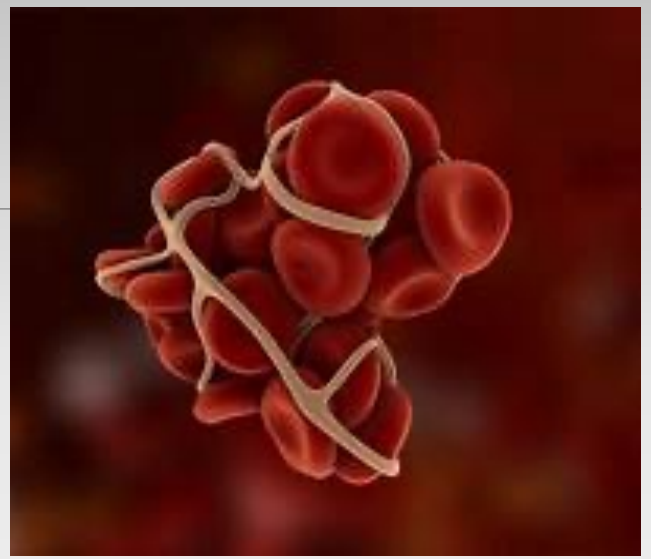
Thrombosis and the Oncology Patient



PAMELA DUDKIEWICZ, DNP, APRN, FNP-BC, AOCNP®

MARCH 3RD, 2023

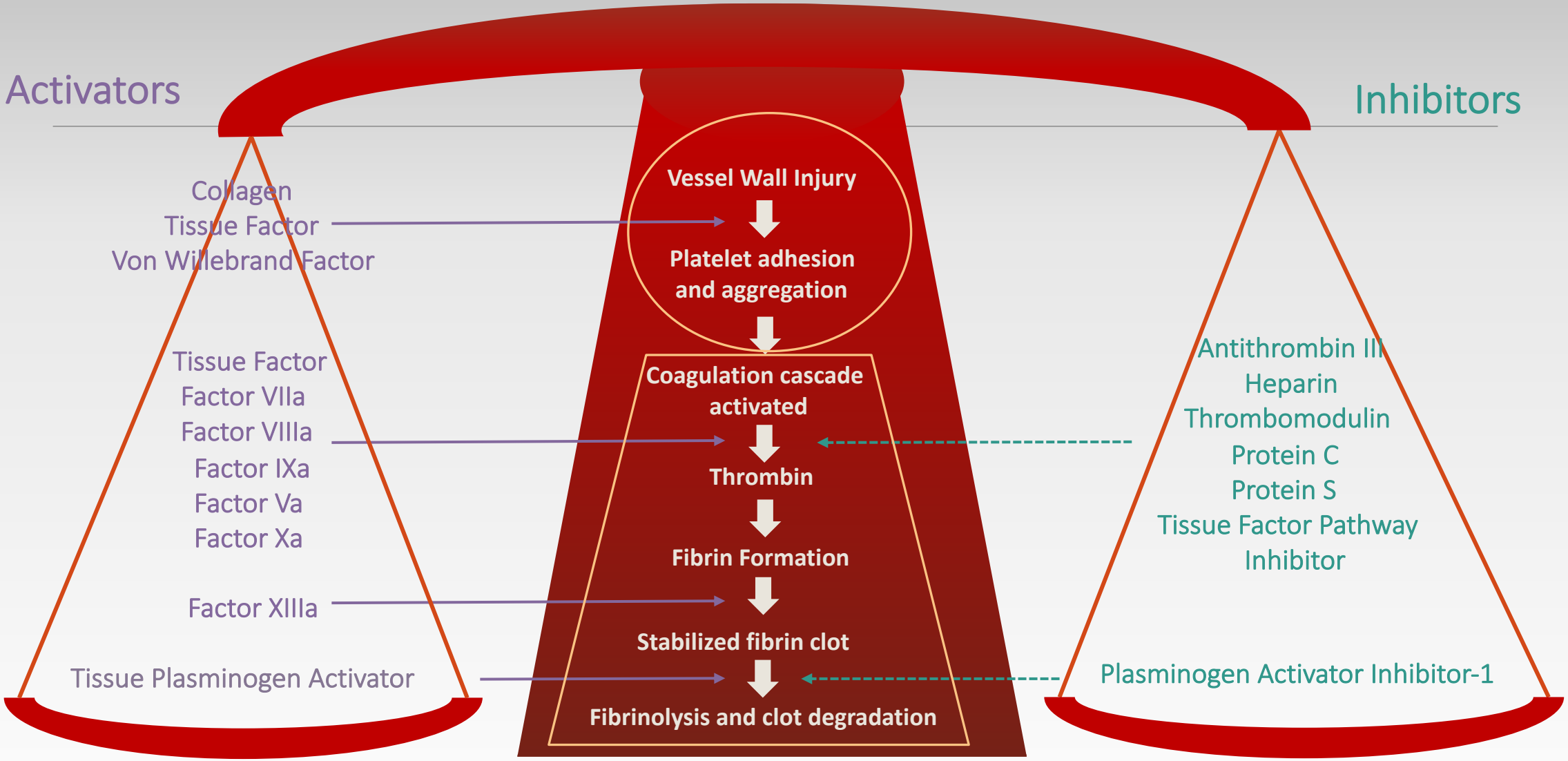
Objectives

- Discuss normal hemostasis and the coagulation cascade
- Discuss an overview of thromboembolism, epidemiology and disease state of and risk for thrombosis
- Discuss the VTE in patients with cancer
- Review currently available antithrombotic agents
- Understand the guidelines for VTE prophylaxis
- Identify high-risk cancer patients and recommendations for treatment

