Cancer-Associated Thrombosis: An Update

David Garcia, MD
April 2019

Disclosure

• Consulting Fees: Janssen; Seattle Genetics

• Research support: Daiichi Sankyo, Incyte
Overview

• primary prevention of VTE among cancer patients undergoing chemotherapy

• treatment of cancer-associated VTE

• perioperative management of anticoagulation

• new VTE treatment/prevention guidelines

Background:
VTE is common in cancer patients

**Background:**

**VTE rate varies by cancer type**

<table>
<thead>
<tr>
<th>Age</th>
<th>First VTE per 100 person-years (95% CI)</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>Hematologic</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>Pancreas</td>
<td>14.6 (12.9–16.5)</td>
</tr>
<tr>
<td>Stomach</td>
<td>10.8 (9.5–12.3)</td>
</tr>
</tbody>
</table>

**Total (N=6592)**

**Common cancer types, n (%):**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Total (N=6592)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate (males)</td>
<td>565 (17.5)</td>
</tr>
<tr>
<td>Breast (females)</td>
<td>506 (15.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>918 (13.9)</td>
</tr>
<tr>
<td>Colon</td>
<td>827 (12.5)</td>
</tr>
<tr>
<td>Haematological</td>
<td>669 (10.1)</td>
</tr>
<tr>
<td>Ovarian (females)</td>
<td>318 (9.5)</td>
</tr>
<tr>
<td>Bladder</td>
<td>319 (4.8)</td>
</tr>
<tr>
<td>Uterus (females)</td>
<td>141 (4.2)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>260 (3.9)</td>
</tr>
<tr>
<td>Stomach</td>
<td>237 (3.6)</td>
</tr>
<tr>
<td>Brain</td>
<td>166 (2.5)</td>
</tr>
</tbody>
</table>

ARS Question 1

In a patient with newly diagnosed metastatic adenocarcinoma of the pancreas who will soon be starting chemotherapy, the benefits of a low-dose DOAC will outweigh the risks.

A) I agree
B) I disagree
C) I am not sure
D) I am somewhat “bummed out” to be sitting in this lecture room rather than on the beach

AVERT study design


No baseline ultrasound exam
AVERT study outcomes

### Primary Composite Efficacy Endpoint
- Symptomatic upper- or lower-extremity proximal DVT
- Symptomatic or incidental pulmonary embolism
- VTE-related death

### Key Secondary Efficacy Endpoint
- All-cause mortality

### Primary Safety Endpoint
- Major bleeding (ISTH-defined)

### Key Secondary Safety Endpoint
- Clinically relevant non-major bleeding

---

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=291)</th>
<th>Placebo (n=283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>61.2± 12.4</td>
<td>61.7 ± 11.3</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>121 (41.6)</td>
<td>119 (42.0)</td>
</tr>
<tr>
<td>Tumor types, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecologic</td>
<td>74 (25.2)</td>
<td>74 (26.1)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>70 (24.1)</td>
<td>69 (24.4)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>37 (12.7)</td>
<td>41 (14.5)</td>
</tr>
<tr>
<td>Khorana score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>186 (63.9)</td>
<td>190 (67.1)</td>
</tr>
<tr>
<td>3</td>
<td>78 (26.8)</td>
<td>68 (24.0)</td>
</tr>
<tr>
<td>4</td>
<td>26 (8.9)</td>
<td>24 (8.5)</td>
</tr>
<tr>
<td>Prior venous thromboembolism, n (%)</td>
<td>9 (3.1)</td>
<td>8 (2.8)</td>
</tr>
</tbody>
</table>

---

AVERT: efficacy outcomes

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=288)</th>
<th>Placebo (n=275)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT*</td>
<td>12 (4.2)</td>
<td>28 (10.2)</td>
<td>0.41</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PE†</td>
<td>7 (2.4)</td>
<td>12 (4.4)</td>
<td>(0.26-0.43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (1.7)</td>
<td>16 (5.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>35 (12.2%)</td>
<td>27 (9.8%)</td>
<td>1.29</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.98-1.71)</td>
<td></td>
</tr>
</tbody>
</table>

*All DVT events were symptomatic (no surveillance ultrasound was performed).
† Includes “incidental” PE events: 3/5 apixaban; 6/16 placebo.

