Cancer Associated Thrombosis:
six months and beyond

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Disclosure

I have no disclosure
The Challenge of Anticoagulation in Patients with Venous Thromboembolism and Cancer

Risk of events in patients receiving anticoagulation therapy for VTE

Recurrent VTE

- Cancer: HR=3.2, cumulative proportion 20.7% at 12 months
- No cancer: cumulative proportion 6.8% at 12 months

Major bleeding*

- Cancer: HR=2.2, cumulative proportion 12.4% at 12 months
- No cancer: cumulative proportion 4.9% at 12 months

*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.

Prandoni P et al, Blood 2002;100:3484–3488
The CLOT Investigators Trial

Cancer patients with acute DVT or PE (n=677)

**Control Group**
- Dalteparin 200 IU/kg OD
- Vitamin K antagonist (INR 2.0 to 3.0) x 6 mo

**Experimental Group**
- Dalteparin 200 IU/kg OD x 1 month
- then ~150 IU/kg OD x 5 mo

5 to 7 days
1 month
6 months

CLOT Study: Reduction in Recurrent VTE

Risk reduction = 52%
p-value = 0.0017

CATCH STUDY: Phase 3, randomised, controlled, multi-centre Tinzaparin Vs VKA.

Patients with a diagnosis of active cancer and symptomatic and objectively confirmed DVT (N=900)

- Tinzaparin 175 anti-Xa IU/kg body weight
- Warfarin + initial (5 to 10 days)
- Tinzaparin (until INR in target)

11 scheduled Clinic Visits:
- Screening Visit – up to 72 hours before randomisation
- Visit 1-3 - every 14 days
- Visit 4-9 - once a month
- Visit 10 - Follow-up visit, 1 month after end-of-study visit

All patients interviewed in between clinic visits by telephone

CATCH STUDY: Results

- **Symptomatic DVT**: 12 patients (2.7%) in the Tinzaparin arm and 24 (5.3%) in the warfarin arm (HR 0.48 [95% CI 0.24–0.96]; \(P=0.04\)).

- **Symptomatic non-fatal PE**: 3 patients in the Tinzaparin arm and 2 in the warfarin arm (and 2 incidental VTE in warfarin arm).

- **Fatal PE**: 17 (3.8%) patients in each arm (HR 0.96 [95% CI 0.49–1.88]; \(P=0.90\)).

- **No difference in major bleeding events** (n=13 [2.7%] in the Tinzaparin arm and 12 [2.4%] in the warfarin arm).

- Significantly less **clinically relevant non-major bleeding** with Tinzaparin than warfarin (50 [11%] and 73 [16%] patients, respectively; \(P=0.004\), HR 0.58).

CATCH: Recurrent VTE in the tinzaparin and warfarin groups

[Graph showing cumulative incidence over days in trial for tinzaparin and warfarin groups]

### Guideline Recommendations for the Treatment of CAT

<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **ESMO 2011**  | - LMWH recommended for long-term (6 months) anticoagulant therapy  
                    - Recommendations for duration of therapy depend on the type of cancer, stage of disease and cancer treatment |
| **ACCP 2016**  | - LMWH preferred over VKA or DOAC therapy  
                    - There is no preference towards VKAs, dabigatran, rivaroxaban, apixaban or edoxaban  
                    - Extended therapy (>3 months) recommended over 3 months of therapy |
| **ESC 2014**   | - LMWH should be considered for the first 3–6 months  
                    - LMWH or VKAs should be considered for extended anticoagulation beyond the first 3–6 months |
| **ASCO 2015**  | - LMWH recommended over UFH for the first 5–10 days  
                    - LMWH preferred over VKAs for the first 6 months of treatment. VKAs are an acceptable alternative if LMWH is not available  
                    - For extended anticoagulation (beyond 6 months) LMWH or VKAs may be considered for selected patients with active cancer  
                    - Use of DOACs is not currently recommended for patients with cancer and VTE owing to limited data |

*Updated ASCO guidelines were published in 2015; reassessment of available new data did not prompt any changes from the 2013 recommendations; such as those with metastatic disease or receiving chemotherapy*

Evidence for treating beyond 6 month
Treatment and 2° Prevention of VTE in Cancer

ASCO: Extended anticoagulation with LMWH or VKA may be considered beyond 6/12 for patients with metastatic disease or patients who are receiving chemotherapy.

