Cancer-associated thrombosis

17th November 2016
Simon Noble
Clinical Professor Palliative Medicine
Cardiff University
Wales, UK
Today

• What is VTE?
• How does CAT differ?
• Initial anticoagulation
• Anticoagulation at 6 months
• New oral agents and cancer
• Patient involvement in decision making
Blood flow to the heart and lungs

Venous clot

Swelling and inflammation below the blockage site

Normal leg  DVT
Saddle PE
Saddle PE

Isolated segmental PE
PE responsible for 10% of deaths in hospital.
Mmmm... A sudden massive PE is a nice way to go!
Post mortem study

- 92 patients where PE identified as cause of death
- 27 (30%) died within 10 minutes of symptoms
- 9 (10%) had no symptoms

Havig (1977)
60% of patients: “gradual deterioration dominated by dyspnoea, tachycardia and fever”

- Correct diagnosis of PE in 10% of cases
- Approximately 2 hours to die
- Treated with diuretics, digoxin, antibiotics
VTE in cancer

- VTE is commonest cause of death in cancer patients undergoing chemotherapy
- VTE is considered to the second leading cause of death in cancer patients
- VTE occurs in ≥ 20% of cancer patient through their lifetime
- VTE may be present in as much as 50% of patients at the time of autopsy series.

Lyman et al JCO 2009;
Lyman et al JCO 2007
Johnson Clin Lab HaemJ 1999
The coagulation pathway

Initiation

Propagation

Clot formation

Fibrinogen ➔ Fibrin
The coagulation pathway

Initiation

Propagation

Clot formation

Inactive factor
Active factor
Transformation
Catalysis

Thrombin

Fibrinogen → Fibrin
The coagulation pathway

Initiation

Propagation

Clot formation

Inactive factor

Active factor

Transformation

Catalysis

Inert factor

Active factor

Transformation

Catalysis

Fibrinogen

Fibrin
Virchow’s triad

- Circulatory stasis
- Endothelial injury
- Hypercoagulable state
Inflammatory Cytokines (TNFα, IL-1) and VEGF

Thrombosis

• Procoagulant molecules
  Tissue factor and others

Cancer

EXTRINSIC FACTORS

Therapies

• Chemotherapy
• Anti-angiogenic
• Hormonal

Platelets

• Surgery
• Central access

• Immobility
• Local stasis
Effect of Malignancy on Risk of Venous Thromboembolism (VTE)

- Population-based case-control (MEGA) study
- N = 3220 consecutive patients with 1st VTE vs. N = 2131 control subjects
- CA patients = 7x OR for VTE vs. non-CA patients

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>0 to 3 months</th>
<th>3 to 12 months</th>
<th>1 to 3 years</th>
<th>5 to 10 years</th>
<th>&gt;15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>28.0</td>
<td>4.9</td>
<td>19.8</td>
<td>53.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Lung</td>
<td>22.2</td>
<td>14.3</td>
<td>3.6</td>
<td>2.6</td>
<td>1.1</td>
</tr>
<tr>
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<td>20.3</td>
<td>3.6</td>
<td>2.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Breast</td>
<td>4.9</td>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
</tr>
</tbody>
</table>

Silver In: The Hematologist - modified from Blom et al. JAMA 2005;293:715.
## Treatment impact on VTE Incidence in Various Tumors

<table>
<thead>
<tr>
<th>Oncology Setting</th>
<th>VTE Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer (Stage I &amp; II) w/o further</td>
<td>0.2%</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
</tr>
<tr>
<td>Advanced cancer (1-year survival=12%)</td>
<td>9%</td>
</tr>
<tr>
<td>High-grade glioma</td>
<td>26%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3-5%</td>
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<td>Renal cell carcinoma</td>
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<tr>
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<td>2%</td>
</tr>
<tr>
<td>Breast cancer (Stage IV) w/ chemo</td>
<td>8%</td>
</tr>
<tr>
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<td>9%</td>
</tr>
<tr>
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TREATMENT OF VTE
• High rate of bleeding in palliative care setting$^1$
• Difficulty controlling INR$^1$
• Multiple drug-drug interactions with commonly used symptom control drugs$^2$
• Impaired quality of life$^3$

