Treatment of Cancer-Associated Venous Thromboembolism:
A new *Rapid Resource* from the AC Forum

Friday | December 11, 2020 | 11:00am-12:00pm EST

**Presenters:**
Marc Carrier, MD, MSc | Nathan Clark, PharmD | Ryan Fleming, PharmD
David Garcia, MD | Tzu-Fei Wang, MD, MPH

[Anticoagulation FORUM Webinar]
Learner Notification

**Accreditation Statement**
In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Anticoagulation Forum. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Presenters

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- Professor, Department of Medicine, University of Ottawa

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- Manager, Thrombosis Service, University of Utah Health

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- Associate Scientist, Ottawa Hospital Research Institute
Disclosures & Notification of Support

Acknowledgement of Financial Commercial Support:
Support for this project provided by BMS-Pfizer Alliance

The below speaker disclosure has the listed relevant financial relationships with commercial interests:

Marc Carrier, MD, MSc

- Bristol-Myers Squibb (BMS) | LEO Pharma | Bayer | Sanofi | Laboratories Servier | Pfizer Pharmaceuticals Inc. (Scientific/Medical Advisory Board Member, Research Grant, Overall Principal Investigator)
Incidence

Annual incidence of VTE in the general population is 117 per 100,000

- Cancer alone was associated with a 4.1-fold risk of thrombosis
- Chemotherapy increased the risk 6.5-fold

Combining these estimates yields an approximate annual incidence of venous thromboembolism (VTE) of 1 per 200 in a population of cancer patients

Cancer and VTE

**Complex Management and Timeline**

- **Hospitalization**
- **Chemotherapy**
- **Metastasis**
- **End of life**

**5.8 (95% CI 5.7 to 6.0)**

- **Risk of VTE in the general population**

Lyman GH, *Cancer* 2010;7:1334–1349
# Incidence of VTE by Cancer Type

Incidence rate (95% CI) of first VTE per 100 person-years by cancer type

<table>
<thead>
<tr>
<th>Age</th>
<th>Total ≥18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>2.7 (2.4–3.0)</td>
</tr>
<tr>
<td>Breast</td>
<td>3.2 (2.9–3.4)</td>
</tr>
<tr>
<td>Colon</td>
<td>6.7 (6.3–7.2)</td>
</tr>
<tr>
<td>Lung</td>
<td>10.1 (9.5–10.8)</td>
</tr>
<tr>
<td>Prostate</td>
<td>4.4 (4.0–4.7)</td>
</tr>
<tr>
<td>Uterus</td>
<td>7.0 (5.9–8.3)</td>
</tr>
<tr>
<td>Haematological</td>
<td>4.5 (4.1–4.8)</td>
</tr>
<tr>
<td>Brain</td>
<td>12.1 (10.3–14.0)</td>
</tr>
<tr>
<td>Ovary</td>
<td>11.9 (10.6–13.2)</td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td><strong>14.6 (12.9–16.5)</strong></td>
</tr>
<tr>
<td>Stomach</td>
<td>10.8 (9.5–12.3)</td>
</tr>
</tbody>
</table>

## Patient Demographics

Patients with active cancer and a first VTE (N=6592)

<table>
<thead>
<tr>
<th>Common cancer types, n (%)</th>
<th>DVT (n=3055)</th>
<th>PE (n=3537)</th>
<th>Total (N=6592)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate (males)</td>
<td>278 (19.1)</td>
<td>287 (16.1)</td>
<td>565 (17.5)</td>
</tr>
<tr>
<td>Breast (females)</td>
<td>225 (14.0)</td>
<td>281 (16.0)</td>
<td>506 (15.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>315 (10.3)</td>
<td>603 (17.0)</td>
<td>918 (13.9)</td>
</tr>
<tr>
<td>Colon</td>
<td>384 (12.6)</td>
<td>443 (12.5)</td>
<td>827 (12.5)</td>
</tr>
<tr>
<td>Haematological</td>
<td>360 (11.8)</td>
<td>309 (8.7)</td>
<td>669 (10.1)</td>
</tr>
<tr>
<td>Ovarian (females)</td>
<td>136 (8.5)</td>
<td>182 (10.3)</td>
<td>318 (9.5)</td>
</tr>
<tr>
<td>Bladder</td>
<td>186 (6.1)</td>
<td>133 (3.8)</td>
<td>319 (4.8)</td>
</tr>
<tr>
<td>Uterus (females)</td>
<td>83 (5.2)</td>
<td>58 (3.3)</td>
<td>141 (4.2)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>129 (4.2)</td>
<td>131 (3.7)</td>
<td>260 (3.9)</td>
</tr>
<tr>
<td>Stomach</td>
<td>104 (3.4)</td>
<td>133 (3.8)</td>
<td>237 (3.6)</td>
</tr>
<tr>
<td>Brain</td>
<td>79 (2.6)</td>
<td>87 (2.5)</td>
<td>166 (2.5)</td>
</tr>
</tbody>
</table>

