Objectives:
1. Identify the relative risk of cancer-associated thrombosis (CAT)
2. List advantages and disadvantages of anticoagulation treatment options for venous thromboembolisms (VTE)
3. Summarize landmark literature and current guidelines for CAT treatment
4. Recommend of refute direct oral anticoagulant (DOAC) use in CAT based on current evidence
Cancer-Associated Thrombosis

I. Definition of Cancer-Associated Thrombosis (CAT)
   A. Venous manifestations\(^1\)
      i. Deep vein thrombosis (DVT)
      ii. Pulmonary embolism (PE)
      iii. Visceral or splanchnic vein thrombosis
   B. Arterial manifestations\(^1\)
      i. Stroke
      ii. Myocardial infarction
   C. First described as Trousseau’s syndrome in 1865 as a migratory superficial thrombophlebitis\(^2\)

II. Epidemiology
   A. Risk/incidence
      i. Malignancy is a hypercoagulable state that leads to a four to seven-fold increased risk of VTE compared to the general population\(^3\)
      ii. Estimated 4 to 20% of patients with cancer will experience CAT\(^4\)
      iii. Approximately one in five cases of VTE in the United States is cancer-associated\(^3\)
      iv. Cumulative incidence of 4.6% reported in 2002-2003 from the US National Hospital Discharge Survey\(^3\)
      v. Increasing frequency of CAT has been reported and is expected to rise\(^3\)
   B. Survival\(^3\)
      i. VTE and thrombotic complications are the second most frequent cause of mortality in cancer
      ii. Study of the Danish National Registry found a one-year survival rate of 12%
      iii. Cancer patients who develop CAT have shorter life expectancies than cancer patients without a VTE or non-cancer patients with VTE
      iv. Diagnosis of VTE among hospitalized cancer patients is associated with a two-fold higher risk for mortality

III. Pathophysiology
   A. Complex interdependent mechanisms involving interactions among cancer cells, host cells, and the coagulation system\(^3\)

\[\text{Figure 1. Pathophysiology of Cancer-associated Thrombosis}^4\]
B. Tumor cells activate blood coagulation through:
   i. Overexpression of tumor cell hemostatic proteins
      a. Procoagulant tissue factor (TF) is constitutively expressed, directly inducing vascular endothelial growth factor (VEGF) expression and forming a complex with factor VIIa to activate factor X and trigger coagulation
      b. Malignant cells express cancer procoagulant (CP), a cysteine protease which directly activates factor X independently of factor VII
         1. Activity seems to be driven by cancer stage
         2. Higher activity at the onset of disease followed by slow decline

ii. Release of proinflammatory and proangiogenic cytokines
    a. Proinflammatory: tumor necrosis factor (TNFa) and Interleukin 1B (IL1B)
       1. Increased expression of TF
       2. Reduced thrombomodulin expression and protein C activation
    b. Proangiogenic: VEGF and basic fibroblast growth factor (bFGF) cytokines lead to increased generation of endothelial cells and expression of TF

iii. Direct interaction with host vascular and blood cells via more adhesion molecules
    a. Tumor cells may release soluble mediators like adenosine diphosphate (ADP), thrombin and other proteases to elicit platelet aggregation
    b. Mucins from adenocarcinoma can cause direct nonenzymatic activation of factor X and interact with adhesion molecules on leukocytes, platelets, and endothelial cells, eliciting coagulation

C. Risk factors
   i. Patient-dependent factors
      a. Female
      b. Older age
      c. African-American ethnicity
      d. Comorbidities (obesity, previous VTE, diabetes, atherosclerosis, etc.)
      e. Decreased performance status and immobility
   ii. Tumor-related factors
      a. Tumor site:
         1. In a pooled analysis of patients with many cancer types, those with tumors originating in the pancreas, stomach, brain, kidney, uterus, lung, and ovary had the highest incidence of VTE
         2. Patients with hematologic malignancies are also at an increased risk

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*Figure 2. Clotting Cascade*
b. Time after diagnosis – VTE occurrence is highest within the first year following diagnosis of cancer³

c. Cancer stage – metastatic disease has a 20-fold increased risk for VTE compared to local disease³

d. Histology – certain histological subtypes of cancers are associated with increased risk of VTE (e.g. adenocarcinoma in non-small-cell lung cancer and ovarian cancer)³

e. Direct compression or invasion of large blood vessels – compression or involvement of vessels increases risk of thrombosis²

iii. Treatment-related factors

a. Chemotherapy – associated with a two to six fold increase of thrombosis compared to the general population¹,¹⁰
   1. Bevacizumab
   2. Thalidomide (or analogs) and/or dexamethasone in multiple myeloma
   3. Hormonal therapy (tamoxifen and aromatase inhibitors)

b. Growth factors – myeloid and erythropoietic growth factors have been associated with an increased risk of VTE, though data has not consistently demonstrated this effect³

c. Central venous catheters (CVC) – Associated with an increased risk of DVT³

d. Major surgery – increases the risk of VTE up to 22-fold in the normal population³

e. Hospitalization – decreased mobility during hospitalization increases the risk of clot³

iv. Biomarkers associated with CAT

a. High TF expression – increased TF-bearing microparticles released by cancer cells are associated with CAT³

b. Thrombocytosis – platelet counts >350,000/mm³ are associated with an increased VTE incidence of 3.98% compared to 1.25% in patients with pre-chemotherapy platelet count of <200,000/mm³³

c. Leukocytosis – leukocyte count >11,000/mm³ is an independent risk factor for CAT

d. Elevated D-dimer – elevated baseline D-dimer levels may confound diagnostic value of D-dimer in VTE and may also predict CAT-associated mortality³

e. High soluble P-selectin – increased plasma levels of this cell adhesion molecule, found on the surface of activated endothelial cells, is strongly associated with CAT³

f. High C-reactive protein (CRP) – higher CRP levels are a predictor of VTE incidence and mortality in cancer patients¹¹