2. Noble. Palliative Medicine 2004
3. Noble and Finlay. Palliative Medicine 2004
The CLOT Trial

*Primary outcome: VTE recurrence*

Risk reduction = 52%

HR 0.48 (95% CI 0.30, 0.77)

log-rank $p = 0.002$

NNT = 13

HR = hazard ratio; NNT = number needed to treat; VKA = vitamin K antagonist; VTE = venous thromboembolism

## LMWH vs warfarin meta analysis

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Intervention Events</th>
<th>VKA Events</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOT</td>
<td>0.51 (0.33, 0.79)</td>
<td>27/336</td>
<td>53/336</td>
<td>41.31</td>
</tr>
<tr>
<td>LITE</td>
<td>0.60 (0.23, 1.59)</td>
<td>6/100</td>
<td>10/100</td>
<td>8.37</td>
</tr>
<tr>
<td>Romera</td>
<td>0.61 (0.11, 3.43)</td>
<td>2/36</td>
<td>3/33</td>
<td>2.66</td>
</tr>
<tr>
<td>ONCENOX</td>
<td>0.66 (0.16, 2.74)</td>
<td>4/61</td>
<td>3/30</td>
<td>3.87</td>
</tr>
<tr>
<td>CATCH</td>
<td>0.69 (0.45, 1.07)</td>
<td>31/449</td>
<td>45/451</td>
<td>41.24</td>
</tr>
<tr>
<td>CANTHANOX</td>
<td>0.70 (0.12, 4.09)</td>
<td>2/71</td>
<td>3/75</td>
<td>2.56</td>
</tr>
</tbody>
</table>

Subtotal (I-squared = 0.0%, p = 0.963): 0.60 (0.45, 0.79) 72/1053 117/1025 100.00
Guideline recommendations:

Standard of treatment for cancer-associated thrombosis is three to six months LMWH

(Grade A)

In patients with ongoing active cancer, consideration should be given to indefinite anticoagulation but decision should be made on a case by case basis, taking into consideration bleeding risk and patient preference.

(Grade D)

DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist
What the evidence covers

- Metastatic disease
- Performance status 0-2
- Estimated prognosis > 3 months
- Platelet count >75,000 mm³
- Weight > 40kg
- No active bleeding
Range of disease

- **CLOT:**
  - 65% metastatic

- **Meyer:**
  - 40% not receiving active treatment
  - 50% metastases

- **LITE**
  - 47% metastatic disease
Carrier M, Khorana AA, Zwicker JI, Noble S, Lee AYY
Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH.
*Journal Thromb and Haem* 2013 September; 11(9) 1760-65
Data in palliative care population

- 2 case series describe use of LMWH for treatment of VTE in advanced cancer patients 1,2

- One qualitative study suggests LMWH to be acceptable to palliative care patients 3

- LMWH now drug of choice for cancer associated VTE in palliative care 4

- LMWH does not accumulate over time 5

1. Noble SIR, Hood K, Finlay IG. Palliative Medicine 2007
3. Noble SIR, Finlay IG. Palliative Medicine 2005
5. Kovacs et al T&H 2005
Is LMWH still acceptable?

• Original paper 2005
• Selection bias?
  o LMWH not custom and practice
  o Most interviewed on LMWH due to warfarin failure
• Representative timeframe?
  o On LMWH for a month
  o Same after 6 months?

Study repeated using same methods
  o LMWH for at least 3 months
Major themes

• Symptoms/ experience of VTE “worse than cancer”
  o Impact on cancer journey
  o Impact on ADLs
• LMWH acceptable within context of illness
  o Necessary inconvenience
  o Fear of recurrence
• Adaptive behaviours and routine

Seaman Pat Pref Adh (2014)
What evidence is there to guide management beyond 6 months?
Effect of Malignancy on Risk of Venous Thromboembolism (VTE)

- Population-based case-control (MEGA) study
- N = 3220 consecutive patients with 1st VTE vs. N = 2131 control subjects
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<th>Adjusted odds ratio</th>
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<td>Hematological</td>
<td>28.0</td>
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<tr>
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<td>20.3</td>
</tr>
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<td>Breast</td>
<td>4.9</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>19.8</td>
</tr>
</tbody>
</table>

