Cancer Associated Thrombosis
Can we use DOACs?

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DIVISION OF HEMATOLOGY
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Faculty/Presenter Disclosure

Speaker: Dr. Cynthia Wu
  ◦ Hematology
  ◦ Thrombosis

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Mitigating Potential Bias

Planning Committee mitigated potential bias by:

◦ Instructing speakers to hold no discussion nor promote products funded by companies listed in slides 1 and 2
◦ Ensuring presentation involves evidence-based topics not directly related to any sponsor
Objectives

Highlight the link between cancer and thrombosis

Briefly review the role for LMWH in cancer associated thrombosis

Discuss the new evidence on the use of DOACs for cancer associated thrombosis (CAT)
The link between cancer and clot
Cancer increases the risk of clot

Annual incident of VTE in the general population is 117/100,000 or roughly 1/1000

Cancer is associated with a 4.1x increased risk

Chemotherapy increases this to 6.5x

Combining these estimates yields an approximate annual incidence of VTE in cancer patients at 1/200

- About 20% of all venous thromboembolism occurs in patients with cancer

Lee A. BJH 2005;128:291-302
Khorana A et al. JTH 2007;5:632-634
Which Cancers?

Those with CAT are most frequently breast, lung and colorectal cancer patients due to the high incidence of these cancers
  - These cancer types are well represented in clinical trials

The most thrombogenic cancers are pancreatic, hematologic and brain
  - These cancer types are poorly represented in clinical trials

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=57591)</td>
<td>3.06 (3.68, 4.27)</td>
</tr>
<tr>
<td>Breast (n=8586)</td>
<td>2.87 (2.30, 3.58)</td>
</tr>
<tr>
<td>Lung (n=7975)</td>
<td>7.27 (5.93, 8.91)</td>
</tr>
<tr>
<td>Colorectal (n=8373)</td>
<td>3.93 (3.28, 4.71)</td>
</tr>
<tr>
<td>Prostate (n=4457)</td>
<td>3.25 (2.56, 4.13)</td>
</tr>
<tr>
<td>Brain (n=1133)</td>
<td>10.40 (5.98, 18.08)</td>
</tr>
<tr>
<td>Bone (n=229)</td>
<td>4.97 (1.46, 16.99)</td>
</tr>
<tr>
<td>Haematological (n=4498)</td>
<td>12.65 (10.04, 15.94)</td>
</tr>
<tr>
<td>Pancreas (n=1671)</td>
<td>15.58 (10.50, 23.00)</td>
</tr>
</tbody>
</table>

CAT Impacts Prognosis

Danish registry on CAT (n=668)

5,371 matched cancer patients without clot

1 year survival
  - 12 % (CAT) vs 36% (controls)
  - $P < 0.001$

VTE is the second leading cause of death in cancer patients.
The evolving options for treatment of CAT
LMWH is superior to warfarin

**CLOT trial (Lee NEJM 2003)**  
* n = 676  
* Dalteparin 200 units/kg x 4 weeks, then 150 units/kg x 5 months  
* 16% VTE  
* 8% VTE  
* Major bleeding ~5%

**CATCH trial (Lee JAMA 2015)**  
* n = 900  
* Tinzaparin 175 units/kg x 6 months (no dose reduction)  
* 10.5% VTE  
* 7.2% VTE  
* Major bleeding ~2.5%

Enoxaparin cancer trials (CANTHANOX, Meyer 2002 and ONCENOX, Deitcher 2006) were stopped early, underpowered and did not demonstrate statistically significant efficacy or safety outcomes
Complex management and timeline

- Risk (odds ratio)
  - Chemotherapy
  - Metastasis
  - Hospitalization
  - Remission or ‘response’
  - Progression
  - End of life
  - Diagnosis

Risk of VTE:
- In the cancer population
- In the general population

Risk levels over time:
- 8
- 7
- 6
- 5
- 4
- 3
- 2
- 1
- 0

Timeline:
- Diagnosis
- Progression
- End of life

Graphic courtesy of Marc Carrier
The classic anticoagulants

Warfarin
- Revolutionized the treatment of thrombotic disorders
- But has several disadvantages including a narrow therapeutic range, multiple food and drug interactions and the resulting need for ongoing INR monitoring
- Many of these issues are compounded in cancer patients

