVC filters in patients severely injured following major trauma, filters did not reduce the incidence of symptomatic PE or death compared to no filter (13.9% vs. 14.4%; HR, 0.99; 95% CI, 0.51–1.94; *P* = .98).[340] Until further data are available, IVC filter placement should only be considered for patients with acute proximal lower-extremity DVT or PE who have absolute contraindications to anticoagulation. The benefit of placing an IVC filter in the absence of a lower-extremity IVC or pelvic DVT is unclear. IVC filters

should only be used in patients in whom the benefits outweigh the risks, and filters should be retrieved as soon as possible.

Evaluation and Treatment of Splanchnic Vein Thrombosis

Splanchnic vein thrombosis (SPVT) refers to a relatively rare group of VTE within the splanchnic vasculature comprising the hepatic (characteristic of Budd-Chiari syndrome), portal, mesenteric, and splenic veins. The presence of SPVT has been associated with decreased survival in patients with cancer. In particular, portal vein thrombosis has been reported in about 20% to 30% of patients with hepatocellular carcinoma at the time of diagnosis and is an independent predictor of poor survival.[341-344] Thrombotic events may occur in multiple segments or in isolated segments within the splanchnic vasculature, with isolated portal vein thrombosis being the most common.[345,346] Thrombosis in multiple segments has been associated with significantly decreased 10-year survival rate compared with thrombosis in a single/isolated segment (48% vs. 68%; $P < .001$).[346] In a retrospective study in patients with extrahepatic portal vein thrombosis, a concurrent diagnosis of mesenteric vein thrombosis was significantly predictive of decreased survival, as well as the presence of cancer.[347] Several smaller retrospective studies have also reported adverse outcomes for patients with mesenteric vein thrombosis, with a 30-day mortality rate of 20%.[348,349] Thromboses in the mesenteric vein can lead to intestinal infarction, which is frequently life-threatening.[348,349] Intestinal infarction has been reported in 30% to 45% of these patients at the time of diagnosis, of which up to 19% were fatal.[345,348]

Risk Factors

Risk factors for SPVT relevant to patients with cancer include recent abdominal surgery (eg, splenectomy),[350-353] abdominal mass, pancreatitis,[354] cirrhosis,[347] paroxysmal nocturnal hemoglobinuria (PNH),[355] myeloproliferative disorders,[356] and *JAK2V617F* mutation with or without overt myeloproliferative disorders.[357,358] In addition, the use of exogenous estrogen, such as oral contraceptives or hormone replacement therapy, has also been linked to SPVT.[347,359] The presence of cancer itself, especially abdominal malignancies, is both a common risk factor for SPVT and a frequent cause of death in patients with SPVT.[346-349] The *JAK2V617F* mutation is detected in a high proportion of patients with polycythemia vera, essential thrombocythemia, and primary myelofibrosis, and now constitutes a part of both diagnostic and prognostic assessment of these myeloproliferative disorders.[360-363] In the absence of overt myeloproliferative disorders, *JAK2V617F* has been detected in approximately 20% to 40% of patients with SPVT.[364-366] Mutations in exon 12 of *JAK2* may also be associated with SPVT in patients without *JAK2V617F*.[367] PNH is a rare acquired clonal hematopoietic disorder resulting in chronic hemolysis, and has been associated with a high propensity for venous thrombosis, particularly in the splanchnic vasculature.[368,369] In a *post hoc* analysis of patients with Budd-Chiari syndrome, those who had underlying PNH more frequently presented with additional SPVT at baseline compared to patients without PNH (47% vs. 10%; $P = .002$).[370]

Evaluation

Clinical manifestations of acute SPVT typically include abdominal pain or mid-abdominal colicky pain, abdominal distention, rebound tenderness, guarding, fever, anorexia, nausea, vomiting, diarrhea, GI bleeding, hepatomegaly, and ascites.[371-375] SPVT may also be an incidental finding. Rebound tenderness, guarding, and fever may be indicative of progression to bowel infarction.[371] Chronic SPVT may often be asymptomatic due to formation of collateral veins,[371,372,376,377] although abdominal pain, nausea, vomiting, anorexia, lower-extremity edema, and splenomegaly have been reported with chronic presentations.[372,375] Weight loss, abdominal distension, and postprandial abdominal pain may also be associated with chronic mesenteric vein thrombosis.[376] Presence of

splenomegaly and/or esophageal varices is a sign of portal hypertension associated with chronic SPVT, and complications may arise due to bleeding from varices.[372,376,378,379] Acute SPVT is associated with presenting signs or symptoms of up to 8-week duration, with no portal cavernoma and no signs of portal hypertension.[373]

The diagnostic evaluation includes medical H&P, based on which further diagnostic testing involving both laboratory testing and imaging can be considered. Additional workup consists of CBC with platelet count and differential, PT, aPTT, basic metabolic profile, hepatic profile, and serum lactate levels. Imaging modalities include abdominal duplex US, CT abdomen/pelvis with contrast, and abdominal MRI with contrast. For suspected cases of SPVT involving the hepatic and/or portal veins, duplex ultrasonography is considered the initial choice of imaging.[365,377-379] CT abdomen/pelvis with contrast is the preferred imaging study for patients with suspected mesenteric vein thrombosis as duplex US can be limited by overlying bowel gas.[371,379] In the case of negative or indeterminate imaging results, other causes should be investigated. If there is continued suspicion of SPVT, repeat imaging is recommended, with consideration of consultation with radiology to optimize imaging techniques/modality.

Treatment

Acute Hepatic Vein Thrombosis

Acute hepatic vein thrombosis is defined by the presence of symptoms for 8 weeks or less. Patients with no contraindication to anticoagulation should undergo anticoagulant therapy with hepatology evaluation. Catheter-directed pharmacomechanical thrombectomy with or without transjugular intrahepatic portosystemic shunt (TIPS) should be considered (see *Thrombolytic Agents* and *Contraindications to Thrombolysis and Indications for Thrombolysis* in the algorithm). TIPs should be considered as one of the treatment options for patients with SPVT and severe symptoms or evidence of portal hypertension. If thrombectomy expertise is not available, consultation with a tertiary medical center is recommended. The decision to offer thrombolysis should be based on local availability/expertise, location of thrombus, and risk of bleeding. The choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues. In the presence of contraindications to anticoagulants, patients should undergo hepatology evaluation, be considered for TIPS or surgical shunt, and regularly be reassessed for contraindications to anticoagulation.

Chronic Hepatic Vein Thrombosis

Chronic hepatic vein thrombosis is defined by the presence of symptoms for more than 8 weeks. Patients should undergo hepatology evaluation and be considered for TIPS (in the setting of portal hypertension) or surgical shunt and anticoagulation. It must be noted that risks/benefits of anticoagulation must be carefully weighed in patients with chronic thrombosis. The duration of anticoagulation should be at least 6 months for triggered events (eg, postsurgical) and indefinite if active cancer, persistent thrombophilic state, or unprovoked thrombotic event is present.

Acute Portal, Mesenteric, and/or Splenic Vein Thrombosis

An acute thrombotic event is defined by the presence of symptoms for 8 weeks or less, with no cavernous transformation/collaterals and no signs of portal hypertension. Anticoagulation and catheter-directed pharmacomechanical thrombectomy with or without TIPS is recommended for patients with no contraindication to anticoagulation with the same considerations as in those with acute hepatic vein thrombosis. Additionally, acute thrombosis involving the mesenteric veins is associated with high risks of intestinal infarction, which is life-threatening and requires immediate surgery to resect necrotic sections of the bowel.[345,348] In the presence of contraindication to anticoagulants, patients should regularly be reassessed for contraindications to anticoagulation, similar to those

with hepatic vein thrombosis, as well as GI/surgery evaluation and subsequent surgery if bowel infarction is present.

Chronic Portal, Mesenteric, and/or Splenic Vein Thrombosis

Chronic thrombosis is defined by the presence of symptoms for longer than 8 weeks or cavernous transformation/collaterals or signs of portal hypertension at the time of diagnosis. Patients should be considered for GI evaluation and surgery if bowel infarction is present, β blockers, variceal banding or sclerosis, and TIPS or surgical shunt and anticoagulation with the same considerations as those with chronic hepatic vein thrombosis.

Anticoagulation for SPVT

Anticoagulation as initial and long-term therapy in patients with SPVT has been reported in several studies.[345,356,374,380] In a study of patients with acute SPVT primarily treated with anticoagulation (LMWH for 7–10 days followed by oral anticoagulation for 6 months), 45% of patients experienced complete recanalization. Patients requiring resection for intestinal infarction, experiencing incomplete recanalization of thrombus, or having inherited thrombophilia were given lifelong oral anticoagulation in this study. Recurrent VTE occurred in 18.5% of patients overall, and only in those who did not receive anticoagulation, and was significantly more frequent among patients with concurrent myeloproliferative disorders at presentation versus those without (70% vs. 13%; $P < .0001$).[345] In a prospective multicenter study in patients with acute portal vein thrombosis treated with anticoagulation (initial therapy with heparin followed by oral anticoagulation for 6 months or long-term in patients with permanent prothrombotic disorders or obstruction of mesenteric vein), the 1-year recanalization rates in the portal vein, mesenteric vein, and splenic vein were 38%, 61%, and 54%, respectively.[374]

Anticoagulation appears to lower the risk for recurrent thrombosis in patients with SPVT without increasing the risk for severe bleeding,[345,356,374,380] including in patients with underlying prothrombotic states.[356] An individual-patient meta-analysis of the effectiveness and safety of anticoagulation for SPVT revealed lower risks of VTE recurrence (HR, 0.42; 95% CI, 0.27–0.64), major bleeding (HR, 0.47; 95% CI, 0.30–0.74), and mortality (HR, 0.23; 95% CI, 0.17–0.31) during anticoagulation therapy compared to off-treatment periods.[381] The study did include patients with cancer (32% of patients had solid cancers, 7.2% had myeloproliferative neoplasms, and 1.2% had leukemia, lymphoma, or multiple myeloma).

In contrast, a large, retrospective cohort study did not find evidence that anticoagulation was beneficial for the prevention of recurrent thrombosis in patients with SPVT. The rate of recurrent VTE was not significantly improved with oral warfarin in terms of 10-year recurrence-free survival rate (89% vs. 77% in the control group; $P = .38$). Hormone therapy was the only independent predictor of recurrence in this study. Moreover, major bleeding events were reported more frequently among patients receiving anticoagulation compared with those who did not (26% vs. 19%; $P < .05$), with gastroesophageal varices and anticoagulation as independent predictors of bleeding.[346] In chronic SPVT, the presence of portal hypertension may increase the risk of bleeding from esophageal varices and splenomegaly may lead to decreased platelet counts, which can further increase the risks of bleeding events in patients treated with anticoagulation.[382] Thus, in the absence of randomized controlled trials, the issue of long-term or lifelong anticoagulation remains somewhat controversial in patients with SPVT. An individual's risk factor(s) for SPVT should be taken into consideration when weighing the risks and benefits of long-term anticoagulation.

Catheter-Directed Thrombolytic Therapy for SPVT

Thrombolytic therapy may be most suitable when administered locally for patients with recent thrombosis; however, this approach should be used

with caution due to risks for major bleeding complications.[383-386] TIPS may be appropriate for patients with an occluded IVC or a portacaval pressure gradient less than 10 mm Hg, and in those with refractory ascites and progressive hepatic dysfunction.[387,388] This procedure is less invasive than surgical interventions, and has been successful in reducing portal hypertension, resolving ascites, and improving hepatic function in patients with Budd-Chiari syndrome.[387-392] Although shunt dysfunction or stenosis is common during follow-up, TIPS is associated with promising long-term outcomes, with 5-year transplant-free survival rates of 74% to 78%.[387,392] On the other hand, surgical portosystemic shunts may be appropriate in patients without an occluded IVC, with a portacaval pressure gradient greater than 10 mm Hg, and with preservation of hepatic function.[393] The impact of surgical shunts versus other interventions on long-term outcomes is unknown[394]; nevertheless, 5-year survival rates range from 75% to 87% in patients with Budd-Chiari syndrome undergoing successful surgical portosystemic shunts.[395-397] This procedure may improve survival outcomes in patients with intermediate-risk prognostic factors as defined by Darwish Murad et al.[398] Of note, surgical shunts appear to have now largely been replaced with TIPS.[388]

β-Blockers and Endoscopic Treatments for SPVT

Gastroesophageal varices may be seen in 35% to 50% of patients with portal vein thrombosis at presentation and remain a significant independent risk factor for major bleeding in patients with SPVT.[346] β-blockers and endoscopic treatments have been evaluated for variceal bleeding in patients at high risk of bleeding events. Even though one study showed visceral banding ligation to be more effective than propranolol in preventing visceral bleeding in patients with cirrhosis with high-risk gastroesophageal varices (7% vs. 30%; *P* = .043),[399] results from several prospective randomized studies found these options to be equally effective (12%–25% vs. 24%–29%), with similar overall mortality rates.[400-402] In one study, ligation was associated with a significantly decreased incidence of esophageal variceal bleeding compared with propranolol (5% vs. 25%; *P* = .027) at the expense of a higher incidence of subcardial variceal bleeding (8% vs. 0%; *P* = .027).[400] Combining the two modalities did not significantly reduce the risks of bleeding (actuarial probability, 7% vs. 11%; *P* = .72) or death (actuarial probability, 8% vs. 15%; *P* = .37).[403] In the context of secondary prophylaxis in patients with noncirrhotic portal hypertension, the incidence of recurrent variceal bleeding was similar between patients receiving ligation versus propranolol (24% vs. 18%; *P* = .625).[404] However, a meta-analysis of randomized studies demonstrated that the combined modality was significantly more effective than endoscopic treatment alone in preventing overall recurrent bleeding (OR, 2.20; 95% CI, 1.69–2.85; *P* < .0001) and in decreasing overall mortality (OR, 1.43; 95% CI, 1.03–1.98; *P* = .03). These data suggest that a combined regimen may be preferred as secondary prophylaxis for esophageal variceal bleeding.[405]

Therapeutic Anticoagulation for VTE in Patients with Cancer

The only placebo-controlled, randomized clinical trial on the use of anticoagulants, in particular heparin followed by warfarin, to treat VTE was performed in 1960.[406] Although most of the subsequent clinical trials evaluating the use of anticoagulation therapy in the prevention and treatment of VTE have not been placebo-controlled, the evidence supporting the effectiveness of such therapies is strong.[407-411]

Anticoagulation agents used in the treatment of VTE are listed in *Therapeutic Anticoagulation for VTE* in the algorithm. U.S. Food and Drug Administration (FDA) indications and NCCN recommendations for these therapies are listed in the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Venous Thromboembolic Disease (for the latest version of the NCCN Compendium, please visit www.NCCN.org). The Panel recommends that agent selection be based on the presence of renal

insufficiency, hepatic disease, inpatient/outpatient status, FDA approval, cost, patient preference, ease of administration, need for therapeutic monitoring, bleeding risk assessment, and reversibility. Suggested dosing schedules were established according to Panel consensus and follow, with several exceptions, manufacturer recommendations. To avoid potential conflicts, users can consult dosing schedules listed in specific institutional standard operating procedure (SOP) documents. Recommendations of the American College of Chest Physicians (ACCP) provide another legitimate source for anticoagulant dosing schedules.[152,313,412-414]

Direct Oral Anticoagulants

Apixaban is an orally administered direct Factor Xa inhibitor approved by the FDA for a variety of indications, including the prevention and initial short- and long-term treatment of VTE.[415-417] Since apixaban is primarily metabolized in the liver and renal elimination accounts for only about 27% of total drug clearance, the drug should be avoided in patients with severe hepatic impairment.[417] Several clinical trials have found apixaban and LMWHs to be equivalent options for the treatment of VTE.[418-421] In fact, apixaban led to lower or similar rates of recurrent VTE compared to dalteparin in the ADAM VTE trial and the Caravaggio study (0.7% vs. 6.3%; HR, 0.099; 95% CI, 0.013–0.780; $P = .0281$ and 5.6% vs. 7.9%; HR, 0.63; 95% CI, 0.37–1.07; $P < .001$ for noninferiority).[419,420] Major bleeding was comparable in both studies and was not higher in the apixaban group.[419-421] The AMPLIFY trial reported a similar rate of recurrent VTE and lower rate of major bleeding in the apixaban group compared to the enoxaparin/warfarin group (3.7% vs. 6.4%; RR, 0.56; 95% CI, 0.13–2.37 and 2.3% vs. 5.0%; RR, 0.45; 95% CI, 0.04–0.78).[418]

Edoxaban is an orally administered direct Factor Xa inhibitor approved by the FDA for the treatment of DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant.[422] Renal clearance accounts for approximately 50% of the total clearance of edoxaban.[423] Clinical trial results indicated edoxaban to be noninferior to dalteparin with respect to the composite outcome of recurrent VTE or major bleeding (12.8% vs. 13.5%; HR, 0.97; 95% CI, 0.70–1.36; $P = .006$ for noninferiority; $P = .87$ for superiority).[424] It must be noted that edoxaban therapy is initiated after initial therapy with LMWH or UFH for at least 5 days. Dabigatran, another DOAC, follows a similar treatment regimen.[425] Renal clearance of dabigatran is 80% of total clearance after oral administration.[425] The clinical benefit of dabigatran in the treatment of cancer-associated VTE was found to be equivalent to warfarin in terms of both efficacy (HR, 0.75; 95% CI, 0.20–2.8 at baseline and HR 0.63; 95% CI, 0.20–2.0 for cancer diagnosed during the study) and safety (major bleeding HR, 4.1; 95% CI 2.2–7.5).[426] However, unlike warfarin, concurrent administration with parenteral anticoagulants is not recommended when transitioning to edoxaban or dabigatran. Prescribing information must be consulted for transitioning protocols between agents.

Rivaroxaban is an orally administered direct Factor Xa inhibitor approved by the FDA for a variety of indications, including the prevention and treatment of VTE.[427-429] The drug is primarily eliminated via the kidneys; thus, rivaroxaban should be avoided in patients with severe renal impairment and used with caution in those with moderate impairment.[429] Subgroup analysis of the EINSTEIN-DVT and EINSTEIN-PE trials in patients with active cancer concluded that rivaroxaban had similar efficacy to prevent VTE recurrence (5% vs. 7%; HR, 0.67; 95% CI, 0.35–1.30) and reduce major bleeding events (2% vs. 5%; HR, 0.42; 95% CI, 0.18–0.99) compared with enoxaparin and vitamin K antagonist.[430] A prospective cohort study reported the 6-month cumulative incidence of new or recurrent VTE to be 4.4% and major bleeding to be 2.2% in patients on rivaroxaban, which were comparable to the EINSTEIN subgroup analysis.[431] Another clinical trial comparing rivaroxaban and dalteparin had similar outcomes, with 6-month cumulative VTE recurrence rates of 4%

and 11% (HR, 0.43; 95% CI, 0.19–0.99), as well as major bleeding rates of 6% and 4% (HR, 1.83; 95% CI, 0.68–4.96) in each respective group.[432]

Based on the quality of evidence presented on apixaban and edoxaban, which include data from large (N > 1000) prospective randomized controlled clinical trials,[418,424] the NCCN Panel assigns category 1 recommendations to these agents in the DVT/PE setting. Although stage IV chronic kidney disease is not listed as a contraindication in the FDA-approved label for apixaban, the NCCN Panel acknowledges that there are insufficient data to support safe apixaban dosing in this setting, especially in the setting of hemodialysis. It must be noted that patients with gastric and gastroesophageal tumors are at increased risk for hemorrhage with DOACs and thus, LMWHs are preferred in this setting. In the Hokusai VTE Cancer Study, the absolute rate of recurrent VTE was found to be 3.4% lower with edoxaban compared to dalteparin, whereas the absolute rate of major bleeding was 2.9% higher. In particular, the excess of major bleeding with edoxaban was confined to patients with GI cancer.[433] On the other hand, results from the Caravaggio study demonstrated that major bleeding occurred in comparable proportions of patients treated with apixaban or dalteparin (3.8% vs. 4.0%). Of note, major bleeding occurred in nine patients with GI cancer in each treatment group.[434] Thus, the NCCN Panel postulates that apixaban may be safer than edoxaban or rivaroxaban for patients with gastric or gastroesophageal lesions (category 2B recommendation).

A recent retrospective study compared the safety and efficacy of DOACs versus LMWH for treatment of VTE in patients with primary brain tumors or secondary metastases to the brain.[435] There was no significant difference in 6-month cumulative bleeding events, including intracranial hemorrhage, in the DOAC arm compared to the LMWH arm (14.3% vs. 27.8%; *P* = .10). Similarly, rates of recurrent VTE events were similar between the DOAC and LMWH arms, at 5.6% and 6.6%, respectively (*P* = .96). These data suggest that DOACs may be a safe and effective treatment option for VTE in this patient population.

Low-Molecular-Weight Heparins

Dalteparin[144] is approved for prevention and treatment of VTE and extended treatment of symptomatic VTE in patients with cancer and enoxaparin[147] is approved by the FDA for the immediate treatment of VTE. A Cochrane review found no significant differences in bleeding, thrombocytopenia, or survival outcomes with LMWH compared with oral vitamin K antagonists for the chronic treatment of VTE in patients with cancer. However, the incidence of VTE was significantly lower for patients receiving LMWH (RR, 0.58; 95% CI, 0.43–0.77).[436] Although each of the two LMWHs has been studied in randomized controlled trials in patients with cancer, the efficacy of dalteparin in this population is supported by the highest quality evidence[408,437] and is the only LMWH approved by the FDA for this indication. NCCN-recommended dosing regimens for dalteparin[408,437,438] and enoxaparin[147,407,439,440] in VTE treatment are based on the results of clinical studies and Panel consensus. Dalteparin has been found to be more effective than a coumarin derivative regarding recurrent VTE (8.0% vs. 15.8%; HR, 0.48; *P* = .002) without increasing the risk of bleeding in a large prospective randomized study.[408] Its safety for cancer-associated VTE has also been monitored for a prolonged period (12 months).[437] On the other hand, the efficacy of enoxaparin for patients with cancer has been confirmed in a small study in comparison with warfarin (combined outcome including major bleeding or recurrent VTE: 10.5% vs. 21.1%; 95% CI, 4.3%–20.3%; *P* = .09).[407] In another study, enoxaparin was found to be a safe and effective option either by itself or in combination with warfarin.[439] Additionally, enoxaparin at fixed dosages of 1.0 mg/kg twice daily or 1.5 mg/kg once daily was reported to be equivalent to dose-adjusted UFH in terms of both symptomatic VTE (2.9% and 4.4% vs. 4.1%) and major hemorrhage (1.3% and 1.7% vs. 2.1%) in a large, prospective, randomized trial. However, this study did not

specifically enroll patients with cancer[440] and long-term treatment with enoxaparin dosing of 1.0 mg/kg SC every 12 hours has not yet been tested in patients with cancer. Thus, the NCCN Panel assigns a category 1 recommendation to dalteparin for DVT/PE.