Length of secondary prophylaxis?

LONGHEVA NCT01184770 - Warfarin vs LMWH (+6 m)

ALICAT ISRCTN37913976 - LMWH vs No anticoagulant (+6 m) - Funded by HTA NIHR

Failed Feasibility - Trial Closed without achieving endpoint -

Failed to Recruit - Downscaled to a Registry
Clinical Question
• Does extending anticoagulation therapy with dalteparin in cancer-associated VTE beyond 6 months have an acceptable safety and adherence profile?

Methods
• Single-arm prospective multi-centre phase IV study (cohort study)
• Determined incidence rates of bleeding and recurrent VTE at month 1, months 2-6, and months 7-12 following enrolment

Duration of therapy
• 185 (55.4%) completed 6 months of therapy
• 109 (32.6%) completed 12 months of therapy
• Mean duration: 210 days

Subjects:
Patients with active cancer and newly diagnosed VTE

Baseline
Dalteparin 200 IU/kg daily sc

Month 1

Month 6
Dalteparin 150 IU/kg daily sc

Month 12

Safety and Efficacy of Long-Term LMWH Therapy: The DALTECAN Study

Recurrent VTE

![Graph showing incidence of recurrent VTE over different months.]

Major bleeding events

![Graph showing incidence of major bleeding events over different months.]

LMWH, low molecular weight heparin; VTE, venous thromboembolism

Safety and Efficacy of Long-Term LMWH Therapy: The DALTECAN Study

Recurrent VTE

- Incidence of new or recurrent VTE: 11.1% (1.4% per patient-month)
- 154 (46.1%) patients died, 115 during the study period (4/115 due to VTE, 2/115 due to bleeding

Major bleeding events

- Incidence of Major Bleeding Events 1.9% per patient month through the whole study (12 months)

Conclusions:

i. Risk of major bleed was greatest in first month of therapy and decreased over the following 11 months.

ii. Risk of VTE recurrence was greatest in first month of therapy and decreased over the following 11 months.

iii. Dalteparin beyond 6 months is not associated with increased bleeding compared to initial period of therapy.

iv. Adherence to dalteparin was high (96% over entire cohort).

Safety and Efficacy of Long-Term LMWH Therapy: The TiCAT Study

Design
- Prospective, multicentre, cohort study in patients with cancer-associated VTE treated with tinzaparin therapy (N=247)
- Objective: to evaluate the rate of clinically relevant bleeding events (major and non-major) and recurrent VTE with short-term versus long-term therapy

Duration of therapy
- 198 (80.2%) completed 6 months of therapy
- 136 (55.1%) completed 12 months of therapy
- Mean duration: 15.6 ± 13.2 months

LMWH, low molecular weight heparin; VTE, venous thromboembolism
Safety and Efficacy of Long-Term LMWH Therapy: The TiCAT Study

Recurrent VTE

Major bleeding events

LMWH, low molecular weight heparin; VTE, venous thromboembolism

Any Predictors for VTE recurrence?

■ Retrospective analysis using the Olmstead county database
■ Development of risk adaptive models- Ottawa Prognostic Score
■ The Cancer DACUS study
■ Biomarker Analyses of the CATCH trial
■ RIETE registry

Relevant studies
Risk of VTE Recurrence May Depend on Tumour Type, Stage of Disease and Co-morbidities

Cumulative incidence of first VTE recurrence

- Active cancer without predictors
- Active cancer with predictors
- Other secondary VTE

Population-based cohort study performed using the Olmstead county database; 477 patients (1533 person-years of follow-up) with cancer and VTE were identified
Chee CE et al, Blood 2014;123:3972–3978

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>

- A total of 139 recurrences were identified with an estimated 10-year cumulative rate of **28.6%**
- Highest recurrence risk in first month of treatment
Extended Treatment of VTE in Cancer Associated Thrombosis: Predicting the Risk of Recurrence