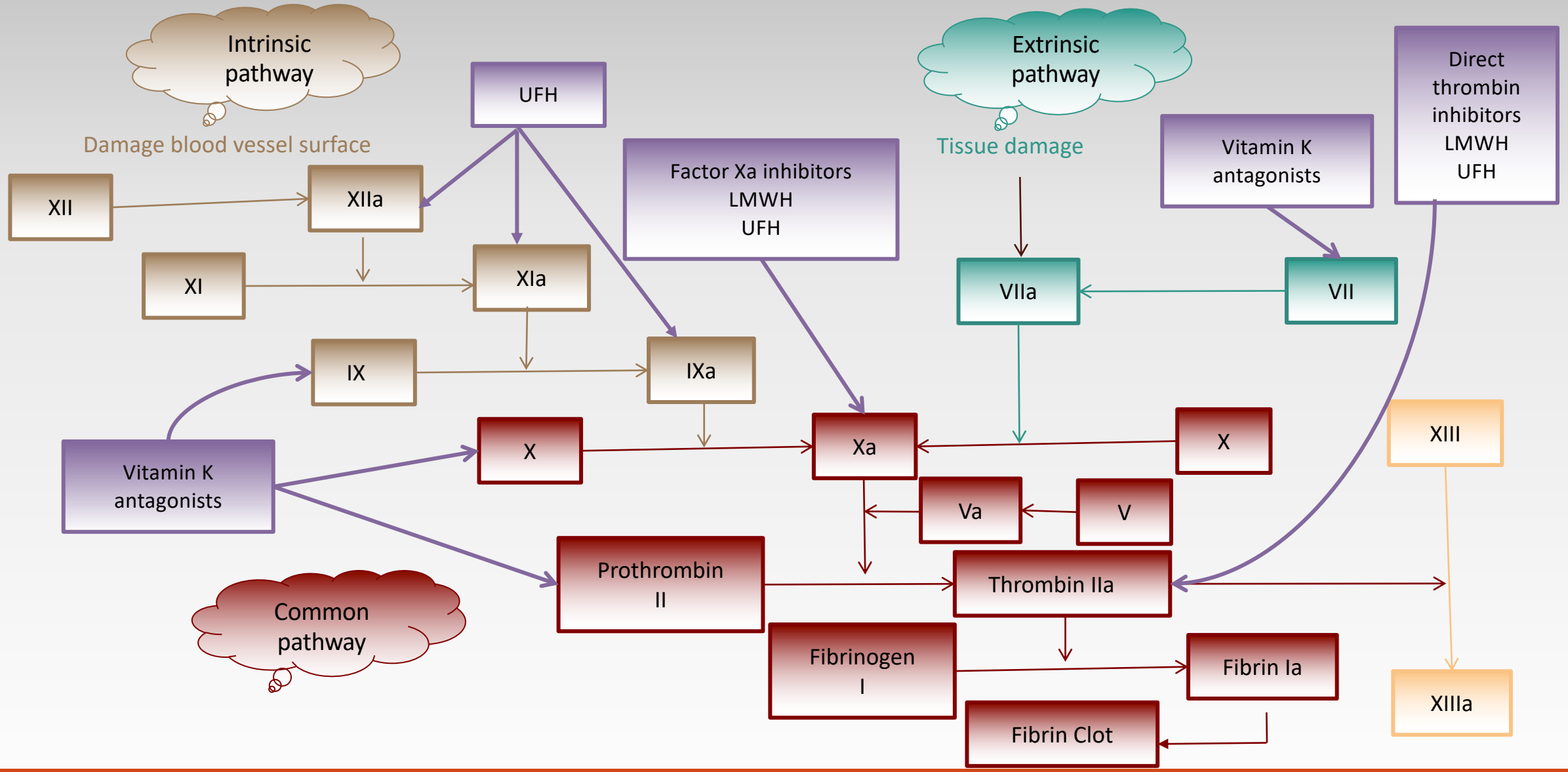
Hemostasis and Coagulation

- Hemostasis: The complex process by which the body stops bleeding upon injury and maintains blood in the vascular system
  - Vessel wall, platelets, and plasma proteins
  - Imbalance= bleeding or thrombosis
- Coagulation: A cascading system of proteins which provides a vital role in hemostasis
  - Consists of three pathways (intrinsic, extrinsic and common)

Hemostasis Overview



Coagulation Cascade



Overview of Thromboembolism

Thrombosis

- A blood clot formed in a blood vessel, obstructing blood flow. The clot does not move to different parts of the body
- Classified as venous (formed in a vein) or arterial (formed in an artery) thrombosis
- Most common
  - DVT
  - PE
- Treatment - anticoagulants

Embolism

- A complete or part of a blood clot that detaches from its site, causing a blockage in a part of the body. This clot can travel through the body.
- Classified as venous embolism and arterial embolism (blocked vessel in any part of body, caused by the moving clot).
- Most common
  - Stroke
  - Heart Attack
- Treatment - antiplatelets

Both conditions are characterized by a blood clot, but are *different* conditions