- Time since cancer diagnosis
  - 0 to 3 months: 53.5
  - 3 to 12 months: 14.3
  - 1 to 3 years: 3.6
  - 5 to 10 years: 2.6
  - >15 years: 1.1

Silver In: The Hematologist - modified from Blom et al. JAMA 2005;293:715.
• Prospective observational safety study of dalteparin at 6 and 12 months anticoagulation for CAT

• 334 patients enrolled,
  • 55.4% (155) completed 6 months of therapy
  • 33% (109) completed 12 months.

CAT = cancer-associated thrombosis

**Major bleeding rate per month**

- Months 1–6: 1.7%
- Months 7–12: 0.7%

**Total VTE recurrence rate**

- Months 1–6: 8.7%
- Months 7–12: 4.1%

- 116 deaths
  - 105 due to cancer
  - 4 due to recurrent PE
  - 2 due to hemorrhage

PE = pulmonary embolism; VTE = venous thromboembolism

Daltecans Efficacy and safety of long-term therapy

- Bleeding was not increased in Months 6–12 compared to Months 2–6.

VTE = venous thromboembolism

What data can guide us?

• CLOT subgroup analysis

• Independent risk factors of VTE recurrence:
  o Lung cancer (HR, 3.51; 95% CI, 1.62–7.62)
  o Metastases (HR, 2.59; 95% CI, 1.29–5.60)

• Lower risk
  o Breast cancer (HR, 0.59; 95% CI, 1.62–7.62)

CI = confidence interval; HR = hazard ratio; VTE = venous thromboembolism

Lee AY et al. J Clin Oncol 27:499s 2009 (suppl abstract 9565)
Risk Model for Recurrent VTE in CAT

**The Ottawa score**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.59</td>
<td>1</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>0.94</td>
<td>1</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>-0.76</td>
<td>-1</td>
</tr>
<tr>
<td>TNM Stage I</td>
<td>-1.74</td>
<td>-2</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>Clinical probability: Low (≤0)</td>
<td></td>
<td>-3 – 0</td>
</tr>
<tr>
<td>Clinical probability: High (≥1)</td>
<td></td>
<td>1 – 3</td>
</tr>
</tbody>
</table>

• Outcome:
  • Patients with a score <0 had a low risk of recurrence: **5.1%**
  • Patients with a score of 0 had an intermediate risk of recurrence: **9.8%**
  • Patients with a score ≥1 had a high risk of recurrence: **15.8%**

• Results have not been fully validated

Louzada ML *et al.* Circulation 2012.

TNM = tumor, node, metastases; VTE = venous thromboembolism
Recurrent VTE Risk in Active Cancer
*Population-based cohort Olmstead County*

- 477 patients with active cancer and VTE (eligible between 1966 and 2000)

**Cumulative Incidence of First VTE Recurrence**

**Multivariate Predictors of VTE Recurrence**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV pancreatic cancer</td>
<td>6.38</td>
<td>2.69, 15.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>4.57</td>
<td>2.07, 10.09</td>
<td>0.0002</td>
</tr>
<tr>
<td>Myeloproliferative or myelodysplastic disorder</td>
<td>3.49</td>
<td>1.59, 7.68</td>
<td>0.002</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>3.22</td>
<td>1.57, 6.59</td>
<td>0.001</td>
</tr>
<tr>
<td>Stage IV cancer (non pancreas)</td>
<td>2.85</td>
<td>1.74, 4.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>2.73</td>
<td>1.63, 4.55</td>
<td>0.0001</td>
</tr>
<tr>
<td>Neurological disease with leg paresis</td>
<td>2.38</td>
<td>1.14, 4.97</td>
<td>0.02</td>
</tr>
<tr>
<td>Cancer stage progression</td>
<td>2.14</td>
<td>1.30, 3.52</td>
<td>0.003</td>
</tr>
<tr>
<td>Warfarin therapy</td>
<td>0.43</td>
<td>0.28, 0.66</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; VTE = venous thromboembolism
## Factors influencing decision whether to extend anticoagulation in CAT