IV. Prevention and Screening

A. Up to 10% of patients with an unprovoked DVT may be diagnosed with cancer within the following year, generating controversy on whether a VTE event should be an indicator for occult cancer screening¹²

B. Risk assessment scores
   i. Various validated risk assessment scores are available to predict risk the of CAT, although they are not routinely utilized to determine need for thromboprophylaxis¹³-¹⁴
ii. Khorana score

**Table 1.** Khorana Score for VTE Risk in Cancer-Associated Thrombosis

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of cancer</td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy platelet count &gt;350,000/mm$^3$</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin level less than 10 g/dl or use of red cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count &gt;11,000/mm$^3$</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index &gt;35 kg/m$^2$ or more</td>
<td>1</td>
</tr>
</tbody>
</table>

*High-risk score = ≥3; Intermediate risk score = 1-2; Low-risk score = 0*

a. Externally validated risk score
   1. Negative predictive value: 98.5%
   2. Positive predictive value of 6.7%
   3. Sensitivity of 35.7%
   4. Specificity of 89.6%

C. Current thromboprophylaxis recommendations
   i. American Society of Clinical Oncology and National Comprehensive Cancer Network
      a. Outpatient: routine outpatient thromboprophylaxis is not recommended
      b. Inpatient: cancer patients require thromboprophylaxis throughout hospitalization
      c. Surgery: patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing up to 4 weeks post-operation

V. Signs and Symptoms

**Table 2.** Signs and Symptoms of VTE

<table>
<thead>
<tr>
<th>DVT</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg swelling</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Pain</td>
<td>Chest pain</td>
</tr>
<tr>
<td>Warmth</td>
<td>Tachypnea</td>
</tr>
<tr>
<td>Redness</td>
<td>Cough</td>
</tr>
<tr>
<td>Sometimes asymptomatic</td>
<td>Syncope</td>
</tr>
</tbody>
</table>

VI. Diagnosis

A. Labs: D-dimer assay
   B. Imaging
      i. Ultrasound
      ii. Computed tomography (CT) angiography
   C. Since D-dimer can be elevated in patients with cancer without thrombosis, clinical suspicion of CAT often demands imaging

VII. Recurrence

A. Cumulative incidence of CAT recurrence in the first 12 months is approximately 20%$^3$
B. Risk of VTE recurrence in cancer patients is approximately 3 times that of noncancer patients (hazard ratio of 3.2; 95% CI, 1.5-5.4)$^3$
C. Cancer patients with initial VTE may require extended, and sometimes lifelong, antithrombotic therapy, thought optimal duration of anticoagulation therapy remains unknown$^{13-14}$
I. Treatment Options of VTE\textsuperscript{13-14,16,18}

A. Parenteral heparins
   i. Unfractionated heparin (UFH)
   ii. Low-molecular weight heparin (LMWH)

B. Parenteral direct thrombin inhibitors (DTI): argatroban, bivalrudin, etc.

C. Parenteral factor Xa Inhibitors: fondaparinux

D. Oral vitamin K antagonist (VKA): warfarin

E. Oral direct oral anticoagulants (DOACs)
   i. Direct thrombin inhibitor: dabigatran
   ii. Factor Xa inhibitors: rivaroxaban, apixaban, edoxaban

Table 3. Selected characteristics of DOACs\textsuperscript{19-20}

<table>
<thead>
<tr>
<th>Target</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Half-Life (hrs)</td>
<td>12-17</td>
<td>5-9</td>
<td>8-15</td>
<td>9-14</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>3-7%</td>
<td>66-100%</td>
<td>50%</td>
<td>50-62%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic; P-gp</td>
<td>Hepatic; CYP3A4, P-gp</td>
<td>Hepatic; CYP3A4, P-gp, BRCP</td>
<td>Hepatic; CYP3A4, P-gp</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal (80%)</td>
<td>Renal (33%)</td>
<td>Renal (25%)</td>
<td>Renal (50%)</td>
</tr>
<tr>
<td>Protein binding</td>
<td>35%</td>
<td>95%</td>
<td>87%</td>
<td>44%</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-gp inhibitors</td>
<td>CYP 3A4 and P-gp inhibitors and inducers</td>
<td>CYP 3A4 and P-gp inhibitors and inducers</td>
<td>P-gp inhibitors</td>
</tr>
</tbody>
</table>

II. Advantages/Disadvantages of VTE Treatment Options

A. Administration route/dosage form\textsuperscript{20-21}
   i. Warfarin: oral, once daily
   ii. LMWH: subcutaneous, once to twice daily
   iii. Fondaparinux: subcutaneous, once daily
   iv. DOACs: oral, once to twice daily

B. Monitoring\textsuperscript{20-21}
   i. Warfarin: INR monitoring required
   ii. LMWH: chronic monitoring not required
   iii. Fondaparinux: chronic monitoring not required
   iv. DOACs: chronic monitoring not required

C. Reversal\textsuperscript{20-22}
   i. Warfarin: vitamin K
   ii. LMWH: protamine
   iii. Fondaparinux: none; difficult due to long half life
   iv. DOACs: idarucizumab, andexanet alpha (currently in clinical trials)

