The management of venous thromboembolism in patients with cancer

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I have the following potential conflicts of interest to report:

- [x] Consulting: ASPEN, Bayer, BMS, Daiichi-Sankyo, LEO
- [ ] Employment in industry
- [ ] Stockholder of a healthcare company
- [ ] Owner of a healthcare company
- [x] Research support: ASPEN, Bayer, BMS, Daiichi-Sankyo, LEO

- [ ] I do not have any potential conflict of interest
Management of VTE in patients with cancer

- Challenges of Cancer-associated thrombosis (CAT)
- Evidence for LMWH
- Evidence for NOACs
- Guidelines
- Practical implications
In cancer:
- VTE => leading cause of death\(^5\)
- VTE => worsened prognosis\(^5\)
- VTE => up to 20% of cancer patients\(^2\)
- VTE in 50% of cancer pts at autopsy\(^3\)

Malignancy and thrombosis: a double-sided clinical relationship


VTE:
- First sign of cancer\(^5\)
- 20% have active cancer\(^4\)
- VTE - prevention & treatment less effective\(^5\)
VTE Risk Associated with Specific Types of Cancer
Frequencies of Various Types of Cancer

Estimated new cases (US: 2014)

VTE Epidemiology Group Study: Incidence of First VTE in Patients with Active Cancer

Patients with active cancer and a first VTE (N=6592). Active cancer was defined as a primary diagnosis of cancer (excluding non-melanoma skin cancer) as a hospital discharge diagnosis or treatment with radiation, chemotherapy or bone marrow transplantation during hospitalization.

*Patients allocated to different cancer types when ≥2 were recorded on the same day. For some, no cancer type was specified.

The Challenge of CAT: Recurrences and Bleeding During Anticoagulation

**Recurrent VTE**

- **Cancer**
  - Cumulative proportion of recurrent VTE, %
  - HR=3.2
  - 20.7%
  - 6.8%

- **No cancer**
  - Cumulative proportion of recurrent VTE, %
  - HR=3.2
  - 12.4%
  - 4.9%

**Major Bleeding**

- **Cancer**
  - Cumulative proportion of recurrent major bleeding, %
  - HR=2.2
  - 12.4%
  - 4.9%

- **No cancer**
  - Cumulative proportion of recurrent major bleeding, %
  - HR=2.2
  - 4.9%

*Defined as overt and associated with either a decrease in the haemoglobin level (at least 2.0 g/dl) or the need for transfusion (≥2 units of blood), if it was retroperitoneal or intracranial, or if the treatment had to be discontinued permanently.

The Challenge of CAT: Long-term LMWH vs VKA: CLOT Study


VKA = vitamin K antagonist; VTE = venous thromboembolism

<table>
<thead>
<tr>
<th>Days 0–5</th>
<th>Months 2–6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral VKA arm</td>
<td>Dalteparin 200 IU/kg OD</td>
</tr>
<tr>
<td>Dalteparin arm</td>
<td>Oral VKA Target INR 2.5</td>
</tr>
<tr>
<td>Oral VKA arm</td>
<td>Dalteparin ~ 150 IU/kg OD</td>
</tr>
</tbody>
</table>

Bleeding (%)

- Major
- Minor

Risk reduction = 52%  
$p = 0.0017$
NOAC Phase III VTE Trials

Inclusion of Patients with Cancer

- Phase III NOAC trials including more than 30,000 patients

<table>
<thead>
<tr>
<th></th>
<th>No cancer</th>
<th>Cancer</th>
<th>%</th>
<th>NOAC</th>
<th>VKA</th>
<th>Recurrent- VTE</th>
<th>Major bleeding or CRNMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>2.6</td>
<td>4.1</td>
<td>2.01</td>
<td>1.29</td>
<td>3.13</td>
<td>6.1</td>
<td>0.66 (0.38, 1.2)</td>
</tr>
<tr>
<td>No cancer</td>
<td>2.5</td>
<td>2.6</td>
<td>0.98</td>
<td>0.83</td>
<td>1.2</td>
<td>2.5</td>
<td>0.98 (0.83, 1.2)</td>
</tr>
</tbody>
</table>

|                | No cancer | Cancer | %     | NOAC | VKA | Major bleeding or CRNMB | | | |
|----------------|-----------|--------|-------|------|-----|-------------------------|------------------------|
| Cancer         | 7.4       | 15.0   | 1.68  | 0.86 | 3.28| 9.1                      | 0.81 (0.64, 1.02)      |
| No cancer      | 9.1       | 7.4    | 1.68  | 0.86 | 3.28| 9.1                      | 0.81 (0.64, 1.02)      |