<table>
<thead>
<tr>
<th>Factor</th>
<th>Favors continuing anticoagulation</th>
<th>Favors stopping anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient preference</td>
<td>• ¹⁰ concern recurrence</td>
<td>• ¹⁰ concern hemorrhage</td>
</tr>
<tr>
<td>Malignancy specific</td>
<td>• Active malignancy</td>
<td>• No evidence of disease</td>
</tr>
<tr>
<td></td>
<td>• High risk cancer e.g., lung</td>
<td>• Low risk cancer e.g., breast</td>
</tr>
<tr>
<td></td>
<td>• Ongoing chemo or ESA</td>
<td></td>
</tr>
<tr>
<td>Previous history of VTE</td>
<td>• Yes</td>
<td>• No</td>
</tr>
<tr>
<td>Nature of initial VTE</td>
<td>• Life-threatening PE</td>
<td>• Non life-threatening PE</td>
</tr>
<tr>
<td></td>
<td>• DVT with severe postphlebitic syndrome</td>
<td>• No residual symptoms</td>
</tr>
<tr>
<td>Risk of hemorrhage</td>
<td>• No</td>
<td>• Yes</td>
</tr>
<tr>
<td>Additional risk factors</td>
<td>• Obesity</td>
<td>• Risk factors other than malignancy when diagnosed e.g., surgery</td>
</tr>
<tr>
<td></td>
<td>• Sex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Poor performance status</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Central venous catheter</td>
<td></td>
</tr>
</tbody>
</table>

¹⁰ = primary; CAT = cancer-associated thrombosis; DVT = deep vein thrombosis; ESA = erythropoiesis stimulating agent; PE = pulmonary embolism

Can we use DOACs yet?
DOAC Pharmacology

**Dabigatran etexilate**
- Hydrolysis
- Bioavailability: 3-7%
- CrCL<30 mL/min: Contraindicated/not recommended:
- \( t_{1/2} = 12–17\) h
- \( \sim 20\% \)

**Rivaroxaban**
- Cyp3A4, Cyp2J2
- Healthy/young
  - \( t_{1/2} = 5–9\) h
- Elderly
  - \( t_{1/2} = 11–13\) h
- Severe hepatic disease: contraindicated
- CrCL<30 mL/min: not recommended:
- \( \sim 65\% \)
- \( \sim 35\% \)

**Apixaban**
- Cyp3A4: minor
- \( t_{1/2} = 12\) h
- Bioavailability: 50%
- \( \sim 73\% \)
- CrCL<30 mL/min: use with caution

**Edoxaban**
- Cyp3A4: minor
- \( t_{1/2} = 9–11\) h
- Bioavailability: 62%
- \( \sim 27\% \)
- \( \sim 50\% \)
- CrCL<15 mL/min: not recommended

Adapted from: Heidbuchel H *et al*. Europace 2013; U.S., Canadian Prescribing Information  CrCl = creatinine clearance
# Oral direct IIa and Xa inhibitors

<table>
<thead>
<tr>
<th></th>
<th>dabigatran</th>
<th>rivaroxaban</th>
<th>apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>IIa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td>$t^{1/2}$</td>
<td>12-17 h</td>
<td>9 h</td>
<td>12 h</td>
</tr>
<tr>
<td>Dose / frequency</td>
<td>150mg bd</td>
<td>20mg od</td>
<td>5mg bd</td>
</tr>
<tr>
<td></td>
<td>110mg bd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal clearance</td>
<td>85%</td>
<td>33%</td>
<td>27%</td>
</tr>
<tr>
<td>Peak</td>
<td>2 h</td>
<td>2-4 h</td>
<td>2-4 h</td>
</tr>
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</table>
DOACs in the treatment of CAT