Thromboembolism as a Cause of Death

- Thromboembolism is the **second leading** cause of death in patients with cancer
- Annual death rate for VTE: 448 per 100,000 cancer outpatients
  - 47-fold increase over the general population

![Cancer Outpatient Mortality](attachment:image.png)

- Thromboembolism: 9%
- Cancer progression: 71%
- Other: 6%
- Infection: 4%
- Aspiration: 1%
- Bleeding: 1%
- Respiratory failure: 1%
- Unknown: 4%

Evolution of Anticoagulant Therapy: Treatments and Trials

Heparin 1916
LMWH 1980s
CLOT (dalteparin vs. warfarin) 2003
CATCH (tinzaparin vs. warfarin) 2015
SELECT-D (rivaroxaban vs. dalteparin) 2018

VKA 1940s
Fondaparinux 2000s
DOACs 1st DOAC 2008
Hokusai-VTE Cancer (edoxaban vs. dalteparin) 2017
CARAVAGGIO (apixaban vs. dalteparin) 2020
Case 1

- A 66-year-old man with metastatic prostate cancer is diagnosed with left femoral and popliteal vein thrombosis
- PMH significant only for hypertension
- His creatinine and CBC are normal
- Medications:
  - leuprolelin (GnRH analogue)
  - Metoprolol

How should his newly diagnosed DVT be treated?
<table>
<thead>
<tr>
<th><strong>DO</strong></th>
<th><strong>DON’T</strong></th>
<th><strong>CONSIDER</strong></th>
<th><strong>CAUTION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Do use a DOAC (apixaban, edoxaban, or rivaroxaban) or LMWH for cancer-associated VTE</td>
<td>• Don’t use warfarin unless patient cannot tolerate or afford DOAC or LMWH</td>
<td>• Consider factors that influence patient preference like route of administration, dose frequency, and affordability</td>
<td>• DOACs should be used with extra caution in patients with high risk of bleeding, such as those with GI/GU cancers or lesions</td>
</tr>
<tr>
<td>• Do use shared decision-making to aid patient preference</td>
<td></td>
<td>• Consider clinical factors like renal and hepatic functions, and overall thrombotic vs. bleeding risks</td>
<td>• Check for clinically important drug-drug interactions prior to using a DOAC</td>
</tr>
</tbody>
</table>
Treatment Algorithm

Patients with Cancer & Acute VTE

- Platelet count greater than 50k/μL
  - Yes
  - High bleeding risk
    - Yes
    - DOAC drug-drug interactions
      - No
      - Patient Preference
        - DOAC
        - Anticoagulation for 3-6 months (continue beyond 6 months if cancer is still active)
      - Yes
      - LMWH

- No
  - DOAC drug-drug interactions
    - No
    - LMWH
Note:

Patients with gastrointestinal (GI) cancer or GI lesions such as gastric/duodenal ulcers, gastritis, etc, or genitourinary lesions/intervention (e.g. nephrostomy tubes). Excess GI/GU bleeding has been observed with some DOACs (compared to LMWH) in some, but not all, clinical trials. Fatal or potentially life-threatening bleeding has occurred infrequently in randomized trials; no differences in the rates of fatal or potentially life-threatening bleeding have been documented.