### Efficacy and Safety of NOACs vs VKA in the Treatment of CAT

#### Recurrent VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN</td>
<td>0.64 (0.23,1.81)</td>
</tr>
<tr>
<td>Hokusai</td>
<td>0.52 (0.16,1.72)</td>
</tr>
<tr>
<td>RE-COVER</td>
<td>0.78 (0.35,1.76)</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>0.58 (0.14,2.34)</td>
</tr>
<tr>
<td>Combined*</td>
<td>0.66 (0.39,1.11)</td>
</tr>
</tbody>
</table>

#### Major Bleeding Events

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN</td>
<td>0.63 (0.22,1.79)</td>
</tr>
<tr>
<td>Hokusai</td>
<td>1.51 (0.37,6.17)</td>
</tr>
<tr>
<td>RE-COVER</td>
<td>0.82 (0.28,2.38)</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>0.46 (0.09,2.44)</td>
</tr>
<tr>
<td>Combined*</td>
<td>0.78 (0.42,1.44)</td>
</tr>
</tbody>
</table>

*Random effects model*  
Hokusai-VTE-Cancer: Study Design

**Short design:** Multinational, prospective, randomized, open-label, blinded endpoint (PROBE), non-inferiority trial

**Study population:**
Patients with cancer* and acute symptomatic or incidental VTE#

- Treatment ≥ 6 and ≤ 12 months
- Patient characteristics (Edoxaban vs LMWH) comparable
- Thrombocytopenia 50.-100.000/µl: 5,3 %
- Metastases: 53,0 %; ECOG ≥3: 22%
- active anti-cancer treatment: 72,3 %

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* Cancer must be other than basal-cell or squamous cell carcinoma of the skin, be active or diagnosed within 2 years prior to randomization and objectively confirmed. Active cancer was defined as any of the following: diagnosis of cancer within the past 6 months; recurrent, regionally advanced or metastatic disease; currently receiving treatment or having received any treatment for cancer during the 6 months prior to randomization; or a haematological malignancy not in complete remission; #symptomatic or incidental VTE; ‡dose adjustment to 30 mg od in patients with a body weight ≤60 kg or CrCl 30–50ml/min, or concomitant use of P-glycoprotein inhibitors

Hokusai-VTE-Cancer: Primary and Secondary Outcomes

Modified Intention-to-treat population for 12 months (N=1046).
Hokusai-VTE-Cancer: GI-bleeding and cancer type

Patients with GI cancer

Patients with non-GI cancer

Hokusai-VTE-Cancer: GI-bleeding and cancer type

Major GI-Bleeding

- Pancreatic
- Hepatobiliary
- Colorectal
- Stomach: All were not resected
- Esophageal

0% 20% 40% 60% 80% 100%

Upper, Lower, None

Cancer-Associated Thrombosis: LMWHs Versus NOACs*

**Recurrent VTE**

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC Events</th>
<th>NOAC Patients</th>
<th>LMWH Events</th>
<th>LMWH Patients</th>
<th>Weight</th>
<th>Risk ratio M-H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hokusai-VTE-Cancer</td>
<td>34</td>
<td>522</td>
<td>46</td>
<td>524</td>
<td>73.4%</td>
<td>0.74 (0.48, 1.14)</td>
</tr>
<tr>
<td>select-d</td>
<td>8</td>
<td>203</td>
<td>18</td>
<td>203</td>
<td>26.6%</td>
<td>0.44 (0.20, 1.00)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>42</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>100.0%</td>
<td>0.65 (0.42, 1.01)</td>
</tr>
</tbody>
</table>

Total events: 42
Heterogeneity: Tau²=0.02; Chi²=1.21, df=1 (p=0.27), I²=17%
Test for overall effect: Z=1.92 (p=0.06)

**Major bleeding**

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC Events</th>
<th>NOAC Patients</th>
<th>LMWH Events</th>
<th>LMWH Patients</th>
<th>Weight</th>
<th>Risk ratio M-H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hokusai-VTE-Cancer</td>
<td>29</td>
<td>522</td>
<td>17</td>
<td>524</td>
<td>73.5%</td>
<td>1.71 (0.95, 3.08)</td>
</tr>
<tr>
<td>select-d</td>
<td>11</td>
<td>203</td>
<td>6</td>
<td>203</td>
<td>26.5%</td>
<td>1.83 (0.69, 4.86)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>725</td>
<td>727</td>
<td>100.0%</td>
<td>1.74 (1.05, 2.88)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 42
Heterogeneity: Tau²=0.00; Chi²=0.01, df=1 (p=0.91), I²=0%
Test for overall effect: Z=2.17 (p=0.03)

