Cancer Associated thrombosis: 6 months and beyond

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National Thrombosis Week
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Risk Factors for cancer associated thrombosis

CANCER RELATED
- Tumour site/ type
- Stage
- Histology
- Time since diagnosis

PATIENT FACTORS
- Age
- High BMI
- Co-morbidities
- Performance status

TREATMENT RELATED
- Chemotherapy
- Immunotherapy
- Hormonal treatments
- Radiation
- Surgery
- Indwelling vascular access
## Guideline recommendations

<table>
<thead>
<tr>
<th></th>
<th>BCSH 2015</th>
<th>ASCO 2013</th>
<th>NICE CG144 2012</th>
<th>ESMO 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial/Acute Treatment</strong></td>
<td>LMWH  Consider oral agent if not tolerated</td>
<td>LMWH for initial 5-10 days if CrCl &gt;30 mL/min</td>
<td>LMWH</td>
<td>LMWH for &gt;5 days</td>
</tr>
<tr>
<td><strong>Long-term Treatment</strong></td>
<td>LMWH  Consider oral agent if not tolerated</td>
<td>LMWH – 1st line VKA (INR 2-3) as alternative</td>
<td>LMWH</td>
<td>LMWH or oral agent</td>
</tr>
<tr>
<td><strong>Duration of Treatment</strong></td>
<td>Minimum 6 months  Extend if active cancer</td>
<td>Minimum 6 months  Extend if metastatic disease or chemotherapy</td>
<td>6 months</td>
<td>Minimum 6 months  Extend if metastatic disease or chemotherapy</td>
</tr>
</tbody>
</table>
Current recommendations

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)

Which patients?
Which agent?
What dose?
What drawbacks?
Patient AB

- 65 year old gentleman
- Oesophageal carcinoma with local node involvement
- Starts pre-operative chemotherapy: ECX
- Incidental PE diagnosed 1 month after starting chemotherapy: treated with Dalteparin 200 iu/kg for 1 month then 150 iu/kg
- Has oesophagectomy, successful resection, good recovery
- Further ECX chemotherapy

- After 6 months Dalteparin, patient is receiving chemotherapy
- Subsequent scans have shown ‘complete resolution’ of the thrombus

- Patient wants to know whether to continue dalteparin?
Patient DE

- 45y female
- Breast carcinoma, with nodal involvement
- Treated with chemotherapy and surgery
- Patient had a proximal DVT during chemotherapy
- Has completed 6 months of dalteparin, cancer successfully resected
- Oncologists want to start tamoxifen
- Does she need secondary prevention?
- Which agent?
What evidence is there to guide management beyond 6 months?
Incidence of VTE recurrence

- The risk of VTE recurrence after stopping anticoagulant therapy depends on the VTE risk factors associated with the initial thrombosis

<table>
<thead>
<tr>
<th>Risk factors (first VTE)</th>
<th>Annual rate of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient/reversible risk factors</td>
<td>~ 3%</td>
</tr>
<tr>
<td>(eg, surgery)</td>
<td></td>
</tr>
<tr>
<td>Continuing risk factors</td>
<td>≥ 10%</td>
</tr>
<tr>
<td>(eg, cancer)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>≥ 10%</td>
</tr>
<tr>
<td>(unprovoked)</td>
<td></td>
</tr>
</tbody>
</table>

Kearon C. Circulation 2003;107:I22-I30.\[^9\]
### Prediction Models for VTE recurrence

<table>
<thead>
<tr>
<th>Model name</th>
<th>Vienna prediction model</th>
<th>DASH score</th>
<th>Rodger or men continue and HER DOO2 score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>929</td>
<td>1,818</td>
<td>646</td>
</tr>
<tr>
<td>Design</td>
<td>Prospective cohort study</td>
<td></td>
<td>Prospective cohort study</td>
</tr>
<tr>
<td>Predictive variables</td>
<td>Male &gt; female, PE &gt; proximal DVT &gt; distal DVT, elevated d-dimer after AC</td>
<td>Patient-level meta-analysis</td>
<td>Men continue. Hyperpigmentation (1 point), Edema (1 point), Redness (1 point), d-dimer ≥250 µg/L during AC (1 point). Obesity (BMI ≥30 kg/m²) (1 point). Old (age ≥65 years) (1 point)</td>
</tr>
<tr>
<td>Total score</td>
<td>0 to 350</td>
<td>-2 to 4</td>
<td>0 to 6</td>
</tr>
<tr>
<td>Annual risk of recurrence</td>
<td>2%–15% depending on total score (nomogram)</td>
<td>Score of ≤1: 3.1%</td>
<td>Women with score of ≤1: 1.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Score of 2: 6.4%</td>
<td>Women with score of ≥2: 14.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Score of ≥3: 12.3%</td>
<td>Men: 13.7%</td>
</tr>
</tbody>
</table>

**Abbreviations:** DVT, deep vein thrombosis; VTE, venous thromboembolism; AC, anticoagulation; BMI, body mass index; PE, pulmonary embolism.