Primary efficacy outcome

[Graph showing patients alive without venous thromboembolism (%) over time for Apixaban and Placebo groups]
Primary safety outcomes

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=288)</th>
<th>Placebo (n=275)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>10 (3.5%)</td>
<td>5 (1.8%)</td>
<td>2.0 (1.01-2.395)</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>21 (7.3%)</td>
<td>15 (5.5%)</td>
<td>1.28 (0.89-1.84)</td>
<td></td>
</tr>
</tbody>
</table>

Most major bleeding events were classified “major” because they were associated with Hgb drop of > 2 g/dL and/or a transfusion of 2 or more units of PRBCs.

Fatal bleeding or bleeding considered to be a clinical emergency was very uncommon:
1 event in apixaban group; 2 events in placebo group

CASSINI Study Design

**Objective:** Assess the efficacy and safety of rivaroxaban versus placebo for thromboprophylaxis in ambulatory cancer patients initiating new systemic regimen and at high risk of VTE

Multinational, multicenter, randomized, double-blind, placebo-controlled phase IIIb superiority study

Patients with various solid tumors/lymphomas initiating new systemic regimen and at high risk of VTE (Khorana score ≥2)

Rivaroxaban 10 mg once daily

Placebo once daily

CUS (compression ultrasonography) (lower extremity)

CASSINI Study Outcomes

<table>
<thead>
<tr>
<th>Primary Composite Efficacy Endpoint</th>
<th>Primary Safety Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic or asymptomatic lower-extremity proximal DVT</td>
<td>Major bleeding (ISTH-defined)</td>
</tr>
<tr>
<td>Symptomatic upper- or lower-extremity distal DVT</td>
<td>Key Secondary Safety Endpoint</td>
</tr>
<tr>
<td>Symptomatic or incidental pulmonary embolism</td>
<td>Clinically relevant non-major bleeding (ISTH-defined)</td>
</tr>
<tr>
<td>VTE-related death</td>
<td>Endpoints were adjudicated by a blinded independent committee</td>
</tr>
</tbody>
</table>

Key Secondary Efficacy Endpoints

- Confirmed arterial thromboembolism
- Confirmed visceral thrombosis
- All-cause mortality

Endpoints were adjudicated by a blinded independent committee.

DVT, deep vein thrombosis; ISTH, International Society on Thrombosis and Haemostasis

Patient Characteristics

<table>
<thead>
<tr>
<th>Placebo (n=421)</th>
<th>Rivaroxaban (n=420)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>62 (28-88)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>206 (48.9)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>346 (82.2)</td>
</tr>
<tr>
<td>Black</td>
<td>18 (4.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Khorana score, n (%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>295 (70.1)</td>
</tr>
<tr>
<td>3</td>
<td>96 (22.8)</td>
</tr>
<tr>
<td>4</td>
<td>25 (5.9)</td>
</tr>
<tr>
<td>Prior VTE, n (%)</td>
<td></td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism
## Patient Characteristics/Primary Site of Cancer

<table>
<thead>
<tr>
<th>Primary tumor site, n (%)</th>
<th>Placebo (n=421)</th>
<th>Rivaroxaban (n=420)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic</td>
<td>138 (32.8%)</td>
<td>136 (32.4%)</td>
</tr>
<tr>
<td>Breast</td>
<td>9 (2.1%)</td>
<td>9 (2.1%)</td>
</tr>
<tr>
<td>Gastric/gastro-esophageal junction</td>
<td>87 (20.7%)</td>
<td>89 (21.2%)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>17 (4.0%)</td>
<td>15 (3.6%)</td>
</tr>
<tr>
<td>Lung</td>
<td>72 (17.1%)</td>
<td>62 (14.8%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>26 (6.2%)</td>
<td>33 (7.9%)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>30 (7.1%)</td>
<td>24 (5.7%)</td>
</tr>
<tr>
<td>Other gastrointestinal</td>
<td>10 (2.4%)</td>
<td>16 (3.8%)</td>
</tr>
<tr>
<td>Other gynecologic</td>
<td>21 (5.0%)</td>
<td>24 (5.7%)</td>
</tr>
<tr>
<td>Others</td>
<td>11 (2.6%)</td>
<td>12 (2.9%)</td>
</tr>
</tbody>
</table>