The impact and clinical significance of P-gp modifiers and CYP3A4 modifiers affecting DOACs varies widely. Consider using Lexicomp® interactions as the preferred drug-drug interaction guidance resource, as well as the AC Forum Rapid Resource on DOAC DDI Guidance.

Patients unable to tolerate or access DOACs or LMWH may be considered for a vitamin K antagonist.
<table>
<thead>
<tr>
<th>Landmark Trial Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td><strong>DOAC</strong></td>
</tr>
<tr>
<td><strong>N</strong></td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
</tr>
<tr>
<td><strong>Study duration</strong></td>
</tr>
<tr>
<td><strong>Incidental VTE</strong></td>
</tr>
<tr>
<td><strong>Cancer diagnosis prior to enrollment</strong></td>
</tr>
<tr>
<td><strong>Active cancer</strong></td>
</tr>
<tr>
<td><strong>Cancer treatment on enrollment</strong></td>
</tr>
<tr>
<td><strong>Solid tumor</strong></td>
</tr>
<tr>
<td><strong>Metastatic cancer</strong></td>
</tr>
<tr>
<td><strong>GI cancer</strong></td>
</tr>
<tr>
<td><strong>Upper GI cancer</strong></td>
</tr>
<tr>
<td><strong>Platelet count cut-off (k/μL) for exclusion</strong></td>
</tr>
<tr>
<td><strong>CrCl cut-off for exclusion</strong></td>
</tr>
</tbody>
</table>
Landmark Trial Meta-Analysis

When compared to LMWH in active cancer patients with acute DVT/PE:

- DOACs decrease the risk of recurrent VTE
- DOACs nonsignificantly increase the risk of major bleeding
- DOACs nonsignificantly decrease the composite risk of recurrent VTE and major bleeding
- DOACs nonsignificantly increase the risk of CRNMB

<table>
<thead>
<tr>
<th>Recurrent VTE†</th>
<th>DOAC</th>
<th>LMWH</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or Subgroup</td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Hokusai VTE Cancer, 2018</td>
<td>34</td>
<td>522</td>
<td>46</td>
<td>524</td>
</tr>
<tr>
<td>Select-D, 2018</td>
<td>8</td>
<td>203</td>
<td>18</td>
<td>203</td>
</tr>
<tr>
<td>Caravaggio, 2020</td>
<td>32</td>
<td>576</td>
<td>46</td>
<td>579</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1301</td>
<td>1306</td>
<td>100.0%</td>
<td>0.68 [0.51, 0.90]</td>
</tr>
<tr>
<td>Total events</td>
<td>74</td>
<td>110</td>
<td>Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 2 (P = 0.54); I² = 0%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.66 (P = 0.008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Bleeding†</th>
<th>DOAC</th>
<th>LMWH</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
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<td>11</td>
<td>203</td>
<td>6</td>
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</tr>
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<td>22</td>
<td>576</td>
<td>23</td>
<td>579</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1301</td>
<td>1306</td>
<td>100.0%</td>
<td>1.36 [0.89, 2.06]</td>
</tr>
<tr>
<td>Total events</td>
<td>62</td>
<td>46</td>
<td>Heterogeneity: Tau² = 0.02; Chi² = 2.36, df = 2 (P = 0.31); I² = 15%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.43 (P = 0.15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† The Forest Plots for recurrent VTE and major bleeding were derived from the 3 landmark trials using the Mantel-Haenszel random effects model. The event rates cited are 6-month event rates.
Case 1 Cont.

• You recommend an oral FXa inhibitor (e.g. apixaban) and he has significant symptomatic improvement.

• However, 2 months later his cancer has progressed and his oncologist proposes starting him on apalutamide.

• *Does this change your treatment plan? Why or why not?*
• A 34 year-old man with a history of “unprovoked” pulmonary embolism (3 years ago) recently received myeloablative chemotherapy and autologous stem cell transplantation to treat refractory diffuse large B-cell lymphoma.

• He has been on rivaroxaban 10 mg daily since he completed 6 months of full-dose anticoagulant therapy for his PE approximately 30 months ago.

