The Role of Direct Oral Anticoagulants for the Treatment and Prevention of Cancer-Associated Venous Thromboembolism

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Objectives

• Describe the findings of recent studies comparing direct oral anticoagulants (DOACs) with low molecular weight heparins for the treatment of cancer-associated thrombosis.
• Describe the studies examining the utility of DOACs for primary prevention of venous thromboembolism in cancer patients.
• Identify cancer patient subpopulations for whom DOACs are optimal and those subpopulations for whom DOACs should be avoided.
• Recognize the unique aspects of the cancer patient population that make anticoagulation higher risk in these patients.

Question 1

A 67-year-old man with metastatic colorectal cancer presents with a new asymptomatic left lower lobe pulmonary embolus found on recent restaging CT scan. He was diagnosed initially with metastatic disease 7 months ago and has received 14 cycles of FOLFOX to treat his malignancy (no surgery or radiation therapy). He weighs 77 kg and has never had a clinically-significant bleeding event. He prefers oral therapy if it is similarly safe and effective. Which of the following is the most appropriate anticoagulant choice?

• A) Dalteparin
• B) Edoxaban
• C) Dabigatran
• D) Warfarin

Question 2

A 61-year-old woman with IDH2-mutant relapsed acute myeloid leukemia currently receiving treatment with enasidenib presents with a new proximal right lower extremity DVT. Her course has been complicated by invasive pulmonary aspergillosis, for which she takes voriconazole. Her platelet count is 89 × 10⁹/L. She weighs 67 kg and has never had a clinically-significant bleeding event. She prefers oral therapy if it is similarly safe and effective. Which of the following is the most appropriate anticoagulant choice?

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Question 3

A 47-year-old woman with triple-negative metastatic breast cancer and a history of prior cancer-associated DVT currently on rivaroxaban presents with a new proximal left lower extremity DVT. She is currently receiving emetogenic platinum-based chemotherapy but denies vomiting and says she has been faithful with her rivaroxaban, never missing a daily dose. Which of the following is the most appropriate anticoagulant choice at this time?

• A) Continue rivaroxaban
• B) Continue rivaroxaban and add aspirin 81 mg daily
• C) Switch to enoxaparin, 1 mg/kg BID
• D) Switch to enoxaparin, 1.2 mg/kg BID (dose-escalated)

Question 4

A 74-year-old man with borderline resectable pancreatic adenocarcinoma presents with a new incidentally-discovered right upper lobe pulmonary embolus while receiving neoadjuvant chemotherapy with FOLFIRINOX. He is an engineer and is requesting data regarding the efficacy and safety of each of his anticoagulant choices. Which of the following is accurate about the bleeding risk of DOACs for the treatment of CAT?

• A) DOACs generally have a lower bleeding risk but higher VTE recurrence risk than LMWH
• B) DOACs generally have a higher bleeding risk but lower VTE recurrence risk than LMWH
• C) DOACs are particularly safe to use in patients with non-metastatic disease, especially localized GU and GI malignancies
• D) DOACs are rarely subject to drug interactions with cancer treatments
Association of Cancer with VTE

- “If the diagnosis of a suspected carcinoma of an internal organ cannot be verified, the sudden and spontaneous appearance of thrombophlebitis in a large vein affords necessary proof for diagnosis.”
- Diagnosed his own gastric cancer after he developed VTE

Epidemiology of Cancer-Associated Thrombosis (CAT)

- 4-7x VTE risk over general population
- VTE complicates course of ~10-20% of all patients with cancer
- Higher risk of death in cancer patients with VTE versus cancer patients without VTE
- Primary risk factors include tumor site of origin, cancer stage, and cancer-directed treatments
  - Metastatic solid tumor ~20x risk
  - Cytotoxic chemotherapeutics—gemcitabine, mitomycin, cisplatin
  - Targeted agents—bevacizumab and certain TKIs (e.g. ponatinib), endocrine therapies (tamoxifen)
  - Surgery and radiation

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Clinical Case I

- A 52-year-old man with metastatic EML4-ALK rearranged non-small cell lung cancer receiving treatment with alectinib presents with acute-onset shortness of breath and tachycardia. A D-dimer is 5592 ng/mL. PE protocol CT scan reveals bilateral segmental and subsegmental pulmonary emboli. Lower extremity duplex ultrasound shows a right femoral vein DVT.
- What is the best anticoagulant choice for this patient?