## CASSINI: efficacy outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Up-to-day-180 period</th>
<th>On-treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=421)</td>
<td>Rivaroxaban (N=420)</td>
</tr>
<tr>
<td>Primary efficacy endpoint</td>
<td>37 (8.79%)</td>
<td>25 (5.95%)</td>
</tr>
<tr>
<td>Symptomatic*</td>
<td>19 (4.51%)</td>
<td>15 (3.57%)</td>
</tr>
<tr>
<td>Asymptomatic*</td>
<td>18 (4.28%)</td>
<td>9 (2.14%)</td>
</tr>
<tr>
<td>Asymptomatic proximal DVT</td>
<td>11 (2.61%)</td>
<td>4 (0.95%)</td>
</tr>
<tr>
<td>Incidental PE</td>
<td>10 (2.38%)</td>
<td>6 (1.43%)</td>
</tr>
<tr>
<td>VTE-related death</td>
<td>3 (0.71%)</td>
<td>1 (0.24%)</td>
</tr>
<tr>
<td>All-cause Death</td>
<td>100 (23.8)</td>
<td>84 (20.0%)</td>
</tr>
</tbody>
</table>
Primary efficacy outcome: All randomized patients

Up to Day 180 (primary)

HR, 0.66; 95% CI, 0.40-1.09; P = 0.101

Placebo, 8.79%
Rivaroxaban, 5.95%

On-treatment

HR, 0.40; 95% CI, 0.20-0.80; P = 0.007

Placebo, 6.41%
Rivaroxaban, 2.62%

Primary safety outcomes

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=405)</th>
<th>Placebo (n=404)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Major bleeding</td>
<td>8 (1.98%)</td>
<td>4 (0.99%)</td>
<td>1.96 (0.59-6.49)</td>
<td>0.265</td>
</tr>
<tr>
<td>Secondary Clinically relevant non-major bleeding</td>
<td>11 (2.72%)</td>
<td>8 (1.98%)</td>
<td>1.34 (0.54-3.32)</td>
<td>0.532</td>
</tr>
</tbody>
</table>

Only 1 fatal bleeding event (rivaroxaban group)
Conclusions (Part 1)

• Cancer patients starting chemotherapy with a Khorana Score $> 2$ have a substantial risk of VTE (at least 10% at 6 months)

• Low-dose DOACs can reduce the risk of VTE by more than 50%

• Primary VTE prophylaxis with low-dose DOACs increases the risk of bleeding, has minimal impact on the risk of fatal bleeding

ARS Question 2

A patient with metastatic adenocarcinoma of the stomach is diagnosed with ‘incidental’ pulmonary embolism (involving more than 1 segmental pulmonary artery). Would you recommend:

A) 5 days of LMWH, followed by edoxaban 60 mg QD
B) Rivaroxaban 15 mg BID x 21 days, followed by 20 mg daily thereafter
C) Long-term LMWH (e.g. enoxaparin 1 mg/kg SC q 12 hours)
D) Ultrasound legs – if no DVT, withhold anticoagulation
"Hokusai VTE-Cancer" Study Design (open label)

Treatment for up to 12 months (at least 6 months)

Efficacy and safety data collected during the entire 12-month study period

Independent blind adjudication of all suspected outcomes

Severity of major bleeding at presentation also adjudicated


SELECT-D Study design (simplified)