Recurrent VTE

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>VKA Events</th>
<th>VKA Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI Year</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-Cover I and II</td>
<td>10</td>
<td>173</td>
<td>12</td>
<td>162</td>
<td>48.4%</td>
<td>0.78 [0.35, 1.76] 2009</td>
<td>0.78 [0.35, 1.76]</td>
</tr>
<tr>
<td>Einstein-DVT</td>
<td>4</td>
<td>118</td>
<td>5</td>
<td>89</td>
<td>19.3%</td>
<td>0.60 [0.17, 2.18] 2010</td>
<td>0.60 [0.17, 2.18]</td>
</tr>
<tr>
<td>Einstein-PE</td>
<td>2</td>
<td>114</td>
<td>3</td>
<td>109</td>
<td>10.2%</td>
<td>0.64 [0.11, 3.74] 2012</td>
<td>0.64 [0.11, 3.74]</td>
</tr>
<tr>
<td>Hokusai</td>
<td>4</td>
<td>109</td>
<td>7</td>
<td>99</td>
<td>22.2%</td>
<td>0.52 [0.16, 1.72] 2013</td>
<td>0.52 [0.16, 1.72]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>514</td>
<td>459</td>
<td>100%</td>
<td></td>
<td></td>
<td>0.66 [0.38, 1.17]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>20</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.94, df = 3 (P = 0.95); I^2 = 0%
Test for overall effect: Z = 1.42 (P = 0.16)

Pooled incidence rates: 4.1% (2.6–6.0) for DOACs
6.1% (4.1–8.5) for VKAs [RR 0.66 (0.38–1.2)]

Recurrent VTE warfarin
Lee A et al. 2003: 16%
Meyer G et al. 2002 17%

Major bleeding or CR-NMB

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<td>20</td>
<td>152</td>
<td>29.5%</td>
<td>1.10 [0.63, 1.92] 2009</td>
<td>1.10 [0.63, 1.92]</td>
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<tr>
<td>Einstein-DVT</td>
<td>17</td>
<td>118</td>
<td>14</td>
<td>88</td>
<td>21.5%</td>
<td>0.91 [0.47, 1.74] 2010</td>
<td>0.91 [0.47, 1.74]</td>
</tr>
<tr>
<td>Einstein-PE</td>
<td>14</td>
<td>114</td>
<td>10</td>
<td>108</td>
<td>15.5%</td>
<td>1.33 [0.62, 2.66] 2012</td>
<td>1.33 [0.62, 2.66]</td>
</tr>
<tr>
<td>Hokusai</td>
<td>20</td>
<td>100</td>
<td>25</td>
<td>99</td>
<td>33.6%</td>
<td>0.73 [0.43, 1.22] 2013</td>
<td>0.73 [0.43, 1.22]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>74</td>
<td>69</td>
<td>100%</td>
<td></td>
<td></td>
<td>0.94 [0.70, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>500</td>
<td>447</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.03, df = 3 (P = 0.57); I^2 = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

### Drug-Drug Interactions with DOACs

**Chemotherapeutic agents and immunosuppressants**

<table>
<thead>
<tr>
<th>Interaction effect*</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases DOAC plasma levels†</td>
<td>P-glycoprotein</td>
<td>P-glycoprotein CYP3A4</td>
<td>P-glycoprotein CYP3A4</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Cyclosporine</td>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Tacrolimus</td>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Tamoxifen</td>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Lapatinib</td>
<td>Lapatinib</td>
<td></td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Nilotinib</td>
<td>Nilotinib</td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Sunitinib</td>
<td>Sunitinib</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>Imatinib</td>
<td>Imatinib</td>
<td></td>
</tr>
<tr>
<td>Reduces DOAC plasma levels‡</td>
<td>Dexamethasone</td>
<td>Dexamethasone</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Doxorubicin</td>
<td>Doxorubicin</td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Vinblastine</td>
<td>Vinblastine</td>
<td></td>
</tr>
</tbody>
</table>

*Clinicians should consult pharmacist; †Drugs that inhibit P-GP or CYP3A4 can increase DOAC levels; ‡Drugs that induce P-GP or CYP3A4 can lower DOAC levels.

CYP3A4 = cytochrome P450 3A4; DOAC = direct oral anticoagulant

Around one third of patients are currently treated with oral medication for their VTE.