VTE Incidence by Tumor Site of Origin/Total Burden of Cancer-Associated VTE

<table>
<thead>
<tr>
<th>Tumor Site of Origin</th>
<th>First VTE rate per 100 person-years (95% CI)</th>
<th>Percent of total Cancer-Associated VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>14.6 (12.9-16.5)</td>
<td>3.9</td>
</tr>
<tr>
<td>Brain</td>
<td>12.1 (10.3-14.0)</td>
<td>2.5</td>
</tr>
<tr>
<td>Ovary</td>
<td>11.9 (10.6-13.2)</td>
<td>9.5</td>
</tr>
<tr>
<td>Stomach</td>
<td>10.2 (9.5-11.3)</td>
<td>6.6</td>
</tr>
<tr>
<td>Lung</td>
<td>10.1 (9.5-10.8)</td>
<td>13.9</td>
</tr>
<tr>
<td>Uterus</td>
<td>7.0 (6.3-7.9)</td>
<td>4.2</td>
</tr>
<tr>
<td>Colon</td>
<td>6.7 (5.9-7.7)</td>
<td>12.5</td>
</tr>
<tr>
<td>Breast</td>
<td>4.4 (4.0-7.7)</td>
<td>17.5</td>
</tr>
<tr>
<td>Breast</td>
<td>3.2 (2.9-3.4)</td>
<td>15.1</td>
</tr>
<tr>
<td>Bladder</td>
<td>2.7 (2.4-3.0)</td>
<td>4.8</td>
</tr>
</tbody>
</table>

CAT Treatment: Historical Perspective

- Initial primary agent was warfarin
- Cancer patients frequently have low TTRs owing to inconsistent dietary intake, nausea, drug-drug interactions, etc.
- 5 randomized trials performed in the 1990s and 2000s comparing LMWH to VKAs

CAT Treatment: VKA vs. LMWH

<table>
<thead>
<tr>
<th>Trial</th>
<th>VTE Recurrence (%)</th>
<th>Major Bleeding (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANTHANOX Warfarin vs enoxaparin (3 months)</td>
<td>No significant difference in primary combined outcome of major bleeding or VTE recurrence. Increased rate of fatal bleeds in warfarin arm (8% vs 0%).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOT VKA vs dalteparin (6 months)</td>
<td>Significant reduction in VTE recurrence with dalteparin. No significant difference in major bleeding or mortality (3-month post-hoc analysis showed a probability of death of 10% in the dalteparin arm compared with 38% in the VKA arm [p&lt;0.05]).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ONCENOX Warfarin vs enoxaparin (7 months)</td>
<td>8.5 vs 10.8</td>
<td>2.9 vs 9.0</td>
<td>32.4 vs 32.8</td>
</tr>
<tr>
<td>LITE VKA vs dalteparin (12 months)</td>
<td>No difference in VTE recurrence or major bleeding after three months. After 12 months of therapy for patients meeting continuation post-hoc analysis showed significantly lower VTE recurrence in the tranexamic acid arm.</td>
<td></td>
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</tr>
<tr>
<td>CATCH VKA vs dalteparin (6 months)</td>
<td>6.1 vs 2.2</td>
<td>2.4 vs 2.7</td>
<td>32.2 vs 34.7</td>
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</tbody>
</table>
CLOT Trial

- 672 patients
- 67% metastatic disease
- 77% receiving cancer-directed therapy
- Warfarin group TTR 46%
  - 20/53 recurrent events occurred with INR <2.0 and most occurred in first month

Warfarin group TTR 46%

13 Lee et al., NEJM 2003

CATCH Trial

- 900 patients
- 55% metastatic disease
- 53% receiving active cancer-directed therapy
- Warfarin group TTR 47%

14 Lee et al., JAMA 2015

CAT Treatment History

- Based on data primarily from CLOT, LMWH was the established standard-of-care for CAT for >15 years
  - Search to explain the reason for this finding
  - The “mythical” properties of heparin
- Meanwhile several studies showed patient compliance with LMWH was clearly suboptimal
  - One real-world analysis of 2941 patients from large insurer databases showing median treatment duration of 3.3 months for LMWH, 7.9 months for warfarin or rivaroxaban
- Clear unmet need for effective, well-tolerated oral therapy