D. Cost (AWP of 30-day supply)\textsuperscript{23}
   i. Warfarin: inexpensive, $76.06
   ii. LMWH: costly, $1,144.80
   iii. Fondaparinux: costly, $4,074.00
   iv. DOACs: costly, rivaroxaban: $431.53
E. Drug and dietary interactions \(^{20-21}\)
   i. Warfarin: many drug interactions, vitamin K dietary considerations
   ii. LMWH: no dietary considerations
   iii. Fondaparinux: no dietary considerations
   iv. DOACs: many P-gp and CYP3A4 interactions, no dietary considerations

F. Renal and hepatic adjustment \(^{20-21}\)
   i. Warfarin: close drug monitoring to adjust for hepatic impairment
   ii. UFH/LMWH: UFH, no renal or hepatic adjustment; LMWH, renal adjustment required with CrCl <30 mL/min
   iii. Fondaparinux: renal adjustment with CrCl 30 to 50 mL/min; no hepatic adjustments
   iv. DOACs: renal adjustment required - rivaroxaban not recommended in CrCl <30 mL/min; hepatic adjustment required – rivaroxaban not recommended in Child-Pugh B or C

G. Bridging/lead-in periods \(^{20}\)
   i. Warfarin: concurrent heparin for 5 days until two therapeutic INR values
   ii. LMWH: not required
   iii. Fondaparinux: not required
   iv. DOACs: heparin required for five days prior to edoxaban and dabigatran; dose reductions after seven days and three weeks for apixaban and rivaroxaban, respectively

H. Heparin-induced thrombocytopenia (HIT) \(^{13-14,20}\)
   i. Warfarin: no risk for HIT
   ii. LMWH: risk for HIT
   iii. Fondaparinux: potential utility in HIT
   iv. DOACs: no risk for HIT

I. Pharmacokinetics \(^{20}\)
   i. Warfarin: unpredictable
   ii. LMWH: predictable
   iii. Fondaparinux: predictable
   iv. DOACs: predictable

III. DOACs in VTE in the General Population
   A. All four direct oral anticoagulants are FDA-approved for the treatment of VTE \(^{20}\)
   B. Current CHEST 2016 guidelines recommend the use of DOACs over VKA therapy in the treatment of VTE in noncancer patients \(^{18}\)
   C. Landmark trials for DOACs have established efficacy and safety in the general population \(^{24-28}\)

**Table 4. Landmark trials for DOACs in VTE \(^{24-28}\)**

<table>
<thead>
<tr>
<th>Landmark Trial</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
</table>
| **AMPLIFY** \(^{24}\) Apixaban vs. enoxaparin + warfarin (TTR: 61%) | **Efficacy:** recurrent symptomatic VTE or VTE mortality  
**Safety:** major bleeding; major bleeding or non-major clinically relevant bleeding (NMCRB) | **Efficacy:**  
2.3% vs. 2.7% (RR 0.84; 95% HR 0.60-1.18; \(P<0.001\) for non-inferiority)  
**Safety:**  
- Major bleeding: 0.6% vs. 1.8% (RR 0.31; 95% CI 0.17-0.55; \(P<0.001\) for superiority; NNT 100)  
- Major bleeding or NMCRB: 4.3% vs. 9.7% (RR 0.44; 95% CI 0.36-0.55; \(P<0.001\) for superiority; NNT 19) |

N=5,395
Table 4. Landmark trials for DOACs in VTE (cont.)^{24-28}

<table>
<thead>
<tr>
<th>Trial</th>
<th>Efficacy: symmetrical recurrent VTE</th>
<th>Efficacy:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EINSTEIN-DVT</strong>^{25}</td>
<td>2.1% vs. 3.0% (HR 0.68; 95% CI 0.44-1.04; P=&lt;0.001 for noninferiority)</td>
<td>8.1% vs. 8.1% (HR 0.97; 95% CI 0.76-1.22; P=0.77)</td>
</tr>
<tr>
<td>Rivaroxaban vs. enoxaparin + warfarin (TTR: 57.7%) N=4,832</td>
<td>Safety: major or non-major clinically relevant bleeding</td>
<td>Safety:</td>
</tr>
<tr>
<td><strong>EINSTEIN-PE</strong>^{26}</td>
<td>2.1% vs. 1.8% (HR 1.12; 95% CI 0.75-1.68; P=0.003 for noninferiority)</td>
<td>10.3% vs. 11.4% (HR 0.90; 95% CI 0.76-1.07; P=0.23)</td>
</tr>
<tr>
<td>Rivaroxaban vs. enoxaparin + warfarin (TTR: 62.7%) N=4,832</td>
<td>Efficacy: symptomatic recurrent VTE</td>
<td>Safety:</td>
</tr>
<tr>
<td><strong>RE-COVER</strong>^{27}</td>
<td>2.7% vs. 2.5% (HR 1.05; 95% CI 0.65-1.70)</td>
<td>Major bleed: 1.6% vs. 1.9% (HR 0.82; 95% CI 0.45-1.48)</td>
</tr>
<tr>
<td>Dabigatran vs. warfarin (TTR: 60%) N=2,564</td>
<td>Efficacy: VTE or VTE related death</td>
<td>Safety: (secondary outcome)</td>
</tr>
<tr>
<td><strong>HOKUSAI-VTE</strong>^{28}</td>
<td>3.2% vs. 3.5% (hazard ratio [HR], 0.89 [95% CI, 0.70-1.13]; P=&lt;0.001 for noninferiority)</td>
<td>8.5% vs. 10.3% (hazard ratio [HR], 0.81 [95% CI, 0.71-0.94]; P=0.004 for superiority)</td>
</tr>
<tr>
<td>Edoxaban vs. warfarin (TTR: 63.5%) N=4,921</td>
<td>Efficacy: symptomatic recurrent VTE</td>
<td>Efficacy:</td>
</tr>
</tbody>
</table>