Extended anticoagulation therapy with LMWHs may require dosage reduction after an initial period. In the CLOT study, the dalteparin dosing was lowered from 200 units/kg daily to 150 units/kg daily after 1 month.[408] In addition, the European Society for Medical Oncology (ESMO) clinical recommendations for management of VTE in patients with cancer specifies using 75% to 80% of the initial dose of LMWH for extended anticoagulation therapy.[441] Limited evidence exists concerning the safety and efficacy of LMWHs in special populations, such as patients with renal insufficiency, patients with BMI >30 kg/m^2, patients weighing <50 kg, patients ≥70 years of age, and patients with cancer.[442] The NCCN Panel suggests that each institution prepare a LMWH dosing algorithm tailored for these subsets of patients. Of the two LMWHs, specific dosing recommendations for patients with severe renal insufficiency (CrCl <30 mL/min) are available only for enoxaparin.[147,443] These recommendations are supported by results from multiple studies showing reduced renal clearance of enoxaparin and its association with a 2- to 3-fold increase in risk of bleeding when administered in standard, unadjusted therapeutic doses to patients with severe renal insufficiency.[178,444,445] On the other hand, available data suggest dalteparin might be sufficiently cleared in patients with renal impairment[176,446]; however, monitoring of peak anti-Xa levels is still recommended in patients with CrCl <30 mL/min.[144] Of the two LMWHs, a specific dosing recommendation for patients with BMI ≥40 kg/m^2 is available only for enoxaparin.[447] This recommendation is supported by a randomized controlled trial of enoxaparin 1 mg/kg versus reduced dose of 0.8 mg/kg every 12 hours in patients with BMI ≥40 kg/m^2. A similar number of patients in both the reduced-dose arm and standard-dose arm reached goal anti-Xa levels, at 89.3% versus 76.9%, respectively (P = .29).[447]

Increased survival rates have been reported for subgroups of patients receiving chronic treatment with LMWH versus other VTE therapies or placebo.[448,449] In the FAMOUS study of patients with advanced cancer without VTE, subgroup analysis of patients with better prognoses suggested that 2- and 3-year survival rates were higher for patients receiving dalteparin compared to those receiving placebo.[448] A post hoc analysis of patients from the CLOT study also indicated that among patients without metastases, 1-year survival rates were higher for those receiving dalteparin versus an oral vitamin K antagonist.[449] Other randomized studies and systematic reviews have provided evidence both for and against the purported survival benefits of LMWHs in patient with cancer.[450-455] Of note, two large randomized prospective trials, as well as a systematic review, reported no overall survival advantage in patients with lung cancer receiving LMWH.[453,455,456]

Fondaparinux

Fondaparinux is a specific indirect Factor Xa inhibitor for the treatment of VTE whose advantages include specific neutralization of factor Xa, elimination of the need to monitor anticoagulant response in most cases, and the lack of cross reactivity with the antibody associated with HIT.[151,414,457] Subgroup analysis of data from the Matisse clinical trials supports the use of fondaparinux in patients with cancer. In these studies, fondaparinux led to a higher 3-month DVT recurrence rate (12.7% vs. 5.4%; absolute difference 7.3%; 95% CI, 0.1–14.5) but a lower PE recurrence rate (8.9% vs. 17.2%; absolute difference, -8.3; 95% CI, -16.7, 0.1) than enoxaparin, with no difference in bleeding or overall survival.[458] The use of fondaparinux in patient populations with renal insufficiency or obesity has not been well-defined, although there is some evidence to support its safe and effective use in patients ≥60 years of age with a broad

range of body weights.[153] The NCCN Panel recommends against the use of fondaparinux in patients with severe renal insufficiency and advises caution for use in patients with renal dysfunction (CrCl 30–50 mL/min) and patients >75 years of age. The Panel also recommends a reduced dose in patients weighing <50 kg and an increased dose in those weighing >100 kg. [151,153]

Unfractionated Heparin

UFH is approved by the FDA for a variety of indications including the treatment of VTE.[459] The initial dosing of UFH in the treatment of VTE is weight-based, with a recommended regimen of 80 units/kg bolus followed by 18 units/kg per hour infusion adjusted to target aPTT or per hospital SOPs.[460] Alternatively, fixed-dose, unmonitored, SC UFH (333 units/kg load, followed by 250 units/kg every 12 hours) has been reported to be comparable to LMWH in the treatment of patients with acute VTE (recurrent VTE 3.8% vs. 3.4%; absolute difference, 0.4%; 95% CI, −2.6% to 3.3%).[461] Patients receiving IV UFH must be hospitalized and monitored for anticoagulant response. The Panel recommends UFH as the agent of choice in patients with CrCl <30 mL/min, because the liver is a main site of heparin biotransformation.[459] Some exceptions include patients with severe renal dysfunction but without IV access, and those with a new diagnosis of VTE despite therapeutic doses of UFH. In a meta-analysis of trials comparing outcomes with anticoagulants (UFH, LMWH, and fondaparinux) as initial treatment of VTE in patients with cancer, LMWH was associated with a significant reduction in mortality rate at 3-month follow-up compared with UFH (RR, 0.66; 95% CI, 0.40–1.10).[462] However, no significant difference was found in VTE recurrence between LMWH and UFH. Furthermore, no statistically significant differences were found between UFH and fondaparinux in terms of mortality, VTE recurrence, or bleeding events.[463]

Warfarin

Warfarin is an option for long-term treatment of VTE in patients with cancer following initial treatment/bridging with UFH,[459] LMWH,[144,147] or fondaparinux.[151] Warfarin can be safely administered to patients with renal insufficiency, although the response to warfarin is accentuated in patients with hepatic insufficiency.[464] If warfarin is selected for chronic anticoagulation, the NCCN Panel recommends initiating warfarin concurrently with the parenteral agent used for acute therapy (at previously recommended doses) and continuing both therapies for at least 5 days and until the International Normalized Ratio (INR) is $\geq$2. During the transition to warfarin monotherapy, the INR should be measured at least twice weekly. Once the patient is on warfarin alone, the INR should be measured initially at least once weekly. Once the patient is on a stable dose of warfarin with an INR of 2–3, INR testing can be gradually decreased to a frequency of no less than once monthly.

Contraindications and Risks to Therapeutic Anticoagulation

Contraindications to anticoagulation can be relative or absolute, and temporary or permanent. Consideration of the degree of contraindication to anticoagulation and its duration are essential when evaluating the risks and benefits of anticoagulation (see *Contraindications to Therapeutic Anticoagulation* in the algorithm). The risks and benefits of anticoagulation and the presence of contraindications must be considered on an individual basis. The Panel recommends frequent re-evaluation of these contraindications and of the risks and benefits of anticoagulation therapy for all patients with cancer.

The use of anticoagulants is complicated by the fact that patients with cancer with VTE have a higher likelihood of developing recurrent VTE and major bleeding than those without malignancy.[60,465] In patients with cancer, bleeding rates were independent of INR values and were high across

different INR categories, whereas recurrence rate was lower when the INR was >2.[465,466] In one prospective follow-up study, the 12-month cumulative incidence of major bleeding was 12.4% and 4.9% in patients with and without cancer, respectively (HR, 2.2; 95% CI, 1.2–4.1). In this study, one-third of all cases of major bleeding occurred during the initial 5 to 10 days of heparin, and the risk of bleeding increased with the extent of cancer.[60] Subsequent randomized controlled studies for the chronic treatment of VTE in patients with cancer demonstrated that LMWHs and vitamin K antagonists are associated with a similar incidence of bleeding events, including major bleeding[407-409]; however, in one study, fatal bleeding was reported in 8% of patients receiving vitamin K antagonists compared with none receiving LMWH.[407] Other risks include osteoporosis and HIT for patients receiving heparins, and drug and food interactions for patients receiving vitamin K antagonists. For example, in patients receiving either a vitamin K antagonist or enoxaparin, decreases in bone mineral density of 1.8% and 3.1% at 1-year follow-up, and 2.6% and 4.8% at 2-year follow-up, respectively, were seen.[467]

Warfarin has a very narrow therapeutic window, and its activity is known to be affected by the administration of many other drugs. For example, a number of antibiotics and antifungal therapies, including trimethoprim-sulfamethoxazole, ciprofloxacin, metronidazole, and fluconazole, potentiate the effect of warfarin, whereas other antibiotics such as rifampin and dicloxacillin antagonize the effect of warfarin.[468,469] Furthermore, certain chemotherapeutic agents, such as 5-fluorouracil and capecitabine, are known to increase the INR in patients undergoing warfarin anticoagulation,[470,471] and drug interactions between warfarin and certain selective estrogen receptor modulators (tamoxifen and raloxifene) have also been reported.[472] Dietary intake of vitamin K and certain dietary supplements can also influence the effects of warfarin.[473,474] Finally, acetaminophen, found in many medications, can increase the therapeutic effects of warfarin when taken in daily doses exceeding 2 g.[475]

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 these agents may not be appropriate for patients who have had significant resections of these portions of the intestinal tract. For additional information on absorption guidance following GI surgical interventions and enteral feeding tube administration, see *Therapeutic Anticoagulation for VTE: DOACs: GI Considerations and Alternative Routes of Administration* in the algorithm.

Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia

Thrombocytopenia is a common consequence of cancer treatment; however, little guidance exists regarding anticoagulation usage in this setting in those with a concurrent or recent VTE diagnosis.[476-478] In a small retrospective cohort study evaluating patients with hematologic malignancy and VTE before or during platelet counts dropping below 50,000/µL, withholding anticoagulation resulted in significantly reduced bleeding (3% vs. 27% in those receiving anticoagulation; incidence rate ratio [IRR], 10.1; 95% CI, 1.5–432.6) but significantly increased recurrent VTE (15% vs. 2%; IRR, 0.17; 95% CI, 0.0–1.51).[229] The NCCN Panel considers anticoagulation to be safe with platelet counts ≥50,000/µL and recommends careful weighing of the risks for recurrent thromboembolism and bleeding. Based on this evaluation, patients at high risk can either continue to receive therapeutic dose anticoagulation with platelet transfusions or undergo placement of a retrievable IVC filter and discontinue anticoagulation. It was demonstrated in a small single-institution observational cohort study that 31 of 59 patients receiving anticoagulation and transfusion support for a platelet goal of 50,000/µL experienced bleeding events. Eleven patients experienced transfusion reactions.[479] Therefore, prospective data are needed to identify an optimal transfusion strategy in this setting.

Patients considered at low risk for VTE recurrence can receive a lower dose of anticoagulation, have their CVAD removed in the case of CVAD-associated DVT, or be monitored for distal DVT with serial US surveillance while being off anticoagulation (see *Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia* in the algorithm). In a prospective cohort study, it was demonstrated that a fixed subtherapeutic dose of LMWH was efficient and safe in patients with cancer requiring interruption of long-term vitamin K antagonist therapy due to treatment-induced thrombocytopenia.[480] In a small, single-institution, retrospective review, enoxaparin at the therapeutic dose was found to be safe to continue, especially if the anticipated duration of platelet count <50,000/µL was less than 7 days.[481] The NCCN Panel outlines enoxaparin dose modification in the setting of thrombocytopenia and does not recommend use of DOACs for platelet counts <50,000/µL due to limited published data.

Progression or New Thrombosis on Therapeutic Anticoagulation

Progression or new thrombosis on therapeutic anticoagulation is defined as extension of DVT or PE, or new DVT or PE, while on recommended anticoagulation therapy (see *Progression or New Thrombosis on Therapeutic Anticoagulation* in the algorithm). An early embolism event might not indicate progression or new thrombosis on therapeutic anticoagulation. An initial determination of whether the INR, aPTT, or LMWH anti-Xa value is within the therapeutic range is important for patients with recurrent VTE who are receiving anticoagulation, as well as assurance of adherence to therapy. When INR, aPTT, or anti-Xa values are subtherapeutic, the solution is to increase the anticoagulant dose to a therapeutic level. INR or aPTT values may also be subtherapeutic due to reasons other than inadequate anticoagulant dosing. For example, warfarin resistance can be due to genetic variability associated with the enzymatic metabolism of warfarin, concomitant administration of medications that interact with warfarin, or pharmacokinetic and biophysical/physiologic limitations of warfarin therapy.[482,483] In this case, an alternative agent should be selected.

Progression or new thrombosis on therapeutic anticoagulation can also occur in the setting of therapeutic INR or aPTT values or, in the case of a DOAC, at therapeutic doses. Causes include cancer-related hypercoagulability, such as Trousseau syndrome; HIT; conditions associated with venous stasis, such as vascular compression by tumors or lymphatic masses or stasis associated with IVC filters; and APS.[484,485] Diagnostic testing to identify the syndromes identified above, when present, is critical to the management of VTE in these settings.[485] In patients with anatomic compression due to congenital or acquired causes, relief of anatomic compression is essential to preventing recurrent thrombosis, after which increasing of anticoagulant dose or switching to an alternative agent can be considered, as renal function allows. For example, a switch to LMWH in the setting of progression or new thrombosis on a DOAC or subtherapeutic INR with warfarin therapy is supported by the results of one study in which a low VTE recurrence rate was reported for patients treated with LMWH following the development of recurrent thromboembolism on warfarin therapy[486] (see *VTE-G 2 of 2 Progression or New Thrombosis on Therapeutic Anticoagulation* in the algorithm).

Although progression or new thrombosis on therapeutic anticoagulation can result if the prescribed anticoagulant dose is inadequate, other factors to consider include adherence to self-administered medications and dosing frequency in patients receiving LMWH.[485] For example, a trend toward an increased risk for VTE recurrence was reported in one study of patients with cancer receiving once-daily enoxaparin in the acute therapy setting.[440] Thus, a twice-daily dosing schedule might be a better option in this setting. A dose increase can also be considered for patients

experiencing recurrent VTE while receiving anticoagulant therapies whose effects are not typically monitored in the laboratory (eg, LMWH and fondaparinux).[487,488]

Thrombolytic Agents

Alteplase and reteplase administered via a catheter or in conjunction with a mechanical thrombectomy device are sometimes used to treat large and/or proximal upper-extremity/intrathoracic or lower-extremity DVT. Thrombolysis with catheter-directed therapies for SPVT is limited to case reports and small studies; the NCCN Panel recommends following local institutional protocols in this setting. The thrombolytic options for PE include systemic thrombolysis using alteplase, reteplase, or tenecteplase (category 2B) or US-assisted CDT using alteplase.

Catheter-directed delivery of thrombolytic agents directly into the clot has allowed more localized targeting of thrombolytic agents and the use of catheter-based thrombectomy devices to accelerate clot removal. CDT with or without mechanical thrombectomy is associated with significantly higher rates of complete clot lysis than conventional anticoagulation.[489] Different FDA-approved catheters and devices exist; however, no single catheter or device has been proven to be superior to another.[490] The extent of thrombus may be an important factor in device and agent selection as well as the likelihood of success.

Effective clot lysis in patients with DVT has been reported with CDT using urokinase, alteplase, reteplase, and tenecteplase.[491-499] It must be noted that for DVT, a post-procedural imaging study is recommended to confirm the results of thrombolysis. A retrospective patient series has demonstrated that patients with cancer can benefit from catheter-directed pharmacomechanical thrombolysis.[328] Other studies also postulated that thrombolysis led to fewer post-thrombotic complications compared with anticoagulation alone (mostly heparin) for patients with DVT.[500-503] However, later data are contradictory regarding this matter. In the CaVenT study, PTS was reported in significantly fewer patients in the CDT arm versus the control arm at 24-month follow-up (41% vs. 56%; P = .047).[494,495] However, the ATTRACT trial, a multicenter randomized study, reported no significant difference in PTS between patients receiving pharmacomechanical CDT and anticoagulation versus those receiving anticoagulation alone.[504] The NCCN Guidelines do not recommend routine use of CDT over anticoagulation alone but suggest that patients with the following factors are most likely to benefit from CDT: iliofemoral DVT; symptom duration less than 14 days; good functional status; life expectancy of ≥1 year; and low risk of bleeding.[313,505] The NCCN Panel believes that CDT and thrombectomy can be considered as a therapeutic option for select patients with limb-threatening/life-threatening acute proximal DVT, particularly when there has been no response to conventional anticoagulation.[314]

In the setting of acute intermediate-risk (submassive) PE, two randomized controlled trials comparing alteplase and tenecteplase to anticoagulation have shown that systemic thrombolysis does not reduce mortality but is associated with an increased risk of bleeding complications.[321,506] In the MOPPET trial, alteplase in conjunction with anticoagulation was shown to be more efficacious in reducing pulmonary hypertension and recurrent PE at 28 months compared to anticoagulation alone (16% vs. 63%; P < .001).[506] In the PEITHO study, patients with intermediate-risk PE were randomized to tenecteplase plus anticoagulation or placebo plus anticoagulation. Death or hemodynamic decompensation occurred in 13 of 506 patients (2.6%) in the tenecteplase group compared to 28 of 499 (5.6%) in the placebo group (OR, 0.44; 95% CI, 0.23–0.87; P = .02). However, the difference between groups was due to a reduced rate of hemodynamic decompensation in the tenecteplase group. Mortality was similar between groups at day 7 and day 30. Extracranial bleeding (32 patients, 6.3% vs. 6 patients, 1.2%; P < .001) and stroke (12 patients,

2.4% vs. 1 patient, 0.2%; *P* = .003) were more common with tenecteplase.[321] Therefore, systemic thrombolytic therapy is reserved for patients with high-risk massive PE.

US-assisted CDT using alteplase has been used for patients with PE[507,508] with ≥50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressure (mean pulmonary artery pressure ≥25 mmHg) or echocardiographic evaluation. Alteplase is administered at a rate of 1 mg/h per drug delivery catheter (2 mg/h for bilateral PE) and infused for 24 hours with one catheter and 12 hours for two catheters.[509] Other US-assisted CDT regimens have been tested, supporting this method's utility in the treatment of acute massive and submassive PE.[332,510]

Similar to anticoagulation, contraindications to thrombolysis include absolute and relative contraindications (see *Contraindications to Thrombolysis and Indications for Thrombolysis* in the algorithm).[313] The risks and benefits of thrombolysis should be assessed on a case-by-case basis by the clinician. The use of a thrombolytic agent may be considered in patients who are pregnant and lactating and with life-threatening thrombosis. Studies examining the safety of thrombolytic therapy during pregnancy or lactation are not available, but thrombolytic agents are unlikely to cross the placenta or transfer to breast milk due to their large molecular weight. Besides the indications mentioned above (limb-threatening/life-threatening acute proximal DVT, symptomatic iliofemoral thrombosis, and massive/life-threatening PE), thrombolysis is also indicated for intestinal SPVT with high risk of ischemia.[511]

Elements to Consider in Decision Not to Treat

The feasibility of invasive or aggressive intervention is not the only consideration for VTE prophylaxis and treatment in patients with cancer.[512] The risks and probability of success of the interventions should be considered as well. Factors to consider before implementing anticoagulation therapy include patient non-acceptance, lack of therapeutic advantage or palliative benefits, whether anticoagulation is associated with an unreasonable burden, and end-of-life/comfort care. Likewise, careful consideration of these issues is also very important in deciding to withhold or withdraw VTE therapy (see *Elements for Consideration in Decision Not to Treat* in the algorithm).

Reversal of Anticoagulation

In the event of life-threatening bleeding, or the need for urgent/emergent invasive procedures, anticoagulant effects must be promptly reversed. It should be noted that all anticoagulation reversal products are associated with a risk of thromboembolism. It is recommended that institutions have treatment pathways or guidelines for the reversal of anticoagulation.

The anticoagulant effects of UFH are fully reversible with protamine sulfate, and the anti-Xa activity of LMWHs are partially reversed by protamine sulfate (up to 60%–75% depending on the LMWH). This agent must be used with caution because it can cause severe hypotension or anaphylactic reactions, particularly if administered too rapidly. Patients with fish allergies and previous exposure to protamine (eg, neutral protamine Hagedorn [NPH] insulin) are at increased risk for allergic reactions (see *Reversal of Anticoagulation* in the algorithm).

IV recombinant human coagulation Factor VIIa (rhFVIIa), which rapidly induces thrombin generation, has been shown to reduce the anticoagulant effects of direct thrombin inhibitors (DTIs) and fondaparinux in laboratory tests.[412,513-520] Although evidence from published studies is limited, available data from *in vitro* models and healthy volunteers support the use of rhFVIIa for management of severe bleeding events with fondaparinux.[412,513-515] Activated prothrombin complex concentrate (aPCC) has also been evaluated as a potential option for reversing the effects of

DTIs by improving hemostatic capacity.[519,521-524] Another proposed strategy for reversal of DTIs is the use of desmopressin acetate, which stimulates release of factor VIII and von Willebrand factor.[525] It is important to remember that desmopressin acetate is effective only for 3 or 4 doses, after which tachyphylaxis develops.[526,527] The DTIs bivalirudin and dabigatran can be removed with hemofiltration and hemodialysis, although clinical data supporting this approach are limited.[518,528,529] Activated charcoal may also be considered for reversal of dabigatran, especially within a few hours of overdose.[530] Idarucizumab was tested and shown in a large, prospective clinical trial to reverse the anticoagulant effects of dabigatran within minutes in both patients who had uncontrolled bleeding and those who were about to undergo an urgent procedure (median maximum percentage reversal 100%; 95% CI, 100–100). Thromboembolic events occurred in 6.3% to 7.4% of patients by day 90.[531,532] Overall, limited information is available on the clinical efficacy of all of these proposed reversal strategies. For life-threatening bleeding, the NCCN Panel currently favors the use of rhFVIIa for bivalirudin reversal, aPCC or rhFVIIa for argatroban reversal, and idarucizumab for dabigatran reversal as first-line agents (see *Reversal of Anticoagulation* in the algorithm).