Rivaroxaban

15 mg bid for 21 days followed by 20 mg od

DOACs vs. LMWH for Cancer-associated Thrombosis

### Recurrent VTE at 6 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOAC Events</th>
<th>LMWH Events</th>
<th>Total</th>
<th>M-H Random, 95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hokusai VTE Cancer 2017</td>
<td>34 522</td>
<td>48 514</td>
<td>73%</td>
<td>0.74 (0.48, 1.14)</td>
<td></td>
</tr>
<tr>
<td>ORBIT-O 2017</td>
<td>0 269</td>
<td>10 209</td>
<td>26.5%</td>
<td>0.44 (0.20, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>[72% 84%]</td>
<td>[64% 100%]</td>
<td></td>
<td>0.65 (0.42, 1.01)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>42</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity Tau²</td>
<td>0.02</td>
<td>1.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.37</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>2.14 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Major Bleeding at 6 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOAC Events</th>
<th>LMWH Events</th>
<th>Total</th>
<th>M-H Random, 95% CI</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hokusai VTE Cancer 2017</td>
<td>29 522</td>
<td>17 524</td>
<td>73.5%</td>
<td>1.71 (0.95, 3.08)</td>
<td></td>
</tr>
<tr>
<td>ORBIT-O 2017</td>
<td>11 203</td>
<td>6 203</td>
<td>26.5%</td>
<td>1.06 (0.86, 1.30)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>[70% 86%]</td>
<td>[64% 100%]</td>
<td></td>
<td>1.74 (1.05, 2.88)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>40</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity Tau²</td>
<td>0.09</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.81</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>2.17 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Apixaban versus Dalteparin in Active Malignancy Associated Venous Thromboembolism (ADAM VTE)

Robert McBane on behalf of the ADAM VTE Investigators

**Study Hypothesis:** Apixaban is associated with a significantly lower rate of *major bleeding* compared to dalteparin in the treatment of patients with active cancer and confirmed DVT or PE
**“ADAM VTE” Study Design**

- **Active cancer plus acute VTE**
- **Dalteparin 200 units/kg for 30 days then 150 units/kg**
- **Apixaban 10 mg BID x 7 days, then 5 mg BID**
- Target Sample Size: 300*

*Powered for safety outcome (bleeding)
† ~15% had arm DVT


---

**Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (N=145)</th>
<th>Dalteparin (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant Metastasis</td>
<td>65%</td>
<td>66%</td>
</tr>
<tr>
<td>Active chemotherapy</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td>Solid tumor, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>Lung</td>
<td>22%</td>
<td>13%</td>
</tr>
<tr>
<td>Pancreatic/Hepatobiliary</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Breast</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Brain</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=145)</th>
<th>Dalteparin (n=142)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding (MB)</td>
<td>0 (0%)</td>
<td>2 (1.4%)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major + Clinically relevant non-major bleeding</td>
<td>9 (6.2%)</td>
<td>9 (6.3%)</td>
<td>0.88</td>
</tr>
<tr>
<td>VTE</td>
<td>1 (0.7%)</td>
<td>9 (6.3%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>


Cancer-Associated VTE Treatment Timeline

2003
“CLOT”
Dalteparin vs. warfarin

2018
“Hokusai Cancer VTE”
Edoxaban vs. Dalteparin

2019
“ADAM VTE”
Apixaban vs. Dalteparin

“Select-D”
Rivaroxaban vs. Dalteparin
How do event rates compare across CAT treatment trials?

<table>
<thead>
<tr>
<th></th>
<th>ADAM (Apixaban)</th>
<th>CLOT (Warfarin)</th>
<th>Hokusai (Edoxaban)</th>
<th>Select-D (Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral agent</td>
<td>0%</td>
<td>4%</td>
<td>5.6%</td>
<td>5.4%</td>
</tr>
<tr>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral agent</td>
<td>0.7%</td>
<td>17%</td>
<td>6.5%</td>
<td>4%</td>
</tr>
</tbody>
</table>

How do event rates compare across CAT treatment trials?

<table>
<thead>
<tr>
<th></th>
<th>ADAM (Apixaban)</th>
<th>CLOT (Warfarin)</th>
<th>Hokusai (Edoxaban)</th>
<th>Select-D (Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral agent</td>
<td>0%</td>
<td>4%</td>
<td>5.6%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>1.4%</td>
<td>6%</td>
<td>8.8%</td>
<td>8.9%</td>
</tr>
<tr>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral agent</td>
<td>0.7%</td>
<td>17%</td>
<td>6.5%</td>
<td>4%</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>6.3%</td>
<td>9%</td>
<td>11.3%</td>
<td>11%</td>
</tr>
</tbody>
</table>
Did the trials enroll the same kinds of patients?