Incidence/Prevalence of Thromboembolism

- VTE affects as many as 500,000 people in the US annually
- Overall incidence is higher in African American populations and lower in Asian populations
- Men>women except women in childbearing years (16-44 years) compared to men of similar age
- 60,000-100,000 is the estimated number of Americans who die each year from DVT/PE
  - 10-30% will die within one month of diagnosis
  - Sudden death is the first symptom in about 25% of people who have a PE
- Of the non-fatal cases of VTE, 40% are from PEs and 60% are from DVTs
- Among people who have had a DVT, ½ will have long-term complications
- 33% will have a recurrence within 10 years

Facts about Thromboembolisms

- ~ 274 people die every day from blood clots
- 70% of all patients with thrombosis are provoked clots
  - Known risk factors
    - Surgery
    - Hospitalization
    - Cancer
    - Medical illness
    - Genetics
  - 2% per year recur after 3 months of anticoagulation therapy
- 30% of all patients with thrombosis are unprovoked clots
  - Absence of identifiable risk factors
  - Idiopathic
  - 7-11% per year recur if anticoagulant therapy stopped after 3, 6, 12, or 24 months

Relationship between cancer and thrombosis

- Armand Trousseau
  - First described the relationship between cancer and thrombosis in 1865

"There appears in the cachexiae…a particular condition of the blood that predisposes it to spontaneous coagulation."

Armand Trousseau

1801-1867

Thromboembolism and Cancer

- Frequently complicates the course of malignancy, especially with medical and surgical anti-cancer treatments
- Can involve both venous and arterial systems
- Venous events- most common
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- Arterial events
  - Stroke
  - Myocardial infarction
- Generally, presents after cancer diagnosis, however, can be the presenting symptom that leads to a cancer diagnosis

Epidemiology of VTE and Cancer

- Of all cases of VTE:
  - 18% occur in cancer patients
  - Annual incidence of VTE is 8/1000 cancer patients/year
  - Up to 7-fold greater risk of VTE development in cancer patients
- Of all cancer patients:
  - 20% will have symptomatic VTE
  - As many as 50% have VTE on autopsy
- Compared to patients without cancer:
  - Higher risk of first and recurrent VTE
  - Higher risk of bleeding on anticoagulants
  - Higher risk of dying

Ay, C et al. Thromb Haemost 2017;117:219-230. Hawbaker S J Adv Pract Oncol 2012;3:23-33

Burden of VTE and Cancer

- Cancer is a strong and independent risk factor for venous thromboembolism (VTE)
- VTE represents one of the most important causes of morbidity and mortality in cancer patients as well as the 2nd leading cause of death in patients with cancer
- Lower survival rates and poorer prognosis in cancer patients with VTE compared to those without
- Healthcare costs are approximately 40-50% higher in cancer patients with VTE compared to those without
- Appropriate prevention and treatment of cancer-associated VTE is vital to reduce its burden on patients and the health system at large

Flanga, A, et al. J Thromb Haema 2013;11:223-233, Mandala, M, et al. Ann Oncology 2011;22(6): vi85-vi92, Lyman, GH. (2011), Cancer, 117::1334-1339

Common VTE in Cancer

Deep Vein Thrombosis

- Symptoms
  - Swelling, pain, warmth, or erythema of unilateral extremity
  - Heaviness in the extremity
  - Unexplained persistent calf cramping
  - Swelling in face, neck, or supraclavicular space
  - Catheter dysfunction
- Signs
  - Dilation of superficial veins and palpable cord
  - + Homan's sign
- Diagnostic studies
  - Duplex venous ultrasonography
  - Contrast-enhanced CT
  - MRI
  - Standard venography
  - Serum D-dimer

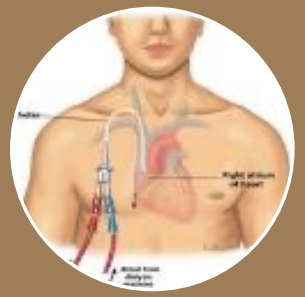
Pulmonary Embolism

- Symptoms
  - Dyspnea (acute onset)
  - Pleuritic chest pain
  - Hemoptysis
  - Cough
  - Pain and/or edema to lower extremity
  - Apprehension
- Signs
  - Tachypnea
  - Signs of DVT
  - Tachycardia
  - Hypoxia
  - Murmur
- Most common
  - CT angiography
  - VQ lung scan
  - Pulmonary angiography