As for the oral direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, the prescribing information indicates that activated charcoal may be considered for reduction of drug absorption.[417,422,429] Due to the high plasma protein binding, these agents are not expected to be dialyzable. Limited data from *in vivo* models and healthy volunteers suggest that prothrombin complex concentrate (PCC) may at least partially reverse the anticoagulation effects.[533-535] The use of rhFVIIa may also be considered, although data are unclear in terms of its benefits (see *Reversal of Anticoagulation* in the algorithm).[519,530] Andexanet alfa was shown in prospective, randomized trials to be a safe and effective option for the reversal of rivaroxaban and apixaban.[536-538] In the small ANNEX-A and the ANNEXA-R clinical trials, apixaban activity was reduced by 94% among those who received andexanet bolus, compared with 21% among those who received placebo ($P < .001$). Rivaroxaban activity was reduced by 92% among those who receive andexanet bolus, versus 18% among those who received placebo ($P < .001$).[537] In the larger ANNEXA-4 trial, among patients who had acute major bleeding, predominantly intracranial or GI, apixaban and rivaroxaban activity both decreased by 92% after andexanet bolus.[538] Andexanet alfa for edoxaban reversal has been examined in healthy volunteers[539,540] and more recently, in patients with acute major bleeding, primarily intracranial.[541] Initial data from this study indicated a median decrease of 69.2% (95% CI, 25.5%–80.2%) in anti-factor Xa activity and 75% excellent or good hemostasis at 12 hours in all patients, and 81.3% in those with intracranial hemorrhage.[541] Overall, andexanet alfa is favored for the treatment of intracranial hemorrhage, whereas PCC can be considered for patients taking factor Xa inhibitors suffering from GI bleeding (or bleeding in other sites). For andexanet alfa dosing and administration, see *Reversal of Anticoagulation* in the algorithm. 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.

The management of a supratherapeutic INR during treatment with warfarin is a common clinical challenge. In many cases, the effects of warfarin therapy in the patient with an elevated INR who is not bleeding can be reversed by withholding or reducing the warfarin dose, and, depending on the INR, the addition of small doses of oral vitamin K_1 for patients who are thought to be at higher risk of bleeding.[464,542-544] It should be noted that a randomized placebo-controlled trial that included 8% of participants with active cancer did not demonstrate any reduction in bleeding or thromboembolic complication with 1.25 mg oral vitamin K for INR reversal in patients without symptoms (with an INR of 4.5–10).[545] Therefore, use of oral vitamin K should be considered on a case-by-case basis. Consistent with the 2012 ACCP Guidelines, the NCCN Panel recommends the use of

oral vitamin K (1–2.5 mg) for patients with an INR greater than 10 on warfarin, and who have no evidence of bleeding[544] (see *Reversal of Anticoagulation* in the algorithm).

For patients requiring rapid warfarin reversal for urgent or emergent surgical procedures, IV administration of vitamin K_1 is preferred over oral vitamin K_1. In a prospective randomized study that compared INR outcomes with IV (0.5 mg) or oral (2.5 mg) vitamin K_1 in patients with baseline INR 6–10 on warfarin, a greater proportion of patients in the IV therapy arm achieved rapid therapeutic INR (2–4) at 6 hours (46% vs. 0%) and at 12 hours (67% vs. 35%) compared with oral therapy.[546] In a prospective study that evaluated vitamin K_1 in patients requiring rapid warfarin reversal for elective surgery, IV vitamin K_1 resulted in an INR $\leq$1.5 on the day of surgery in nearly all patients (94%).[547] Thus, for patients on warfarin requiring reversal within 24 hours of surgery, IV vitamin K1 (1–2.5 mg slowly) is recommended. INR assessment should be repeated prior to surgery to determine the need for supplemental plasma. For patients requiring reversal within 48 hours of surgery, 2.5 mg of oral vitamin K_1 can be given. In these cases, INR measurements should be repeated at 24 and 48 hours to determine the need for additional vitamin K or plasma. Patients with serious or life-threatening bleeding require 10 mg of IV vitamin K_1 and the 4-factor PCC.[542,548,549] Close monitoring of INR is required. If 4-factor PCC is unavailable, or the patient is allergic to heparin or had experienced HIT within 1 year, a 3-factor PCC without heparin may be used.[550] Other alternatives include fresh frozen plasma (FFP) and rhFVIIa.[542,551] There is a small risk for anaphylaxis (~1 in 3000 doses) associated with the IV administration of vitamin K_1, especially when it is administered more rapidly than 1 mg per minute.[552] PCC, rhFVIIa, and plasma have been associated with a low risk for thromboembolic events[553-555] (see *Reversal of Anticoagulation* in the algorithm).

Perioperative Management of Anticoagulation and Antithrombotic Therapy

Management of surgery-associated bleeding in patients with cancer is complicated by the need for anticoagulation in many of these patients due to their malignancy, cancer therapy, and/or comorbidities. It was shown in a large prospective study that patients with cancer chronically anticoagulated for VTE experienced higher rates of both periprocedural VTE (2% vs. 0.16%; $P = .02$) and major bleeding (3.7% vs. 0.6%; $P < .001$) compared to patients with cancer not chronically anticoagulated for VTE.[556] Another retrospective study found a high 30-day rate of VTE and major bleeding, both 4.1%, in patients with cancer-associated VTE requiring interruption of anticoagulation perioperatively.[557] Therefore, a balance of the thrombotic risk and bleeding risk is important. The Panel prefers to use shorter half-life and more easily reversible anticoagulants in the early post-procedural period, particularly for procedures with a high bleeding risk or in a critical site (eg, central nervous system). Bridging anticoagulation therapy refers to the use of short-acting anticoagulants (LMWH or UFH) for 10 to 20 days during the periprocedural period.[558] In the case of emergent surgery, anticoagulation should be reversed (see *Reversal of Anticoagulation* in the algorithm). The timing of reinitiation of anticoagulation after surgery is influenced by the bleeding risk of the procedure and thrombotic risk factors of the individual (see *Bleeding Risk Assessment*, *Thromboembolic Risk Assessment for Arterial Thromboembolism and VTE*, and *Perioperative Management of Anticoagulation in Patients with Cancer* in the algorithm).

If the surgical procedure is non-emergent, an assessment of the bleeding risk should be performed before the procedure. For procedures associated with a very low risk of bleeding, including but not limited to minor dermatologic procedures, joint or soft tissue injections, GI endoscopy without biopsy or polypectomy, and minor dental procedures, anticoagulation can continue leading up to surgery.[413] Use of local

hemostatic agents, such as topical tranexamic acid, aminocaproic acid, or thrombin-soaked absorbable gelatin powder, is encouraged in the event of bleeding during minor dental procedures. Patients at low, moderate, and high bleeding risk should undergo thromboembolic risk assessment. Based on these results, patients at low thromboembolic risk should stop anticoagulation without bridging therapy.[413,559,560] Of note, it is preferable to continue warfarin without discontinuation for some low-risk procedures, such as pacemaker or automatic implantable cardioverter defibrillator placement.[413] Patients at moderate or high thromboembolic risk should stop anticoagulation and bridging therapy should be considered[413]; however, in most circumstances bridging anticoagulation is not necessary for those taking DOACs, as the duration of interruption is shorter than with warfarin.[560] See *Table 3: Periprocedural Management of Oral Anticoagulants: Hold Times* in the algorithm for specific recommendations on recommended hold times for DOACs, warfarin, and LMWHs.

Postoperative anticoagulation based on bleeding risk and thromboembolic risk should ensue after surgery. All patients should receive standard VTE thromboprophylaxis once hemostasis is adequate (generally within 12–24 hours postoperatively), and thromboprophylaxis can be continued until therapeutic dose anticoagulation is resumed.[413,560,561] See the section on *Post-Procedural Resumption of Anticoagulation* in the algorithm for recommended timing of resumption for DOACs, warfarin, and LMWHs based on procedural bleeding risk. An IVC filter (retrievable filter preferred) should be considered if VTE (eg, lower-extremity DVT with or without PE) occurred within 1 month of planned surgery. Patients should be assessed periodically for filter retrieval once anticoagulation is safely resumed.

If the surgical procedure is emergent, anticoagulation should be reversed prior to surgery and postoperative anticoagulation should be started based on bleeding risk and thromboembolism risk. An IVC filter should be considered with the same considerations as for those undergoing non-emergent surgeries.

Bleeding risk can be attributed to both procedural and patient-specific factors. Providing a risk stratification system for surgeries and procedures in the context of perioperative antithrombotic drug use is challenging due to limited evidence.[558] However, several guidelines have classified higher-bleeding-risk surgeries and procedures to include GI procedures, percutaneous coronary interventions, neuraxial anesthesia and other neurosurgical procedures, and major orthopedic surgeries, among others. Dental procedures, cutaneous procedures, and selected cardiac procedures such as cardiac implantable devices and endovascular procedures and catheter ablation are considered operations with lower-bleeding risk[413,562-565] (for an exhaustive list of estimated bleeding risk for various surgical procedures, see *Bleeding Risk Assessment* in the algorithm). In terms of patient-specific factors, several scoring systems have been developed, such as the HAS-BLED score,[566,567] the ORBIT bleeding risk score,[568] and the biomarker-based ABC-bleeding risk score[569]; however, these scores have not been prospectively validated in the perioperative setting, particularly among patients with cancer.

In terms of thromboembolic risk assessment,[413] it must be noted that event rates per risk category may be higher in patients with cancer. Cancers associated with high thrombotic risk include pancreatic, liver, biliary, lung, stomach, brain, and esophageal cancers.[2] Additionally, the CHADS2 and CHADS2Vasc scoring systems were developed for patients with atrial fibrillation without cancer and may not be valid in patients with cancer.[570,571] Patients with atrial fibrillation may have additional risk factors for arterial thrombosis, including stroke or transient ischemic attack within 3 months and rheumatic heart valve disease.[413,560] The perioperative risk of recurrent thromboembolism in patients with VTE is influenced by the time of their thrombotic event (<3 months, within 3–12 months, >12

months) and the presence of thrombophilia, including: deficiencies in protein C, protein S, or antithrombin; gene mutations in factor V Leiden or prothrombin; or APS[413] (see the section on *Thromboembolic Risk Assessment for Arterial Thromboembolism and VTE* in the algorithm). The impact of these risk factors on the overall thromboembolic risk category should be assessed on a case-by-case basis in patients with cancer.

Overall, these Guidelines are meant to supplement but should not supersede clinical judgment. Careful attention to each individual's clinical situation is the best guide to management. For guidance on specific anticoagulation (warfarin, apixaban, dabigatran, edoxaban, fondaparinux, and rivaroxaban), see *Perioperative Management of Anticoagulation in Patients with Cancer* in the algorithm.

This section is based upon the Panel's assessment of the current literature on perioperative anticoagulation management in patients with cancer. There were considerable differences of opinions on management in many areas, which reflects the limited information on perioperative outcomes in patients with cancer on anticoagulation, who are likely to be at higher bleeding and thrombotic risk compared to patients without cancer. Since the risk of perioperative bleeding or thrombosis can be influenced by a large number of variables, including but not limited to the patient's cancer site and stage, proposed invasive procedure, antithrombotic medications, and concurrent medical conditions, periprocedural anticoagulation management should be determined on a case-by-case basis. For optimal outcomes, it is essential to develop a perioperative anticoagulation plan in advance in conjunction with the patient's proceduralist.

Heparin-Induced Thrombocytopenia

Evaluation

HIT is caused by a relatively common immunologic reaction to heparin-based products.[414,572] In a surveillance study, the incidence of HIT was 0.2% for all patients receiving heparin therapy and 1.2% in those exposed to heparin for more than 4 days.[573] HIT is triggered when UFH or LMWH binds to platelet factor 4 (PF4) and forms an immunogenic PF4-heparin complex.[414,574] The end result is a consumptive thrombocytopenia and profound prothrombotic state that triggers symptomatic thromboembolism in as many as 75% of patients.[414,574] Results of some studies indicate that the frequency of HIT with LMWH and UFH is similar,[575,576] whereas other studies suggest a lower incidence of HIT in patients receiving LMWH.[577-580] There is some evidence that patients with cancer are at increased risk of developing HIT and HIT-related VTE,[581,582] although this has not been firmly established. It has been suggested that factors such as anticoagulant dose and whether the patient is treated in the medical or surgical setting may account for these conflicting results, since a lower relative incidence of HIT with LMWH was observed for patients treated in the surgical setting receiving prophylactic doses of anticoagulant therapy.[583]

Clinical evidence of HIT includes development of thrombocytopenia, formation of necrotic lesions at injection sites, arterial thromboembolic complications, and/or development of VTE.[584,585] Most commonly, HIT occurs 5 to 10 days following initial exposure to heparin-based products. Rapid-onset HIT can occur within 1 day following administration of heparin in a patient with previous exposure to such agents within a period of 100 days.[414,576] Delayed-onset HIT is less common, and can occur days or weeks after heparin therapy has been discontinued.[574] A diagnosis of HIT is based on both clinical and serologic evidence.[414] The presence of both clinical sequelae of HIT, including thrombosis and thrombocytopenia (defined as a drop in platelet count by >50%) and anti-PF4/heparin antibodies, are needed for a diagnosis. Since most HIT antibodies do not activate platelets, a negative test result is more useful for excluding the diagnosis than a positive test result is for confirming it.[586] The specificity of functional platelet activation assays, such as the serotonin release assay

(SRA), is higher than antigen assays, such as the heparin-PF4 ELISA, which detects the presence of HIT antibodies but does not assess their ability to activate platelets.[414] The diagnosis of HIT is complicated by the high frequency of heparin use in hospitals, possible delays in obtaining serologic test results, and other causes of thrombocytopenia in patients receiving heparin-based products. In addition, there are increased bleeding risks associated with substitution of a DTI for heparin. Therefore, it is critically important that a high level of clinical suspicion is present before a patient is treated for HIT.[586]

The 4T score is a simple, validated tool designed to assess the probability of HIT based on specific characteristics of four clinical parameters: **t**hrombocytopenia, the **t**iming of the onset of platelet fall, the presence of **t**hrombosis or other clinical sequelae, and evidence of o**t**her potential causes of thrombocytopenia (see *HIT Pre-test Probability Score Assessment Tool* in the algorithm).[587-589] Evidence suggests that the negative predictive value of this assessment tool is considerably higher than its positive predictive value; hence, this tool is more likely to be useful in identifying patients at low risk for HIT.[588,590] Cuker and colleagues developed an alternative pre-test probability model based on broad expert opinion of HIT diagnosis known as the HIT Expert Probability (HEP) score. In a validation patient cohort, the HEP score demonstrated greater inter-observer reliability and correlation with laboratory test results and expert assessment of the probability of HIT diagnosis than the 4T score.[591] It has been suggested that while the HEP and 4T scores are excellent screening pretest probability models for HIT,[592] the HEP score might be superior to the 4Ts score among less experienced physicians and in patients in the ICU.[593] For patients who develop suspected HIT after cardiac surgery, the cardiopulmonary bypass (CPB) score should be consider for risk assessment.[594] The CPB score was superior to the 4T score and the HEP score for identification of HIT in patients following cardiac surgery in a recent retrospective study.[595] None of the HIT pre-test probability models has been prospectively assessed in patients with cancer and may have less utility in this population, particularly in patients receiving chemotherapy who have alternative causes for thrombocytopenia.[596]

The Panel recommends evaluation using any of the above scoring systems if HIT is suspected. For patients classified as being at low risk for HIT, options include: continue UFH/LMWH, consider alternative causes of thrombocytopenia, monitor clinical status, and consider HIT antibody testing by ELISA in select patients based on clinical judgment. In the case of a negative ELISA test (estimated HIT probability 0%[597,598]), patients should continue UFH/LMWH and be monitored for clinical status. Based on clinical judgment, initiation of argatroban, bivalirudin, or fondaparinux in place of UFH/LMWH may be warranted in select patients. In the case of a positive ELISA test (estimated HIT probability 1.5%[597,598]), the Panel recommends SRA or P-selectin expression assay (PEA) testing and reassessment of risks and benefits of UFH/LMWH versus alternative non-heparin anticoagulant. In the case of a positive SRA/PEA test, the patients should be treated for HIT. In the case of a negative SRA/PEA test, HIT diagnosis and other causes of thrombocytopenia should be reconsidered, and the use of UFH/LMWH can resume.

Patients classified as being at intermediate/high risk for HIT should initially be treated as having a diagnosis of HIT while awaiting confirmatory ELISA test results. UFH/LMWH exposure should be eliminated from all sources (ie, treatment, prophylaxis, line flushes, coated catheters). Warfarin should be discontinued and reversed with vitamin K. Alternative non-heparin anticoagulant should be started. For patients without an indication for therapeutic anticoagulation who are judged to be at high risk of bleeding and moderate risk of HIT, a prophylactic dose of a non-heparin anticoagulant may be considered while awaiting the results of initial testing.[39] Platelet transfusions should be avoided unless the patient is

actively bleeding or is at high risk of bleeding. In the case of a negative ELISA test and intermediate 4T score (estimated HIT probability 0.6%[597,598]), HIT diagnosis and other causes of thrombocytopenia should be reconsidered, and the use of UFH/LMWH can resume. In the case of a negative ELISA test and high 4T/HEP/CPB score (estimated HIT probability 6.6%[597,598]), the Panel recommends continuation of alternative non-heparin anticoagulant and repeat ELISA/SRA/PEA test. Institution-specific ELISA optical density value thresholds should be considered when determining whether to send for SRA/PEA testing. In the event of a positive test result, the patient should be treated for HIT. A negative repeat ELISA/SRA/PEA test result warrants reconsideration of HIT diagnosis and other causes of thrombocytopenia, as well as resumption of UFH/LMWH. In the case of a positive ELISA test and intermediate or high 4T score (estimated HIT probability 54%–93%, respectively[597,598]), or high HEP/CPB score, the patient should be treated for HIT.

Anticoagulants for the Treatment of HIT

Direct Thrombin Inhibitors

Argatroban is approved by the FDA for the immediate treatment of HIT.[599] Argatroban is primarily metabolized by the liver, and prolonged clearance of this agent has been seen in patients with hepatic insufficiency.[599] Thus, its use should be avoided in patients with hepatic failure. The manufacturer-recommended dose for argatroban, similar to that of many anticoagulants, may be too high for the treatment of HIT in patients who are critically ill, and thus should be lowered.[600-602] In a prospective randomized trial, argatroban significantly reduced the combined endpoint of death, limb amputation, and occurrence of new thrombotic events among patients with HIT without thrombosis compared with historical controls (25.6% vs. 38.8%; *P* = .014). No significant differences in the combined endpoint were noted with argatroban versus control among patients with HIT and thrombosis.[603] Similarly, results from the second trial of argatroban showed significantly decreased incidence of the combined endpoint with argatroban compared with historical controls in patients with HIT without thrombosis (28.0% vs. 38.8%; *P* = .04), but not in patients with HIT and thrombosis (41.5% vs. 56.5%; *P* = .07).[604] In both trials, argatroban was shown to significantly decrease the incidence of death due to thrombosis, as well as the incidence of new thrombosis compared with controls (*P* < .05), regardless of concurrent thrombosis status.[603,604]

Bivalirudin is another DTI recommended for the off-label treatment of HIT. Similar to argatroban, dose reductions are suggested for bivalirudin in patients with HIT and hepatic and/or renal insufficiency or critical illness.[605,606] Besides smaller retrospective studies,[605,606] data regarding bivalirudin use in HIT are limited. The largest retrospective study of bivalirudin included 386 patients with suspected or confirmed HIT. Of these, 57.8% had thrombosis at HIT diagnosis and 4.6% developed new thrombosis while on bivalirudin. Major bleeding occurred in 7.6% of patients, with a significant increase in the population with critical illness (13.1%; OR, 2.4; 95% CI, 1.2–4.9; *P* = .014); the 30-day all-cause mortality rate was 14.5% with 1.7% of deaths being HIT-related.[607] It is important to note that bivalirudin has been associated with anaphylaxis. Overall, no head-to-head trials comparing different DTIs in the treatment of HIT have been published. Clinician experience and comfort level with the agents used should be a consideration in the choice of therapy.