TTR = time in therapeutic range

IV. Cancer-specific Considerations

A. Clinical experience^{13-14,16}
   i. Warfarin: long history of use in CAT
   ii. LMWH: current treatment of choice for CAT
   iii. Fondaparinux: limited evidence in treatment of CAT
   iv. DOACs: limited evidence for safety and efficacy in CAT

B. Thrombocytopenia^{3,21}
   i. Commonly observed adverse effect of chemotherapy or in advanced stages of malignancy
   ii. Leads to increased bleeding risk with limited data suggesting dose adjustments in patients with platelet counts less than 50 x 10^{9}/L

C. Drug interactions^{20-21}
   i. DOACs have drug interactions with agents frequently used in cancer patients (azole antifungals, fluoroquinolones, etc.)
   ii. Limited recommendations exists on adjustments for p-gp interactions, as edoxaban is the only DOAC studied with dose reductions for specific p-gp drug interactions

D. Brain tumors and metastases^{29-30}
   i. Patients with brain malignancy and metastases are known to be at increased relative risk of clot due to the latent hypercoagulable state, particularly in the post-operative period
   ii. Risk for coagulation is opposed by increased risk of spontaneous intracerebral hemorrhage associated with brain malignancies
E. Malnutrition/cachexia\textsuperscript{20,31}
   i. Minimal subcutaneous tissue for drug administration and modified gut wall function in cachexia: may require risk/benefit consideration of oral agents or LMWH
   ii. Altered body mass index: optimal dosing in extreme weights are unclear
   iii. Low protein and albumin: may influence the protein binding of DOACs and warfarin

F. Long term management: no data available on “indefinite anticoagulation”\textsuperscript{3,13-14}

V. CAT Landmark Trials
   A. CLOT (2003)\textsuperscript{32}
      i. Trial evaluating treatment of symptomatic VTE in cancer patients (N=676)
      ii. Initial dalteparin followed by 6 months of dalteparin or warfarin therapy
      iii. Established superiority of LMWH in treatment of CAT
   
   B. CATCH (2015)\textsuperscript{33}
      i. Trial designed to mirror CLOT to further support recommendations for LMWH in CAT
      ii. Initial tinzaparin followed by 6 months of full dose tinzaparin or warfarin therapy
      iii. Failure to detect significant difference in VTE recurrence after 6 months was attributed to a “healthier” patient population with fewer VTE risk factors, higher performance status, less metastatic disease, less systemic anticancer treatment, and lower history of thrombosis
      iv. Significant decrease in symptomatic DVTs with tinzaparin, but not powered for this secondary outcome
      v. No difference in major bleeding or mortality, but significantly less NMCRB
      vi. Trial raises question of appropriateness of LMWH therapy as first line VTE treatment in CAT for all types of cancer patients

Table 5. Landmark Trials for the Treatment of CAT\textsuperscript{29-30}

<table>
<thead>
<tr>
<th>Landmark Trial</th>
<th>Primary Outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
</table>
| CLOT (2003)\textsuperscript{32}  
Dalteparin vs. warfarin  
N=676 | **Efficacy**: recurrent DVT, nonfatal PE, or fatal PE at 6 months | **Efficacy**:  
Recurrent: 8% vs. 15.8% (HR 0.48; 95% CI 0.30-0.77; \(P=0.002\))  
Secondary outcomes:  
Major bleed: 6% vs. 4% (\(P=0.27\))  
Any bleed: 14% vs. 19% (\(P=0.09\))  
Mortality: 39% vs. 41% (\(P=0.53\)) | • TTR: 46%  
• Time in supratherapeutic INR: 24%  
• Dalteparin dose was reduced by 25% after one month into the trial |
| CATCH (2015)\textsuperscript{33}  
Tinzaparin vs. warfarin  
N=900 | **Efficacy**: recurrent VTE | **Efficacy**:  
Recurrent VTE: 7.2% vs. 10.5% (hazard ratio [HR], 0.65 [95% CI, 0.41-1.03]; \(P=.07\))  
Secondary outcomes:  
Symptomatic DVT: 2.7% vs. 5.3% (hazard ratio [HR], 0.48 [95% CI, 0.24-0.96]; \(P=.04\))  
Major bleed: 2.7% vs. 2.4% (HR, 0.89 [95% CI, 0.40-1.99]; \(P=.77\))  
NMCRB: 10.9% vs. 15.3% (HR, 0.58 [95% CI, 0.40-0.84]; \(P=.004\))  
Mortality: 34.7% vs. 32.2% (HR, 1.08 [95% CI, 0.85-1.36]; \(P=.54\)) | • TTR: 47%  
• Lower incidence of recurrent VTE in the warfarin group compared to the CLOT trial (10.5% vs. 15.8%) |
VI. Current Recommendations in CAT

A. American Society of Clinical Oncology (ASCO) 2014\textsuperscript{13-14}
   i. Acute VTE: LMWH preferred over UFH for initial 5-10 days of treatment in patients with CrCl > 30 mL/min
   ii. Long term anticoagulation: LMWH preferred over VKA, with VKA as acceptable alternative; DOACs not recommended
   iii. Therapy duration: at least 6 months, with extended therapy considered for patients with persistent high risk of recurrence

B. National Comprehensive Cancer Network (NCCN) 2016\textsuperscript{16}
   i. Acute VTE: LMWH, UFH, or fondaparinux
   ii. Long term anticoagulation: LMWH preferred over VKA, with VKA as acceptable alternative; DOACs not recommended
   iii. Therapy duration: minimum 3 months to indefinitely in patients with persistent risk factors