15 Khorana et al, Res Pract Thromb Haemost 2018

Pivotal DOAC VTE Trials

- Pivotal trials of DOACs vs. VKA for VTE in the general population included some “cancer” patients
- As large trials, several hundred “cancer” patients were treated in these studies, facilitating comparison between DOAC and VKA
- Why “cancer”? Several trials excluded active cancer patients or certain groups
- Two meta-analysis examined this:
  - One meta-analysis of 1581 cancer patients out of a total of 27,023 enrolled patients found a lower VTE recurrence rate in DOAC-treated patients
  - Another meta-analysis of 1132 “active” cancer patients found no difference

16 Van Es et al., Blood 2014

Vedovati et al., Chest 2015

MSKCC QI Initiative: Clinical DOAC Pathway

- 1072 patients with CAT treated with rivaroxaban
- 92% solid tumor (75% metastatic disease)
- 6-month cumulative incidence of recurrent VTE 4.2%, major bleeding 2.2%, CRNMB 5.5%
  - 73.1% of bleeds occurred in the GI tract
- Carefully selected patient population—numerous exclusion criteria

17 Soffet et al., Res Pract Thromb Haemost 2019

MSKCC QI Initiative: Clinical DOAC Pathway EXCLUSION CRITERIA

- Active bleeding or a perceived high risk of bleeding
- Uncontrolled severe organ system primary or metastatic lesion
- Systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg
- Childbearing potential without proper contraceptive measure, pregnancy, or breast-feeding
- Creatinine clearance >10 ml/min as determined with the Cockcroft-Gault formula
- Body weight <50 kg or >150 kg
- Clinically significant liver disease
- Concurrent use of any antiplatelet agent other than aspirin 81 mg daily
- Ongoing microscopic hematuria or known untreated urinary tract lesion
- Ongoing gastrointestinal bleeding or known untreated gastrointestinal lesion
- Expected or gastrointestinal disruption (post-surgical deviation of the gastrointestinal tract or medical condition known to result in malabsorption) or need for medications to be administered by tube feedings
- Unacceptable Drug Interactions at time of initiation of Rivaroxaban
  - Use of HIV protease inhibitor or new azole antifungal (e.g. voriconazole, posaconazole)
  - Any “X” rated interaction as determined by Lexicomp, except dexamethasone.
  - Other potential significant drug interaction, as determined on a case-by-case basis
- Patients with an anticipated period of chemotherapy-induced thrombocytopenia of <25,000/mcL for 7 days or longer. This includes patients with Acute Myeloid Leukemia, Acute Lymphocytic Leukemia, or Post-Stem Cell Transplant.

18 Soffet et al., Res Pract Thromb Haemost 2019
Final Published Studies of Randomized Trials Comparing LMWH with DOACs

<table>
<thead>
<tr>
<th>Study</th>
<th>Hokusai VTE Cancer (6 mo outcomes)</th>
<th>SELECT-D (6 mo outcomes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arm</td>
<td>Edoxaban</td>
<td>Dalteparin</td>
</tr>
<tr>
<td>Recurrent VTE (%)</td>
<td>6.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>5.6</td>
<td>3.2</td>
</tr>
<tr>
<td>CRNMB (%)</td>
<td>12.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>26.8</td>
<td>24.2</td>
</tr>
<tr>
<td>Cancer therapy (%)</td>
<td>71.6</td>
<td>73.1</td>
</tr>
<tr>
<td>Metastatic disease (%)</td>
<td>52.5</td>
<td>53.4</td>
</tr>
</tbody>
</table>

Hokusai VTE Cancer Study

- 1050 cancer patients with acute symptomatic or incidental PE or proximal DVT
- Randomized to LMWH x 5 days followed by edoxaban or dalteparin for 6-12 months
- Composite primary endpoint of recurrent VTE or major bleeding at 12 months: edoxaban non-inferior to dalteparin (HR 0.97, P=0.006 for noninferiority)
- Recurrent VTE: 7.9% edoxaban arm, 11.3% dalteparin arm, P=0.09
- Major bleeding: 6.9% edoxaban arm, 4.0 dalteparin arm, P=0.04
- CRNMB: 14.6% edoxaban arm, 11.1% dalteparin arm, NS
- No difference in overall survival