Indirect Factor Xa Inhibitor

Fondaparinux is a recommended alternative to parenteral DTIs in HIT treatment. There have been rare reports of fondaparinux use and development of HIT, although in most cases patients had prior exposure to UFH or LMWH.[608-611] Thus, the NCCN Panel recommends fondaparinux as a second-line agent. The two largest retrospective studies demonstrating fondaparinux safety and efficacy for HIT treatment enrolled 84 and 133 patients, respectively.[612,613] In the first study, thrombosis and

bleeding occurred in 16.5% and 21.1% of patients in the fondaparinux group, compared with 21.4% and 20% in the control group (treated with argatroban or danaparoid).[613] In the second study, HIT-specific complications and all-cause in-hospital mortality occurred in 0% of patients in the fondaparinux group, compared with 11.7% and 6.3% of patients treated with argatroban, lepirudin, or danaparoid.[612] Fondaparinux has also been used in case reports and smaller studies for patients with HIT and generally appears to be safe.[614-617]

Direct Oral Anticoagulants

Apixaban, rivaroxaban, dabigatran, and edoxaban are rarely used for the initial treatment of HIT; however, they may be a reasonable option for patients who have stabilized on initial treatment for HIT using a DTI or fondaparinux, have no procedures planned, and have no contraindications. The use of apixaban[618-624] and dabigatran[624-627] for HIT treatment is limited to case reports and small retrospective studies that included very small numbers of patients with cancer. The most evidence supporting the use of DOACs is with rivaroxaban, which includes case reports, a systematic review, and a small prospective study.[623,624,628-636] In the systematic review, a thrombosis rate of 1 of 46 patients (2.2%; 95% CI, 0.4%–11.3%) and no major hemorrhage were reported in patients treated with rivaroxaban during acute HIT; similar results were reported for apixaban and dabigatran.[636] The only literature report on the use of edoxaban for HIT treatment is a case study of one patient who underwent surgery for esophageal cancer.[637]

Warfarin

The Panel recommends that warfarin should not be initiated in patients with HIT until after platelet count recovery because of the potential for skin necrosis and/or venous gangrene.[414,638] After platelet recovery, warfarin should be overlapped with a DTI or fondaparinux for at least 5 days; the DTI or fondaparinux should be discontinued only after the INR has reached the intended target range (INR 2–3) for 24 hours. Since both DTIs and warfarin reduce thrombin activity, coadministration of a DTI and warfarin produces a combined effect on laboratory measurements of both aPTT and INR. However, concurrent therapy, compared with warfarin monotherapy, exerts no additional effect on vitamin K-dependent factor X activity. Therefore, the anticoagulation impact of warfarin may be underestimated in the presence of a DTI. DTIs can prolong the INR during co-therapy with warfarin. Since argatroban has the lowest affinity for thrombin of the two DTIs, higher molar plasma concentrations of argatroban are needed to prolong the aPTT; hence, prolongation of INR is more pronounced with argatroban compared with the other DTIs.[639,640] A higher target INR should therefore be achieved before argatroban is discontinued.[414,599,640] Once the DTI is discontinued, a repeat INR and aPTT should be obtained 2 to 6 hours later to determine whether the INR is therapeutic on warfarin monotherapy. Alternatively, chromogenic factor X levels (which are not affected by DTIs) can be used to monitor warfarin activity during transition from co-therapy with argatroban.[641,642]

Platelet Transfusions

As noted above, platelet transfusions should be avoided unless the patient is actively bleeding or is at high risk of bleeding.

Patient Resources for VTE Management

- National Blood Clot Alliance - www.stoptheclot.org
- ClotCare Online Resource - http://www.clotcare.com/
- North American Thrombosis Forum - http://natfonline.org/patients

References

1. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005;293:715-722. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15701913.

2. Mulder FI, Horvath-Puho E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood 2021;137:1959-1969. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33171494.

3. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer 2013;119:648-655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22893596.

4. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5:632-634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17319909.

5. Khorana AA, Francis CW, Culakova E, et al. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 2007;110:2339-2346. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17918266.

6. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism in hospitalized neutropenic cancer patients. J Clin Oncol 2006;24:484-490. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16421425.

7. Fotopoulou C, duBois A, Karavas AN, et al. Incidence of venous thromboembolism in patients with ovarian cancer undergoing platinum/paclitaxel-containing first-line chemotherapy: an exploratory analysis by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group. J Clin Oncol 2008;26:2683-2689. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18509180.

8. Chew HK, Wun T, Harvey D, et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 2006;166:458-464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16505267.

9. Chew HK, Wun T, Harvey DJ, et al. Incidence of venous thromboembolism and the impact on survival in breast cancer patients. J Clin Oncol 2007;25:70-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17194906.

10. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000;343:1846-1850. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11117976.

11. Kuderer NM, Francis CW, Culakova E, et al. Venous thromboembolism and all-cause mortality in cancer patients receiving chemotherapy (abstract). J Clin Oncol 2008;26(Suppl 15):Abstract 9521. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/9521.

12. Martino MA, Williamson E, Siegfried S, et al. Diagnosing pulmonary embolism: experience with spiral CT pulmonary angiography in gynecologic oncology. Gynecol Oncol 2005;98:289-293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15950268.

13. Agnelli G, Bolis G, Capussotti L, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg 2006;243:89-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16371741.

14. Ohashi Y, Ikeda M, Kunitoh H, et al. Venous thromboembolism in cancer patients: report of baseline data from the multicentre, prospective Cancer-VTE Registry. Jpn J Clin Oncol 2020;50:1246-1253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32715307.

15. Rickles FR, Levine MN. Epidemiology of thrombosis in cancer. Acta Haematol 2001;106:6-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11549771.

16. Key NS, Khorana AA, Kuderer NM, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2020;38:496-520. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31381464.

17. Farge D, Bounameaux H, Brenner B, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol 2016;17:e452-e466. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27733271.

18. Heit JA, Silverstein MD, Mohr DN, et al. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med 1999;159:445-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10074952.

19. Aggarwal A, Fullam L, Brownstein AP, et al. Deep vein thrombosis (DVT) and pulmonary embolism (PE): awareness and prophylaxis practices reported by patients with cancer. Cancer Invest 2015;33:405-410. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26181096.

20. Secin FP, Jiborn T, Bjartell AS, et al. Multi-institutional study of symptomatic deep venous thrombosis and pulmonary embolism in prostate cancer patients undergoing laparoscopic or robot-assisted laparoscopic radical prostatectomy. Eur Urol 2008;53:134-145. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17597288.

21. Girard P, Decousus M, Laporte S, et al. Diagnosis of pulmonary embolism in patients with proximal deep vein thrombosis: specificity of symptoms and perfusion defects at baseline and during anticoagulant therapy. Am J Respir Crit Care Med 2001;164:1033-1037. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11587992.

22. Anderson FA, Jr., Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991;151:933-938. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2025141.

23. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. JAMA 2014;311:717-728. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24549552.

24. PubMed Overview. Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed June 5, 2024.

25. Ageno W, Squizzato A, Garcia D, Imberti D. Epidemiology and risk factors of venous thromboembolism. Semin Thromb Hemost 2006;32:651-658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17024592.

26. Connolly GC, Khorana AA. Emerging risk stratification approaches to cancer-associated thrombosis: risk factors, biomarkers and a risk score. Thromb Res 2010;125 Suppl 2:1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20433985.

27. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:4902-4907. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18216292.

28. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med 2005;118:978-980. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16164883.

29. Borch KH, Hansen-Krone I, Braekkan SK, et al. Physical activity and risk of venous thromboembolism. The Tromso study. Haematologica 2010;95:2088-2094. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20801904.

30. Cheng YJ, Liu ZH, Yao FJ, et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. PLoS Med 2013;10:e1001515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24068896.

31. Enga KF, Braekkan SK, Hansen-Krone IJ, et al. Cigarette smoking and the risk of venous thromboembolism: the Tromso Study. J Thromb Haemost 2012;10:2068-2074. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22882779.

32. Hansson PO, Eriksson H, Welin L, et al. Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: "the study of men born in 1913". Arch Intern Med 1999;159:1886-1890. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10493318.

33. Danin-Mankowitz H, Ugarph-Morawski A, Braunschweig F, Wandell P. The risk of venous thromboembolism and physical activity level, especially high level: a systematic review. J Thromb Thrombolysis 2021;52:508-516. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33389612.

34. van Stralen KJ, Doggen CJ, Lumley T, et al. The relationship between exercise and risk of venous thrombosis in elderly people. J Am Geriatr Soc 2008;56:517-522. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18179500.

35. Mahmoodi BK, Brouwer JL, Ten Kate MK, et al. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. J Thromb Haemost 2010;8:1193-1200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20230415.

36. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996;88:3698-3703. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8916933.

37. Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019-1027. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11953980.

38. Ginsburg KS, Liang MH, Newcomer L, et al. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. Ann Intern Med 1992;117:997-1002. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1443986.

39. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv 2018;2:3360-3392. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30482768.

40. Segal JB, Streiff MB, Hofmann LV, et al. Management of venous thromboembolism: a systematic review for a practice guideline. Ann Intern Med 2007;146:211-222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17261856.

41. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance--United States, 1991--1999. MMWR Surveill Summ 2003;52:1-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12825542.

42. Rogers MA, Levine DA, Blumberg N, et al. Triggers of hospitalization for venous thromboembolism. Circulation 2012;125:2092-2099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22474264.

43. Schmidt M, Horvath-Puho E, Thomsen RW, et al. Acute infections and venous thromboembolism. J Intern Med 2012;271:608-618. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22026462.

44. Mandalà M, Barni S, Prins M, et al. Acquired and inherited risk factors for developing venous thromboembolism in cancer patients receiving adjuvant chemotherapy: a prospective trial. Ann Oncol 2010;21:871-876. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19713246.

45. Lu HY, Liao KM. Increased risk of deep vein thrombosis in end-stage renal disease patients. BMC Nephrol 2018;19:204. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30115029.

46. Monreal M, Falga C, Valle R, et al. Venous thromboembolism in patients with renal insufficiency: findings from the RIETE Registry. Am J Med 2006;119:1073-1079. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17145252.

47. Wattanakit K, Cushman M, Stehman-Breen C, et al. Chronic kidney disease increases risk for venous thromboembolism. J Am Soc Nephrol 2008;19:135-140. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18032796.

48. Borvik T, Braekkan SK, Enga K, et al. COPD and risk of venous thromboembolism and mortality in a general population. Eur Respir J 2016;47:473-481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26585434.

49. Kim V, Goel N, Gangar J, et al. Risk factors for venous thromboembolism in chronic obstructive pulmonary disease. Chronic Obstr Pulm Dis 2014;1:239-249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25844397.

50. Piazza G, Goldhaber SZ, Kroll A, et al. Venous thromboembolism in patients with chronic obstructive pulmonary disease. Am J Med 2012;125:1010-1018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22884176.

51. Bertoletti L, Quenet S, Laporte S, et al. Pulmonary embolism and 3-month outcomes in 4036 patients with venous thromboembolism and chronic obstructive pulmonary disease: data from the RIETE registry. Respir Res 2013;14:75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23865769.

52. Tang L, Wu YY, Lip GY, et al. Heart failure and risk of venous thromboembolism: a systematic review and meta-analysis. Lancet Haematol 2016;3:e30-44. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26765646.

53. Leizorovicz A, Turpie AG, Cohen AT, et al. Epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis. The SMART study. J Thromb Haemost 2005;3:28-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15634263.

54. Eliasson A, Bergqvist D, Bjorck M, et al. Incidence and risk of venous thromboembolism in patients with verified arterial thrombosis: a population study based on 23,796 consecutive autopsies. J Thromb Haemost 2006;4:1897-1902. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16881933.

55. Hong C, Zhu F, Du D, et al. Coronary artery calcification and risk factors for atherosclerosis in patients with venous thromboembolism. Atherosclerosis 2005;183:169-174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15939424.

56. Prandoni P, Bilora F, Marchiori A, et al. An association between atherosclerosis and venous thrombosis. N Engl J Med 2003;348:1435-1441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12686699.

57. Darze ES, Latado AL, Guimaraes AG, et al. Incidence and clinical predictors of pulmonary embolism in severe heart failure patients admitted to a coronary care unit. Chest 2005;128:2576-2580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16236926.

58. Kroger K, Weiland D, Ose C, et al. Risk factors for venous thromboembolic events in cancer patients. Ann Oncol 2006;17:297-303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16282243.

59. Prandoni P, Lensing AWA, Prins MH, et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. Ann Intern Med 2002;137:955-960. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12484710.

60. Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484-3488. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393647.

61. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med 2002;162:1245-1248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12038942.

62. Beam DM, Courtney DM, Kabrhel C, et al. Risk of thromboembolism varies, depending on category of immobility in outpatients. Ann Emerg Med 2009;54:147-152. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19135280.

63. Flinterman LE, van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Body height, mobility, and risk of first and recurrent venous thrombosis. J Thromb Haemost 2015;13:548-554. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25627967.

64. Venous thromboembolism in adult hospitalizations - United States, 2007-2009. MMWR Morb Mortal Wkly Rep 2012;61:401-404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22672974.

65. Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore) 1999;78:285-291. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10499070.

66. Ogren M, Bergqvist D, Wahlander K, et al. Trousseau's syndrome - what is the evidence? A population-based autopsy study. Thromb Haemost 2006;95:541-545. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16525584.

67. Sallah S, Wan JY, Nguyen NP. Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. Thromb Haemost 2002;87:575-579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12008937.

68. Hall IE, Andersen MS, Krumholz HM, Gross CP. Predictors of venous thromboembolism in patients with advanced common solid cancers. J Cancer Epidemiol 2009;2009:182521-182521. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20445797.

69. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. Cancer 2000;89:640-646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10931464.

70. Khorana AA, Francis CW, Menzies KE, et al. Plasma tissue factor may be predictive of venous thromboembolism in pancreatic cancer. J Thromb Haemost 2008;6:1983-1985. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18795992.

71. Khorana AA, Ahrendt SA, Ryan CK, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. Clin Cancer Res 2007;13:2870-2875. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17504985.

72. Andtbacka RHI, Babiera G, Singletary SE, et al. Incidence and prevention of venous thromboembolism in patients undergoing breast cancer surgery and treated according to clinical pathways. Ann Surg 2006;243:96-9101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16371742.

73. Carrier M, Le Gal G, Tay J, et al. Rates of venous thromboembolism in multiple myeloma patients undergoing immunomodulatory therapy with thalidomide or lenalidomide: a systematic review and meta-analysis. J Thromb Haemost 2011;9:653-663. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21255254.

74. De Stefano V, Sora F, Rossi E, et al. The risk of thrombosis in patients with acute leukemia: occurrence of thrombosis at diagnosis and during treatment. J Thromb Haemost 2005;3:1985-1992. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16102104.

75. Mohren M, Markmann I, Jentsch-Ullrich K, et al. Increased risk of thromboembolism in patients with malignant lymphoma: a single-centre analysis. Br J Cancer 2005;92:1349-1351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15798767.

76. Ottinger H, Belka C, Kozole G, et al. Deep venous thrombosis and pulmonary artery embolism in high-grade non Hodgkin's lymphoma: incidence, causes and prognostic relevance. Eur J Haematol 1995;54:186-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7720839.

77. Hicks LK, Cheung MC, Ding K, et al. Venous thromboembolism and nonsmall cell lung cancer: a pooled analysis of National Cancer Institute of

Canada Clinical Trials Group trials. Cancer 2009;115:5516-5525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19711465.

78. Sandhu R, Pan C-X, Wun T, et al. The incidence of venous thromboembolism and its effect on survival among patients with primary bladder cancer. Cancer 2010;116:2596-2603. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20336780.

79. Gade IL, Braekkan SK, Naess IA, et al. The impact of initial cancer stage on the incidence of venous thromboembolism: the Scandinavian Thrombosis and Cancer (STAC) Cohort. J Thromb Haemost 2017;15:1567-1575. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28585779.

80. Hammond J, Kozma C, Hart JC, et al. Rates of venous thromboembolism among patients with major surgery for cancer. Ann Surg Oncol 2011;18:3240-3247. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21584837.

81. Toledano TH, Kondal D, Kahn SR, Tagalakis V. The occurrence of venous thromboembolism in cancer patients following major surgery. Thromb Res 2013;131:e1-5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23174626.

82. Baarslag HJ, Koopman MMW, Hutten BA, et al. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med 2004;15:503-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15668085.

83. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 2000;160:809-815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10737280.

84. Prandoni P, Polistena P, Bernardi E, et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med 1997;157:57-62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8996041.

85. Lee AYY, Levine MN, Butler G, et al. Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. J Clin Oncol 2006;24:1404-1408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16549834.

86. Gerber DE, Segal JB, Levy MY, et al. The incidence of and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation: implications for VTE prevention. Blood 2008;112:504-510. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18480425.

87. Joffe HV, Goldhaber SZ. Upper-extremity deep vein thrombosis. Circulation 2002;106:1874-1880. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12356644.

88. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol 2003;21:3665-3675. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14512399.

89. van Rooden CJ, Schippers EF, Barge RMY, et al. Infectious complications of central venous catheters increase the risk of catheter-related thrombosis in hematology patients: a prospective study. J Clin Oncol 2005;23:2655-2660. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15837979.

90. Lordick F, Hentrich M, Decker T, et al. Ultrasound screening for internal jugular vein thrombosis aids the detection of central venous catheter-related infections in patients with haemato-oncological diseases: a prospective observational study. Br J Haematol 2003;120:1073-1078. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12648081.

91. Khorana AA, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 2005;104:2822-2829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16284987.

92. Otten HM, Mathijssen J, ten Cate H, et al. Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an

underestimated phenomenon. Arch Intern Med 2004;164:190-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14744843.

93. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999;281:2189-2197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10376571.

94. Decensi A, Maisonneuve P, Rotmensz N, et al. Effect of tamoxifen on venous thromboembolic events in a breast cancer prevention trial. Circulation 2005;111:650-656. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15699284.

95. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652-1662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16288118.

96. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371-1388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9747868.

97. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res (Phila) 2010;3:696-706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20404000.

98. Leaf AN, Propert K, Corcoran C, et al. Phase III study of combined chemohormonal therapy in metastatic prostate cancer (ECOG 3882): an Eastern Cooperative Oncology Group study. Med Oncol 2003;20:137-146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12835516.

99. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701-1712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15082697.

100. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12117397.

101. Blanco-Molina A, Trujillo-Santos J, Tirado R, et al. Venous thromboembolism in women using hormonal contraceptives. Findings from the RIETE Registry. Thromb Haemost 2009;101:478-482. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19277408.

102. Lidegaard O, Nielsen LH, Skovlund CW, et al. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22027398.

103. Manzoli L, De Vito C, Marzuillo C, et al. Oral contraceptives and venous thromboembolism: a systematic review and meta-analysis. Drug Saf 2012;35:191-205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22283630.

104. Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ 2011;342:d2151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21511805.

105. Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ 2011;342:d2139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21511804.

106. Tepper NK, Dragoman MV, Gaffield ME, Curtis KM. Nonoral combined hormonal contraceptives and thromboembolism: a systematic

review. Contraception 2017;95:130-139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27771476.

107. El Accaoui RN, Shamseddeen WA, Taher AT. Thalidomide and thrombosis. A meta-analysis. Thromb Haemost 2007;97:1031-1036. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17549307.

108. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133-2142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18032763.

109. Zangari M, Siegel E, Barlogie B, et al. Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. Blood 2002;100:1168-1171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12149193.

110. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 2008;299:914-924. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18314434.

111. Connolly GC, Dalal M, Lin J, Khorana AA. Incidence and predictors of venous thromboembolism (VTE) among ambulatory patients with lung cancer. Lung Cancer 2012;78:253-258. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23026639.

112. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. Blood 2010;116:5377-5382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20829374.

113. Mandala M, Clerici M, Corradino I, et al. Incidence, risk factors and clinical implications of venous thromboembolism in cancer patients treated within the context of phase I studies: the 'SENDO experience'. Ann Oncol 2012;23:1416-1421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22052988.

114. Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol 2011;29:3466-3473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21810688.

115. Kearney JC, Rossi S, Glinert K, Henry DH. Venous Thromboembolism (VTE) and Survival in a Cancer Chemotherapy Outpatient Clinic: A Retrospective Chart Review Validation of a VTE Predictive Model [abstract]. Blood 2009;114:Abstract 2503. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/2503.

116. Price LH, Nguyen MB, Picozzi VJ, Kozarek RA. Portal vein thrombosis in pancreatic cancer: Natural history, risk factors, and implications for patient management [abstract]. Proceedings of the Gastrointestinal Cancers Symposium 2010:Abstract 143. Available at: https://meetinglibrary.asco.org/content/1359-72.

117. Pabinger I, van Es N, Heinze G, et al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. Lancet Haematol 2018;5:e289-e298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29885940.

118. Verso M, Agnelli G, Barni S, et al. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med 2012;7:291-292. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22547369.

119. Pelzer U, Sinn M, Stieler J, Riess H. [Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy?]. Dtsch Med Wochenschr 2013;138:2084-2088. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24085361.

120. Cella CA, Di Minno G, Carlomagno C, et al. Preventing venous thromboembolism in ambulatory cancer patients: The ONKOTEV study.

Oncologist 2017;22:601-608. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28424324.

121. Munoz Martin AJ, Ortega I, Font C, et al. Multivariable clinical-genetic risk model for predicting venous thromboembolic events in patients with cancer. Br J Cancer 2018;118:1056-1061. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29588512.

122. Gerotziafas GT, Taher A, Abdel-Razeq H, et al. A Predictive Score for Thrombosis Associated with Breast, Colorectal, Lung, or Ovarian Cancer: The Prospective COMPASS-Cancer-Associated Thrombosis Study. Oncologist 2017;22:1222-1231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28550032.

123. van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica 2017;102:1494-1501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28550192.

124. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med 2019;380:720-728. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30786186.

125. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 2019;380:711-719. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30511879.

126. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:381S-453S. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18574271.

127. Kahn SR, Morrison DR, Diendere G, et al. Interventions for implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism. Cochrane Database Syst Rev 2018;4:CD008201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29687454.

128. Kakkar VV, Corrigan TP, Fossard DP, et al. Prevention of Fatal Postoperative pulmonary embolism by low doses of heparin. Reappraisal of results of international multicentre trial. Lancet 1977;1:567-569. Available at: https://www.ncbi.nlm.nih.gov/pubmed/65660.

129. Mismetti P, Laporte S, Darmon JY, et al. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001;88:913-930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11442521.

130. Agnelli G, Bergqvist D, Cohen AT, et al. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg 2005;92:1212-1220. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16175516.

131. Kakkar AK, Levine M, Pinedo HM, et al. Venous thrombosis in cancer patients: insights from the FRONTLINE survey. Oncologist 2003;8:381-388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12897335.

132. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008;371:387-394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18242412.