Risk for VTE

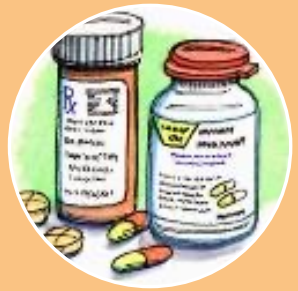
Age

History



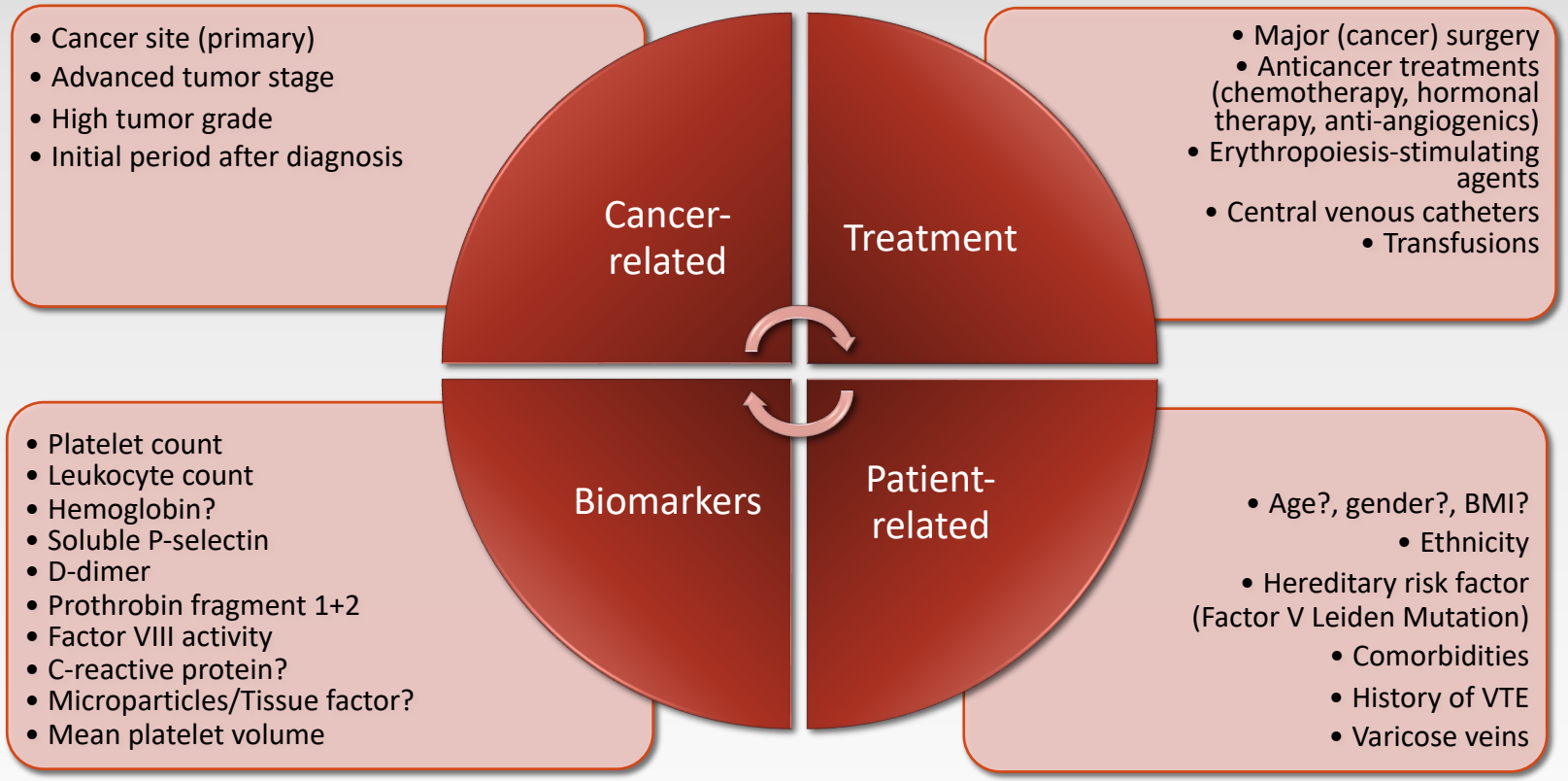
Vascular Stasis

Hypercoagulable State

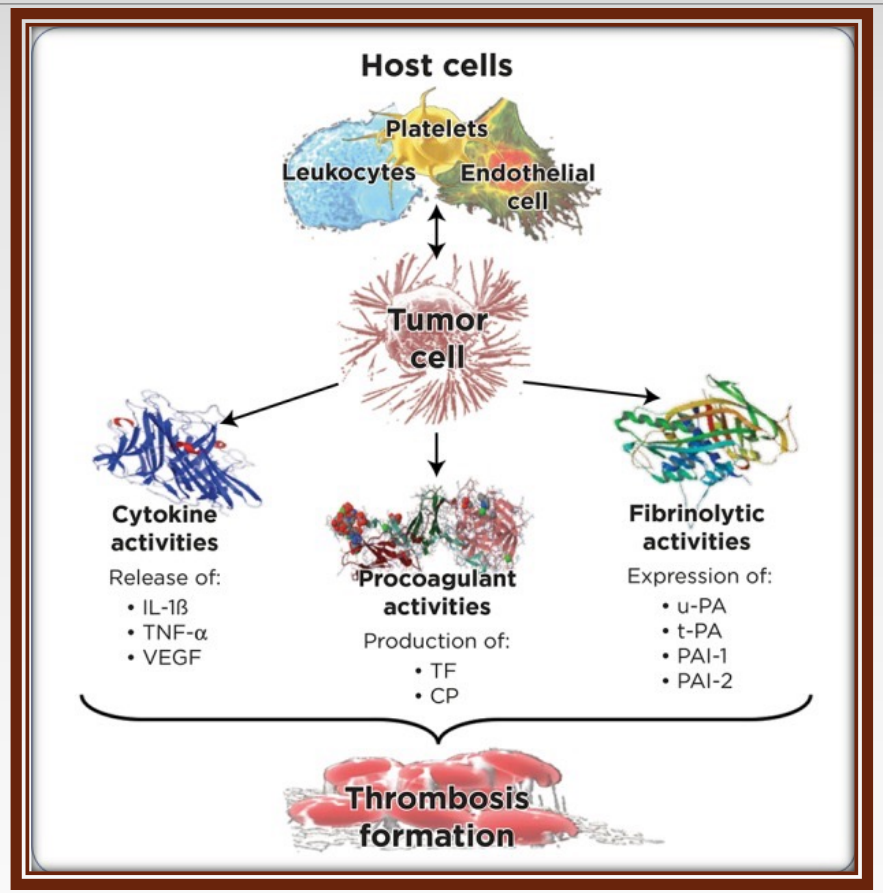


Medication

Risk Factors for VTE in Patients with Cancer



Pathogenesis of Cancer-Associated VTE

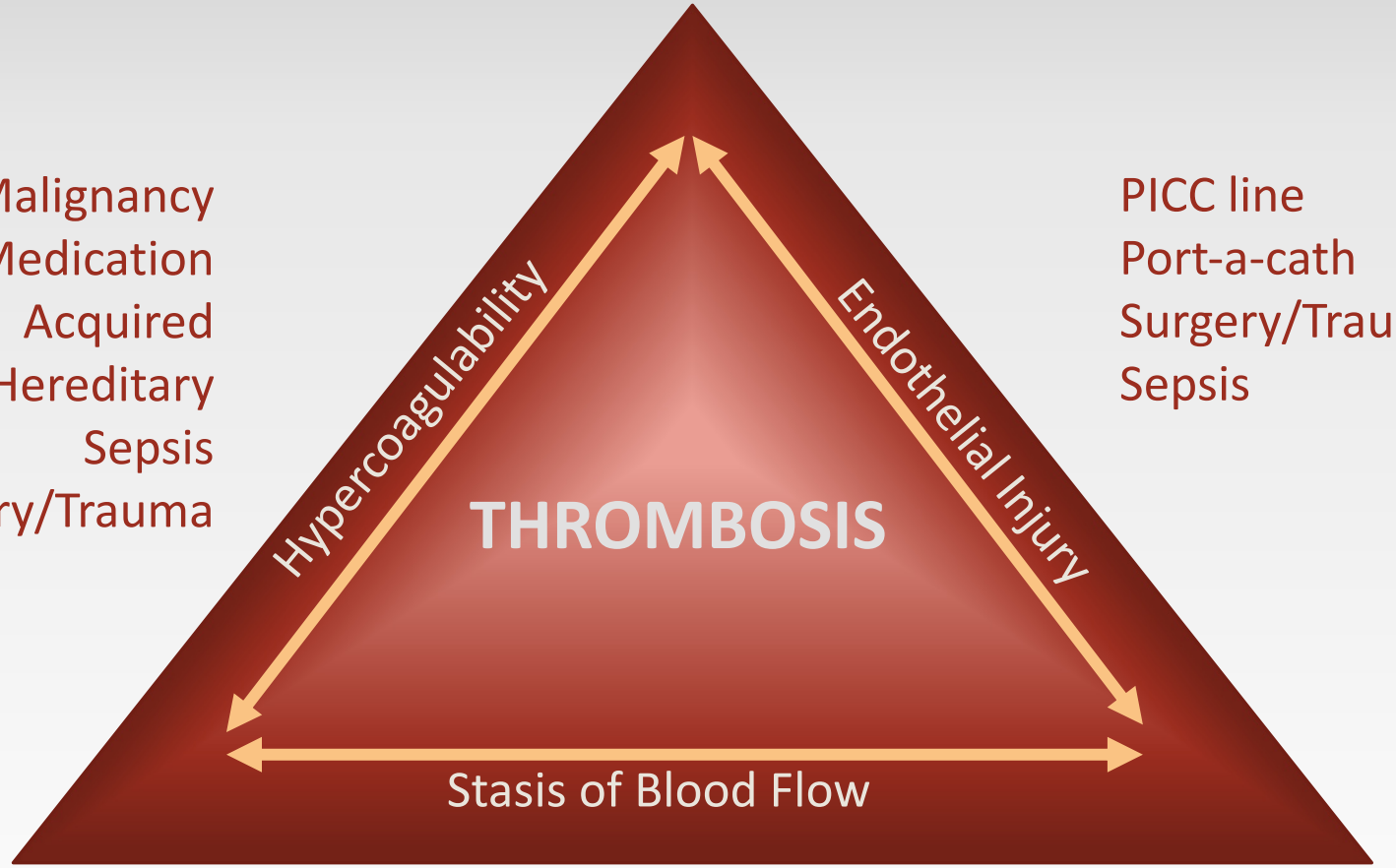


Mechanism	Function
Procoagulant activity	Production of: • Tissue factor • Cancer procoagulant
Fibrinolytic activity	Expression of: • Urokinase-type activator • Tissue-type plasminogen activator • Plasminogen activator inhibitor-1 • Plasminogen activator inhibitor-2
Cytokine activity	Release of: • Interleukin-1β • Tumor necrosis factor-α • Vascular endothelial growth factor
Host cell-tumor cell activity	Interaction with: • Endothelial cells • Leukocytes; monocytes and macrophages • Platelets • Tumor cells

Hawbaker, S. J Adv Pract Oncol 2012;3:23-33 Used with permission

Virchow's Triad

Malignancy
Medication
Acquired
Hereditary
Sepsis
Surgery/Trauma



PICC line
Port-a-cath
Surgery/Trauma
Sepsis

Immobility, Age, Heart or Lung Failure

Clinical Issues and Thrombosis

Prevention

- Identification of patients at high risk
- Determine strategy for prevention

Diagnosis

- Recognition of signs and symptoms
- Evaluation of patient and treatment factors
- Diagnosis of thrombosis

Management

- Acute management
- Chronic management
- Prevention

Currently Available Anticoagulants for Prevention and Treatment of VTE

Anticoagulant Options for Treatment of VTE

- Heparin (UFH) – IV, SC
- Low Molecular Weight Heparin (LMWH)
  - Dalteparin - SC
  - Enoxaparin - SC
- Vitamin K Antagonist
  - Warfarin - PO
- Factor Xa Inhibitors
  - Apixaban - PO
  - Rivaroxaban - PO
  - Fondaparinux - SC
- Direct Thrombin Inhibitors
  - Dabigatran - PO