• His platelet count was 256,000/µL pre-transplant but has dropped to 56,000. It is expected that his platelet count will drop below 50,000 soon and remain less than 50,000/ µL for the next 1-2 weeks. **How should this be managed?**
  • Platelet transfusions? To what threshold?
  • Interrupt rivaroxaban?
  • Reduce rivaroxaban dose?
Case 3

- A 72 year-old woman is diagnosed with colon cancer after she was discovered to have iron-deficiency anemia.

- In preparation for colectomy and resection of a solitary hepatic metastasis, she begins neoadjuvant chemotherapy with capecitabine and oxaliplatin.

- One week after starting chemotherapy, she is diagnosed with acute right common femoral vein thrombosis.

**How should she be treated?**
- FXa inhibitor? LMWH? Warfarin?
- Why?
- What about 1 month after surgery?
## Guideline Recommendations

<table>
<thead>
<tr>
<th></th>
<th>2020 NCCN&lt;sup&gt;1&lt;/sup&gt;</th>
<th>2020 ASCO&lt;sup&gt;2&lt;/sup&gt;,*</th>
<th>2018 ISTH&lt;sup&gt;3&lt;/sup&gt;,*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute VTE Treatment</strong></td>
<td>DOAC (edoxaban, apixaban, and rivaroxaban) preferred for patients without gastric or gastroesophageal lesions</td>
<td>Initial anticoagulation (first 5–10 days): LMWH or rivaroxaban preferred</td>
<td>DOACs (edoxaban and rivaroxaban) suggested for low risk of bleeding and no drug-drug interaction, LMWH suggested otherwise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-term (at least 6 months): LMWH, edoxaban or rivaroxaban preferred</td>
<td></td>
</tr>
<tr>
<td><strong>GI/GU Cancer</strong></td>
<td>LMWH preferred for patients with gastric or gastroesophageal lesions</td>
<td>There is an increase in major bleeding risk with DOACs, particularly observed in GI and potentially GU malignancies</td>
<td>LMWH suggested in patients with luminal GI cancers with an intact primary, patients at risk of bleeding from the GU tract, bladder, or nephrostomy tubes, or patients with active GI mucosal abnormalities</td>
</tr>
</tbody>
</table>

*The recommendations from ASCO and ISTH were made before apixaban was compared to LMWH*
Landmark Trial Meta-Analysis

When compared to LMWH in active cancer patients with acute DVT/PE:

- DOACs decrease the risk of recurrent VTE\(^\dagger\)
- DOACs nonsignificantly increase the risk of major bleeding\(^\dagger\)
- DOACs nonsignificantly decrease the composite risk of recurrent VTE and major bleeding\(^7\)
- DOACs nonsignificantly increase the risk of CRNMB\(^7\)

\(^\dagger\) The Forest Plots for recurrent VTE and major bleeding were derived from the 3 landmark trials using the Mantel-Haenszel random effects model. The event rates cited are 6-month event rates.
Oral Anticoagulation for Primary VTE Prevention in Ambulatory Patients with Active Cancer

- Khorana Score for Prediction of VTE in Ambulatory Cancer Patients
- Cumulative Risk of VTE According to Khorana Score
- Guideline Recommendation Summary
- Landmark Trial Characteristics
- Meta-Analysis of Randomized Controlled Trials of Low-Dose DOAC vs. Placebo for Primary VTE Prevention

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Current Reversal and Treatment Strategies for DOAC-related Bleeding

Tuesday | January 19, 2021 | 6:00 PM ET

Faculty: Megan Barra, PharmD, BCPS, BCCCP | Adam Cuker, MD, MS | Scott Kaatz, DO, MSc | Ronni Nemeth, PharmD, CACP, DPLA | Kelly Rudd, PharmD, FCCP, BCPS, CACPP

Vascular Protection in Patients with CAD/PAD

Friday | February 16, 2021 | 4:00 PM ET

Faculty: Geoffrey Barnes, MD, MSc | Marc Bonaca, MD, MPH | Henry Han, MD | Eva Kline-Rogers, MS, NP | Bishoy Ragheb, PharmD | Nichole Sherwood, PharmD

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acforum.org/education-webinars
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