133. Tapson VF, Decousus H, Pini M, et al. Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. Chest 2007;132:936-945. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17573514.

134. Couban S, Goodyear M, Burnell M, et al. Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. J Clin Oncol 2005;23:4063-4069. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15767639.

135. Karthaus M, Kretzschmar A, Kroning H, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. Ann Oncol 2006;17:289-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16317012.

136. Verso M, Agnelli G, Bertoglio S, et al. Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. J Clin Oncol 2005;23:4057-4062. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15767643.

137. Young AM, Billingham LJ, Begum G, et al. Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. Lancet 2009;373:567-574. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19217991.

138. Li A, Brandt W, Brown C, et al. Efficacy and safety of primary thromboprophylaxis for the prevention of venous thromboembolism in patients with cancer and a central venous catheter: A systematic review and meta-analysis. Thromb Res 2021;208:58-65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34715510.

139. Brandt W, Brown C, Wang TF, et al. Efficacy and safety of apixaban for primary prevention of thromboembolism in patients with cancer and a central venous catheter: A subgroup analysis of the AVERT Trial. Thromb Res 2022;216:8-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35660801.

140. Spyropoulos AC, Anderson FA, Jr., Fitzgerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest 2011;140:706-714. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21436241.

141. Grant PJ, Greene MT, Chopra V, et al. Assessing the Caprini Score for Risk Assessment of Venous Thromboembolism in Hospitalized Medical Patients. Am J Med 2016;129:528-535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26551977.

142. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost 2010;8:2450-2457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20738765.

143. Greene MT, Spyropoulos AC, Chopra V, et al. Validation of risk assessment models of venous thromboembolism in hospitalized medical patients. Am J Med 2016;129:1001.e9-1001.e18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27107925.

144. Prescribing information for dalteparin sodium injection, for subcutaneous use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020287Orig1s076lbl.pdf. Accessed June 5, 2024.

145. Kucher N, Leizorovicz A, Vaitkus PT, et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005;165:341-345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15710801.

146. Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874-879. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15289368.

147. Prescribing information for enoxparin sodium injection, for subcutaneous and intravenous use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020164s129lbl.pdf. Accessed June 5, 2024.

148. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999;341:793-800. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10477777.

149. Lederle FA, Sacks JM, Fiore L, et al. The prophylaxis of medical patients for thromboembolism pilot study. Am J Med 2006;119:54-59. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16431185.

150. Kakkar AK, Cimminiello C, Goldhaber SZ, et al. Low-molecular-weight heparin and mortality in acutely ill medical patients. N Engl J Med 2011;365:2463-2472. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22204723.

151. Prescribing information for fondaparinux sodium injection, for subcutaneous use. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021345Orig1s043lbl.pdf. Accessed June 5, 2024.

152. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e195S-226S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22315261.

153. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006;332:325-329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16439370.

154. Belch JJ, Lowe GD, Ward AG, et al. Prevention of deep vein thrombosis in medical patients by low-dose heparin. Scott Med J 1981;26:115-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7291971.

155. Dentali F, Douketis JD, Gianni M, et al. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med 2007;146:278-288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17310052.

156. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg 1988;208:227-240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2456748.

157. Kovacs MJ, Kahn SR, Rodger M, et al. A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (The Catheter Study). J Thromb Haemost 2007;5:1650-1653. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17488349.

158. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. Lancet 1975;2:45-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/49649.

159. Gruber UF, Duckert F, Fridrich R, et al. Prevention of postoperative thromboembolism by dextran 40, low doses of heparin, or xantinol nicotinate. Lancet 1977;1:207-210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/64746.

160. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P, et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. J Thromb Haemost 2006;4:2384-2390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16881934.

161. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002;346:975-980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11919306.

162. Turpie AG, Bauer KA, Caprini JA, et al. Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison. J Thromb Haemost 2007;5:1854-1861. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17723125.

163. Kakkar VV, Boeckl O, Boneu B, et al. Efficacy and safety of a low-molecular-weight heparin and standard unfractionated heparin for prophylaxis of postoperative venous thromboembolism: European multicenter trial. World J Surg 1997;21:2-8; discussion 8-9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8943170.

164. Koppenhagen K, Adolf J, Matthes M, et al. Low molecular weight heparin and prevention of postoperative thrombosis in abdominal surgery. Thromb Haemost 1992;67:627-630. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1324534.

165. McLeod RS, Geerts WH, Sniderman KW, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial. Ann Surg 2001;233:438-444. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11224634.

166. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. ENOXACAN Study Group. Br J Surg 1997;84:1099-1103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9278651.

167. Guntupalli SR, Brennecke A, Behbakht K, et al. Safety and efficacy of apixaban vs enoxaparin for preventing postoperative venous thromboembolism in women undergoing surgery for gynecologic malignant neoplasm: A randomized clinical trial. JAMA Netw Open 2020;3:e207410. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32589230.

168. Becattini C, Pace U, Pirozzi F, et al. Rivaroxaban vs placebo for extended antithrombotic prophylaxis after laparoscopic surgery for colorectal cancer. Blood 2022;140:900-908. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35580191.

169. McGowan KE, Makari J, Diamantouros A, et al. Reducing the hospital burden of heparin-induced thrombocytopenia: impact of an avoid-heparin program. Blood 2016;127:1954-1959. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26817956.

170. Akl EA, Terrenato I, Barba M, et al. Low-molecular-weight heparin vs unfractionated heparin for perioperative thromboprophylaxis in patients with cancer: a systematic review and meta-analysis. Arch Intern Med 2008;168:1261-1269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18574082.

171. DeBernardo RL, Perkins RB, Littell RD, et al. Low-molecular-weight heparin (dalteparin) in women with gynecologic malignancy. Obstet Gynecol 2005;105:1006-1011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15863537.

172. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother 2009;43:1064-1083. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19458109.

173. Becker RC, Spencer FA, Gibson M, et al. Influence of patient characteristics and renal function on factor Xa inhibition pharmacokinetics and pharmacodynamics after enoxaparin administration in non-ST-segment elevation acute coronary syndromes. Am Heart J 2002;143:753-759. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12040334.

174. Bazinet A, Almanric K, Brunet C, et al. Dosage of enoxaparin among obese and renal impairment patients. Thromb Res 2005;116:41-50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15850607.

175. Chow SL, Zammit K, West K, et al. Correlation of antifactor Xa concentrations with renal function in patients on enoxaparin. J Clin Pharmacol 2003;43:586-590. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12817521.

176. Shprecher AR, Cheng-Lai A, Madsen EM, et al. Peak antifactor Xa activity produced by dalteparin treatment in patients with renal impairment compared with controls. Pharmacotherapy 2005;25:817-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15927900.

177. Polkinghorne KR, McMahon LP, Becker GJ. Pharmacokinetic studies of dalteparin (Fragmin), enoxaparin (Clexane), and danaparoid sodium (Orgaran) in stable chronic hemodialysis patients. Am J Kidney Dis 2002;40:990-995. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12407644.

178. Lim W, Dentali F, Eikelboom JW, Crowther MA. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal

insufficiency. Ann Intern Med 2006;144:673-684. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16670137.

179. Spinler SA, Inverso SM, Cohen M, et al. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J 2003;146:33-41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12851605.

180. Thorevska N, Amoateng-Adjepong Y, Sabahi R, et al. Anticoagulation in hospitalized patients with renal insufficiency: a comparison of bleeding rates with unfractionated heparin vs enoxaparin. Chest 2004;125:856-863. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15006942.

181. Collet JP, Montalescot G, Agnelli G, et al. Non-ST-segment elevation acute coronary syndrome in patients with renal dysfunction: benefit of low-molecular-weight heparin alone or with glycoprotein IIb/IIIa inhibitors on outcomes. The Global Registry of Acute Coronary Events. Eur Heart J 2005;26:2285-2293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15932908.

182. Fox KA, Bassand JP, Mehta SR, et al. Influence of renal function on the efficacy and safety of fondaparinux relative to enoxaparin in non ST-segment elevation acute coronary syndromes. Ann Intern Med 2007;147:304-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17785485.

183. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. Obes Surg 2002;12:19-24. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11868291.

184. Borkgren-Okonek MJ, Hart RW, Pantano JE, et al. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. Surg Obes Relat Dis 2008;4:625-631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18261965.

185. Simone EP, Madan AK, Tichansky DS, et al. Comparison of two low-molecular-weight heparin dosing regimens for patients undergoing laparoscopic bariatric surgery. Surg Endosc 2008;22:2392-2395. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18594915.

186. Frederiksen SG, Hedenbro JL, Norgren L. Enoxaparin effect depends on body-weight and current doses may be inadequate in obese patients. Br J Surg 2003;90:547-548. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12734859.

187. Martinez L, Burnett A, Borrego M, et al. Effect of fondaparinux prophylaxis on anti-factor Xa concentrations in patients with morbid obesity. Am J Health Syst Pharm 2011;68:1716-1722. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21880887.

188. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). Circulation 1997;96:61-68. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9236418.

189. Simoneau MD, Vachon A, Picard F. Effect of prophylactic dalteparin on anti-factor Xa levels in morbidly obese patients after bariatric surgery. Obes Surg 2010;20:487-491. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18931882.

190. Gaborit B, Moulin PA, Bege T, et al. Lean body weight is the best scale for venous thromboprophylaxis algorithm in severely obese patients undergoing bariatric surgery. Pharmacol Res 2018;131:211-217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29452290.

191. Freeman AL, Pendleton RC, Rondina MT. Prevention of venous thromboembolism in obesity. Expert Rev Cardiovasc Ther 2010;8:1711-1721. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21108553.

192. Escalante-Tattersfield T, Tucker O, Fajnwaks P, et al. Incidence of deep vein thrombosis in morbidly obese patients undergoing laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis 2008;4:126-130. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18359453.

193. Kardys CM, Stoner MC, Manwaring ML, et al. Safety and efficacy of intravascular ultrasound-guided inferior vena cava filter in super obese bariatric patients. Surg Obes Relat Dis 2008;4:50-54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18065293.

194. Rowan BO, Kuhl DA, Lee MD, et al. Anti-Xa levels in bariatric surgery patients receiving prophylactic enoxaparin. Obes Surg 2008;18:162-166. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18165884.

195. Steib A, Degirmenci SE, Junke E, et al. Once versus twice daily injection of enoxaparin for thromboprophylaxis in bariatric surgery: effects on antifactor Xa activity and procoagulant microparticles. A randomized controlled study. Surg Obes Relat Dis 2016;12:613-621. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26686309.

196. Brunetti L, Wassef A, Sadek R, et al. Anticoagulant activity of enoxaparin and unfractionated heparin for venous thromboembolism prophylaxis in obese patients undergoing sleeve gastrectomy. Surg Obes Relat Dis 2019;15:363-373. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30713119.

197. Celik F, Huitema AD, Hooijberg JH, et al. Fixed-dose enoxaparin after bariatric surgery: the influence of body weight on peak anti-Xa levels. Obes Surg 2015;25:628-634. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25223871.

198. Ojo P, Asiyanbola B, Valin E, Reinhold R. Post discharge prophylactic anticoagulation in gastric bypass patient-how safe? Obes Surg 2008;18:791-796. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18386108.

199. Singh K, Podolsky ER, Um S, et al. Evaluating the safety and efficacy of BMI-based preoperative administration of low-molecular-weight heparin in morbidly obese patients undergoing Roux-en-Y gastric bypass surgery. Obes Surg 2012;22:47-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21476124.

200. Rondina MT, Wheeler M, Rodgers GM, et al. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-Ill patients. Thromb Res 2010;125:220-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19272635.

201. Al Otaib N, Bootah Z, Al Ammari MA, et al. Assessment of anti-factor Xa activity of enoxaparin for venous thromboembolism prophylaxis in morbidly obese surgical patients. Ann Thorac Med 2017;12:199-203. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28808492.

202. Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. Am J Hematol 2012;87:740-743. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22565589.

203. Deremiah E, Franco-Martinez C, Gamboa C, et al. Effectiveness and safety of high-dose thromboprophylaxis in morbidly obese major trauma patients. Hosp Pharm 2023;58:92-97. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36644743.

204. Vaughns JD, Ziesenitz VC, Williams EF, et al. Prophylactic use of enoxaparin in adolescents during bariatric surgery-a prospective clinical study. Obes Surg 2020;30:63-68. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31463801.

205. Steele KE, Canner J, Prokopowicz G, et al. The EFFORT trial: Preoperative enoxaparin versus postoperative fondaparinux for thromboprophylaxis in bariatric surgical patients: a randomized double-blind pilot trial. Surg Obes Relat Dis 2015;11:672-683. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25620436.

206. Buckheit D, Lefemine A, Sobieraj DM, Hobbs L. Venous thromboembolism prophylaxis in underweight hospitalized patients. Clin Appl Thromb Hemost 2021;27:10760296211018752. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34080451.

207. Sebaaly J, Covert K. Enoxaparin dosing at extremes of weight: Literature review and dosing recommendations. Ann Pharmacother 2018;52:898-909. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29592538.

208. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e737S-e801S. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22315277.

209. Warad D, Rao AN, Mullikin T, et al. A retrospective analysis of outcomes of dalteparin use in pediatric patients: a single institution experience. Thromb Res 2015;136:229-233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26026634.

210. Singer GA, Riggi G, Karcutskie CA, et al. Anti-Xa-guided enoxaparin thromboprophylaxis reduces rate of deep venous thromboembolism in high-risk trauma patients. J Trauma Acute Care Surg 2016;81:1101-1108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27488490.

211. Clarke-Pearson DL, Synan IS, Dodge R, et al. A randomized trial of low-dose heparin and intermittent pneumatic calf compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. Am J Obstet Gynecol 1993;168:1146-1153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8475960.

212. Ramirez JI, Vassiliu P, Gonzalez-Ruiz C, et al. Sequential compression devices as prophylaxis for venous thromboembolism in high-risk colorectal surgery patients: reconsidering American Society of Colorectal Surgeons parameters. Am Surg 2003;69:941-945. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14627252.

213. Collaboration CT, Dennis M, Sandercock P, et al. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet 2013;382:516-524. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23727163.

214. CLOTS Trials Collaboration, Dennis M, Sandercock PA, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet 2009;373:1958-1965. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19477503.

215. Martino MA, Borges E, Williamson E, et al. Pulmonary embolism after major abdominal surgery in gynecologic oncology. Obstet Gynecol 2006;107:666-671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16507939.

216. Arabi YM, Al-Hameed F, Burns KEA, et al. Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. N Engl J Med 2019;380:1305-1315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30779530.

217. Amaragiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev 2000:CD001484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10908501.

218. Sachdeva A, Dalton M, Lees T. Graduated compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev 2018;11:CD001484. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30390397.

219. Cohen AT, Skinner JA, Warwick D, Brenkel I. The use of graduated compression stockings in association with fondaparinux in surgery of the hip. A multicentre, multinational, randomised, open-label, parallel-group comparative study. J Bone Joint Surg Br 2007;89:887-892. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17673580.

220. Shalhoub J, Lawton R, Hudson J, et al. Graduated compression stockings as adjuvant to pharmaco-thromboprophylaxis in elective surgical patients (GAPS study): randomised controlled trial. BMJ 2020;369:m1309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32404430.

221. Spencer FA, Lessard D, Emery C, et al. Venous thromboembolism in the outpatient setting. Arch Intern Med 2007;167:1471-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17646600.

222. Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer 2012;48:1283-1292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22100906.

223. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: Outcomes from the CONKO-004 trial. J Clin Oncol 2015;33:2028-2034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25987694.

224. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e227S-277S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22315263.

225. Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev 2019;8:CD004318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31449321.

226. Napolitano M, Saccullo G, Marietta M, et al. Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and venous thromboembolism: an expert consensus. Blood Transfus 2019;17:171-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30418130.

227. Khanal N, Bociek RG, Chen B, et al. Venous thromboembolism in patients with hematologic malignancy and thrombocytopenia. Am J Hematol 2016;91:E468-E472. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27489982.

228. Herishanu Y, Misgav M, Kirgner I, et al. Enoxaparin can be used safely in patients with severe thrombocytopenia due to intensive chemotherapy regimens. Leuk Lymphoma 2004;45:1407-1411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15359641.

229. Houghton DE, Key NS, Zakai NA, et al. Analysis of anticoagulation strategies for venous thromboembolism during severe thrombocytopenia in patients with hematologic malignancies: a retrospective cohort. Leuk Lymphoma 2017;58:2573-2581. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28393576.

230. Cervera R, Khamashta MA, Shoenfeld Y, et al. Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2009;68:1428-1432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18801761.

231. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. JAMA 2006;295:1050-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16507806.

232. Palfreyman SJ, Michaels JA. A systematic review of compression hosiery for uncomplicated varicose veins. Phlebology 2009;24 Suppl 1:13-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19307438.

233. Decousus H, Quere I, Presles E, et al. Superficial venous thrombosis and venous thromboembolism: a large, prospective epidemiologic study. Ann Intern Med 2010;152:218-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20157136.

234. Gorty S, Patton-Adkins J, DaLanno M, et al. Superficial venous thrombosis of the lower extremities: analysis of risk factors, and recurrence and role of anticoagulation. Vasc Med 2004;9:1-6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15230481.

235. Periard D, Monney P, Waeber G, et al. Randomized controlled trial of peripherally inserted central catheters vs. peripheral catheters for middle duration in-hospital intravenous therapy. J Thromb Haemost 2008;6:1281-1288. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18541001.

236. Galanaud JP, Blaise S, Sevestre MA, et al. Long-term outcomes of isolated superficial vein thrombosis in patients with active cancer. Thromb Res 2018;171:179-186. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29789147.

237. Hirmerova J, Seidlerova J, Subrt I, Hajsmanova Z. Prevalence of cancer in patients with superficial vein thrombosis and its clinical importance. J Vasc Surg Venous Lymphat Disord 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34089942.

238. van Weert H, Dolan G, Wichers I, et al. Spontaneous superficial venous thrombophlebitis: does it increase risk for thromboembolism? A historic follow-up study in primary care. J Fam Pract 2006;55:52-57. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16388768.

239. Lutter KS, Kerr TM, Roedersheimer LR, et al. Superficial thrombophlebitis diagnosed by duplex scanning. Surgery 1991;110:42-46. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1866693.

240. Sullivan V, Denk PM, Sonnad SS, et al. Ligation versus anticoagulation: treatment of above-knee superficial thrombophlebitis not involving the deep venous system. J Am Coll Surg 2001;193:556-562. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11708514.

241. Chengelis DL, Bendick PJ, Glover JL, et al. Progression of superficial venous thrombosis to deep vein thrombosis. J Vasc Surg 1996;24:745-749. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8918318.

242. Barco S, Pomero F, Di Minno MND, et al. Clinical course of patients with symptomatic isolated superficial vein thrombosis: the ICARO follow-up study. J Thromb Haemost 2017;15:2176-2183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28871623.

243. Galanaud JP, Bosson JL, Genty C, et al. Superficial vein thrombosis and recurrent venous thromboembolism: a pooled analysis of two observational studies. J Thromb Haemost 2012;10:1004-1011. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22429908.

244. Beyer-Westendorf J, Schellong SM, Gerlach H, et al. Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 3b trial. Lancet Haematol 2017;4:e105-e113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28219692.

245. Kearon C, Carrier M, Gu CS, et al. Rivaroxaban compared to placebo for the treatment of leg superficial vein thrombosis: A randomized trial. Semin Thromb Hemost 2020;46:977-985. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33368114.

246. Decousus H, Prandoni P, Mismetti P, et al. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. N Engl J Med 2010;363:1222-1232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20860504.

247. Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8644983.

248. Galanaud JP, Sevestre MA, Pernod G, et al. Long-term outcomes of cancer-related isolated distal deep vein thrombosis: the OPTIMEV study. J Thromb Haemost 2017;15:907-916. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28266773.

249. Poudel SK, Park DY, Jia X, et al. Clinical outcomes of isolated distal deep vein thrombosis versus proximal venous thromboembolism in cancer patients: The Cleveland Clinic experience. J Thromb Haemost 2020;18:651-659. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31808607.

250. Dentali F, Pegoraro S, Barco S, et al. Clinical course of isolated distal deep vein thrombosis in patients with active cancer: a multicenter cohort study. J Thromb Haemost 2017;15:1757-1763. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28639418.

251. Decousus H, Bourmaud A, Fournel P, et al. Cancer-associated thrombosis in patients with implanted ports: a prospective multicenter French cohort study (ONCOCIP). Blood 2018;132:707-716. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29980524.

252. Bleker SM, van Es N, van Gils L, et al. Clinical course of upper extremity deep vein thrombosis in patients with or without cancer: a systematic review. Thromb Res 2016;140 Suppl 1:S81-88. Available at:

253. Munoz FJ, Mismetti P, Poggio R, et al. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE Registry. Chest 2008;133:143-148. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17925416.

254. Agnelli G, Verso M, Ageno W, et al. The MASTER registry on venous thromboembolism: description of the study cohort. Thromb Res 2008;121:605-610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17692901.

255. Beck-Razi N, Kuzmin A, Koren D, et al. Asymptomatic deep vein thrombosis in advanced cancer patients: the value of venous sonography. J Clin Ultrasound 2010;38:232-237. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20461778.

256. Birdwell BG, Raskob GE, Whitsett TL, et al. The clinical validity of normal compression ultrasonography in outpatients suspected of having deep venous thrombosis. Ann Intern Med 1998;128:1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9424975.

257. Taffoni MJ, Ravenel JG, Ackerman SJ. Prospective comparison of indirect CT venography versus venous sonography in ICU patients. AJR Am J Roentgenol 2005;185:457-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16037520.

258. Lim K-E, Hsu W-C, Hsu Y-Y, et al. Deep venous thrombosis: comparison of indirect multidetector CT venography and sonography of lower extremities in 26 patients. Clin Imaging 2004;28:439-444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15531146.