### Administration of medication (%)

- **Tablet**
  - Total: 30%
  - Germany: 50%
  - Other: 10%

- **Injection under the skin**
  - Total: 70%
  - Germany: 50%
  - Other: 90%*

- **Other**
  - Total: 0%
  - Germany: 0%
  - Other: 0%

*Significant difference to Germany

**Base:** all respondents  
**Multiple answers**
Interference with cancer treatment is the most important attribute to patients, followed by efficacy of VTE therapy.

Relative importance of attributes* - Total

- Efficacy: 24%
- Risk of minor bleeding: 1%
- Risk of major bleeding: 2%
- Administration form: 39%
- Interference with cancer treatment: 19%
- Frequency of administration: 13%
- Monitoring through blood test: 2%

*n = 100

* Impact / weight of each attribute on the overall preference / choice behavior
When asked directly, patients allocate almost the same importance to efficacy and interference with cancer treatment.

**Direct importance of characteristics for treatment decision (means)**

*Base: all respondents*

*Multiple answers*

*Please distribute 100 points in total to the features according to their importance*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Total n = 100</th>
<th>German n = 50</th>
<th>British n = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>32</td>
<td>38*</td>
<td>27</td>
</tr>
<tr>
<td>Risk of minor bleeding</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Risk of major bleeding</td>
<td>7</td>
<td>7*</td>
<td>6</td>
</tr>
<tr>
<td>Administration form</td>
<td>28</td>
<td>24</td>
<td>33*</td>
</tr>
<tr>
<td>Interference with cancer treatment</td>
<td>4</td>
<td>2</td>
<td>6*</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>4</td>
<td>6*</td>
<td>6*</td>
</tr>
<tr>
<td>Monitoring through blood tests</td>
<td>4</td>
<td>2</td>
<td>6*</td>
</tr>
</tbody>
</table>

*Significant difference to UK / Germany*
Current guidelines recommend LMWH for the treatment of patients with cancer and VTE.

There are four active phase III trials of direct Xa inhibitors vs. LMWH that should be completed in the next 2–3 years.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparator</th>
<th>Study design elements</th>
<th>1° Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban(^1,2)</td>
<td>Dalteparin</td>
<td>Outcomes measured after both 6 months and 12 months of therapy</td>
<td>Composite of recurrent VTE and major bleeding</td>
</tr>
<tr>
<td>Rivaroxaban(^3)</td>
<td>Dalteparin</td>
<td>After randomization of active therapy for 6 months, patients are randomized to rivaroxaban vs. placebo for a further 6 months</td>
<td>Recurrent VTE</td>
</tr>
<tr>
<td>Rivaroxaban(^4)</td>
<td>Any LMWH</td>
<td>Randomized for 3 months</td>
<td>Patient-reported treatment satisfaction</td>
</tr>
<tr>
<td>Apixaban(^5)</td>
<td>Dalteparin</td>
<td>Randomized for 6 months</td>
<td>Safety</td>
</tr>
</tbody>
</table>

LMWH = low molecular weight heparin; VTE venous thromboembolism.

• Patients place great reliance on their doctors advice regarding treatment of CAT.¹

• Discussing options with patients should include:
  o Strength of evidence
  o Potential benefits
  o Potential complications

CAT = cancer-associated thrombosis

So is there any role for DOACs in cancer now?

• Efficacy of LMWH most marked in first 3 months
The CLOT Trial

Primary outcome: VTE recurrence

Risk reduction = 52%

HR 0.48 (95% CI 0.30, 0.77)

log-rank $p = 0.002$

NNT = 13

HR = hazard ratio; NNT = number needed to treat; VKA = vitamin K antagonist; VTE = venous thromboembolism

So is there any role for DOACs in cancer now?

- Efficacy of LMWH most marked in first 3 months
- No studies have demonstrated superiority after 6 months
- Arguably, one can justify any of the anticoagulants
• At six months (if patient warrants indefinite anticoagulation)
• DOAC if
  o Patient wants to stop injections
  o Not receiving chemo
  o Renal function satisfactory

CAT = Cancer-associated thrombosis
When the evidence is lacking:

- Management should be guided by an appreciation of
  - Pathophysiology of CAT
  - Thrombogenicity of respective cancer
  - Thrombogenicity of respective chemotherapy
  - Bleeding risks
  - Patient views

CAT = Cancer-associated thrombosis
THANKYOU