Unfractionated Heparin

- MOA
  - acts at multiple sites in the coagulation process; binds to antithrombin III, catalyzing inactivation of thrombin and other clotting factors
- Dosage
  - VTE Prophylaxis- 5000 units SC Q 8-12 h
  - VTE Treatment- 18 units/kg/h IV
- Therapeutic monitoring
  - aPTT (1.5 – 2.5 x mean normal value)
- Reversal agent-
  - 100% neutralization *Protamine sulfate*
  - Removed by Hemodialysis- partial

Low Molecular Weight Heparin (LMWH)

- MOA
  - Binds to antithrombin III and accelerates activity, inhibiting thrombin and factor Xa
- Dosage
  - VTE Prophylaxis:
    - 40 mg SC (enoxaparin)
    - 5000 IU SC qd (dalteparin)
  - VTE Treatment:
    - Enoxaparin 1mg/kg SC q12h or 1.5 mg/kg qd
    - Dalteparin 200 IU/kg SC qd
- Therapeutic monitoring
  - Minimal effect on aPTT
  - Anti-Xa activity in select populations (pregnancy, obesity, renal dysfunction, children)
- Reversal Agent
  - Partially reversed with *protamine sulfate* (~60%)
  - Removed by Hemodialysis- ~ 20%

Enoxaparin
Dalteparin

Vitamin K Antagonists

- MOA
  - Inhibits the synthesis of vitamin K dependent clotting factors (factors II, VII, IX, protein C/S)
- Dosing
  - Initially administered with parenteral UFH, LMWH or fondaparinux for at least 5 days until INR is 2 or greater
- Prophylaxis
  - Start 2-5 mg daily and adjust for a target INR of 2-3 (A fib) or INR 2.5-3.5 (mechanical valves)
- Treatment
  - Start 2-5 mg along with parenteral bridging x 5 days`
- Therapeutic Monitoring
  - PT/INR
- Reversal agent
  - *Vitamin K*
  - *Fresh frozen plasma (FFP)*
  - *Prothrombin complex concentrate (PCC)*
  - *Recombinant activated factor VII*

Warfarin

Factor Xa Inhibitors

- MOA
  - (synthetic) selectively binds to AT-III potentiating FXa neutralization and inhibiting thrombin formation
- Dosage: weight based
  - Prophylaxis: 2.5 mg SC qd
  - Treatment: <50 kg- 5 mg SC qd
    - 50-100 kg- 7.5 mg SC qd
    - >100 kg- 10 mg SC qd
- Therapeutic monitoring
  - Fondaparinux specific anti-FXa activity, seldom indicated.
  - Monitor renal functions periodically
- Reversal agent
  - Consider *rFVIIa* for reversal; but no proven benefit
  - Removed by Hemodialysis- No

Fondaparinux

Oral Factor Xa Inhibitors

- MOA
  - Selective inhibitor of FXa, inhibiting free and clot-based FXa, decreasing thrombin generation
- Dosing
  - Prophylaxis
    - 10 mg qd PO (knee/hip) (rivaroxaban)
    - 20 mg qd PO A .fib
    - 2.5 mg bid PO (knee/hip) (apixaban)
    - 5 mg bid PO A. fib
  - Treatment
    - 15 mg bid PO x 21 days, then 20 mg qd (rivaroxaban)
    - 10 mg bid PO x 7 days, then 5mg bid (apixaban)
- Therapeutic Monitoring
  - Rivaroxaban or apixaban specific anti-FXa activity
  - Monitor renal functions periodically
- Reversal Agent
  - Consider *4-factor PCC*
  - *Andexanet alfa* - **Life-threatening bleeding only**
  - Removed by Hemodiaysis- No

Rivaroxaban
Apixaban

Direct Thrombin Inhibitor

- MOA
  - Directly inhibits thrombin by reversibly binding to free and clot-based thrombin and inhibiting thrombin-induced platelet aggregation
- Dosing
  - Prophylaxis
    - 110 mg PO 1-4 h x1 postop, then 220 mg qd x 28-35 days (hip replacement)
    - 150 mg bid PO (A fib)
  - Treatment*
    - 150 mg bid PO
- Therapeutic Monitoring
  - Dilute thrombin time (dTT)
  - Ecarin clotting time (ECT)
  - aPTT
- Reversal agent
  - Activated charcoal (if within 2 hours of ingestion)
  - Consider *4-factor PCC*
  - *Idarucizumab* - **Life-threatening bleeding or emergency surgery**
  - Removed by Hemodialysis- ~ 65%

Dabigatran

*Crcl 15-30: 75 mg bid; CrCl <15: not defined

Prophylaxis of VTE in Cancer Patients

- Identifying at-risk populations
  - Hospitalized patients
    - Adult medical and surgical patients
    - Diagnosis of cancer or suspicion of cancer
- Ambulatory cancer patients
  - Surgical oncology patients: high-risk abdominal or pelvic cancer patients
  - Multiple myeloma patients on IMiD therapy

IMiD = immunomodulatory drug

Current Guidelines

- VTE prophylaxis guidelines have been published by several groups
  - American Society of Clinical Oncology (ASCO)
  - National Comprehensive Cancer Network (NCCN)
  - European Society of Medical Oncology (ESMO)

Guidance Questions to be Considered

- What is the appropriate workup to search for occult malignancy in patients with idiopathic VTE?
- How can high-risk cancer patients be identified for primary thromboprophylaxis?
- What is the appropriate immediate and long-term treatment for cancer patients with acute VTE including DOACs?
- What is the appropriate duration of anticoagulation?
- What is the appropriate treatment strategy in patients with recurrent VTE on anticoagulation?