LMWH
- Addressed many of the issues that faced warfarin use in cancer as they do not interact with food and drugs
- But the expensive and parenteral nature of LMWH limit its use particularly for those who need long term anticoagulation
DOACs in CAT specific populations

Clinical trials are finally emerging

- Hokusai VTE cancer trial - edoxaban vs dalteparin - published Dec 2017
- Select-D pilot study - rivaroxaban vs dalteparin - published May 2018
- Casta Diva (NCT 02746185) - rivaroxaban vs dalteparin
- Adam (NCT 02585713) - apixaban vs dalteparin - presented at ASH 2018
- Canvas (NCT 02744092) - any DOAC vs any LMWH
- Caravaggio (NCT 03045406) - apixaban vs dalteparin

- Other trials for extended treatment of CAT with DOAC as well as for prophylaxis with DOAC in ambulatory CAT patients undergoing chemotherapy
Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D.,
Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D.,
Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D.,
Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D.,
Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D.,
Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D.,
for the Hokusai VTE Cancer Investigators*

February 15, 2018
DOI: 10.1056/NEJMoa1711948
Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)

Annie M. Young, Andrea Marshall, Jenny Thirlwall, Oliver Chapman, Anand Lokare, Catherine Hill, Danielle Hale, Janet A. Dunn, Gary H. Lyman, Charles Hutchinson, Peter MacCallum, Ajay Kakkar, F.D. Richard Hobbs, Stavros Petrou, Jeremy Dale, Christopher J. Poole, Anthony Maraveyas, and Mark Levine
What we are starting to know...

DOACs appear equal to LMWH

DOACs appear equal to LMWH

**Hokusai trial (Raskob NEJM 2018) n = 1050**
- 5+ days of LMWH then
- Either dalteparin 200 units/kg x 4 weeks, then 150 units/kg
- Or edoxaban 60mg daily*

**SELECT-D trial** (Young JCO 2018) n = 406
- dalteparin 200 units/kg x 4 weeks, then 150 units/kg
- Vs rivaroxaban 15mg BID x 3 weeks then 20mg daily

*Hokusai: edoxaban was dose reduced to 30mg daily if CrCl 30-50, body weight ≤60kg, potent p-glycoprotein inhibitor
**SELECT-D: after first 220 patients, esophageal and GE junction cancers were excluded due to excessive bleeding risk on DOAC
What we are starting to know... but DOACs appear less safe than LMWH

Hokusai trial (Raskob NEJM 2018)  n = 1050
5+ days of LMWH then
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Or edoxaban 60mg daily*

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**SELECT-D: after first 220 patients, esophageal and GE junction cancers were excluded due to excessive bleeding risk on DOAC
Treatment algorithm in cancer-associated thrombosis: Canadian expert consensus

M. Carrier MD MSc, N. Blais MD MSc, M. Crowther MD MSc, P. Kavan MD PhD, G. Le Gal MD PhD, O. Moodley MD, S. Shivakumar MD, V. Tagalakis MD MSc, C. Wu MD, and A.Y.Y. Lee MD MSc

General tips:

Check for major contraindications to each agent

Ensure patient is able to absorb PO medications prior to started any oral anticoagulant