C. American College of Chest Physicians (ACCP) 2016\textsuperscript{18}
   i. Acute VTE: Not addressed
   ii. Long term anticoagulation: LMWH over VKA and DOACs, with no preference to VKA or DOACs if LMWH is not used
   iii. Therapy duration: Continue same agent for first three months of treatment; unnecessary to switch after 3 months

D. International Initiative on Thrombosis and Cancer (ITAC-CME) 2016\textsuperscript{34}
   i. Acute VTE: LMWH is preferred over UFH and fondaparinux due to ease of use
   ii. Long term anticoagulation: LMWH preferred over VKAs
      a. DOACs can be considered for VTE treatment of patients with stable cancer not receiving systemic anticancer therapy
      b. DOACs can be considered in cases where VKA is acceptable but not an available treatment choice
   iii. Therapy duration: minimum of 3 months

VII. Meta-analyses

A. Derived data from subanalyses of the landmark trials for DOACs\textsuperscript{35-36}

B. Posch et al. 2015\textsuperscript{35}
   i. Network meta-analysis comparing the relative efficacy and safety of VKA, DOAC, and LMWH for the long-term treatment of VTE in patients with cancer
   ii. Included ten randomized controlled trials comparing two interventions (VKA, DOAC, or LMWH) with a minimum treatment period of three months
      a. Compared 3242 total cancer patients in six studies comparing VKA with LMWH, five studies comparing VKA with DOAC
      b. Included recent CATCH trial comparing VKA with LMWH
   iii. Efficacy outcome: recurrent VTE – no difference between DOAC and LMWH: RR=1.08 (95% CI: 0.59-1.95, p=0.81)
   iv. Safety outcome: major bleeding – no difference between DOAC and LMWH: RR=0.67 (95%CI: 0.31-1.46, p=0.31)
   v. Adjustment analysis for six month risks of recurrent VTE or bleeding covariate performed
      a. Efficacy – no difference between DOAC and LMWH: RR=0.71 (95%CI: 0.14-3.51, p=0.68)
      b. Safety – no difference between DOAC and LMWH: RR=0.30 (95%CI: 0.15-1.10, p=0.08)
C. Sardar et al. 2015\textsuperscript{36}
   i. Meta analysis evaluating the efficacy and safety of DOACs in patients with cancer
   ii. Included six randomized controlled trials including patients with cancer comparing DOACs with any control (VKA, LMWH, or placebo)
   iii. Included subgroup analysis by DOAC agent
      a. Rivaroxaban contained the largest sample size out of all the DOACs
      b. 434 total cancer patients on rivaroxaban in the EINSTEIN, EINSTEIN-PE, AND MAGELLAN trials
   iv. Efficacy outcome: VTE or VTE-related death
      a. No difference: 4.6% in the DOAC group vs. 5.5% in the control group (OR, 0.9; 95% CI, 0.39-1.65)
      b. No difference: 6.0% with rivaroxaban vs. 5.7% in the control group (OR, 1.08; 95% CI, 0.6-1.94)
   v. Safety outcome: clinically relevant bleeding
      a. No difference: 8.6% in the DOAC group vs. 5.8% in the control group (OR 1.49; 95% CI, 0.73-3.06)
      b. No difference: 8.9% in the rivaroxaban group vs. 6.0% in the control group (OR 1.49; 95% CI, 0.73-3.06)

D. Meta-analyses data suggest there is no difference in efficacy or safety between DOACs and LMWH

E. Favors rivaroxaban as the agent with the greatest potential for use in cancer-associated thrombosis

VIII. Clinical Question
   a. What is the efficacy of rivaroxaban compared to LMWH in cancer associated thrombosis?
   b. What is the safety of rivaroxaban compared to LMWH in cancer associated thrombosis?
Endpoints

**Primary efficacy:**
- Symptomatic recurrent VTE (composite of fatal PE, non-fatal PE or DVT)

**Primary safety outcome:**
- Clinically relevant bleeding (composite of major and non-major clinically relevant bleeding)

**Secondary outcomes:**
- Net clinical benefit (composite of primary efficacy outcome and major bleeding)
- Major bleeding
- Mortality

Study Sample

Of the 655 (8%) patients with any active cancer (new diagnosis of cancer or recurrence of cancer after randomization), 462 (6%) presented with the diagnosis at baseline and 193 (2%) were diagnosed during the study.

- All demographic characteristics between the rivaroxaban group and the enoxaparin + VKA groups were similar

Table 6. Demographic information

<table>
<thead>
<tr>
<th></th>
<th>Active cancer at baseline</th>
<th>Active cancer diagnosed during the study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban (n=258)</td>
<td>Enoxaparin and VKA (n=204)</td>
</tr>
<tr>
<td>Male Sex – n (%)</td>
<td>152 (59)</td>
<td>109 (53)</td>
</tr>
<tr>
<td>Age – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>109 (42)</td>
<td>77 (38)</td>
</tr>
<tr>
<td>65-75 years</td>
<td>80 (31)</td>
<td>77 (38)</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>69 (27)</td>
<td>50 (25)</td>
</tr>
<tr>
<td>Treatment duration – n (%)</td>
<td>19 (7)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>3 months</td>
<td>168 (65)</td>
<td>127 (62)</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>&gt; 80 mL/min</td>
<td>125 (48)</td>
<td>97 (48)</td>
</tr>
<tr>
<td>50-80 mL/min</td>
<td>98 (38)</td>
<td>71 (35)</td>
</tr>
<tr>
<td>&lt;50 mL/min</td>
<td>34 (13)</td>
<td>35 (17)</td>
</tr>
<tr>
<td>Recurrent or metastatic cancer – n (%)</td>
<td>49 (19)</td>
<td>52 (25)</td>
</tr>
<tr>
<td>Chemotherapy – n (%)</td>
<td>74 (29)</td>
<td>62 (30)</td>
</tr>
</tbody>
</table>

