MANAGEMENT OF CANCER ASSOCIATED THROMBOSIS

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A 67-year-old man receiving palliative chemotherapy for metastatic colon carcinoma is admitted to the acute medical assessment unit complaining of dyspnea and pleuritic chest pain.

He undergoes a CT pulmonary angiogram (CTPA) which confirms a pulmonary embolism.
Questions?

1. Why did this occur?
2. What is the influence in patient’s prognosis?
3. What is the optimal management of this patient?
4. Should this patient be managed differently if this were an incidental finding?
5. Could this have been prevented?
Question 1

Why did this occur?
THE LEGACY OF ARMAND TROUSSEAU

Cancer and Venous Thromboembolism (VTE)

Professor Armand Trousseau
*Lectures in Clinical Medicine*

(1801–1867)

“I have always been struck with the frequency with which cancerous patients are affected with **painful edema** of the superior or inferior extremities…”

New Syndenham Society – 1865

Armand Trousseau first described this finding in the **1860s**; he later found the same sign in himself, was subsequently diagnosed with **gastric cancer** and died soon thereafter.

Clinique Medicale de l'Hotel-Dieu de Paris. 1865;3.
Of all cases of VTE:
- About 20% occur in cancer patients

Of all cancer patients:
- 20% will have symptomatic VTE
- 50% have VTE at autopsy

Compared with patients without cancer:\(^2\)
- Higher risk of first and recurrent VTE (3.2-fold)
- Higher risk of bleeding on anticoagulants (2.2-fold)
- Higher risk of dying (2.2-fold)
- VTE is the second leading cause of death in cancer
- Incidence of Cancer Associated Thrombosis (CAT) increasing

Patients with cancer approximately 19.8%

All patients with VTE and PE

Incidence of VTE in patients hospitalised with cancer increasing significantly compared with non-cancer patients\(^2,3\)

VIRCHOW'S TRIAD IN CANCER PATIENTS

- Prolonged bed rest – patient immobility
- Surgical procedures
- Extrinsic compression of blood vessels by tumour
- Increased blood viscosity
- Direct invasion by tumour
- Prolonged use of CVC
- Endothelial damage by chemotherapy
- Effect of tumour cytokines on vascular endothelium

Changed blood composition

- More procoagulation factors due to hypoxia and/or inflammation
- Microparticles with Tissue Factor
- Pro angiogenic factors
- Increase in overall platelet activity
- Decrease in anticoagulant activities
- Decrease in fibronolytic activity

RISK FACTORS

- Primary Site
- Histology
- Grade
- Initial period

Cancer-related

- Platelet counts
- Leukocyte counts
- Hemoglobin
- Tissue factor
- D-dimer
- P-selectin
- Thrombin generation potential

Treatment-related

- Surgery/hospitalisation
- Chemotherapy
- Anti-angiogenics
- CVCs
- ESA/transfusions

Patient-related

- Age
- Ethnicity
- Comorbidities

Biomarkers

Khorana presentation in HeSMO Conference 2017, Athens
RISK FOR VTE BY TYPE OF MALIGNANCY

Fold increase in risk vs. patients without malignancy

- ENT: 1.6
- Prostate: 2.2
- Cervix: 2.9
- Ovarian: 3.1
- Skin: 3.8
- Breast: 4.9
- Kidney: 6.2
- Brain: 6.7
- Other: 6.9
- GI: 20.3
- Lung: 22.2
- Haematological: 28.0

VTE WITHIN 2 YEARS OF DIAGNOSIS OF 5 DIFFERENT TYPES OF CANCER (235,149 cancer cases)

Regional-stage disease at the time of diagnosis

Metastatic-stage disease at the time of diagnosis

Reproduced with permission from Arch Intern Med 2006;166(4):458-464. Copyright 2006 American Medical Association. All rights reserved
Patients with cancer have a 4- to 6-fold increased risk for VTE

Risk factor assessment is an ongoing process

Unprovoked VTE may be the earliest sign of cancer

Up to 10% of patients will be diagnosed with cancer in the year after

More than 60% of occult cancers are diagnosed shortly after the diagnosis of unprovoked VTE

The incidence rate of cancer diagnosis returns to the rate in the general population after 1 year
The pathogenesis of a prothrombotic state in cancer involves:

- Production of procoagulants by tumour cells
- Suppression of fibrinolytic activity
- Platelet activation

There is a close link between malignant transformation, tumour angiogenesis, metastasis and thrombosis
Cancer-mediated hypercoagulability occurs as a consequence of direct activation of procoagulant pathways by cancer cells (mediated by aberrant tumour cell TF expression, release of tumour cell-derived, TF-expressing microparticles, cancer procoagulant and other cell surface proteases) or from indirect systemic effects of cancer on a variety of cell types, including leucocyte, endothelial cells and platelets.