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>ADAM (Apixaban)</th>
<th>Hokusai (Edoxaban)</th>
<th>Select-D (Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper GI tumor (%)</td>
<td>4-5</td>
<td>5</td>
<td>10*</td>
</tr>
<tr>
<td>Pancreas (%)</td>
<td>12</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Metastases (%)</td>
<td>65</td>
<td>52</td>
<td>58</td>
</tr>
<tr>
<td>6-month mortality</td>
<td>16</td>
<td>40</td>
<td>25</td>
</tr>
</tbody>
</table>

* Patients with esophageal or gastroesophageal tumors were excluded midway through the Select-D study because, in this subgroup, the DSMB noted a statistically nonsignificant difference in major bleeding between the treatment arms.

Caravaggio Study (apixaban vs. dalteparin)
ClinicalTrials.gov Identifier: NCT03045406

Randomized, open-label, PROBE, non-inferiority study
Treatment period: 6 months

Primary Outcome: Composite of: DVT or PE (symptomatic, incidental or fatal).

Recruitment target: 1168 pts.
As of March 13th: 1025 pts randomized.
Results expected: late 2019.

Agnelli G. et al Thromb Haemost. 2018 Sep;118(9):1668-1678
Can we use DOACs in patients with gastrointestinal cancer?

• 2018 ISTH Guidance Statement:

  • We suggest the use of specific DOACs (edoxaban and rivaroxaban) for cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no drug–drug interactions with current systemic therapy.

  • We suggest the use of LMWHs for cancer patients with an acute diagnosis of VTE and a high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis. Edoxaban and rivaroxaban are acceptable alternatives if there are no drug–drug interactions with current systemic therapy.

* Khorana A, et al, JTH 2018

Gl cancer (top) vs. Non-Gl cancer (bottom)

**GI vs. other Major Bleeding in the Select-D trial**

<table>
<thead>
<tr>
<th>Type of Bleed</th>
<th>Dalteparin (n = 203)</th>
<th>Rivaroxaban (n = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Sites of major bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Stomach</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lower GI</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Site unknown</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hematuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Intraoperative hemorrhage</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hematoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal hematoma related to surgical clip</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>


**Major Bleeding events in the Hokusai VTE trial**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Edoxaban (n = 32)</th>
<th>Dalteparin (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal bleeding, n (%)</td>
<td>0</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Hospitalization due to bleeding, n (%)</td>
<td>29 (62.5)</td>
<td>13 (81.3)</td>
</tr>
<tr>
<td>Admission to intensive care unit</td>
<td>18 (56.3)</td>
<td>12 (75.0)</td>
</tr>
<tr>
<td>Duration of hospitalization, d, median (IQR)</td>
<td>6 (4–12)</td>
<td>8 (5–23)</td>
</tr>
<tr>
<td>Bleeding management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red blood cell transfusion, n (%)</td>
<td>22 (58.8)</td>
<td>8 (56.0)</td>
</tr>
<tr>
<td>1 unit</td>
<td>5 (15.6)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>2 units</td>
<td>11 (34.3)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>3 or more units</td>
<td>6 (18.8)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Procedure, n (%)</td>
<td>7 (21.9)</td>
<td>3 (19)</td>
</tr>
</tbody>
</table>

Major Bleeding events in the Hokusai VTE trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Edoxaban (n = 32)</th>
<th>Dalteparin (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study drug interruption due to bleeding, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5 (15.6)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Temporary</td>
<td>19 (59.4)</td>
<td>9 (56.3)</td>
</tr>
<tr>
<td>Permanent</td>
<td>8 (25.0)</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Cancer treatment interrupted or withdrawn due to bleeding, n (%)</td>
<td>9 (28.1)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Clinical course severity category&lt;sup&gt;a&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category 1</td>
<td>5 (15.6)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Category 2</td>
<td>24 (75.0)</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Category 3</td>
<td>3 (9.4)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Category 4</td>
<td>0</td>
<td>1 (6.3)</td>
</tr>
</tbody>
</table>