SELECT-D Study

- 40% cancer patients with acute symptomatic or incidental PE or symptomatic proximal DVT
- Randomized to rivaroxaban or dalteparin for 6 months
- Recurrent VTE (primary endpoint): 4% rivaroxaban arm, 11% dalteparin arm, HR 0.43, 95% CI 0.19-0.99
- Major bleeding: 6% rivaroxaban arm, 4 dalteparin arm, HR 1.83, 95% CI 0.68-4.96
- CRNMB: 13% rivaroxaban arm, 4% dalteparin arm, HR 3.76, 95% CI 1.63-8.69
- No difference in overall survival

The Other Big Story from Hokusai VTE Cancer and SELECT-D

- Subgroup analysis in Hokusai VTE Cancer revealed most major bleeding was in GI tract, primarily luminal GI cancers
- Close to 1 in 8 patients with a GI cancer randomized to edoxaban had a major bleeding event
- DSMB for SELECT-D halted enrollment of patients with upper GI cancers at an interim analysis due to unacceptable rates of bleeding in these patients
- Take-home point: Until additional data is available, DOACs are not considered optimal for patients with luminal GI malignancies and a primary still in place.

Other Studies Comparing DOAC and LMWH

- ADAM-VTE: Compared apixaban vs. dalteparin in 300 patients; primary endpoint was safety (bleeding)
  - Abstract published at ASH 2018 showed study had met primary endpoint of similar bleeding rates between two arms with a lower VTE recurrence rate for apixaban arm
  - Still awaiting final publication
- Caravaggio: Large randomized trial, apixaban vs. dalteparin
- CANVAS: Compares DOAC therapy (rivaroxaban, apixaban, edoxaban, or dabigatran, by investigator choice) with LMWH with or without transition to warfarin
- Many others

Current Recommendations from NCCN and ISTH (as of August 2019)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Preferred Options</th>
<th>Alternative Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCCN</strong></td>
<td>Category 1</td>
<td>Category 2A</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Enoxaparin</td>
<td>UFH IV then UFH SC</td>
</tr>
<tr>
<td>LMWH x 5 days</td>
<td>Rivaroxaban</td>
<td>UFH SC load then UFH</td>
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<tr>
<td>education</td>
<td>Fondaparinux</td>
<td>UFH SC</td>
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<tr>
<td>Apixaban</td>
<td>UFH 5 days then</td>
<td>UFH SC</td>
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<td>Edoxaban</td>
<td>LMWH or fondaparinux x 5 days then warfarin</td>
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| **ISTH**       | DOAC (edoxaban or rivaroxaban) high evidence of low bleeding risk and no drug-DOAC interactions |
|----------------|LMWH in patients with low bleeding risk |
| DOAC (apixaban or rivaroxaban) high evidence of low bleeding risk and no drug-DOAC interactions |
| LMWH if high bleeding risk or potential drug-DOAC interactions |
Recurrent CAT while on Anticoagulation: What to do?

<table>
<thead>
<tr>
<th>Anticoagulant during breakthrough VTE</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Full-dose weight-based LMWH (enoxaparin 1 mg/kg twice daily or dalteparin 200 units/kg daily)</td>
</tr>
<tr>
<td>Direct oral anticoagulant</td>
<td>Low-dose LMWH (enoxaparin 0.5 mg/kg twice daily or dalteparin 5,000 units twice daily)</td>
</tr>
<tr>
<td>Low-dose LMWH (enoxaparin 1 mg/kg twice daily or dalteparin 200 units/kg daily)</td>
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<tr>
<td>Intermediate-dose LMWH (enoxaparin 1 mg/kg twice daily or dalteparin 5,000 units twice daily)</td>
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<tr>
<td>Three-quarters intensity LMWH (enoxaparin 1.5 mg/kg/day or dalteparin 150 units/kg/day)</td>
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<tr>
<td>Prophylactic-dose fondaparinux (2.5 mg/day)</td>
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<tr>
<td>Full-dose weight-based fondaparinux (5-10 mg daily)</td>
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<td>Full-dose weight-based LMWH (enoxaparin 1 mg/kg twice daily or dalteparin 200 units/kg daily)</td>
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<tr>
<td>Dose-escalated LMWH (120-125% full weight-based dose)</td>
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<tr>
<td>Full-dose weight-based fondaparinux (5-10 mg daily)</td>
<td></td>
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<tr>
<td>Dose-escalated fondaparinux (full weight-based dose plus 2.5 mg)</td>
<td></td>
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<tr>
<td>Dose-escalated LMWH (120-125% full weight-based dose) or fondaparinux (full weight-based dose plus 2.5 mg)</td>
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<tr>
<td>Experimental approaches: Consider addition of antiplatelet agent or second anticoagulant with distinct mechanisms of action</td>
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</tbody>
</table>