In various malignancies, neutrophils are “primed” to release their contents in the form of NETs, resulting in direct activation of procoagulant pathways, platelet activation and inhibition of naturally occurring anticoagulant pathways, including tissue factor pathway inhibitor. As a consequence of these various direct and indirect mechanisms, patients with cancer have an elevated risk for venous thromboembolism.
Tissue factor (TF), a transmembrane glycoprotein, is a procoagulant expressed by tumour cells.

Over expression of TF spontaneously releases microparticles into the bloodstream and these microparticles are procoagulant.

TF induces production of vascular endothelial growth factor (VEGF) in human tumour cells, independently of its ability to activate factor Xa-catalysed conversion of prothrombin.
CANCER CELLS EXERT A PROCOAGULANT ACTIVITY IN THEIR MICROENVIRONMENT

The TF–VIIa complex and factor Xa are among the known activators of G-protein-coupled protease-activated receptor-2 (PAR-2) in tumour cells, while the TF–VIIa–Xa complex and thrombin efficiently activate PAR-1.

Both PARs have been implicated in signalling pathways leading to angiogenesis and metastasis.

The genetic mechanism responsible for malignant transformation, such as oncogene activation (RAS or MET), or tumour suppressor gene inactivation (P53 or PTEN), also directly induces the expression of genes regulating haemostasis.
Plasminogen activator inhibitor-1 is a potent inhibitor of the fibrinolytic system, promoting tumour growth and angiogenesis.

Proinflammatory cytokines such as tumour necrosis factor, interleukin-1, interleukin-6 and interferons activate coagulation.

Platelet P-selectin leads to platelet aggregation and platelet-rich thrombus formation.

Chemotherapy induces endothelial cell activation, leading to increased TF expression, elevated levels of plasma von Willebrand factor and factor VIII coagulant protein, and decreased level of antithrombin and protein C and S.
THROMBOSIS AND CANCER

Question 2

What is the influence in patient’s prognosis?

A blood clot in the pulmonary artery

Image: Medical Images RM / STEVE OH, MS CMI
WHY YOU SHOULD CARE

VTE and mortality

- Thrombo-embolism: 9%
- Infection: 9%
- Respiratory failure: 4%
- Bleeding: 1%
- Aspiration: 1%
- Other: 6%
- Unknown: 4%
- Cancer progression: 71%

2\textsuperscript{nd} leading cause of death in cancer patients

- Accounts for 9\% of deaths\textsuperscript{1}
- Associated with early mortality during chemotherapy (HR=6.98)\textsuperscript{2}
- 47-fold increased risk of mortality from VTE\textsuperscript{1}

VTE and mortality

VTE is an independent risk factor for mortality very early during the first 4 cycles chemotherapy in cancer patients of all stages.

*K Adjusted for major confounders: Age, gender, race, cancer type, stage, year of therapy, chemotherapy type and dose intensity, major laboratory abnormalities, PS, BMI, and comorbid conditions

WHAT IS THE RISK FOR DEATH IN PATIENTS WITH VTE AND MALIGNANCY?

- An analysis of >1.2 million US Medicare (age ≥65) patients admitted to the hospital with a malignancy

**Cumulative probability of death within 183 days of initial hospitalisation by cohort**

HOW COMMON IS RECURRENT VTE IN PATIENTS WITH CANCER?

Medicare hospital discharge data
- 46,848 cases with DVT/PE
- 1,211,944 admissions for malignancy
- 8,177,634 admissions for nonmalignant disease

Cumulative probability of re-admission with DVT/PE within 183 days of initial hospitalisation

THROMBOSIS AND CANCER

Question 3

What is the optimal management of this patient?
AIMS OF VTE TREATMENT

Prevention of acute and chronic complications:
- Fatal PE
- Thrombus extension and embolisation
- Early and late recurrences of VTE

Anticoagulation is the cornerstone of VTE treatments!
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

Probability of recurrent VTE (%)

Days Post Randomization

0% 5% 10% 15% 20% 25%

VKA

Dalteparin

15.8%
8.0%

NNT, number needed to treat; VKA, vitamin K antagonist
### THE CLOT TRIAL

#### Results: Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin N=338</th>
<th>VKA N=335</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed</td>
<td>19 (5.6%)</td>
<td>12 (3.6%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Associated with death</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Critical site*</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Transfusion of ≥2 units of RBC</td>
<td>14</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>or drop in Hb ≥2 g/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any bleed</td>
<td>46 (13.6%)</td>
<td>62 (18.5%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Intracranial, intraspinal, pericardial, retroperitoneal, intra-ocular, intra-articular