Khorana, AA, et al. J Thromb Thrombolysis 2016;41:81-91

Occult Malignancy and Idiopathic VTE

- Unprovoked VTE have a 4-fold risk of underlying cancer
- Up to 10% of patients with unprovoked VTE may be diagnosed with cancer within the 1st year following VTE
- Recommendations
  - Patients with unprovoked VTE should undergo a thorough medical history and physical exam, basic labs studies (CBC, metabolic profile and LFTs) and chest x-ray
  - Patients should undergo, if not up-to-date, age-specific and gender-specific cancer screening (cervical, breast, prostate and colon)
- Further clinical trials are required to assess the risk and benefits of more extensive occult cancer screening in patient s with unprovoked VTE

Identifying High-Risk Cancer Patients

- VTE estimate in general cancer population the risk is
- DOACs and LMWH are pharmacokinetically similar ~ 13/1000 person-years
- VTE estimate in metastatic disease or those on thrombogenic regimens the risk is 68/1000 person-years and as high as 200/1000 person-years amongst patients with primary brain tumors
- Utilizing a validated risk assessment tool can be helpful

Predictive Model for VTE (The Khorana Score)

Patient Characteristics	Risk Score
Site of cancer Very high-risk (stomach, pancreas) High-risk (lung, lymphoma, gynecologic, bladder, testicular)	 2 1
Prechemotherapy platelet count $\geq$ 350,000/mm^3	1
Hemoglobin level less than 10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count > 11,000/mm^3	1
Body mass index $\geq$ 35 kg/m^2 or more	1
High-risk score $\geq$ 3 Intermediate risk score 1-2 Low-risk score 0	

Yan, AR, et al, Healthcare. 2021 Jun21; 9(6):778.

Identifying High-Risk Cancer Patients

- Recommendations
  - No routine VTE prophylaxis in unselected and low-risk outpatients and in patients with high-risk for bleeding (primary brain tumors)
  - Outpatient LMWH in high-risk (Score $\geq$ 3 or advanced pancreatic cancer) patients receiving chemotherapy as well as aspirin or LMWH in myeloma patients on IMiD-based regimens
  - Inpatient VTE prophylaxis with LMWH or UFH in hospitalized cancer patients with an acute medical illness
  - Inpatient VTE prophylaxis with LMWH or UFH in cancers patients undergoing major surgery
  - Post-op VTE prophylaxis with LMWH up to 4 weeks in patients undergoing abdominal/pelvic surgery for cancer with high-risk features (immobility, obesity, and VTE history)

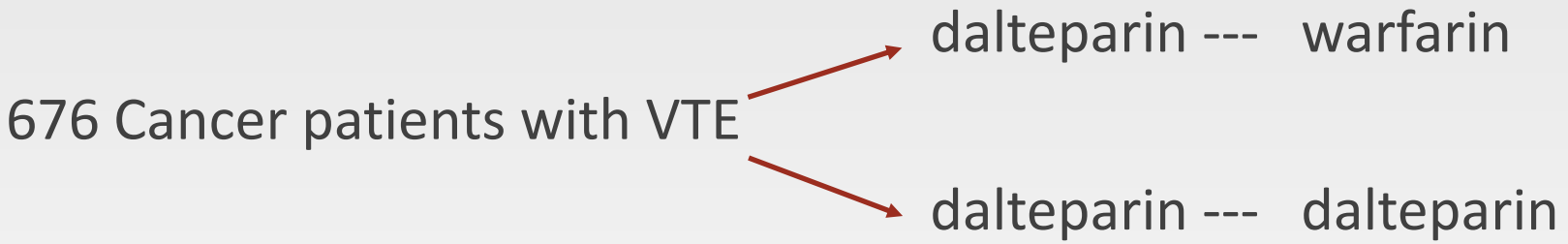
Fondaparinux should be considered in patients with contraindication to UFH or LMWH

Immediate and Long-Term Treatment

- Cancer patients with VTE have higher rates of complications, including 12% annual risk of bleeding complications and up to 21% annual risk of recurrent VTE
- Cancer-associated VTE may be resistant to warfarin and extended therapy with LMWH have shown superiority
- DOACs efficacy and safety in cancer-associated VTE remains uncertain.
  - LMWH showed significant reduction in recurrence whereas DOACs did not
  - LMWH showed a non-significant increase in bleeding risk whereas DOACs showed a non-significant reduction in bleeding risk

CLOT Trial

- Multicenter, open-label, randomized study (N=676)
- Initial therapy- dalteparin followed by 6 months of either dalteparin or warfarin with target INR 2.5



- Results- Symptomatic recurrent DVT/PE including death r/t PE was 27 patients (7%) in dalteparin group and 53 patients (15%) in warfarin group. No difference in major bleeding.
- What is the appropriate treatment strategy in patients with recurrent VTE on anticoagulation?