**BUT**

Limited validation studies

Are these scores relevant to cancer patients?
Prediction models for VTE in cancer

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Risk Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of cancer</td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy platelet count $\geq 350,000/mm^3$</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin level $&lt;100$ g/L or use of red cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count $&gt;11,000/mm^3$</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index $\geq 35$ kg/m$^2$</td>
<td>1</td>
</tr>
</tbody>
</table>

*High-risk score $\geq 3$; intermediate-risk score $= 1–2$; low-risk score $= 0$.


"RISK OF VTE:"

- Score 0 = 0.5%
- Score 1–2 = 2%
- Score $\geq 3$ = 7%

Only validated for initial VTE event and not recurrent events after 6 months of chemotherapy
What data can guide us?

CLOT Study: randomised LMWH vs warfarin in patients with CAT subgroup analysis

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

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

Lee AY et al. J Clin Oncol 27:499s 2009 (suppl abstract 9565)
Recurrent VTE Risk in Active Cancer
Population-based cohort Olmstead County

Cumulative Incidence of First VTE Recurrence

- 477 patients with active cancer and VTE (eligible between 1966 and 2000)
- Highest risk amongst pancreatic cancer, CNS tumours, ovarian, lung and any metastatic tumour
- Warfarin reduced recurrence: Hazard ratio 0.43 (0.28-0.66)

### 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 et al, Circulation 2012
Role of residual vein thrombosis

P=0.175

- 242 patients with residual vein thrombosis
  - (non-compressibility of 40% vein diameter)
- Randomly assigned to further 6 month LMWH
- 15% vs 22% recurrence in 12 month follow up
- Absence of residual vein thrombosis: 2.8% recurrence off anticoagulation
- Residual vein thrombosis NOT a useful tool for deciding to continue anticoagulation

Cancer treatment and thrombosis

Hormonal therapies:
- oestrogen receptor modulators (tamoxifen)
- Progestins
- Aromatase inhibitors
- Thalidomide analogs
- Cisplatin
- Anti-angiogenic agents and growth factor inhibitors
DALTECAN: Efficacy and safety of long-term therapy

334 patients enrolled assessing dalteparin at 6 (55%) or 12 months (33%)

- 116 deaths: 105 cancer; 4 recurrent PE; 2 haemorrhage

DALTECAN: *Efficacy and safety of long-term therapy*

- Bleeding was not increased in Months 6–12 compared to Months 2–6.
Feasibility study
RCT to explore anticoagulation > 6 months in those with ongoing cancer

Qualitative component
- Willingness of patients to be randomised
- Willingness of clinicians to recruit

Deemed not feasible

DATA STILL LACKING AND HARD TO OBTAIN.....
Direct Oral anticoagulants

Subgroup analysis: non-inferior to warfarin with respect to recurrent VTE
Direct oral anticoagulants: bleeding

Clinically Relevant Bleeding

Major bleeding

Guy’s and St Thomas’ NHS Foundation Trust
What can we learn from our patients?

- Symptomatic CAT is a distressing experience\(^1\)
- Patients are given insufficient information about risks of CAT during chemotherapy\(^2\)
- LMWH injections acceptable within context of illness\(^1\)
- Develop habits and rituals to normalize daily injections\(^2\)

CAT = cancer-associated thrombosis; LMWH = low molecular weight heparin
An ideal anticoagulant for patients in order of preference

1. Least interference with cancer treatments
2. Lowest thrombosis recurrence rate
3. Minimal bleeding risk
4. Oral
5. Once a day
6. No need for monitoring

Noble S et al Haematologica 2015.
There is limited evidence on which to make decisions

- Prior thrombosis, severity, recurrence on anticoagulation
- Thrombogenicity of cancer
- Thrombogenicity of treatments: chemotherapy, immunotherapy, hormone therapy
- Bleeding risks: tumour type; concurrent illness
- Patient views
## 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>• 1° concern recurrence</td>
<td>• 1° 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>
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</tbody>
</table>
Patient AB

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- Oesophageal carcinoma with local node involvement
- Starts pre-operative chemotherapy: ECX
- Incidental PE diagnosed 1 month after starting chemotherapy: treated with Dalteparin 200 iu/kg for 1 month then 150 iu/kg
- Has oesophagectomy, successful resection, good recovery
- Further ECX chemotherapy

- After 6 months Dalteparin, patient is receiving chemotherapy
- Subsequent scans have shown ‘complete resolution’ of the thrombus
- Patient wants to know whether to continue dalteparin?

Outcome: Patient continued with prophylactic dalteparin dose

Stopped once completed chemotherapy and confirmed cancer in remission
No further thrombosis
Patient BC

- 45y female
- Breast carcinoma, with nodal involvement
- Treated with chemotherapy and surgery
- Patient had an intracardiac thrombosis during chemotherapy, possibly due to line

- Has completed 6 months of dalteparin, cancer successfully resected
- Oncologists want to start tamoxifen

- Does she need secondary prevention?
- Which agent?

- **OUTCOME**: Patient chose to take rivaroxaban 20mg as secondary prevention until tamoxifen complete
Thanks for listening

- Questions and thoughts?