Statistics

Intention to treat analysis with Cox proportional hazards model stratified according to qualifying DVT or PE and intended duration of treatment

Results

**Table 7. Outcomes in patients with active cancer**

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=354)</th>
<th>Enoxaparin and vitamin K antagonist (N=301)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE n (%)</td>
<td>16 (5)</td>
<td>20 (7)</td>
<td>0.67 (0.35-1.30)</td>
<td>0.24</td>
</tr>
<tr>
<td>Clinically relevant bleeding n (%)</td>
<td>48 (14)</td>
<td>49 (16)</td>
<td>0.8 (0.54-1.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>Major bleeding n (%)</td>
<td>8 (2)</td>
<td>15 (5)</td>
<td>0.42 (0.18-0.99)</td>
<td>0.047</td>
</tr>
<tr>
<td>Mortality n (%)</td>
<td>58 (16)</td>
<td>53 (18)</td>
<td>0.93 (0.64-1.35)</td>
<td>0.7</td>
</tr>
<tr>
<td>Net clinical benefit n (%)</td>
<td>25 (7)</td>
<td>38 (13)</td>
<td>0.54 (0.33-0.9)</td>
<td>0.018</td>
</tr>
</tbody>
</table>
**Author's Conclusions**
- Rivaroxaban is associated with similar rates of recurrent VTE, clinically relevant bleeding, and mortality compared to VKA therapy in patients with active cancer.
- Rivaroxaban is associated with significantly less major bleeding and significantly greater net clinical benefit compared to VKA therapy in patients with active cancer.

**Critique**
- Strengths
  - Inclusion of cancer patients from original landmark trials to determine similar efficacy and improved safety of rivaroxaban compared to LMWH + VKA in treatment of VTE
- Limitations
  - Subgroup analysis of EINSTEIN trials; not powered for primary outcomes
  - Diagnosis of active cancer was required to be reclassified
  - Inclusion of active basal-cell or squamous-cell skin carcinoma
  - Exclusion of many cancer patient due to life expectancy of <3 months

**Application**
- Rivaroxaban may be a safe and effective alternative to vitamin K antagonists for CAT treatment.

---

**Table 8. Baseline Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cancer (n=118)</th>
<th>No cancer (n=178)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (mean ± SD)</td>
<td>66 ± 10</td>
<td>55 ± 15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>60 (51)</td>
<td>84 (47)</td>
<td>0.41</td>
</tr>
<tr>
<td>DVT only, n (%)</td>
<td>73 (62)</td>
<td>118 (66)</td>
<td>0.24</td>
</tr>
<tr>
<td>PE only, n (%)</td>
<td>28 (24)</td>
<td>20 (11)</td>
<td>0.0002</td>
</tr>
<tr>
<td>DVT+PE, n (%)</td>
<td>17 (14)</td>
<td>41 (23)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Table 8. Baseline Data (cont.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cancer (n=118)</th>
<th>No cancer (n=178)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²) (mean ± SD)</td>
<td>29 ± 6</td>
<td>35 ± 15</td>
<td>0.08</td>
</tr>
<tr>
<td>CrCl &lt;50 mL/min, n (%)</td>
<td>6 (5)</td>
<td>4 (2)</td>
<td>0.20</td>
</tr>
<tr>
<td>Chemotherapy at time of VTE, n (%)</td>
<td>90 (76)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Recent surgery, n (%)</td>
<td>13 (11)</td>
<td>29 (16)</td>
<td>0.21</td>
</tr>
<tr>
<td>Thrombophilia, n (%)</td>
<td>1 (0.5)</td>
<td>11 (6)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hormonal therapy, n (%)</td>
<td>0</td>
<td>10 (6)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

- Genitourinary (23.6%), gastrointestinal (20.3%), and lung (13.5%) were the top three most common cancer locations

Statistics
- Continuous variables were compared using the Wilcoxon rank-sum test
- Categorical factors were compared using chi-squared test for independence

Results

Table 9. Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cancer (n=118)</th>
<th>No cancer (n=178)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE recurrence, n (%)</td>
<td>4 (3.3)</td>
<td>5 (2.8)</td>
<td>0.53</td>
</tr>
<tr>
<td>DVT, n</td>
<td>3</td>
<td>4</td>
<td>1.000</td>
</tr>
<tr>
<td>PE, n</td>
<td>1</td>
<td>1</td>
<td>1.000</td>
</tr>
<tr>
<td>Major bleed, n (%)</td>
<td>3 (2.5)</td>
<td>0</td>
<td>0.06</td>
</tr>
<tr>
<td>NMCRRB, n (%)</td>
<td>4 (3.4)</td>
<td>1 (0.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Major and NMCRRB, n (%)</td>
<td>7 (5.9)</td>
<td>1 (0.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Minor bleed, n (%)</td>
<td>3 (2.5)</td>
<td>3 (1.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>37 (31)</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NMCRRB = nonmajor clinically relevant bleeding
- Two events occurred during anticoagulation interruption for an procedure
- No arterial thrombotic events occurred
- None of the deaths were due to VTE or bleeding complications
- 3-month post-therapy survey cited ease and comfort (60%) the most common reason for rivaroxaban therapy, followed by minimal food and drug interactions (41%) and cost (12%)