CARAVAGGIO: Study Design
Prospective, randomized, open-label, multicentre study

Treatment period 6 months

- Patients with symptomatic or unsuspected proximal DVT or PE and cancer

N=1170

Apixaban
10 mg bid for 1 week, followed by 5 mg bid for 6 months

Dalteparin
200 IU/kg daily for 1 month, followed by 150 IU/kg for 5 months

Primary outcome: objectively confirmed recurrent VTE occurring during the study period, defined as the composite of proximal DVT of the lower limbs (symptomatic or unsuspected), DVT of the upper limb (symptomatic) and PE (symptomatic or unsuspected)

bid, twice daily; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

Agnelli G et al, Thromb Haemost 2018;118:1668–1678
Management of VTE in patients with cancer

- Challenges of Cancer-associated thrombosis (CAT)
- Evidence for LMWH
- Evidence for NOACs
- Guidelines
- Practical implications
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH should be considered for the first 6 months over VKAs</td>
<td>Ila</td>
</tr>
<tr>
<td>Edoxaban considered as an alternative to LMWH in patients without GI cancer</td>
<td>Ila B</td>
</tr>
<tr>
<td>Rivaroxaban considered as an alternative to LMWH in patients without GI cancer</td>
<td>Ila C</td>
</tr>
<tr>
<td>Extended AC (&gt; 6 mts) considered for indefinite period (or until cancer is cured)</td>
<td>Ila B</td>
</tr>
<tr>
<td>Consider to manage incidental PE in the same manner as symptomatic PE (segmental or multiple subsegmental)</td>
<td>Ila B</td>
</tr>
</tbody>
</table>

ISTH Guidance for Treatment of Cancer-Associated VTE

— NOACs suggested for patients with CAT and **low risk of bleeding** and no DDI with current systemic therapy

— Edoxaban and rivaroxaban are the only NOACs with RCT evidence compared with LMWH in CAT

— LMWH remains acceptable alternative

— LMWH suggested for patients with CAT and **high risk of bleeding**, including:
  - luminal GI cancers with intact primary, or with active GI mucosal abnormalities (duodenal ulcers, gastritis, esophagitis, or colitis…)

— NOACs may be acceptable alternative if no DDI with current systemic Tx

ISTH, International Society of Thrombosis and Haemostasis; LMWH, low molecular weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; VTE, venous thromboembolism
Summary

- Patients with active cancer have a high risk of VTE recurrence
  - Prevalence and incidence of CAT vary by cancer type

- Randomized clinical trials suggest that NOACs are as effective as LMWH for the treatment of CAT to prevent VTE recurrence

- Current clinical guidance/guidelines recommended the use of NOACs and LMWH for treatment of patients with CAT, based on the individual clinical profile and patient preferences

In patients with high risk of bleeding LMWH are preferred over NOACs. NOACS are contraindicated in case of malignant neoplasms at high risk of bleeding.

**NOACs in Treatment of CAT: Treatment matrix**

<table>
<thead>
<tr>
<th>LMWH</th>
<th>Unstable; high bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• E.g. acute leukaemia, active GI/UG lesion, oesophagus/stomach, not resected</td>
<td>• ECOG 4, poor prognosis</td>
</tr>
<tr>
<td>• CrCl &lt;30 ml/min; LFT &gt;3x ULN</td>
<td>• Acute chemotherapy; sepsis; vomiting; mucositis; platelets &lt;50,000 per μl</td>
</tr>
<tr>
<td>• Antiplatelet agent</td>
<td>• Post-surgery &lt;2 weeks</td>
</tr>
<tr>
<td>• CNS neoplasm: primary/metastatic</td>
<td>• DDI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Stable; low bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pancreatic cancer</td>
<td>• Preventive radiotherapy</td>
</tr>
<tr>
<td>• Hepatic/renal cancer</td>
<td>• Chronic chemotherapy</td>
</tr>
<tr>
<td>• Prostate cancer</td>
<td>• No active anticancer treatment; stable disease</td>
</tr>
<tr>
<td>• Thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>• Lung/ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>• Chronic leukaemia</td>
<td></td>
</tr>
<tr>
<td>• Uterine/breast cancer</td>
<td></td>
</tr>
<tr>
<td>• Melanoma</td>
<td></td>
</tr>
</tbody>
</table>

**LMWH vs NOAC: no permanent decision!**

Adjustment to type/phase of malignancy and treatment, patient situation:
- Unstable, chemotherapy, vomiting, thrombocytopenia: NOAC → LMWH
- Stable, low risk for complications and high QoL: LMWH → NOAC

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Thank you very much for your attention!
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10. FRANKFURTER GERINNUNGSSYMPOSIUM

6. - 7. SEPTEMBER 2019
Thank you very much for your attention!