CATCH STUDY

Results: Incidence of VTE recurrence

HR 0.65 (95% CI 0.41, 1.03)
p=0.07
Risk Reduction = 35%

Warfarin  
\( n = 451 \)  
10.5%

Tinzaparin  
\( n = 449 \)  
6.9%

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## CATCH STUDY

### Bleedings

<table>
<thead>
<tr>
<th>Bleeding event</th>
<th>Tinzaparin</th>
<th>Warfarin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>2.9%</td>
<td>2.7%</td>
<td>No difference</td>
</tr>
<tr>
<td>Non-major bleeding</td>
<td>11.1%</td>
<td>16.2%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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META-ANALYSIS

LMWH better than VKA for the long term treatment

8 randomised control trials

- Statistically significant reduction in VTE (HR = 0.47; 95% CI 0.32, 0.71)
- No difference in bleeding (RR = 0.91; 95% CI 0.64, 1.31)
- No survival benefit (HR = 0.96; 95% CI 0.81, 1.14)

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014

Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines

International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer
Chronic management:
- LMWH is preferred for the first six months as monotherapy without warfarin in patients with proximal DVT or PE and prevention of recurrent VTE in patients with recurrent or metastatic cancer

Duration of anticoagulation:
- Minimum time of 3 months
- For non-catheter-associated DVT or PE recommended indefinite anticoagulation while cancer is active, under treatment or if risk factors for recurrence persist.
VENOUS THROMBOEMBOLISM PROPHYLAXIS AND TREATMENT IN PATIENTS WITH CANCER

- LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE who does not have severe renal impairment
- For long-term anticoagulation, LMWH for at least 6 months is preferred because of improved efficacy over VKAs
- Anticoagulation with LMWH or VKA beyond the initial 6 months may be considered for selected patients with active cancer, such as those with metastatic disease or those receiving chemotherapy
- Use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not recommended at this time
GUIDANCE FOR MANAGING PATIENTS BEYOND 6 MONTHS

Indefinite anticoagulation while cancer is active, under treatment, or if risk factors for recurrence persist

<table>
<thead>
<tr>
<th></th>
<th>Favours Continuing Anticoagulation</th>
<th>Favours Stopping Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient preference</strong></td>
<td>Primary concern is recurrence</td>
<td>Primary concern is hemorrhage</td>
</tr>
<tr>
<td><strong>Malignancy specific</strong></td>
<td>Active malignancy</td>
<td>No evidence of disease</td>
</tr>
<tr>
<td></td>
<td>Ongoing chemotherapy or ESA</td>
<td>Lower-risk diagnosis (eg, breast cancer)</td>
</tr>
<tr>
<td></td>
<td>High-risk diagnosis (e.g., lung cancer)</td>
<td></td>
</tr>
<tr>
<td><strong>Previous history of VTE</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Nature of initial VTE</strong></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><strong>Increased risk for hemorrhage</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Additional risk factors</strong></td>
<td>Obesity</td>
<td>Risk factors other than malignancy present when VTE diagnosed (eg, recent 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>

*Extrapolated in part from unprovoked non–cancer-related VTE; †Before development of cancer-associated VTE.
MANAGEMENT OF RECURRENCE

For patients already on anticoagulation

- If the patient is on sub-therapeutic dose of warfarin, change the dose to achieve a target INR of 2–3. If INR is therapeutic, switch from warfarin to LMWH
- If the patient is on LMWH, check anti-factor Xa level at 4 hours since last dose
- If the peak anti-factor Xa level is sub-therapeutic (<0.5 units), adjust dose of LMWH to achieve a peak anti-factor Xa level of 0.5–1.5 units
- If the peak anti-factor Xa level is therapeutic, then increase the dose of LMWH by 20%
- If the anti-factor Xa level is therapeutic and the patient is symptomatic from VTE, then consider IVC filter
DO DIRECT FACTOR XA OR IIA INHIBITORS HAVE A ROLE IN CANCER-ASSOCIATED VTE?

Apixaban, rivaroxaban, and dabigatran approved for

- the prevention of VTE during major orthopedic surgery
- the prevention of stroke in atrial fibrillation

Rivaroxaban for the treatment of VTE
DIRECT ORAL ANTICOAGULANTS (DOACs)

- DOACs are now approved by the US Food and Drug Administration and European Medicines Agency for selected indications in VTE prevention and treatment, but are not routinely recommended in cancer patients. These agents inhibit activated factor X (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran etexilate).