Thrombocytopenia and Anticoagulation for CAT

Clinical Case II

- A 56-year-old man with metastatic gastric adenocarcinoma presents for evaluation prior to initiating chemotherapy. His CBC is within normal limits with a hemoglobin of 13.9 g/dL, platelet count of 390 × 10^9/L, and WBC of 10.2 × 10^9/L. His BMI is 36. He is a biology professor at a local university and has read about potential complications of his cancer. He understands that he will receive antiemetics with chemotherapy to deal with nausea but asks how we will prevent blood clots given his gastric cancer and impending cytotoxic chemotherapy, which he knows predisposes him to clots.
- Is he a potential candidate for primary thromboprophylaxis with a DOAC?

Primary Prophylaxis of CAT with DOACs

- Numerous risk prediction scores exist for CAT
- Most common is Khorana score:
  - Site of Cancer: Very high risk: stomach, pancreas
  - High risk: lung, lymphoma, gynecologic, bladder, testicular
  - Prechemotherapy platelet count ≥ 350 x 10^9/L
  - Hemoglobin level < 10 g/dL or use of red cell growth factors
  - Prechemotherapy leukocyte count > 11 x 10^9/L
  - Body mass index ≥ 35 kg/m^2

AVERT and CASSINI Trials: Primary Thromboprophylaxis for CAT

<table>
<thead>
<tr>
<th>Trial</th>
<th>VTE Occurrence (%)</th>
<th>Major Bleeding (%)</th>
<th>Clinically Relevant Nonmajor Bleeding (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVERT</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Apixaban vs Placebo</td>
<td>4.2 vs 10.2</td>
<td>3.5 vs 1.8</td>
<td>7.3 vs 5.5</td>
<td>12.2 vs 9.8</td>
</tr>
<tr>
<td>CASSINI</td>
<td></td>
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<tr>
<td>Rivaroxaban vs Placebo</td>
<td>2.60 vs 6.41</td>
<td>1.98 vs 0.99</td>
<td>2.72 vs 1.98</td>
<td>20.0 vs 23.8</td>
</tr>
</tbody>
</table>

Apixaban significantly reduced the rate of VTE compared to placebo. Major bleeding was higher in the intention to treat analysis. There was no difference in nonmajor bleeding.

Rivaroxaban significantly reduced the rate of VTE compared to placebo during the on-treatment period. There was no difference in rate of major or nonmajor bleeding.
Summary: Choice of Anticoagulant for CAT

**DOAC**

**Relative Indications**
- Patient without GI malignancy
- Low risk for major bleeding
- Ease of treatment for patient is a priority
- No strong drug-drug interactions

**Relative contraindications**
- Active GI malignancy
- History of GI bleeding
- Extremes of weight (<50 kg or >150 kg)
- Renal insufficiency/fluctuating renal status

**LMWH**

**Relative Indications**
- Frequent emetogenic chemotherapy, nausea and vomiting, difficulty with oral intake
- Concerns for GI absorption (feeding tubes, gastric or bowel resections)
- Drug-drug interactions with DOAC or VKA
- Motivated patient willing to use for extended durations
- Known increased bleeding risk
- Recurrent CAT while on anticoagulants

**Relative contraindications**
- Strong aversion or inability to use injectable therapy
- Renal insufficiency/fluctuating renal status (unless regular anti-Xa monitoring with dose-adjustment is feasible)
- Extremes of weight (<50 kg or >150 kg)

**VKA**

**Relative Indications**
- Any situation in which close anticoagulant monitoring is necessary (e.g., multiple prior bleeds) or concern for absorption and metabolism
- Advanced chronic kidney disease
- Extremes of weight (<50 kg or >150 kg)

**Relative contraindications**
- Lack of access to dedicated anticoagulation monitoring service with experience caring for cancer patients

**Question 1**
A 67-year-old man with metastatic colorectal cancer presents with a new asymptomatic left lower lobe pulmonary embolus found on recent restaging CT scan. He was diagnosed initially with metastatic disease 7 months ago and has received 14 cycles of FOLFOX to treat his malignancy (no surgery or radiation therapy). He weighs 77 kg and has never had a clinically-significant bleeding event. He prefers oral therapy if it is similarly safe and effective. Which of the following is the most appropriate anticoagulant choice?
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