Author’s Conclusions
- The low rate of VTE recurrence appears to be similar in cancer and non-cancer patient groups with rivaroxaban for treatment of VTE
- The rate of major bleeding is similar in cancer and non-cancer patient groups with rivaroxaban for treatment of VTE
  - The rate of major and NMCRRB was significantly greater in the cancer group
- Similar rates of VTE recurrence and bleeding as the EINSTEIN trial subanalyses

Critique
- Strengths
  - Consecutive CAT recruitment is representative of real-life results
  - More patients with high-risk cancers (37%), compared to EINSTEIN trial subanalyses
- Limitations
  - Not a randomized control trial to determine noninferiority of rivaroxaban for VTE treatment in cancer and non-cancer patients
  - Significant demographic differences affecting risk between comparator groups

Application
- Rivaroxaban is similar in safety and efficacy in the cancer population compared to the non-cancer population, with relatively low anticipated rates of VTE recurrence and major bleeding
- Long-term data needed to determine optimal duration of anticoagulants in CAT
Objective
To evaluate the efficacy and safety of rivaroxaban for CAT through the use of a Clinical Pathway guide as part of a Quality Assessment Initiative (QAI) at Memorial Sloan Kettering (MSK)

Study Design
Prospective cohort study

Enrollment

**Inclusion:**
- Patients with cancer associated DVT and/or PE treated with a plan for at least 6 months of rivaroxaban treatment
- Relative contraindications:
  - CrCl <30 mL/min
  - LFT >3×ULN
  - Expected malabsorption in stomach or small bowl
  - Active genitourinary or gastrointestinal lesions

**Exclusion:**
- Untreated primary CNS neoplasm
- Weight <50 or >150 kg
- Use of antiplatelet agents other than aspirin 81 mg daily
- Any significant drug interaction

Relatives contraindications:
- CrCl <30 mL/min
- LFT >3×ULN
- Expected malabsorption in stomach or small bowl
- Active genitourinary or gastrointestinal lesions
- Untreated primary CNS neoplasm
- Weight <50 or >150 kg
- Use of antiplatelet agents other than aspirin 81 mg daily
- Any significant drug interaction

Interventions
Use of the Clinical Pathway for treatment of VTE with rivaroxaban
- Starting dose: 15 mg PO BID x3 weeks followed by 20 mg daily
- Dose reductions (10 mg PO BID x3 weeks followed by 15 mg daily)
  - > 75 years or older
  - Platelets 25,000/mcL-50,000/mcL

Holding parameters
- Platelets < 25,000/mcL

Endpoints
- Recurrent VTE (as defined in the CLOT trial)
- Major bleeding (as defined by the International Society on Thrombosis and Haemostasis)
- NMCRRB leading to discontinuation of rivaroxaban
- Death from any cause

Study Sample
- 200 patients with CAT planned for at least 6 months of rivaroxaban treatment, regardless of compliance with Clinical Pathway, followed until time to an endpoint or at least 6 months

Table 10. Demographic Information

<table>
<thead>
<tr>
<th>Selected Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in years)</td>
<td>63</td>
</tr>
<tr>
<td>Sex (n=200); n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80 (40)</td>
</tr>
<tr>
<td>Female</td>
<td>120 (60)</td>
</tr>
<tr>
<td>VTE (n=200); n (%)</td>
<td></td>
</tr>
<tr>
<td>PE, with or without DVT</td>
<td>136 (68)</td>
</tr>
<tr>
<td>Proximal, symptomatic lower extremity DVT</td>
<td>64 (32)</td>
</tr>
<tr>
<td>Cancer stage (of solid tumors, excluding brain) (n=180); n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (2)</td>
</tr>
<tr>
<td>1</td>
<td>5 (3)</td>
</tr>
<tr>
<td>2</td>
<td>7 (4)</td>
</tr>
<tr>
<td>3</td>
<td>23 (13)</td>
</tr>
<tr>
<td>4</td>
<td>142 (78)</td>
</tr>
</tbody>
</table>
Table 10. Demographic Information (cont.)

<table>
<thead>
<tr>
<th>Cancer type, (n=200); n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>34 (17)</td>
</tr>
<tr>
<td>Gynecological</td>
<td>26 (13)</td>
</tr>
<tr>
<td>Lung</td>
<td>23 (12)</td>
</tr>
<tr>
<td>Breast</td>
<td>22 (11)</td>
</tr>
<tr>
<td>GU/prostate</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Hematological</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Stomach/esophagus</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>33 (17)</td>
</tr>
</tbody>
</table>

Table 11. Six-month cumulative incidence estimates

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Cancer (N=200)</th>
<th>Age &gt; 75 years (subanalysis, N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE recurrence, % [95% CI]</td>
<td>4.4 [1.4-7.4]</td>
<td>5.3 [0-12.1]</td>
</tr>
<tr>
<td>Major bleed, % [95% CI]</td>
<td>2.2 [0-4.2]</td>
<td>2.6 [0-7.4]</td>
</tr>
<tr>
<td>NMCRB leading to discontinuation of rivaroxaban, % [95% CI]</td>
<td>3.8 [1.0-6.5]</td>
<td>3 [0-8.7]</td>
</tr>
<tr>
<td>All-cause mortality % [95% CI]</td>
<td>17.6 [11.7-23]</td>
<td>---</td>
</tr>
</tbody>
</table>

- 19 cancer-related deaths and 12 deaths of unknown cause

Table 12. Management of rivaroxaban anticoagulation in specific events

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose reduction (n)</th>
<th>Drug held (n)</th>
<th>No change (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMCRB</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count &lt;50,000/mcL (n=11)</td>
<td>1</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>CrCl &lt;30 mL/min (n=7)</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Elevated liver enzymes (AST, ALT, or bilirubin &gt;3xULN) (n=18)</td>
<td>0</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Invasive procedures (n=70)</td>
<td>0</td>
<td>65</td>
<td>4</td>
</tr>
</tbody>
</table>