259. Sampson FC, Goodacre SW, Thomas SM, van Beek EJ. The accuracy of MRI in diagnosis of suspected deep vein thrombosis: systematic review and meta-analysis. Eur Radiol 2007;17:175-181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16628439.

260. Evans AJ, Sostman HD, Witty LA, et al. Detection of deep venous thrombosis: prospective comparison of MR imaging and sonography. J Magn Reson Imaging 1996;6:44-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8851402.

261. Laissy JP, Cinqualbre A, Loshkajian A, et al. Assessment of deep venous thrombosis in the lower limbs and pelvis: MR venography versus duplex Doppler sonography. AJR Am J Roentgenol 1996;167:971-975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8819396.

262. Dupas B, el Kouri D, Curtet C, et al. Angiomagnetic resonance imaging of iliofemorocaval venous thrombosis. Lancet 1995;346:17-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7603138.

263. Fraser DGW, Moody AR, Davidson IR, et al. Deep venous thrombosis: diagnosis by using venous enhanced subtracted peak arterial MR venography versus conventional venography. Radiology 2003;226:812-820. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12601180.

264. Carpenter JP, Holland GA, Baum RA, et al. Magnetic resonance venography for the detection of deep venous thrombosis: comparison with contrast venography and duplex Doppler ultrasonography. J Vasc Surg 1993;18:734-741. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8230557.

265. Joffe HV, Kucher N, Tapson VF, Goldhaber SZ. Upper-extremity deep vein thrombosis: a prospective registry of 592 patients. Circulation 2004;110:1605-1611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15353493.

266. Verso M, Agnelli G, Kamphuisen PW, et al. Risk factors for upper limb deep vein thrombosis associated with the use of central vein catheter in cancer patients. Intern Emerg Med 2008;3:117-122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18317868.

267. Baarslag H-J, van Beek EJR, Koopman MMW, Reekers JA. Prospective study of color duplex ultrasonography compared with contrast venography in patients suspected of having deep venous thrombosis of the upper extremities. Ann Intern Med 2002;136:865-872. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12069560.

268. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet 2014;383:880-888. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24315521.

269. Gould MK, Dembitzer AD, Doyle RL, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute

deep venous thrombosis. A meta-analysis of randomized, controlled trials. Ann Intern Med 1999;130:800-809. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10366369.

270. van Dongen CJ, van den Belt AG, Prins MH, Lensing AW. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev 2004:CD001100. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15495007.

271. Napolitano M, Saccullo G, Malato A, et al. Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study. J Clin Oncol 2014;32:3607-3612. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25267738.

272. Moik F, Colling M, Mahe I, et al. Extended anticoagulation treatment for cancer-associated thrombosis-Rates of recurrence and bleeding beyond 6 months: A systematic review. J Thromb Haemost 2022;20:619-634. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34816583.

273. Di Nisio M, van Es N, Carrier M, et al. Extended treatment with edoxaban in cancer patients with venous thromboembolism: A post-hoc analysis of the Hokusai-VTE Cancer study. J Thromb Haemost 2019;17:1866-1874. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31271705.

274. Davies GA, Lazo-Langner A, Gandara E, et al. A prospective study of Rivaroxaban for central venous catheter associated upper extremity deep vein thrombosis in cancer patients (Catheter 2). Thromb Res 2018;162:88-92. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28416213.

275. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386-1389. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10227218.

276. Kanne JP, Lalani TA. Role of computed tomography and magnetic resonance imaging for deep venous thrombosis and pulmonary embolism. Circulation 2004;109:15-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15051664.

277. Schoepf UJ, Costello P. CT angiography for diagnosis of pulmonary embolism: state of the art. Radiology 2004;230:329-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14752178.

278. Schoepf UJ, Kucher N, Kipfmueller F, et al. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. Circulation 2004;110:3276-3280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15533868.

279. Plasencia-Martinez JM, Carmona-Bayonas A, Calvo-Temprano D, et al. Prognostic value of computed tomography pulmonary angiography indices in patients with cancer-related pulmonary embolism: Data from a multicenter cohort study. Eur J Radiol 2017;87:66-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28065377.

280. Anderson DR, Kahn SR, Rodger MA, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA 2007;298:2743-2753. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18165667.

281. Calvo-Romero JM, Lima-Rodriguez EM, Bureo-Dacal P, Perez-Miranda M. Predictors of an intermediate ventilation/perfusion lung scan in patients with suspected acute pulmonary embolism. Eur J Emerg Med 2005;12:129-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15891446.

282. Kearon C, Ginsberg JS, Douketis J, et al. An evaluation of D-dimer in the diagnosis of pulmonary embolism: a randomized trial. Ann Intern Med 2006;144:812-821. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16754923.

283. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003;349:1227-1235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14507948.

284. Sohne M, Kruip MJHA, Nijkeuter M, et al. Accuracy of clinical decision rule, D-dimer and spiral computed tomography in patients with malignancy, previous venous thromboembolism, COPD or heart failure and in older patients with suspected pulmonary embolism. J Thromb Haemost 2006;4:1042-1046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16689757.

285. Knowlson L, Bacchu S, Paneesha S, et al. Elevated D-dimers are also a marker of underlying malignancy and increased mortality in the absence of venous thromboembolism. J Clin Pathol 2010;63:818-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20671046.

286. Maestre A, Trujillo-Santos J, Visona A, et al. D-dimer levels and 90-day outcome in patients with acute pulmonary embolism with or without cancer. Thromb Res 2014;133:384-389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24438941.

287. Douma RA, van Sluis GL, Kamphuisen PW, et al. Clinical decision rule and D-dimer have lower clinical utility to exclude pulmonary embolism in cancer patients. Explanations and potential ameliorations. Thromb Haemost 2010;104:831-836. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20664894.

288. Righini M, Le Gal G, De Lucia S, et al. Clinical usefulness of D-dimer testing in cancer patients with suspected pulmonary embolism. Thromb Haemost 2006;95:715-719. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16601844.

289. Di Nisio M, Sohne M, Kamphuisen PW, Buller HR. D-Dimer test in cancer patients with suspected acute pulmonary embolism. J Thromb Haemost 2005;3:1239-1242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15946214.

290. Jimenez D, Aujesky D, Moores L, et al. Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism. Thorax 2011;66:75-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20978032.

291. Jimenez D, Yusen RD, Otero R, et al. Prognostic models for selecting patients with acute pulmonary embolism for initial outpatient therapy. Chest 2007;132:24-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17625081.

292. Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: the prep study, a prospective multicenter cohort study. Am J Respir Crit Care Med 2010;181:168-173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19910608.

293. Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol 1997;30:1165-1171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9350909.

294. Jimenez D, Diaz G, Molina J, et al. Troponin I and risk stratification of patients with acute nonmassive pulmonary embolism. Eur Respir J 2008;31:847-853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18094010.

295. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007;116:427-433. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17606843.

296. Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002;106:1263-1268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12208803.

297. Jimenez D, Aujesky D, Diaz G, et al. Prognostic significance of deep vein thrombosis in patients presenting with acute symptomatic pulmonary embolism. Am J Respir Crit Care Med 2010;181:983-991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20110556.

298. Pruszczyk P, Torbicki A, Kuch-Wocial A, et al. Diagnostic value of transoesophageal echocardiography in suspected haemodynamically significant pulmonary embolism. Heart 2001;85:628-634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11359740.

299. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, et al. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. Am Heart J 1997;134:479-487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9327706.

300. Aujesky D, Roy PM, Le Manach CP, et al. Validation of a model to predict adverse outcomes in patients with pulmonary embolism. Eur Heart J 2006;27:476-481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16207738.

301. Donze J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index. A clinical prognostic model for pulmonary embolism. Thromb Haemost 2008;100:943-948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18989542.

302. Weeda ER, Kohn CG, Peacock WF, et al. External validation of the hestia criteria for identifying acute pulmonary embolism patients at low risk of early mortality. Clin Appl Thromb Hemost 2017;23:769-774. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27225840.

303. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006;144:165-171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16461960.

304. Ahn S, Lee YS, Kim WY, et al. Prognostic Value of Treatment Setting in Patients With Cancer Having Pulmonary Embolism: Comparison With the Pulmonary Embolism Severity Index. Clin Appl Thromb Hemost 2017;23:615-621. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26759372.

305. den Exter PL, Gomez V, Jimenez D, et al. A clinical prognostic model for the identification of low-risk patients with acute symptomatic pulmonary embolism and active cancer. Chest 2013;143:138-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22814859.

306. Kline JA, Roy PM, Than MP, et al. Derivation and validation of a multivariate model to predict mortality from pulmonary embolism with cancer: The POMPE-C tool. Thromb Res 2012;129:e194-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22475313.

307. Carmona-Bayonas A, Jimenez-Fonseca P, Font C, et al. Predicting serious complications in patients with cancer and pulmonary embolism using decision tree modelling: the EPIPHANY Index. Br J Cancer 2017;116:994-1001. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28267709.

308. Font C, Carmona-Bayonas A, Beato C, et al. Clinical features and short-term outcomes of cancer patients with suspected and unsuspected pulmonary embolism: the EPIPHANY study. Eur Respir J 2017;49:1600282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28052954.

309. Ahn S, Cooksley T, Banala S, et al. Validation of the EPIPHANY index for predicting risk of serious complications in cancer patients with incidental pulmonary embolism. Support Care Cancer 2018;26:3601-3607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29725804.

310. Li X, Hu Y, Lin P, et al. Comparison of different clinical prognostic scores in patients with pulmonary embolism and active cancer. Thromb Haemost 2021;121:834-844. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33450779.

311. Font C, Carmona-Bayonas A, Fernandez-Martinez A, et al. Outpatient management of pulmonary embolism in cancer: data on a prospective cohort of 138 consecutive patients. J Natl Compr Canc Netw 2014;12:365-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24616542.

312. Carmona-Bayonas A, Font C, Jimenez-Fonseca P, et al. On the necessity of new decision-making methods for cancer-associated, symptomatic, pulmonary embolism. Thromb Res 2016;143:76-85. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27208461.

313. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical

Practice Guidelines. Chest 2012;141:e419S-494S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22315268.

314. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123:1788-1830. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21422387.

315. Weingart S. AHA PE Guidelines. EMCrit Blog 2011. Available at: https://emcrit.org/emcrit/aha-pulmonary-embolism-guidelines-2011/.

316. Pasrija C, Kronfli A, George P, et al. Utilization of veno-arterial extracorporeal membrane oxygenation for massive pulmonary embolism. Ann Thorac Surg 2018;105:498-504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29174781.

317. Streiff MB. Thrombosis in the setting of cancer. Hematology Am Soc Hematol Educ Program 2016;2016:196-205. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27913480.

318. Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347:1143-1150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12374874.

319. Ashton RW, Daniels CE, Ryu JH. Thrombolytic therapy in patients with submassive pulmonary embolism. N Engl J Med 2003;348:357-359; author reply 357-359. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12540653.

320. Thabut G, Logeart D. Thrombolysis for pulmonary embolism in patients with right ventricular dysfunction: con. Arch Intern Med 2005;165:2200-2203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16246981.

321. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402-1411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24716681.

322. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA 2014;311:2414-2421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24938564.

323. Dong BR, Hao Q, Yue J, et al. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev 2009:CD004437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19588357.

324. Tardy B, Venet C, Zeni F, et al. Short term effect of recombinant tissue plasminogen activator in patients with hemodynamically stable acute pulmonary embolism: results of a meta-analysis involving 464 patients. Thromb Res 2009;124:672-677. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19493561.

325. Agnelli G, Becattini C, Kirschstein T. Thrombolysis vs heparin in the treatment of pulmonary embolism: a clinical outcome-based meta-analysis. Arch Intern Med 2002;162:2537-2541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12456225.

326. Thabut G, Thabut D, Myers RP, et al. Thrombolytic therapy of pulmonary embolism: a meta-analysis. J Am Coll Cardiol 2002;40:1660-1667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12427420.

327. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation 2004;110:744-749. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15262836.

328. Kim HS, Preece SR, Black JH, et al. Safety of catheter-directed thrombolysis for deep venous thrombosis in cancer patients. J Vasc Surg 2008;47:388-394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18241762.

329. Aklog L, Williams CS, Byrne JG, Goldhaber SZ. Acute pulmonary embolectomy: a contemporary approach. Circulation 2002;105:1416-1419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11914247.

330. Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg 2005;129:1018-1023. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15867775.

331. Thistlethwaite PA, Kemp A, Du L, et al. Outcomes of pulmonary endarterectomy for treatment of extreme thromboembolic pulmonary hypertension. J Thorac Cardiovasc Surg 2006;131:307-313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16434258.

332. Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014;129:479-486. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24226805.

333. Stein PD, Kayali F, Olson RE. Twenty-one-year trends in the use of inferior vena cava filters. Arch Intern Med 2004;164:1541-1545. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15277286.

334. Streiff MB. Vena caval filters: a comprehensive review. Blood 2000;95:3669-3677. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10845895.

335. Streiff MB. Vena caval filters: a review for intensive care specialists. J Intensive Care Med 2003;18:59-79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15189653.

336. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. Circulation 2005;112:416-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16009794.

337. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med 1998;338:409-415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9459643.

338. Elting LS, Escalante CP, Cooksley C, et al. Outcomes and cost of deep venous thrombosis among patients with cancer. Arch Intern Med 2004;164:1653-1661. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15302635.

339. Mismetti P, Laporte S, Pellerin O, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. JAMA 2015;313:1627-1635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25919526.

340. Ho KM, Rao S, Honeybul S, et al. A multicenter trial of vena cava filters in severely injured patients. N Engl J Med 2019;381:328-337. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31259488.

341. Connolly GC, Chen R, Hyrien O, et al. Incidence, risk factors and consequences of portal vein and systemic thromboses in hepatocellular carcinoma. Thromb Res 2008;122:299-306. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18045666.

342. Greten TF, Papendorf F, Bleck JS, et al. Survival rate in patients with hepatocellular carcinoma: a retrospective analysis of 389 patients. Br J Cancer 2005;92:1862-1868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15870713.

343. Rabe C, Pilz T, Klostermann C, et al. Clinical characteristics and outcome of a cohort of 101 patients with hepatocellular carcinoma. World J Gastroenterol 2001;7:208-215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11819762.

344. Cabibbo G, Enea M, Attanasio M, et al. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology 2010;51:1274-1283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20112254.

345. Amitrano L, Guardascione MA, Scaglione M, et al. Prognostic factors in noncirrhotic patients with splanchnic vein thromboses. Am J Gastroenterol 2007;102:2464-2470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17958760.

346. Thatipelli MR, McBane RD, Hodge DO, Wysokinski WE. Survival and recurrence in patients with splanchnic vein thromboses. Clin Gastroenterol Hepatol 2010;8:200-205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19782767.

347. Janssen HL, Wijnhoud A, Haagsma EB, et al. Extrahepatic portal vein thrombosis: aetiology and determinants of survival. Gut 2001;49:720-724. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11600478.

348. Acosta S, Alhadad A, Svensson P, Ekberg O. Epidemiology, risk and prognostic factors in mesenteric venous thrombosis. Br J Surg 2008;95:1245-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18720461.

349. Hedayati N, Riha GM, Kougias P, et al. Prognostic factors and treatment outcome in mesenteric vein thrombosis. Vasc Endovascular Surg 2008;42:217-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18332399.

350. Acosta S, Ogren M, Sternby NH, et al. Mesenteric venous thrombosis with transmural intestinal infarction: a population-based study. J Vasc Surg 2005;41:59-63. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15696045.

351. Krauth MT, Lechner K, Neugebauer EA, Pabinger I. The postoperative splenic/portal vein thrombosis after splenectomy and its prevention--an unresolved issue. Haematologica 2008;93:1227-1232. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18556406.

352. Stamou KM, Toutouzas KG, Kekis PB, et al. Prospective study of the incidence and risk factors of postsplenectomy thrombosis of the portal, mesenteric, and splenic veins. Arch Surg 2006;141:663-669. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16847237.

353. Ageno W, Dentali F, Squizzato A. How I treat splanchnic vein thrombosis. Blood 2014;124:3685-3691. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25320239.

354. Butler JR, Eckert GJ, Zyromski NJ, et al. Natural history of pancreatitis-induced splenic vein thrombosis: a systematic review and meta-analysis of its incidence and rate of gastrointestinal bleeding. HPB (Oxford) 2011;13:839-845. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22081918.

355. Valla D, Dhumeaux D, Babany G, et al. Hepatic vein thrombosis in paroxysmal nocturnal hemoglobinuria. A spectrum from asymptomatic occlusion of hepatic venules to fatal Budd-Chiari syndrome. Gastroenterology 1987;93:569-575. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3609666.

356. Condat B, Pessione F, Hillaire S, et al. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology 2001;120:490-497. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11159889.

357. Dahabreh IJ, Zoi K, Giannouli S, et al. Is JAK2 V617F mutation more than a diagnostic index? A meta-analysis of clinical outcomes in essential thrombocythemia. Leuk Res 2009;33:67-73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18632151.

358. Dentali F, Squizzato A, Brivio L, et al. JAK2V617F mutation for the early diagnosis of Ph- myeloproliferative neoplasms in patients with venous thromboembolism: a meta-analysis. Blood 2009;113:5617-5623. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19273837.

359. Valla D, Le MG, Poynard T, et al. Risk of hepatic vein thrombosis in relation to recent use of oral contraceptives. A case-control study. Gastroenterology 1986;90:807-811. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3949113.

360. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet

2005;365:1054-1061. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15781101.

361. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature 2005;434:1144-1148. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15793561.

362. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 2005;352:1779-1790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15858187.

363. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell 2005;7:387-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15837627.

364. De Stefano V, Fiorini A, Rossi E, et al. Incidence of the JAK2 V617F mutation among patients with splanchnic or cerebral venous thrombosis and without overt chronic myeloproliferative disorders. J Thromb Haemost 2007;5:708-714. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17263783.

365. De Stefano V, Martinelli I. Splanchnic vein thrombosis: clinical presentation, risk factors and treatment. Intern Emerg Med 2010;5:487-494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20532730.

366. Regina S, Herault O, D'Alteroche L, et al. JAK2 V617F is specifically associated with idiopathic splanchnic vein thrombosis. J Thromb Haemost 2007;5:859-861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17403204.

367. Colaizzo D, Amitrano L, Tiscia GL, et al. A new JAK2 gene mutation in patients with polycythemia vera and splanchnic vein thrombosis. Blood 2007;110:2768-2769. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17881638.

368. Hillmen P, Lewis SM, Bessler M, et al. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med 1995;333:1253-1258. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7566002.

369. Socie G, Mary JY, de Gramont A, et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology. Lancet 1996;348:573-577. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8774569.

370. Hoekstra J, Leebeek FW, Plessier A, et al. Paroxysmal nocturnal hemoglobinuria in Budd-Chiari syndrome: findings from a cohort study. J Hepatol 2009;51:696-706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19664836.

371. Kumar S, Sarr MG, Kamath PS. Mesenteric venous thrombosis. N Engl J Med 2001;345:1683-1688. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11759648.

372. Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. N Engl J Med 2004;350:578-585. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14762185.

373. Parikh S, Shah R, Kapoor P. Portal vein thrombosis. Am J Med 2010;123:111-119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20103016.

374. Plessier A, Darwish-Murad S, Hernandez-Guerra M, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology 2010;51:210-218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19821530.

375. Sogaard KK, Astrup LB, Vilstrup H, Gronbaek H. Portal vein thrombosis; risk factors, clinical presentation and treatment. BMC Gastroenterol 2007;7:34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17697371.

376. Bradbury MS, Kavanagh PV, Bechtold RE, et al. Mesenteric venous thrombosis: diagnosis and noninvasive imaging. Radiographics

2002;22:527-541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12006685.

377. Hoekstra J, Janssen HL. Vascular liver disorders (I): diagnosis, treatment and prognosis of Budd-Chiari syndrome. Neth J Med 2008;66:334-339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18809980.

378. Hoekstra J, Janssen HL. Vascular liver disorders (II): portal vein thrombosis. Neth J Med 2009;67:46-53. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19299846.

379. Ponziani FR, Zocco MA, Campanale C, et al. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. World J Gastroenterol 2010;16:143-155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20066733.

380. Dentali F, Ageno W, Witt D, et al. Natural history of mesenteric venous thrombosis in patients treated with vitamin K antagonists: a multi-centre, retrospective cohort study. Thromb Haemost 2009;102:501-504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19718470.

381. Candeloro M, Valeriani E, Monreal M, et al. Anticoagulant therapy for splanchnic vein thrombosis: an individual patient data meta-analysis. Blood Adv 2022;6:4516-4523. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35613465.

382. Martinelli I, Franchini M, Mannucci PM. How I treat rare venous thromboses. Blood 2008;112:4818-4823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18805965.

383. Hollingshead M, Burke CT, Mauro MA, et al. Transcatheter thrombolytic therapy for acute mesenteric and portal vein thrombosis. J Vasc Interv Radiol 2005;16:651-661. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15872320.

384. Kim HS, Patra A, Khan J, et al. Transhepatic catheter-directed thrombectomy and thrombolysis of acute superior mesenteric venous thrombosis. J Vasc Interv Radiol 2005;16:1685-1691. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16371536.

385. Sharma S, Texeira A, Texeira P, et al. Pharmacological thrombolysis in Budd Chiari syndrome: a single centre experience and review of the literature. J Hepatol 2004;40:172-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14672630.

386. Smalberg JH, Spaander MV, Jie KS, et al. Risks and benefits of transcatheter thrombolytic therapy in patients with splanchnic venous thrombosis. Thromb Haemost 2008;100:1084-1088. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19132234.

387. Garcia-Pagan JC, Heydtmann M, Raffa S, et al. TIPS for Budd-Chiari syndrome: long-term results and prognostics factors in 124 patients. Gastroenterology 2008;135:808-815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18621047.

388. Darwish Murad S, Plessier A, Hernandez-Guerra M, et al. Etiology, management, and outcome of the Budd-Chiari syndrome. Ann Intern Med 2009;151:167-175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652186.