- The major concerns about DOACs in cancer patients include unpredictable absorption and higher risk of GI bleeding in patients with mucositis, inability to measure the anticoagulant activity by using standard assays, potential interaction with hormonal and chemotherapeutic agents, altered metabolism in patients with renal dysfunction or hepatic metastasis, and lack of antidote when patients are actively bleeding.
The DOACs, including the direct factor IIa inhibitor dabigatran and the factor Xa inhibitors apixaban, rivaroxaban, and edoxaban, are being investigated for use in cancer patients.

These agents offer many benefits over traditional anticoagulants, including no requirement for laboratory monitoring, feasibility of oral administration and a reduced risk for food-drug interactions.

All three agents have received regulatory approval for the treatment of acute VTE in the general population, but there remains a paucity of data on the efficacy and safety of these agents in patients with cancer and European regulatory authorities have advised against the use of apixaban for the treatment of cancer-associated VTE.
A recent meta-analysis evaluated 9 RCTs and included 2,310 patients treated with DOACs.

This analysis demonstrated a reduction in recurrent VTE in patients treated with LMWH compared with those receiving warfarin (RR, 0.52; 95% CI, 0.36–0.74).

Conversely, compared with warfarin, DOACs were not associated with a significant reduction in recurrent VTE (RR, 0.66; 95% CI, 0.39–1.11).

In this study, LMWH was associated with a nonsignificant increase in major bleeding (RR, 1.06; 95% CI, 0.5–2.23), whereas DOACs showed a nonsignificant decrease (RR, 0.78; 95% CI, 0.42–1.44).

Overall, in light of the paucity of data demonstrating the safety and efficacy of these agents in cancer patients and lack of appropriate control arms, current published consensus guidelines do not recommend their use in patients with cancer.
## NOVEL ANTICOAGULANTS (NOACs) TRIALS: OUTCOMES IN CANCER PATIENTS

### Prespecified subgroup analyses

<table>
<thead>
<tr>
<th>NOAC Trial</th>
<th>Patients with active cancer</th>
<th>Recurrent VTE</th>
<th>Clinically</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EINSTEIN-DVT</strong></td>
<td>Rivaroxaban = 6.8%</td>
<td>Rivaroxaban = 3.4%</td>
<td>Rivaroxaban = 14.4%</td>
</tr>
<tr>
<td></td>
<td>VKA = 5.2%</td>
<td>VKA = 5.6%</td>
<td>VKA = 15.9%</td>
</tr>
<tr>
<td><strong>EINSTEIN-PE</strong></td>
<td>Rivaroxaban = 4.7%</td>
<td>Rivaroxaban = 1.8%</td>
<td>Rivaroxaban = 12.3%</td>
</tr>
<tr>
<td></td>
<td>VKA = 4.5%</td>
<td>VKA = 2.8%</td>
<td>VKA = 9.3%</td>
</tr>
<tr>
<td><strong>EINSTEIN-EXT</strong></td>
<td>Rivaroxaban = 4.5%</td>
<td>Not reported</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>VKA = 4.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AMPLIFY</strong></td>
<td>Apixaban = 2.5%</td>
<td>Not reported</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>VKA = 2.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AMPLIFY-EXT</strong></td>
<td>Placebo = 2.2%</td>
<td>Not reported</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Apixaban 2.5 mg = 1.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apixaban 5 mg = 1.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RE-COVER</strong></td>
<td>Dabigatran = 5.0%</td>
<td>Dabigatran = 3.1%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>VKA = 4.5%</td>
<td>VKA = 5.3%</td>
<td></td>
</tr>
<tr>
<td><strong>RE-MEDY</strong></td>
<td>Dabigatran = 4.2%</td>
<td>Dabigatran = 3.3%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>VKA = 4.1%</td>
<td>VKA = 1.7%</td>
<td></td>
</tr>
<tr>
<td><strong>HOKUSAI-VTE</strong></td>
<td>Edoxaban = 2.6%</td>
<td>Edoxaban = 3.7%</td>
<td>Edoxaban = 18.3%</td>
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<tr>
<td></td>
<td>VKA = 2.4%</td>
<td>VKA = 7.1%</td>
<td>VKA = 25.3%</td>
</tr>
</tbody>
</table>