- 1 episode of major bleed occurred after dose reduction with initial NMCRB
- 1 episode of NMCRB and 1 death associated with elevated LFTs
- 1 recurrent VTE associated with invasive procedures in a high-risk patient

Author’s Conclusions

There is no evidence for loss of efficacy or safety with use of rivaroxaban for treatment of CAT
- Risk of VTE recurrence (4.4%) and major bleed (2.2%) is less than 6-month risk of recurrent VTE (8.7 and 9%) and major bleed (6 and 10.2%) found in two published trials of dalteparin
- Similar rates of recurrent VTE (5%) and major bleeding (2%) as recent EINSTEIN subgroup analysis in cancer patients
- Risk of recurrent VTE and bleeding in patients >75 years is comparable to ages <75 years

Critique

Strengths:
- Studied the use of rivaroxaban specifically taking into account cancer-associated factors and limitations such as thrombocytopenia, interruption procedure, and organ dysfunction
- Inclusion of high VTE risk patients, as 78% of patient had metastatic disease compared to 67% in the CLOT trial
- Establishes guidance for dose adjustments in specific events
Critique
(cont.)
Limitations
• Not a randomized controlled trial; no comparator group
• Indirect comparison of efficacy and safety with CLOT trial
• Non-evidence based dose reductions performed
• No stated definition of “significant drug interactions”

Application
Rivaroxaban can be used safely and effectively in cancer patients, with appropriate dose adjustments, despite cancer-specific factors and limitations

Recommendations

I. Recommendations
   i. LMWH is still first-line therapy in the treatment of CAT
   ii. Provide routine patient education on anticoagulation options (LMWH, warfarin, rivaroxaban)
   iii. Administer LMWH (enoxaparin 1 mg/kg q12h) in the following indications:
       a. Expected physiologic malabsorption (e.g. gastrointestinal resection)
       b. AST/ALT >3xULN
       c. Severe nausea and vomiting
   iv. In patients who are not amenable to subcutaneous injections with LMWH anticoagulation
       and are suboptimal candidates for warfarin therapy, recommend rivaroxaban (15 mg PO BID
       x3 weeks followed by 20 mg daily) in patients without the following rivaroxaban contraindications:
       a. CrCl <30 mL/hr
       b. Significant drug interactions with rivaroxaban
       c. High risk for bleeding/active bleeding (i.e. active GU or GI lesions, CNS lesions or
          metastasis, platelets <50,000/mcL etc.)
   v. Suboptimal candidates for warfarin:
      a. History of labile INR despite compliance
      b. Unpredictable dietary habits due to social disposition or lack of appetite
      c. Unsuitable for routine INR monitoring and follow up (social disposition, palliative
         care, etc.)
   vi. In patients receiving rivaroxaban, recommend dose reduction (10 mg PO BID x3 weeks
       followed by 15 mg daily) in patients ≥75 years old
II. Future Directions

A. Pending trials for rivaroxaban use in cancer patients

Table 13. Pending rivaroxaban trials in cancer-associated thrombosis\textsuperscript{40-43}

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Design</th>
<th>Comparators</th>
<th>Primary outcomes</th>
<th>Estimated completion</th>
</tr>
</thead>
</table>
| CASTA-DIVA\textsuperscript{40} | Prospective, randomized, non-inferiority, open-label, multicenter trial | Rivaroxaban vs. dalteparin | • Symptomatic DVT  
  • Symptomatic PE  
  • Unsuspected PE and DVT  
  • Worsening of pulmonary vascular or venous obstruction | May 2017             |
| SELECT-D\textsuperscript{41}  | Prospective, randomized, open-label, multicenter pilot trial | Rivaroxaban vs. dalteparin | • Recurrent VTE | December 2018 |
| CONKO-011\textsuperscript{42} | Prospective, randomized, open-label trial | Rivaroxaban vs. LMWH | • Patient-reported treatment satisfaction | March 2018 |
| CANVAS\textsuperscript{43}  | Prospective, randomized, open-label trial | DOACs vs. LMWH | • Cumulative VTE recurrence at 6 months | September 2019 |

B. CAT treatment primarily based on patient specific factors (cost, patient dexterity, patient preference, emetogenic issues, etc.)

III. Summary

A. Rivaroxaban has the most potential for use in CAT based on current available evidence
   i. Rivaroxaban is the only DOAC thus far with prospective studies specifically in cancer associated thrombosis
   ii. Observed rates of VTE recurrence and major bleeding are similar to those seen in the EINSTEIN trials and the CLOT trial

B. Rivaroxaban vs. VKA therapy
   i. Rivaroxaban is associated with similar rates of recurrent VTE compared to VKA therapy
   ii. Significantly less bleeding and significantly greater net clinical benefit compared to VKA therapy in patients with active cancer

C. Rivaroxaban in cancer patients in prospective cohort studies
   i. Noncancer patients vs. cancer patients
      a. Rivaroxaban use in cancer patients is not associated with an increased risk of recurrent VTE compared to use in noncancer patients
      b. The rate of major and NMCRR with rivaroxaban was significantly increased in cancer patients (5.9%), but less than that of dalteparin in the CLOT trial (14%)
   ii. Rivaroxaban in cancer patients
      a. Dose adjustments and/or holding parameters can compensate for elderly age, liver dysfunction, renal dysfunction, and thrombocytopenia in CAT without apparent compromise in efficacy or safety of rivaroxaban
      b. Patients with advanced cancers can be successfully treated for CAT with rivaroxaban