389. Eapen CE, Velissaris D, Heydtmann M, et al. Favourable medium term outcome following hepatic vein recanalisation and/or transjugular intrahepatic portosystemic shunt for Budd Chiari syndrome. Gut 2006;55:878-884. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16174658.

390. Mancuso A, Fung K, Mela M, et al. TIPS for acute and chronic Budd-Chiari syndrome: a single-centre experience. J Hepatol 2003;38:751-754. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12763367.

391. Perello A, Garcia-Pagan JC, Gilabert R, et al. TIPS is a useful long-term derivative therapy for patients with Budd-Chiari syndrome uncontrolled by medical therapy. Hepatology 2002;35:132-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11786969.

392. Rossle M, Olschewski M, Siegerstetter V, et al. The Budd-Chiari syndrome: outcome after treatment with the transjugular intrahepatic portosystemic shunt. Surgery 2004;135:394-403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15041963.

393. Hemming AW, Langer B, Greig P, et al. Treatment of Budd-Chiari syndrome with portosystemic shunt or liver transplantation. Am J Surg 1996;171:176-180; discussion 180-171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8554136.

394. Zeitoun G, Escolano S, Hadengue A, et al. Outcome of Budd-Chiari syndrome: a multivariate analysis of factors related to survival including surgical portosystemic shunting. Hepatology 1999;30:84-89. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10385643.

395. Panis Y, Belghiti J, Valla D, et al. Portosystemic shunt in Budd-Chiari syndrome: long-term survival and factors affecting shunt patency in 25 patients in Western countries. Surgery 1994;115:276-281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8128351.

396. Pisani-Ceretti A, Intra M, Prestipino F, et al. Surgical and radiologic treatment of primary Budd-Chiari syndrome. World J Surg 1998;22:48-53; discussion 53-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9465761.

397. Slakey DP, Klein AS, Venbrux AC, Cameron JL. Budd-Chiari syndrome: current management options. Ann Surg 2001;233:522-527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11303134.

398. Darwish Murad S, Valla DC, de Groen PC, et al. Determinants of survival and the effect of portosystemic shunting in patients with Budd-Chiari syndrome. Hepatology 2004;39:500-508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14768004.

399. Psilopoulos D, Galanis P, Goulas S, et al. Endoscopic variceal ligation vs. propranolol for prevention of first variceal bleeding: a randomized controlled trial. Eur J Gastroenterol Hepatol 2005;17:1111-1117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16148558.

400. Perez-Ayuso RM, Valderrama S, Espinoza M, et al. Endoscopic band ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhotic patients with high risk esophageal varices. Ann Hepatol 2010;9:15-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20308718.

401. Lay CS, Tsai YT, Lee FY, et al. Endoscopic variceal ligation versus propranolol in prophylaxis of first variceal bleeding in patients with cirrhosis. J Gastroenterol Hepatol 2006;21:413-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16509867.

402. Schepke M, Kleber G, Nurnberg D, et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. Hepatology 2004;40:65-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15239087.

403. Sarin SK, Wadhawan M, Agarwal SR, et al. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. Am J Gastroenterol 2005;100:797-804. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15784021.

404. Sarin SK, Gupta N, Jha SK, et al. Equal efficacy of endoscopic variceal ligation and propranolol in preventing variceal bleeding in patients with noncirrhotic portal hypertension. Gastroenterology 2010;139:1238-1245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20547163.

405. Funakoshi N, Segalas-Largey F, Duny Y, et al. Benefit of combination beta-blocker and endoscopic treatment to prevent variceal rebleeding: a meta-analysis. World J Gastroenterol 2010;16:5982-5992. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21157975.

406. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1960;1:1309-1312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13797091.

407. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study.

Arch Intern Med 2002;162:1729-1735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12153376.

408. Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12853587.

409. Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med 2006;119:1062-1072. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17145251.

410. Akl EA, Kahale L, Neumann I, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev 2014;6:CD006649. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24945634.

411. Lee AY, Kamphuisen PW, Meyer G, et al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. JAMA 2015;314:677-686. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26284719.

412. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e24S-43S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22315264.

413. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy: An American College of Chest Physicians clinical practice guideline. Chest 2022;162:e207-e243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35964704.

414. Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:340S-380S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18574270.

415. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23808982.

416. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23216615.

417. Prescribing information for apixaban tablets, for oral use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202155s034lbl.pdf. Accessed June 3, 2024.

418. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. J Thromb Haemost 2015;13:2187-2191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26407753.

419. McBane RD, 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost 2020;18:411-421. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31630479.

420. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. N Engl J Med 2020;382:1599-1607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32223112.

421. Ageno W, Vedovati MC, Cohen A, et al. Bleeding with Apixaban and Dalteparin in Patients with Cancer-Associated Venous Thromboembolism: Results from the Caravaggio Study. Thromb Haemost 2021;121:616-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33202447.

422. Prescribing information for edoxaban tablets, for oral use. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203049s007lbl.pdf. Accessed June 5, 2024.

423. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. J Clin Pharmacol 2010;50:743-753. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20081065.

424. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29231094.

425. Prescribing information for dabigatran etexilate capsules, for oral use. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/022512s047lbl.pdf. Accessed June 5, 2024.

426. Schulman S, Goldhaber SZ, Kearon C, et al. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. Thromb Haemost 2015;114:150-157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25739680.

427. Investigators E, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-2510. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21128814.

428. Investigators E-P, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-1297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22449293.

429. Prescribing information for rivaroxaban tablets, for oral use and for oral suspension. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022406s041lbl.pdf. Accessed June 5, 2024.

430. Prins MH, Lensing AW, Brighton TA, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. Lancet Haematol 2014;1:e37-46. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27030066.

431. Mantha S, Laube E, Miao Y, et al. Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease: a prospective cohort study. J Thromb Thrombolysis 2017;43:166-171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27696084.

432. Young AM, Marshall A, Thirlwall J, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol 2018;36:2017-2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29746227.

433. Kraaijpoel N, Di Nisio M, Mulder FI, et al. Clinical impact of bleeding in cancer-associated venous thromboembolism: Results from the Hokusai VTE cancer study. Thromb Haemost 2018;118:1439-1449. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30060256.

434. Ageno W, Vedovati MC, Cohen A, et al. Bleeding with Apixaban and Dalteparin in Patients with Cancer-Associated Venous Thromboembolism: Results from the Caravaggio Study. Thromb Haemost 2021;121:616-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33202447.

435. Lee A, Oley F, Jr., Lo M, et al. Direct oral anticoagulants or low-molecular-weight heparins for venous thromboembolism in patients with brain tumors. Thromb Res 2021;208:148-155. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34798446.

436. Kahale LA, Hakoum MB, Tsolakian IG, et al. Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. Cochrane Database Syst Rev 2018;6:CD006650. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29920657.

437. Francis CW, Kessler CM, Goldhaber SZ, et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. J Thromb Haemost 2015;13:1028-1035. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25827941.

438. Wells PS, Anderson DR, Rodger MA, et al. A randomized trial comparing 2 low-molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. Arch Intern Med 2005;165:733-738. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15824291.

439. Deitcher SR, Kessler CM, Merli G, et al. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost 2006;12:389-396. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17000884.

440. Merli G, Spiro TE, Olsson CG, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med 2001;134:191-202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11177331.

441. Mandalà M, Falanga A, Roila F. Management of venous thromboembolism in cancer patients: ESMO clinical recommendations. Ann Oncol 2008;19 Suppl 2:126-127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18456750.

442. Cook LM, Kahn SR, Goodwin J, Kovacs MJ. Frequency of renal impairment, advanced age, obesity and cancer in venous thromboembolism patients in clinical practice. J Thromb Haemost 2007;5:937-941. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17461927.

443. Sanderink GJ, Guimart CG, Ozoux ML, et al. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. Thromb Res 2002;105:225-231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11927128.

444. Hulot JS, Montalescot G, Lechat P, et al. Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. Clin Pharmacol Ther 2005;77:542-552. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15961985.

445. Kruse MW, Lee JJ. Retrospective evaluation of a pharmacokinetic program for adjusting enoxaparin in renal impairment. Am Heart J 2004;148:582-589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15459586.

446. Douketis J, Cook D, Meade M, et al. Prophylaxis against deep vein thrombosis in critically ill patients with severe renal insufficiency with the low-molecular-weight heparin dalteparin: an assessment of safety and pharmacodynamics: the DIRECT study. Arch Intern Med 2008;168:1805-1812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18779469.

447. Curry MA, LaFollette JA, Alexander BR, et al. Evaluation of treatment-dose enoxaparin in acutely ill morbidly obese patients at an academic medical center: A randomized clinical trial. Ann Pharmacother 2019;53:567-573. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30574790.

448. Kakkar AK, Levine MN, Kadziola Z, et al. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). J Clin Oncol 2004;22:1944-1948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15143088.

449. Lee AYY, Rickles FR, Julian JA, et al. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. J Clin Oncol 2005;23:2123-2129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15699480.

450. Altinbas M, Coskun HS, Er O, et al. A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer. J Thromb Haemost 2004;2:1266-1271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15304029.

451. Klerk CP, Smorenburg SM, Otten HM, et al. The effect of low molecular weight heparin on survival in patients with advanced malignancy. J Clin Oncol 2005;23:2130-2135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15699479.

452. Akl EA, van Doormaal FF, Barba M, et al. Parenteral anticoagulation may prolong the survival of patients with limited small cell lung cancer: a Cochrane systematic review. J Exp Clin Cancer Res 2008;27:4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18577254.

453. Meyer G, Besse B, Doubre H, et al. Anti-tumour effect of low molecular weight heparin in localised lung cancer: a phase III clinical trial. Eur Respir J 2018;52:1801220. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30262574.

454. Sanford D, Naidu A, Alizadeh N, Lazo-Langner A. The effect of low molecular weight heparin on survival in cancer patients: an updated systematic review and meta-analysis of randomized trials. J Thromb Haemost 2014;12:1076-1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24796727.

455. Ek L, Gezelius E, Bergman B, et al. Randomized phase III trial of low-molecular-weight heparin enoxaparin in addition to standard treatment in small-cell lung cancer: the RASTEN trial. Ann Oncol 2018;29:398-404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29106448.

456. Montroy J, Lalu MM, Auer RC, et al. The efficacy and safety of low molecular weight heparin administration to improve survival of cancer patients: A systematic review and meta-analysis. Thromb Haemost 2020;120:832-846. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32369854.

457. Savi P, Chong BH, Greinacher A, et al. Effect of fondaparinux on platelet activation in the presence of heparin-dependent antibodies: a blinded comparative multicenter study with unfractionated heparin. Blood 2005;105:139-144. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15388575.

458. van Doormaal FF, Raskob GE, Davidson BL, et al. Treatment of venous thromboembolism in patients with cancer: subgroup analysis of the Matisse clinical trials. Thromb Haemost 2009;101:762-769. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19350123.

459. Prescribing information for heparin sodium injection, for intravenous or subcutaneous use. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/017029s159lbl.pdf. Accessed June 5, 2024.

460. Hirsh J, Bauer KA, Donati MB, et al. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:141S-159S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18574264.

461. Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. JAMA 2006;296:935-942. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16926353.

462. Hakoum MB, Kahale LA, Tsolakian IG, et al. Anticoagulation for the initial treatment of venous thromboembolism in people with cancer. Cochrane Database Syst Rev 2018;1:CD006649. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29363105.

463. Akl EA, Vasireddi SR, Gunukula S, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev 2011;2:CD006649. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21328285.

464. Prescribing information for warfarin sodium tablets, for oral use 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009218s118lbl.pdf. Accessed June 5, 2024.

465. Hutten BA, Prins MH, Gent M, et al. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol 2000;18:3078-3083. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10963635.

466. Palareti G, Legnani C, Lee A, et al. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous

thromboembolic disease in patients with or without malignancy. Thromb Haemost 2000;84:805-810. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11127860.

467. Wawrzynska L, Tomkowski WZ, Przedlacki J, et al. Changes in bone density during long-term administration of low-molecular-weight heparins or acenocoumarol for secondary prophylaxis of venous thromboembolism. Pathophysiol Haemost Thromb 2003;33:64-67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14624046.

468. Aronson J. Serious drug interactions. Practitioner 1993;237:789-791. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7903448.

469. Lacey CS. Interaction of dicloxacillin with warfarin. Ann Pharmacother 2004;38:898-898. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15054148.

470. Saif MW. An adverse interaction between warfarin and fluoropyrimidines revisited. Clin Colorectal Cancer 2005;5:175-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16197620.

471. Shah HR, Ledbetter L, Diasio R, Saif MW. A retrospective study of coagulation abnormalities in patients receiving concomitant capecitabine and warfarin. Clin Colorectal Cancer 2006;5:354-358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16512995.

472. Morello KC, Wurz GT, DeGregorio MW. Pharmacokinetics of selective estrogen receptor modulators. Clin Pharmacokinet 2003;42:361-372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12648026.

473. Nutescu EA, Shapiro NL, Ibrahim S, West P. Warfarin and its interactions with foods, herbs and other dietary supplements. Expert Opin Drug Saf 2006;5:433-451. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16610971.

474. Sconce E, Khan T, Mason J, et al. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation. Thromb Haemost 2005;93:872-875. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15886802.

475. Wittkowsky AK, Boccuzzi SJ, Wogen J, et al. Frequency of concurrent use of warfarin with potentially interacting drugs. Pharmacotherapy 2004;24:1668-1674. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15585436.

476. Samuelson BT, Gernsheimer T, Estey E, Garcia DA. Variability in management of hematologic malignancy patients with venous thromboembolism and chemotherapy-induced thrombocytopenia. Thromb Res 2016;141:104-105. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26994682.

477. Chalayer E, Cavalieri D, Martignoles JA, et al. Antithrombotic therapy and platelet transfusions in hematologic malignancy patients presenting chemotherapy-induced thrombocytopenia: a French survey. Transfusion 2017;57:1717-1723. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28439927.

478. Kopolovic I, Lee AY, Wu C. Management and outcomes of cancer-associated venous thromboembolism in patients with concomitant thrombocytopenia: a retrospective cohort study. Ann Hematol 2015;94:329-336. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25190031.

479. Samuelson Bannow BT, Walter RB, Gernsheimer TB, Garcia DA. Patients treated for acute VTE during periods of treatment-related thrombocytopenia have high rates of recurrent thrombosis and transfusion-related adverse outcomes. J Thromb Thrombolysis 2017;44:442-447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28884390.

480. Saccullo G, Malato A, Raso S, et al. Cancer patients requiring interruption of long-term warfarin because of surgery or chemotherapy induced thrombocytopenia: the use of fixed sub-therapeutic doses of low-molecular weight heparin. Am J Hematol 2012;87:388-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22374861.

481. Liu J, Krishnan J, Diep L, Shah M. Enoxaparin use during chemotherapy induced thrombocytopenic phase in cancer patients with venous thromboembolism. J Clin Oncol 2018;36:e18852-e18852.

Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.e18852.

482. Schwarz UI, Ritchie MD, Bradford Y, et al. Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med 2008;358:999-991008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18322281.

483. Teefy AM, Martin JE, Kovacs MJ. Warfarin resistance due to sulfasalazine. Ann Pharmacother 2000;34:1265-1268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11098339.

484. Anderson JA, Saenko EL. Heparin resistance. Br J Anaesth 2002;88:467-469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12066718.

485. Streiff MB. Long-term therapy of venous thromboembolism in cancer patients. J Natl Compr Canc Netw 2006;4:903-910. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17020668.

486. Luk C, Wells PS, Anderson D, Kovacs MJ. Extended outpatient therapy with low molecular weight heparin for the treatment of recurrent venous thromboembolism despite warfarin therapy. Am J Med 2001;111:270-273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11566456.

487. Carrier M, Le Gal G, Cho R, et al. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. J Thromb Haemost 2009;7:760-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19245418.

488. Ihaddadene R, Le Gal G, Delluc A, Carrier M. Dose escalation of low molecular weight heparin in patients with recurrent cancer-associated thrombosis. Thromb Res 2014;134:93-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24835673.

489. Mewissen MW, Seabrook GR, Meissner MH, et al. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. Radiology 1999;211:39-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10189452.

490. Chopard R, Ecarnot F, Meneveau N. Catheter-directed therapy for acute pulmonary embolism: navigating gaps in the evidence. Eur Heart J Suppl 2019;21:I23-I30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31777454.

491. Castaneda F, Li R, Young K, et al. Catheter-directed thrombolysis in deep venous thrombosis with use of reteplase: immediate results and complications from a pilot study. J Vasc Interv Radiol 2002;13:577-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12050297.

492. Grunwald MR, Hofmann LV. Comparison of urokinase, alteplase, and reteplase for catheter-directed thrombolysis of deep venous thrombosis. J Vasc Interv Radiol 2004;15:347-352. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15064337.

493. Razavi MK, Wong H, Kee ST, et al. Initial clinical results of tenecteplase (TNK) in catheter-directed thrombolytic therapy. J Endovasc Ther 2002;9:593-598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12431142.

494. Enden T, Klow NE, Sandvik L, et al. Catheter-directed thrombolysis vs. anticoagulant therapy alone in deep vein thrombosis: results of an open randomized, controlled trial reporting on short-term patency. J Thromb Haemost 2009;7:1268-1275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19422443.

495. Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 2012;379:31-38. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22172244.

496. Vedantham S, Vesely TM, Sicard GA, et al. Pharmacomechanical thrombolysis and early stent placement for iliofemoral deep vein thrombosis. J Vasc Interv Radiol 2004;15:565-574. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15178716.

497. Bush RL, Lin PH, Bates JT, et al. Pharmacomechanical thrombectomy for treatment of symptomatic lower extremity deep venous thrombosis: safety and feasibility study. J Vasc Surg 2004;40:965-970. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15557912.

498. Lin PH, Zhou W, Dardik A, et al. Catheter-direct thrombolysis versus pharmacomechanical thrombectomy for treatment of symptomatic lower extremity deep venous thrombosis. Am J Surg 2006;192:782-788. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17161094.

499. Kim HS, Patra A, Paxton BE, et al. Adjunctive percutaneous mechanical thrombectomy for lower-extremity deep vein thrombosis: clinical and economic outcomes. J Vasc Interv Radiol 2006;17:1099-1104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16868161.

500. Goldhaber SZ, Meyerovitz MF, Green D, et al. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. Am J Med 1990;88:235-240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2106783.

501. Schweizer J, Kirch W, Koch R, et al. Short- and long-term results after thrombolytic treatment of deep venous thrombosis. J Am Coll Cardiol 2000;36:1336-1343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11028492.

502. Turpie AG, Levine MN, Hirsh J, et al. Tissue plasminogen activator (rt-PA) vs heparin in deep vein thrombosis. Results of a randomized trial. Chest 1990;97:172S-175S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2108855.

503. Broderick C, Watson L, Armon MP. Thrombolytic strategies versus standard anticoagulation for acute deep vein thrombosis of the lower limb. Cochrane Database Syst Rev 2021;1:CD002783. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33464575.

504. Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med 2017;377:2240-2252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29211671.

505. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020;4:4693-4738. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33007077.

506. Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol 2013;111:273-277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23102885.

507. McCabe JM, Huang PH, Riedl L, et al. Usefulness and safety of ultrasound-assisted catheter-directed thrombolysis for submassive pulmonary emboli. Am J Cardiol 2015;115:821-824. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25633189.

508. Sharifi M, Awdisho A, Schroeder B, et al. Retrospective comparison of ultrasound facilitated catheter-directed thrombolysis and systemically administered half-dose thrombolysis in treatment of pulmonary embolism. Vasc Med 2019;24:103-109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30834822.

509. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: The OPTALYSE PE trial. JACC Cardiovasc Interv 2018;11:1401-1410. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30025734.

510. Piazza G, Hohlfelder B, Jaff MR, et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: The SEATTLE II Study. JACC Cardiovasc Interv 2015;8:1382-1392. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26315743.

511. Benmassaoud A, AlRubaiy L, Yu D, et al. A stepwise thrombolysis regimen in the management of acute portal vein thrombosis in patients with evidence of intestinal ischaemia. Aliment Pharmacol Ther 2019;50:1049-1058. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31489698.

512. Noble S. Management of venous thromboembolism in the palliative care setting. Int J Palliat Nurs 2007;13:574-579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18399382.

513. Bijsterveld NR, Moons AH, Boekholdt SM, et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. Circulation 2002;106:2550-2554. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12427650.

514. Elmer J, Wittels KA. Emergency reversal of pentasaccharide anticoagulants: a systematic review of the literature. Transfus Med 2012;22:108-115. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22171588.

515. Lisman T, Bijsterveld NR, Adelmeijer J, et al. Recombinant factor VIIa reverses the in vitro and ex vivo anticoagulant and profibrinolytic effects of fondaparinux. J Thromb Haemost 2003;1:2368-2373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14629471.

516. Vavra KA, Lutz MF, Smythe MA. Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. Ann Pharmacother 2010;44:718-726. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20233918.

517. Young G, Yonekawa KE, Nakagawa PA, et al. Recombinant activated factor VII effectively reverses the anticoagulant effects of heparin, enoxaparin, fondaparinux, argatroban, and bivalirudin ex vivo as measured using thromboelastography. Blood Coagul Fibrinolysis 2007;18:547-553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17762530.

518. Warkentin TE, Margetts P, Connolly SJ, et al. Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. Blood 2012;119:2172-2174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22383791.

519. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers. Thromb Haemost 2012;108:217-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22627883.

520. Zatta A, McQuilten Z, Kandane-Rathnayake R, et al. The Australian and New Zealand Haemostasis Registry: ten years of data on off-licence use of recombinant activated factor VII. Blood Transfus 2015;13:86-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24960661.

521. Diehl KH, Romisch J, Hein B, et al. Investigation of activated prothrombin complex concentrate as potential hirudin antidote in animal models. Haemostasis 1995;25:182-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7557657.