### Ottawa prognostic score for recurrent VTE risk in CAT¹

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>Points</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>0.40</td>
<td>1</td>
</tr>
</tbody>
</table>

- **Clinical probability low**: score ≤0 (-3–0)
- **Clinical probability high**: score ≥1 (1–3)

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*Retrospective analysis of 419 adult patients with VTE and concomitant active cancer from a multicentre observational cohort study (2001–2010)

Tissue Factor As a Predictor of Recurrent Venous Thromboembolism in Malignancy: Biomarker Analyses of the CATCH Trial

- CATCH- multicentre RCT that investigated Tinzaparin or dose adjusted warfarin for 6 month.
- 805 patients had had sample for TF assay.
- Patients in the highest quartile of TF experienced the greatest VTE recurrence (> 64.6 pg/mL; 38 [19%] of 203 patients v 34 [6%] of 602 patients; relative risk, 3.3; 95% CI, 2.1 to 5.1; P < .001).

Subdistributional hazard ratios (SHRs; and 95% CIs) in the combined competing risk regression model.

Alok A. Khorana; Pieter W. Kamphuisen; Guy Meyer; Rupert Bauersachs; Mette S. Janas; Mikala F. Jarner; Agnes Y.Y. Lee; JCO 2017, 35, 1078-1085. DOI: 10.1200/JCO.2016.67.4564
Long-term Management of VTE in Cancer Patients: The Cancer-DACUS Study

Pure DVT study (No PE)
Long-term Management of VTE in Cancer Patients: The Cancer-DACUS Study

Nadroparin maintained at 75% dose. BD regimen
Extended Treatment in Cancer Associated Thrombosis: Challenges in the Real World

RIETE Registry: Duration of anticoagulant therapy by risk factors for VTE

DOAC for CAT

?For how long
**Hokusai VTE - Cancer Study Design**

**Objectively Confirmed VTE**
- Stratified randomization for
  - Bleeding Risk
  - Dose Adjustment
- PROBE design
- **114 sites** North America, Europe, Australia, New Zealand

Day 0
- Dalteparin 200 IU/kg

Day 30
- Dalteparin 150 IU/kg

Month 12
- LMWH
  - Edoxaban 60mg QD*

N: ~1000
N: ~500
N: ~500
Hokusai VTE Cancer Recurrent VTE and Major Bleeding – 12 Months

A

B

SELECTeD: Study Design (1)
Randomized, Open-Label, Multi-Centre, Pilot trial

Population:
Active cancer with symptomatic DVT and/or any PE
ECOG PS ≤2

Rivaroxaban 15 mg bid for 21 days then 20 mg od

Dalteparin 200 IU/kg od s.c. for the 30 days then
150 IU/kg od

N=530

6 months

Young A et al, ASH 2017; Abstract 625; Available at: http://www.clinicaltrialresults.org/; select-d protocol. https://warwick.ac.uk/fac/med/research/ctu/trials/cancer/select-d/select-d_protocol_v2.0_09-apr-2013.pdf [accessed 21 Mar 2018]
SELECTeD: Study Design (2)

Population: PE index event or residual CUS DVT at ~5 months

N=300

Rivaroxaban

Population: No residual CUS DVT at ~5 months

Placebo

No treatment

6 months

12 months

Aug. 2016. Second randomization closed n=92 patients

VTE recurrence

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin (n=203)</th>
<th>Rivaroxaban (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE recurrences within 6 months, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT or PE</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Other location</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6-month VTE recurrence rate, % (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-month lower limb DVT or PE recurrence rate</td>
<td>11% (7–16%)</td>
<td>4% (2–9%)</td>
</tr>
<tr>
<td></td>
<td>9% (6–15%)</td>
<td>3% (1–7%)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td>0.43 (0.19-0.99)</td>
</tr>
</tbody>
</table>

SELECTeD
### Major bleeds

<table>
<thead>
<tr>
<th>Months from trial entry</th>
<th>Dalteparin (n=203)</th>
<th>Rivaroxaban (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
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</tbody>
</table>

- **Major bleed**, n
  - Dalteparin: 6
  - Rivaroxaban: 11

- **6 month major bleed rate, % (95% CI)**
  - Dalteparin: 4% (2-8%)
  - Rivaroxaban: 6% (3-11%)