Immediate and Long-Term Treatment

- Recommendations
  - Patients with active cancer (known disease or receiving anti-cancer treatment) and VTE be treatment) and VTE be treated with LMWH for at least 6 months
  - Patients with incidentally diagnosed VTE be treated similarly to patients with VTE based on symptoms with at least 6 months of LMWH monotherapy, with the exceptions of isolated subsegmental PE where treatment made on case-by-case basis

Appropriate Duration and Preferred Agent

- Optimal duration of anticoagulation has not been assessed beyond 6 months
- Consensus is to continue for at least 6 months and reassess
- Recommendations
  - Anticoagulation with LMWH for a minimum of 6 months after a diagnosis of cancer-associated VTE and should continue beyond if patient has active malignancy or ongoing anti-cancer therapy
  - Patients low-risk for recurrence should be discontinued after 6 months in the absence of active malignancy (cured or complete remission)
  - Patients with high-risk for recurrence should continue with anticoagulation with periodic reevaluation

Strategy in Patient with Recurrent VTE

- Recurrent VTE is not uncommon in malignancies even with patients receiving appropriate anticoagulation, however no randomized trials to provide evidence-based approach
- Empirical approaches have been described
- Inferior vena cava (IVC) filters should only be used temporarily in patients with acute VTE and anticoagulation is contraindicated
  - Prospective randomized study of patients who received filters had short-term protection from PE, but higher rates of DVT and filter-site thrombosis
  - IVC filters were associated with increased metastases and reduced survival in cancer patients

Strategy in Patient with Recurrent VTE

- Cancer patients with symptomatic recurrent VTE despite therapeutic anticoagulation with an agent other than LMWH; transition to therapeutic LMWH, assuming no contraindications
- Cancer patients with symptomatic recurrent VTE despite optimal anticoagulation with LMWH continue LMWH at a higher dose, starting at an increase of ~25% of the current dose or resuming therapeutic weight-adjusted dose if the patient was at a non-therapeutic dose at the time of the recurrence
- Advise against IVC filters except in the presence of absolute contraindications to pharmacologic anticoagulation and only retrievable filters should be used

Conclusion

- For more than 150 years, clinicians have recognized that cancer patients are at an increased risk for developing VTE events
- VTE is a very prevalent issue in cancer patients affecting quality of life, overall survival and healthcare costs
- Despite an increasing awareness of cancer-associated VTE and the publications of evidence - based guidelines, recommendations are not followed sufficiently
- Many factors are involved in determining if and when to hold anticoagulation, how soon before surgery and the timing to resume after
- It is essential, as providers to be proactive and promote the use of evidence-based guidelines similar to those developed by the NCCN, ASCO, and ESMO to improve patient outcomes

Hawbaker S J Adv Pract Oncol 2012;3:23-33; Ay, C, et al. Thromb Haemost 2017: 219-230

References

- Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). *Chest*. 2012;141:e44S-e88S.
- Ay, C et al. Cancer-associated venous thromboembolism: burden, mechanisms, and management. *Thromb Haemost* 2017;117(2):219-230.
- Barnes GD, Ageno W, Ansell J, et al. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. *J Throm Haemost.* 2015 Jun;13(6):1154-6.
- Bartholomew JR. Update on the management of venous thromboembolism. *Cleveland Clinic Journal of medicine*.2017 December; 84(3):39-46.
- Flanga, A, et al. Coagulation and cancer: biological and clinical aspects. *J Thromb Haema* 2013;11(2):223-233.
- Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants, antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012 Feb;141(suppl 2):e24S-43S.
- Hawbaker S. Venous thromboembolism in the cancer population: pathology, risk, and prevention. *J Adv Pract Oncol;* 2012;3(1):23-33
- Heit, JA; Epidemiology of venous thromboembolism. *Nature Review Cardiology.* 2015;12(8):464–474.
- Jaffer, AK. An overview of venous thromboembolism:impact, risks, and issues in prophylaxis. *Cleveland Clinic Journal of Medicine* 2008 April;75(3):S3-S6.
- Kearon C, Akl EA, Omelas J, et al. Antithrombotic therapy for VTE disease. CHEST guideline and expert panel report. Chest. 2016 Feb;149(2):315-52.
- Khorana, AA, et al. Guidance for the prevention and treatment of cancer-associated venous thromboembolism. *J Thromb Thrombolysis* 2016;41(1):81-91.
- Lyman, GH. Venous thromboembolism in the patient with cancer: focus on burden of disease and benefits of thromboprophylaxis. *Cancer.* 2011;117(7):1334-1349.
- Lyman, GH, et al., Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. *The Oncologist.*2013;18(12):1231-1329.
- Mandala, M, et al. Management of venous thromboembolism (VTE) in cancer patients: ESMO clinical practice guidelines. *Ann Oncology* 2011;22(6): vi85-vi92.
- Nigel, SK, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *J Clinical Oncology*. 2020; 38(5): 496-520.
- Nutescu EA, Burnett A, Fanikos J, et al. Pharmacology of anticoagulants used in the treatment of venous thromboembolism. *J Thromb Thrombolysis.* 2016 Jan;41(1):15-31.
- Schulman s, Ageno W, Konstantinides SV. Venous thromboembolism: past, present and future. *Thromb Haemost. 2017;117:1219-1229.*
- Song, AB, et al. Direct oral anticoagulants for treatment and prevention of venous thromboembolism in cancer patients. *Vasc Health Risk Manag.* 2019 Jun 21;15:175-186.
- Witt DM, Clark NP, Kaatz S, et al. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. *J Thromb Thrombolysis.* 2016 Jan;41(1):187-205.
- Yan, AR, et al. Risk factors and prediction models for venous thromboembolism in ambulatory patients with lung cancer. *Healthcare.* 2021 Jun 21;9(6):778.

Thank you!