522. Elg M, Carlsson S, Gustafsson D. Effect of activated prothrombin complex concentrate or recombinant factor VIIa on the bleeding time and thrombus formation during anticoagulation with a direct thrombin inhibitor. Thromb Res 2001;101:145-157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11228338.

523. Sorensen B, Ingerslev J. A direct thrombin inhibitor studied by dynamic whole blood clot formation. Haemostatic response to ex-vivo addition of recombinant factor VIIa or activated prothrombin complex concentrate. Thromb Haemost 2006;96:446-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17003921.

524. Dager WE, Roberts AJ, Nishijima DK. Effect of low and moderate dose FEIBA to reverse major bleeding in patients on direct oral anticoagulants. Thromb Res 2019;173:71-76. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30476716.

525. Bove CM, Casey B, Marder VJ. DDAVP reduces bleeding during continued hirudin administration in the rabbit. Thromb Haemost 1996;75:471-475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8701410.

526. Prescribing information for desmopressin acetate injection, for intravenous or subcutaneous use. 2022. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/018938Orig1s039lbl.pdf. Accessed June 5, 2024.

527. Mannucci PM, Bettega D, Cattaneo M. Patterns of development of tachyphylaxis in patients with haemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP). Br J Haematol 1992;82:87-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1419807.

528. Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet 2010;49:259-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20214409.

529. Koster A, Buz S, Krabatsch T, et al. Effect of modified ultrafiltration on bivalirudin elimination and postoperative blood loss after on-pump coronary artery bypass grafting: assessment of different filtration strategies. J Card Surg 2008;23:655-658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18793221.

530. Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am J Hematol 2012;87 Suppl 1:S141-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22473649.

531. Pollack CV, Jr., Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med 2017;377:431-441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28693366.

532. Pollack CV, Jr., Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26095746.

533. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011;124:1573-1579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21900088.

534. Godier A, Miclot A, Le Bonniec B, et al. Evaluation of prothrombin complex concentrate and recombinant activated factor VII to reverse rivaroxaban in a rabbit model. Anesthesiology 2012;116:94-102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22042412.

535. Schulman S, Gross PL, Ritchie B, et al. Prothrombin complex concentrate for major bleeding on Factor Xa inhibitors: A prospective cohort study. Thromb Haemost 2018;118:842-851. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29564837.

536. Siegal D, Lu G, Leeds JM, et al. Safety, pharmacokinetics, and reversal of apixaban anticoagulation with andexanet alfa. Blood Adv 2017;1:1827-1838. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29296829.

537. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of Factor Xa inhibitor activity. N Engl J Med 2015;373:2413-2424. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26559317.

538. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with Factor Xa inhibitors. N Engl J Med 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30730782.

539. Crowther M, Levy GG, Lu G, et al. A phase 2 randomized, double-blind, placebo-controlled trial demonstrating reversal of edoxaban-induced anticoagulation in healthy subjects by andexanet alfa (PRT064445), a universal antidote for Factor Xa (fxa) inhibitors. Blood 2014;124:4269-4269. Available at: https://doi.org/10.1182/blood.V124.21.4269.4269.

540. Lu G, Conley PB, Leeds JM, et al. A phase 2 PK/PD study of andexanet alfa for reversal of rivaroxaban and edoxaban anticoagulation in healthy volunteers. Blood Adv 2020;4:728-739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32092140.

541. Benz AP, Xu L, Eikelboom JW, et al. Abstract P3: Andexanet alfa for acute bleeding during treatment with edoxaban. Stroke 2021;52:AP3-AP3. Available at: https://www.ahajournals.org/doi/abs/10.1161/str.52.suppl_1.P3

542. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:160S-198S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18574265.

543. Makris M, van Veen JJ, Maclean R. Warfarin anticoagulation reversal: management of the asymptomatic and bleeding patient. J Thromb Thrombolysis 2010;29:171-181. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19882303.

544. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e152S-184S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22315259.

545. Crowther MA, Ageno W, Garcia D, et al. Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin: a randomized trial. Ann Intern Med 2009;150:293-300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19258557.

546. Lubetsky A, Yonath H, Olchovsky D, et al. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med 2003;163:2469-2473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14609783.

547. Burbury KL, Milner A, Snooks B, et al. Short-term warfarin reversal for elective surgery--using low-dose intravenous vitamin K: safe, reliable and convenient*. Br J Haematol 2011;154:626-634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21751986.

548. Sarode R, Milling TJ, Jr., Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234-1243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23935011.

549. Goldstein JN, Refaai MA, Milling TJ, Jr., et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet 2015;385:2077-2087. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25728933.

550. Holland L, Warkentin TE, Refaai M, et al. Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supratherapeutic international normalized ratio due to warfarin overdose. Transfusion 2009;49:1171-1177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19210325.

551. Ilyas C, Beyer GM, Dutton RP, et al. Recombinant factor VIIa for warfarin-associated intracranial bleeding. J Clin Anesth 2008;20:276-279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18617125.

552. Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K1): a 5-year retrospective review. Ann Allergy Asthma Immunol 2002;89:400-406. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12392385.

553. Ehrlich HJ, Henzl MJ, Gomperts ED. Safety of factor VIII inhibitor bypass activity (FEIBA): 10-year compilation of thrombotic adverse events. Haemophilia 2002;8:83-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11952842.

554. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2005;352:777-785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15728810.

555. Bucklin MH, Acquisto NM, Nelson C. The effects of recombinant activated factor VII dose on the incidence of thromboembolic events in patients with coagulopathic bleeding. Thromb Res 2014;133:768-771. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24636870.

556. Tafur AJ, Wysokinski WE, McBane RD, et al. Cancer effect on periprocedural thromboembolism and bleeding in anticoagulated patients.

Ann Oncol 2012;23:1998-2005. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22473596.

557. Shaw JR, Douketis J, Le Gal G, Carrier M. Periprocedural interruption of anticoagulation in patients with cancer-associated venous thromboembolism: An analysis of thrombotic and bleeding outcomes. J Thromb Haemost 2019;17:1171-1178. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31038838.

558. Valsami S, Asmis LM. A brief review of 50 years of perioperative thrombosis and hemostasis management. Semin Hematol 2013;50:79-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24216167.

559. Clark NP, Witt DM, Davies LE, et al. Bleeding, recurrent venous thromboembolism, and mortality risks during warfarin interruption for invasive procedures. JAMA Intern Med 2015;175:1163-1168. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26010033.

560. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol 2017;69:871-898. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28081965.

561. Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J 2013;34:2094-2106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23625209.

562. Albaladejo P, Bonhomme F, Blais N, et al. Management of direct oral anticoagulants in patients undergoing elective surgeries and invasive procedures: Updated guidelines from the French Working Group on Perioperative Hemostasis (GIHP) - September 2015. Anaesth Crit Care Pain Med 2017;36:73-76. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27659969.

563. Spyropoulos AC, Al-Badri A, Sherwood MW, Douketis JD. Periprocedural management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. J Thromb Haemost 2016;14:875-885. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26988871.

564. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. Eur Heart J 2017;38:2137-2149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27282612.

565. Sticherling C, Marin F, Birnie D, et al. Antithrombotic management in patients undergoing electrophysiological procedures: a European Heart Rhythm Association (EHRA) position document endorsed by the ESC Working Group Thrombosis, Heart Rhythm Society (HRS), and Asia Pacific Heart Rhythm Society (APHRS). Europace 2015;17:1197-1214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26105732.

566. Omran H, Bauersachs R, Rubenacker S, et al. The HAS-BLED score predicts bleedings during bridging of chronic oral anticoagulation. Results from the national multicentre BNK Online bRiDging REgistRy (BORDER). Thromb Haemost 2012;108:65-73. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22534746.

567. Zhu W, He W, Guo L, et al. The HAS-BLED Score for Predicting Major Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis. Clin Cardiol 2015;38:555-561. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26418409.

568. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. Eur Heart J 2015;36:3258-3264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26424865.

569. Hijazi Z, Oldgren J, Lindback J, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. Lancet 2016;387:2302-2311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27056738.

570. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263-272. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19762550.

571. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004;110:2287-2292. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15477396.

572. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e495S-530S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22315270.

573. Andreescu AC, Possidente C, Hsieh M, Cushman M. Evaluation of a pharmacy-based surveillance program for heparin-induced thrombocytopenia. Pharmacotherapy 2000;20:974-980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10939559.

574. Arepally GM, Ortel TL. Heparin-induced thrombocytopenia. Annu Rev Med 2010;61:77-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20059332.

575. Morris TA, Castrejon S, Devendra G, Gamst AC. No difference in risk for thrombocytopenia during treatment of pulmonary embolism and deep venous thrombosis with either low-molecular-weight heparin or unfractionated heparin: a metaanalysis. Chest 2007;132:1131-1139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17646239.

576. Prandoni P, Siragusa S, Girolami B, Fabris F. The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study. Blood 2005;106:3049-3054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16030191.

577. Levine RL, McCollum D, Hursting MJ. How frequently is venous thromboembolism in heparin-treated patients associated with heparin-induced thrombocytopenia? Chest 2006;130:681-687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16963663.

578. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005;106:2710-2715. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15985543.

579. Pouplard C, May MA, Iochmann S, et al. Antibodies to platelet factor 4-heparin after cardiopulmonary bypass in patients anticoagulated with unfractionated heparin or a low-molecular-weight heparin : clinical implications for heparin-induced thrombocytopenia. Circulation 1999;99:2530-2536. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10330384.

580. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995;332:1330-1335. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7715641.

581. Opatrny L, Warner MN. Risk of thrombosis in patients with malignancy and heparin-induced thrombocytopenia. Am J Hematol 2004;76:240-244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15224359.

582. Prandoni P, Falanga A, Piccioli A. Cancer, thrombosis and heparin-induced thrombocytopenia. Thromb Res 2007;120 Suppl 2:137-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18023709.

583. Greinacher A, Alban S, Omer-Adam MA, et al. Heparin-induced thrombocytopenia: a stoichiometry-based model to explain the differing immunogenicities of unfractionated heparin, low-molecular-weight heparin, and fondaparinux in different clinical settings. Thromb Res 2008;122:211-220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18262226.

584. Greinacher A, Farner B, Kroll H, et al. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A

retrospective analysis of 408 patients. Thromb Haemost 2005;94:132-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16113796.

585. Warkentin TE, Roberts RS, Hirsh J, Kelton JG. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome: a nested cohort study. Chest 2005;127:1857-1861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15888871.

586. Greinacher A. Heparin-induced thrombocytopenia. J Thromb Haemost 2009;7 Suppl 1:9-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19630757.

587. Crowther MA, Cook DJ, Albert M, et al. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. J Crit Care 2010;25:287-293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20149589.

588. Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006;4:759-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16634744.

589. Warkentin TE, Aird WC, Rand JH. Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program 2003:497-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14633796.

590. Pouplard C, Gueret P, Fouassier M, et al. Prospective evaluation of the '4Ts' score and particle gel immunoassay specific to heparin/PF4 for the diagnosis of heparin-induced thrombocytopenia. J Thromb Haemost 2007;5:1373-1379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17362241.

591. Cuker A, Arepally G, Crowther MA, et al. The HIT Expert Probability (HEP) Score: a novel pre-test probability model for heparin-induced thrombocytopenia based on broad expert opinion. J Thromb Haemost 2010;8:2642-2650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20854372.

592. Joseph L, Gomes MP, Al Solaiman F, et al. External validation of the HIT Expert Probability (HEP) score. Thromb Haemost 2015;113:633-640. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25588983.

593. Pishko AM, Fardin S, Lefler DS, et al. Prospective comparison of the HEP score and 4Ts score for the diagnosis of heparin-induced thrombocytopenia. Blood Adv 2018;2:3155-3162. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30463915.

594. Lillo-Le Louet A, Boutouyrie P, Alhenc-Gelas M, et al. Diagnostic score for heparin-induced thrombocytopenia after cardiopulmonary bypass. J Thromb Haemost 2004;2:1882-1888. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15550015.

595. Allan KA, Crow JR, Chasler JE, et al. Comparison of Clinical Scoring Tools to Predict Heparin-Induced Thrombocytopenia in Cardiac Surgery. Semin Thorac Cardiovasc Surg 2022;34:570-580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34102291.

596. Wong M, Oo TH, Qiao W, et al. Performance of 4T score and heparin-platelet factor 4 antibody in the diagnosis of heparin-induced thrombocytopenia (HIT) in cancer. J Thromb Thrombolysis 2017;44:261-266. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28677022.

597. Cuker A. Does my patient have HIT? There should be an app for that. Blood 2016;127:522-524. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26847066.

598. Nagler M, Bachmann LM, ten Cate H, ten Cate-Hoek A. Diagnostic value of immunoassays for heparin-induced thrombocytopenia: a systematic review and meta-analysis. Blood 2016;127:546-557. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26518436.

599. Prescribing information for argatroban injection, for intravenous infusion only. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203049s007lbl.pdf. Accessed June 5, 2024.

600. Begelman SM, Baghdasarian SB, Singh IM, et al. Argatroban anticoagulation in intensive care patients: effects of heart failure and multiple organ system failure. J Intensive Care Med 2008;23:313-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18701526.

601. Kiser TH, Jung R, MacLaren R, Fish DN. Evaluation of diagnostic tests and argatroban or lepirudin therapy in patients with suspected heparin-induced thrombocytopenia. Pharmacotherapy 2005;25:1736-1745. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16305293.

602. Reichert MG, MacGregor DA, Kincaid EH, Dolinski SY. Excessive argatroban anticoagulation for heparin-induced thrombocytopenia. Ann Pharmacother 2003;37:652-654. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12708939.

603. Lewis BE, Wallis DE, Berkowitz SD, et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 2001;103:1838-1843. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11294800.

604. Lewis BE, Wallis DE, Leya F, et al. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med 2003;163:1849-1856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12912723.

605. Kiser TH, Fish DN. Evaluation of bivalirudin treatment for heparin-induced thrombocytopenia in critically ill patients with hepatic and/or renal dysfunction. Pharmacotherapy 2006;26:452-460. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16553502.

606. Kiser TH, Burch JC, Klem PM, Hassell KL. Safety, efficacy, and dosing requirements of bivalirudin in patients with heparin-induced thrombocytopenia. Pharmacotherapy 2008;28:1115-1124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18752382.

607. Joseph L, Casanegra AI, Dhariwal M, et al. Bivalirudin for the treatment of patients with confirmed or suspected heparin-induced thrombocytopenia. J Thromb Haemost 2014;12:1044-1053. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24766902.

608. Chong BH, Chong JJ. Heparin-induced thrombocytopenia associated with fondaparinux. Clin Adv Hematol Oncol 2010;8:63-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20351686.

609. Ratuapli SK, Bobba B, Zafar H. Heparin-induced thrombocytopenia in a patient treated with fondaparinux. Clin Adv Hematol Oncol 2010;8:61-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20351685.

610. Rota E, Bazzan M, Fantino G. Fondaparinux-related thrombocytopenia in a previous low-molecular-weight heparin (LMWH)-induced heparin-induced thrombocytopenia (HIT). Thromb Haemost 2008;99:779-781. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18392338.

611. Warkentin TE, Maurer BT, Aster RH. Heparin-induced thrombocytopenia associated with fondaparinux. N Engl J Med 2007;356:2653-2655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17582083.

612. Schindewolf M, Steindl J, Beyer-Westendorf J, et al. Use of fondaparinux off-label or approved anticoagulants for management of heparin-induced thrombocytopenia. J Am Coll Cardiol 2017;70:2636-2648. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29169470.

613. Kang M, Alahmadi M, Sawh S, et al. Fondaparinux for the treatment of suspected heparin-induced thrombocytopenia: a propensity score-matched study. Blood 2015;125:924-929. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25515959.

614. Blackmer AB, Oertel MD, Valgus JM. Fondaparinux and the management of heparin-induced thrombocytopenia: the journey continues. Ann Pharmacother 2009;43:1636-1646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19737996.

615. Grouzi E, Kyriakou E, Panagou I, Spiliotopoulou I. Fondaparinux for the treatment of acute heparin-induced thrombocytopenia: a single-center experience. Clin Appl Thromb Hemost 2010;16:663-667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19825921.

616. Lobo B, Finch C, Howard A, Minhas S. Fondaparinux for the treatment of patients with acute heparin-induced thrombocytopenia. Thromb Haemost 2008;99:208-214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18217156.

617. Wester JP, Leyte A, Oudemans-van Straaten HM, et al. Low-dose fondaparinux in suspected heparin-induced thrombocytopenia in the critically ill. Neth J Med 2007;65:101-108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17387236.

618. Ezekwudo DE, Chacko R, Gbadamosi B, et al. Apixaban for treatment of confirmed heparin-induced thrombocytopenia: a case report and review of literature. Exp Hematol Oncol 2017;6:21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28725494.

619. Khalid S, Daw H. The Role of Apixaban in the Treatment of Heparin-Induced Thrombocytopenia. Cureus 2017;9:e1428. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28884054.

620. Anusim N, Ionescu F, Konde AS, et al. Outcomes in heparin-induced thrombocytopenia managed with direct oral anticoagulants. Blood 2019;134:4975-4975. Available at: https://doi.org/10.1182/blood-2019-129485.

621. Walenga JM, Prechel M, Hoppensteadt D, et al. Apixaban as an alternate oral anticoagulant for the management of patients with heparin-induced thrombocytopenia. Clin Appl Thromb Hemost 2013;19:482-487. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23780399.

622. Larsen PB, Jorgensen M, Friis-Hansen L, Ingeberg S. Apixaban used for the management of heparin-induced thrombocytopenia in a 72-year-old woman with lung cancer. Clin Case Rep 2015;3:987-989. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26732728.

623. Kunk PR, Brown J, McShane M, et al. Direct oral anticoagulants in hypercoagulable states. J Thromb Thrombolysis 2017;43:79-85. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27632140.

624. Sharifi M, Bay C, Vajo Z, et al. New oral anticoagulants in the treatment of heparin-induced thrombocytopenia. Thromb Res 2015;135:607-609. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25613925.

625. Mirdamadi A. Dabigatran, a direct thrombin inhibitor, can be a life-saving treatment in heparin-induced thrombocytopenia. ARYA Atheroscler 2013;9:112-114. Available at: https://pubmed.ncbi.nlm.nih.gov/23690810/.

626. Tardy-Poncet B, Piot M, Montmartin A, et al. Delayed-onset heparin-induced thrombocytopenia without thrombosis in a patient receiving postoperative thromboprophylaxis with rivaroxaban. Thromb Haemost 2015;114:652-654. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26062524.

627. Bircan HA, Alanoglu EG. Massive Pulmonary Embolism in a Patient with Heparin Induced Thrombocytopenia: Successful Treatment with Dabigatran. Eurasian J Med 2016;48:65-68. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27026768.

628. Hantson P, Lambert C, Hermans C. Rivaroxaban for arterial thrombosis related to heparin-induced thrombocytopenia. Blood Coagul Fibrinolysis 2015;26:205-206. Available at: https://pubmed.ncbi.nlm.nih.gov/25255239/.

629. Aon M, Al-Shammari O. Rivaroxaban treatment for heparin-induced thrombocytopenia: A case report and a review of the current experience. Case Rep Hematol 2020;2020:8885256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32953186.

630. Samos M, Bolek T, Ivankova J, et al. Heparin-induced thrombocytopenia presenting with deep venous thrombosis and pulmonary embolism successfully treated with rivaroxaban: Clinical case report and review of current experiences. J Cardiovasc Pharmacol 2016;68:391-394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27464495.

631. Casan JM, Grigoriadis G, Chan N, Chunilal S. Rivaroxaban in treatment refractory heparin-induced thrombocytopenia. BMJ Case Rep 2016;2016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27520997.

632. Sartori M, Favaretto E, Cini M, et al. Rivaroxaban in the treatment of heparin-induced thrombocytopenia. J Thromb Thrombolysis 2015;40:392-394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25804370.

633. Abouchakra L, Khabbaz Z, Abouassi S, Badaoui G. Rivaroxaban for treatment of heparin-induced thrombocytopenia after cardiac surgery: A case report. J Thorac Cardiovasc Surg 2015;150:e19-20. Available at: https://pubmed.ncbi.nlm.nih.gov/26055438/.

634. Ng HJ, Than H, Teo EC. First experiences with the use of rivaroxaban in the treatment of heparin-induced thrombocytopenia. Thromb Res 2015;135:205-207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24974053.

635. Kopolovic I, Warkentin TE. Progressive thrombocytopenia after cardiac surgery in a 67-year-old man. CMAJ 2014;186:929-933. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24756626.

636. Warkentin TE, Pai M, Linkins LA. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. Blood 2017;130:1104-1113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28646118.

637. Kanamoto R, Hiromatsu S, Anegawa T, et al. Use of Edoxaban for the Treatment of Heparin-Induced Thrombocytopenia. Case Rep Vasc Med 2020;2020:2367095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32963878.

638. Srinivasan AF, Rice L, Bartholomew JR, et al. Warfarin-induced skin necrosis and venous limb gangrene in the setting of heparin-induced thrombocytopenia. Arch Intern Med 2004;164:66-70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14718324.

639. Gosselin RC, Dager WE, King JH, et al. Effect of direct thrombin inhibitors, bivalirudin, lepirudin, and argatroban, on prothrombin time and INR values. Am J Clin Pathol 2004;121:593-599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15080313.

640. Warkentin TE, Greinacher A, Craven S, et al. Differences in the clinically effective molar concentrations of four direct thrombin inhibitors explain their variable prothrombin time prolongation. Thromb Haemost 2005;94:958-964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16363236.

641. Arpino PA, Demirjian Z, Van Cott EM. Use of the chromogenic factor X assay to predict the international normalized ratio in patients transitioning from argatroban to warfarin. Pharmacotherapy 2005;25:157-164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15767231.

642. Austin JH, Stearns CR, Winkler AM, Paciullo CA. Use of the chromogenic factor x assay in patients transitioning from argatroban to warfarin therapy. Pharmacotherapy 2012;32:493-501. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22511112.