- **Hazard ratio major bleeds (95% CI)**
  - 1.83 (0.68-4.96)

*1 fatal bleed in each arm*

### Numbers at Risk:

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers at Risk</td>
<td>203</td>
<td>203</td>
</tr>
<tr>
<td>Months from trial entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>176</td>
<td>147</td>
</tr>
<tr>
<td>1</td>
<td>172</td>
<td>149</td>
</tr>
<tr>
<td>2</td>
<td>176</td>
<td>147</td>
</tr>
<tr>
<td>3</td>
<td>172</td>
<td>149</td>
</tr>
<tr>
<td>4</td>
<td>176</td>
<td>147</td>
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<tr>
<td>5</td>
<td>172</td>
<td>149</td>
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<tr>
<td>6</td>
<td>176</td>
<td>147</td>
</tr>
</tbody>
</table>

SELECTeD
<table>
<thead>
<tr>
<th></th>
<th>Hokusai-VTE-Cancer¹</th>
<th>select-d²-⁴</th>
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</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Non-inferiority</td>
<td>Randomized pilot</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>Active cancer</td>
<td>Active cancer</td>
</tr>
<tr>
<td><strong>Rx</strong></td>
<td>LMWH 5 days edoxaban po od</td>
<td>Rivaroxaban po od</td>
</tr>
<tr>
<td></td>
<td>Dalteparin s.c. od</td>
<td>Dalteparin s.c. od</td>
</tr>
<tr>
<td></td>
<td>6 months and up to 12 months</td>
<td>6 months and second randomization</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Composite of recurrent VTE or major bleeding</td>
<td>Primary: recurrent VTE Secondary: major bleeding and CRNM bleeding</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>1050</td>
<td>406</td>
</tr>
<tr>
<td><strong>Results</strong> (difference % between NOAC and LMWH)</td>
<td>Recurrent VTE: 3.4% in favour of edoxaban</td>
<td>Recurrent VTE: 7.0% in favour of rivaroxaban</td>
</tr>
<tr>
<td></td>
<td>Major bleeding: 2.9% in favour of dalteparin</td>
<td>Major bleeding: 2.0% in favour of dalteparin</td>
</tr>
<tr>
<td>Median duration of treatment: 211 days for edoxaban and 184 days for dalteparin, ( p=0.01 )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Real World Data
Higher Persistence on Index Therapy in Cancer Patients Using Rivaroxaban or Warfarin versus LMWH

*Discontinuation was defined as a gap of no more than 60 days between the end of the days of supply of a dispensing and the start date of he next dispensing of the index therapy, if any.

Higher Risk of Discontinuation of Index Therapy on LMWH versus Rivaroxaban or Warfarin

<table>
<thead>
<tr>
<th>Drug</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>0.38</td>
<td>0.32–0.46</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.33</td>
<td>0.28–0.38</td>
<td></td>
</tr>
<tr>
<td>LMWH</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Risk of discontinuation with rivaroxaban or warfarin versus LMWH

Favours rivaroxaban or warfarin

Favours LMWH

• **Warfarin** is still the most commonly used anticoagulant.

• **Rivaroxaban** is as commonly used as LMWH despite guideline recommendation

• Patients on **LMWH** had significantly lower persistence and shorter duration

• Patients initiating on **oral agents** are at significantly lower risk to discontinue therapy relative to LMWH
Inconveniences of Long-Term LMWH Therapy

- Reluctance of patients to have a drug injected parenterally beyond the first weeks
- Reluctance of physicians to prescribe such an expensive therapy beyond the first weeks
- Country-based regulations that may not reimburse LMWH treatment beyond the initial treatment

LMWH, low molecular weight heparin
Kearon C et al, Chest 2016;149:315–352; Author’s opinion
To conclude -

- Current guidelines are expected to change.
- Data that may help to individualize treatment is still lacking and risk adaptive models are not validated.
- Evidence for both LMWH and DOAC identifies the first month to be at greatest risk for recurrent VTE and major bleed.
- Not much difference in the rate composite outcome of recurrent venous thromboembolism or major bleeding between DOAC and LMWH.
Thank you