Sort out drug coverage!
## Clot and cancer burden

<table>
<thead>
<tr>
<th></th>
<th>Hokusai VTE Cancer 2018 (sx or incidental PE/DVT)</th>
<th>SELECTd 2018 (sx PE/DVT + incidental PE)</th>
<th>CLOT 2003 (sx PE/DVT)</th>
<th>CATCH 2015 (sx PE/DVT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulant</strong></td>
<td>edoxaban</td>
<td>rivaroxaban</td>
<td>dalteparin</td>
<td>warfarin</td>
</tr>
<tr>
<td></td>
<td>dalteparin</td>
<td>dalteparin</td>
<td>dalteparin</td>
<td>tinzaparin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>warfarin</td>
</tr>
<tr>
<td><strong>Clot at enrolment</strong></td>
<td>33% incidental VTE</td>
<td>50% incidental VTE</td>
<td><strong>Symptomatic VTE only</strong></td>
<td>Symptomatic VTE only (included incidental VTE for recurrences)</td>
</tr>
<tr>
<td><strong>Metastatic cancer (%)</strong></td>
<td>52.4</td>
<td>53.4</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>66</td>
<td>68.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53.3</td>
</tr>
<tr>
<td><strong>Cancer tx (%)</strong> Chemo/RT/Sx</td>
<td>71.6</td>
<td>73.1</td>
<td>69</td>
<td>78.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>76.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55</td>
</tr>
<tr>
<td><strong>ECOG (%)</strong></td>
<td>0-1 = 76.3</td>
<td>0-1 = 75.1</td>
<td>0-1 = 76</td>
<td>0-1 = 63.6</td>
</tr>
<tr>
<td></td>
<td>2 = 23.6</td>
<td>2 = 23.7</td>
<td>2 = 21</td>
<td>2 = 34.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 = 26</td>
<td>2 = 36.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-1 = 76.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 = 23.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 = 22.8</td>
</tr>
<tr>
<td><strong>Death (%)</strong></td>
<td>39.5 (12 mos)</td>
<td>36.6 (12 mos)</td>
<td>30 (6 mos)</td>
<td>39 (6 mos)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 (6 mos)</td>
<td>41 (6 mos)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33.4 (6 mos)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30.6 (6 mos)</td>
</tr>
</tbody>
</table>
Bleeding risk assessment

Statistically significantly higher rate of major bleeding on both rivaroxaban and edoxaban compared to dalteparin.

Patients with more risk factors for bleeding were at even higher risk of major bleeding on DOAC vs LMWH.

This may be due to the ability to titrate/adjust the dose of LMWH with greater flexibility than oral anticoagulation or possibly due to the shorter half life of LMWH compared to OAC.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Major bleeding (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Edoxaban</td>
<td>Dalteparin</td>
</tr>
<tr>
<td>Urothelial cancer</td>
<td>13.2</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine clearance 30–50 mL/min</td>
<td>10.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Platelets 50–100×10^3/mL</td>
<td>12.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Use of antiplatelet agents</td>
<td>11.5</td>
<td>3.2</td>
</tr>
<tr>
<td>3 Risk factors^a</td>
<td>13.5</td>
<td>4.1</td>
</tr>
<tr>
<td>4 Or more risk factors^a</td>
<td>10.5</td>
<td>4.2</td>
</tr>
</tbody>
</table>

^a Defined as surgery within the preceding 2 weeks, use of antiplatelet agents, primary or metastatic brain tumour, regionally advanced or metastatic cancer, gastrointestinal or urothelial cancer diagnosed within the preceding 6 months, or treatment with bevacizumab within the preceding 6 weeks. NA = not available.
Type of cancer

Specific cancer groups had a much bigger difference in major bleeding

**GI cancer**

- Hokusai trial: in GI cancer patients (any GI malignancy), major GI bleeding occurred in 18/136 (13.2%) of edoxaban patients and 3/125 (2.4%) of dalteparin patients
- SELECTd trial: major GI bleeding occurred in 8/203 (3.9%) of rivaroxaban patients and 4/203 (2.0%) of dalteparin patients

  After the first 220 patients were enrolled, the protocol call was amended to exclude all UGI cancer patients due to excessive major bleeding

**Urothelial cancer**

- Hokusai trial: for urothelial cancer patients, major GU bleeding occurred in 5/38 (13.2%) in edoxaban patients and 0/31 in dalteparin patients
- SELECTd trial: major GU bleeding was reported as 1/203 in rivaroxaban patients and 0/203 in dalteparin patients with clinically relevant non major bleeding (mainly GI and GU bleeding) reported in 25/203 (12.3%) rivaroxaban patients and 7/203 (3.4%) dalteparin patients
**Drug interactions**