Major Bleeding events in the Select-D trial

<table>
<thead>
<tr>
<th>Type of Bleed</th>
<th>Dalteparin (n = 203)</th>
<th>Rivaroxaban (n = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Criteria to define major bleeding&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically overt and decrease in hemoglobin level of ≥ 2 g/dL over 24 hours</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Clinically overt and transfusion of ≥ 2 units of packed red cells</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Clinically overt and critical site (eg, intracranial, retroperitoneal)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clinically overt and contributes to death</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Mayo Clinic VTE Registry: 604 consecutive patients with cancer-associated VTE
(March 2013-Nov 2018): **124 (21%) GI malignancy**

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (N=171)</th>
<th>Rivaroxaban (N=138)</th>
<th>LMWH (N=295)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI malignancy</td>
<td>35 (20.5%)</td>
<td>24 (17.5%)</td>
<td>65 (22.0%)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>90 (52.6%)</td>
<td>78 (56.5%)</td>
<td>179 (60.7%)</td>
</tr>
<tr>
<td>PE</td>
<td>84 (49.1%)</td>
<td>58 (42.0%)</td>
<td>143 (48.5%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>115 (67.6%)</td>
<td>86 (62.8%)</td>
<td>197 (67.9%)</td>
</tr>
<tr>
<td>Surgery &lt;6 mo</td>
<td>32 (18.7%)</td>
<td>29 (21.0%)</td>
<td>31 (10.5%)</td>
</tr>
<tr>
<td>Bleeding* &lt;3 mo</td>
<td>6 (3.5%)</td>
<td>11 (8.0%)</td>
<td>11 (3.7%)</td>
</tr>
</tbody>
</table>

*Major bleeding or clinically-relevant non-major bleeding

Houghton et al, 2018 ASH Abstract #362

Rates of bleeding for **all cancer types**: non-randomized comparisons

- Major bleeding: **HR 1.44** (95% CI, 0.71-2.92)
- Clinically relevant non-major bleeding: **HR 3.82** (95% CI, 1.26-11.6)

Houghton et al, Abstract #362
Rates of bleeding by anticoagulant for GI cancer

<table>
<thead>
<tr>
<th></th>
<th>DOAC (N=59)</th>
<th>LMWH (N=65)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>5 (8.5%)</td>
<td>2 (3.1%)</td>
<td>2.9 (0.57-14.78)</td>
</tr>
<tr>
<td></td>
<td><strong>10.33 per 100 PY</strong></td>
<td>3.44 per 100 PY</td>
<td></td>
</tr>
<tr>
<td>CRNMB</td>
<td>1 (1.7%)</td>
<td>1 (1.5%)</td>
<td>1.18 (0.07-20.55)</td>
</tr>
<tr>
<td></td>
<td><strong>1.97 per 100 PY</strong></td>
<td>1.71 per 100 PY</td>
<td></td>
</tr>
<tr>
<td>MB+CRNMB</td>
<td>6 (10.2%)</td>
<td>3 (4.6%)</td>
<td>2.35 (0.59-9.42)</td>
</tr>
<tr>
<td></td>
<td><strong>12.64 per 100 PY</strong></td>
<td>5.17 per 100 PY</td>
<td></td>
</tr>
</tbody>
</table>

- **Limitations**: Small numbers, non-randomized, analysis not adjusted for other variables

Conclusions (Part 2)

- Edoxaban (after 5-day LMWH lead-in) and Rivaroxaban are effective treatments for cancer-associated DVT/PE
  - Preliminary data re: apixaban is encouraging but more evidence would be desirable
- Patients with acute cancer-associated VTE should be aware that treatment with a DOAC may increase the risk of bleeding (compared to LMWH)
  - Approximately 1 “extra” major bleed caused for every 50 patients treated with DOAC (instead of LMWH) for 6 mos.
  - The “number needed to harm” may be lower in patients with GI or GU cancers (more evidence is needed)