## Anticoagulants as substrates for major pathways

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>CYP3A4 (metabolic)</th>
<th>P-gp (transport)</th>
<th>Other CYP metabolizing enzymes (2C9, 2C19, 2C8, 2C18, 1A2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>VKA</td>
<td>Major</td>
<td>No/Minor</td>
<td>All (Major: CYP2C9)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Major</td>
<td>Major</td>
<td>Minor: 1A2, 2C8, 2C9, 2C19</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Minor</td>
<td>Major</td>
<td>No</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Major</td>
<td>Major</td>
<td>No</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>No</td>
<td>Moderate</td>
<td>No</td>
</tr>
</tbody>
</table>

*Table courtesy of Marc Carrier*

**Remember:**
Cancer patients are usually on ever changing and cycling multidrug regimens which makes calculating and tracking drug interactions very tricky.
Regular reassessment

Clinical course, treatment and prognosis of cancer patients often change throughout the cancer journey.

Initial treatment choices may not be the best option in future situations.

Compliance is also a well known issue with any anticoagulated population but for cancer it has very striking consequences.

- In the Hokusai and SELECTd trials, the efficacy curve started to split in favor of DOACs after the acute phase (3 months) was finished. While there was less data to analyze in SELECTd, in the Hokusai trial, 10% less patients were still on LMWH compared to edoxaban by the end of the trial.

- Historical data notes a 21%/year risk of recurrent VTE if anticoagulation is inadequate and cancer is still active.

Prandoni P et al. Blood 2002;100:3483-3488
What do patients really think?

Be aware that doctor preference and how we inform our patients can impact patient preference.

Table 4. Relative importance of VTE treatment attributes in % (obtained from the CBC).

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Relative importance in % (Total n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interference with cancer treatment (e.g. requiring postponement of surgery)</td>
<td>39</td>
</tr>
<tr>
<td>Efficacy (risk of new/recurring blood clot)</td>
<td>24</td>
</tr>
<tr>
<td>Risk of major bleeding (e.g. requiring transfusion, hospitalization)</td>
<td>19</td>
</tr>
<tr>
<td>Administration form</td>
<td>13</td>
</tr>
<tr>
<td>Monitoring through blood tests (with potential dose adjustment)</td>
<td>2</td>
</tr>
<tr>
<td>Risk of minor bleeding (e.g. bruising, nose bleeds)</td>
<td>2</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>1</td>
</tr>
</tbody>
</table>
**Duration of anticoagulation**

No trials presently exist specifically addressing duration of anticoagulation in CAT

Risk of recurrent VTE is high if cancer remains active

It is presently recommended that anticoagulation should continue in the absence of contraindications until the cancer is no longer considered active

Prandoni P et al. Blood 2002;100:3483-3488
DALTECAN: Francis CW et al. JTH 2015;13(6):1028-1035
Canadian expert consensus 2018

Cancer-associated thrombosis without contraindication to anticoagulation (both incidental and symptomatic, lower limb DVT and PE)

Risk of bleeding?
(Consider well-documented risk factors for bleeding including GI toxicity [i.e., GI comorbidity, previous GI bleed, treatment associated with GI toxicity], thrombocytopenia [<50,000 platelets/mL], renal impairment [GFR per the Cockcroft-Gault formula of 20-50 mL/min], recent and/or life-threatening bleeding, intracranial lesion and use of antiplatelet agents)

High risk

Active GI or urothelial tumours

Non-high risk

Type of cancer?

Other types, non-active GI/urothelial tumours

Yes

Drug-drug interactions with DOACs based on pharmacist-led pharmacokinetic review?

No

LMWH

DOAC*

Reassess on a regular basis (at least every 3 months or if there are changes in management or patient condition)

Cancer status: still active?

Yes

No

Consider stopping
Bringing the Story to an End
Final Thoughts

Cancer associated thrombosis is common

It carries weight for both the cancer and its treatment as well as the clot and its treatment

With newer anticoagulant regimens now available, the decision process has become more complex and a rational approach is essential

- Be wary of DOACs in GI/urothelial, high bleeding risk cancer patients
- Be wary of drug interactions and the changing course of a cancer patients
- DOACs are an exciting new option for CAT otherwise and may enhance long term compliance
Questions?