---

## DOACs INTERACTIONS WITH ANTICANCER THERAPIES

<table>
<thead>
<tr>
<th>Interaction effect*</th>
<th>Dabigatran P-glycoprotein</th>
<th>Rivaroxaban P-glycoprotein CYP3A4</th>
<th>Apixaban P-glycoprotein CYP3A4</th>
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</thead>
<tbody>
<tr>
<td>Increases DOAC plasma levels†</td>
<td></td>
<td></td>
<td></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>
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<tr>
<td>Tamoxifen</td>
<td>Tamoxifen</td>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td>Lopatinib</td>
<td>Lopatinib</td>
<td>Lopatinib</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>Taxol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduces DOAC plasma levels§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Dexamethasone</td>
<td>Dexamethasone</td>
<td></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>

†Inhibitors of pgp transport and CYP3A4 pathway; §Inducers-lower DOAC levels.
## INJECTABLE ANTICOAGULANTS DIFFERENTIATION

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Average molecular weight (Daltons)</th>
<th>Manufacturing process</th>
<th>Mode of action/activity</th>
<th>Anti-Xa activity neutralised (%)</th>
<th>Dosing</th>
<th>Use in renal insufficiency</th>
<th>CAT long term treatment indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>6.000</td>
<td>Chemical cleavage - nitrous acid</td>
<td>FXa&gt;FlHa 1000/384 IUs</td>
<td>74</td>
<td>Prophylaxis: OD Treatment: OD</td>
<td>Dose adjustment</td>
<td>Yes</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>6.500</td>
<td>Enzymatic cleavage - heparinase</td>
<td>FXa&gt;FlHa 1000/500 IUs</td>
<td>86</td>
<td>Prophylaxis: OD Treatment: OD</td>
<td>CrCl &gt;30 ml/min No accumulation &gt;20 ml/min can be used</td>
<td>Yes</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4.500</td>
<td>Chemical cleavage - alkaline</td>
<td>FXa&gt;FlHa 1000/233 IUs</td>
<td>54</td>
<td>Prophylaxis: OD Treatment: BID</td>
<td>CrCl &lt;30 ml/min Dose adjustment CrCl 30-80 ml/min Clinical surveillance</td>
<td>No (Only initial treatment -10 days SmPC)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>1.700</td>
<td>Synthetic</td>
<td>FXa only</td>
<td>-</td>
<td>Prophylaxis: OD Treatment: OD</td>
<td>CrCl 20-50 ml/min Dose reduction by 50%</td>
<td>No</td>
</tr>
</tbody>
</table>
Should this patient be managed differently if this were an incidental finding?
WHAT IS THE TRUE BURDEN OF VTE IN MEDICAL ONCOLOGY
Medical oncology versus other settings

60–70% of fatal PE detected post-mortem are not suspected or diagnosed\(^1,2\)

Fatal PE is the leading cause of sudden death among hospitalised patients and contributes to up to 10% of in-hospital deaths\(^3\)

---

INCIDENTAL VTE

VTE that was diagnosed on a CT scan performed for another reason than the clinical suspicion of VTE, usually for tumour staging or to assess the response to chemotherapy.

Recommendations: Treat incidental VTE as symptomatic VTE

135 pancreatic cancer patients / 1,151 radiologic exams

35% experienced VTE

Multivariate analysis / all associated with mortality

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>25; 10, 63</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>8.9; 2.5, 31.7</td>
<td>p=0.007</td>
<td></td>
</tr>
<tr>
<td>Incidental visceral events</td>
<td>2.6; 1.6, 4.2</td>
<td>p=0.0001</td>
<td></td>
</tr>
</tbody>
</table>

WHETHER SYMPTOMATIC OR INCIDENTAL, VTE IS STRONGLY ASSOCIATED WITH WORSENED MORTALITY

CLINICAL OUTCOME OF PATIENTS WHO WERE INCIDENTALLY DIAGNOSED WITH AND TREATED FOR PE

Cumulative risk of recurrent PE

Kaplan-Meier cumulative survival curve

12-month: **13.3%** in the incidental PE group and **16.9%** in the symptomatic

12-month mortality rate **52.9 vs. 53.3%**

EFFECT OF INCIDENTAL AND SYMPTOMATIC VTE ON OVERALL SURVIVAL

- Incidental VTE vs. no VTE (23.4 months vs. 45.8 months; HR, 2.4; 95% CI, 1.2-4.9; P=0.01)
- Incidental VTE vs. symptomatic VTE (HR, 1.2; 95% CI, 0.4-2.0; P=0.7)

Reprinted from Clinic Lung Cancer 14(6), Connolly GC, et al., Prevalence and clinical significance of incidental and clinically suspected venous thromboembolism in lung cancer patients, 713–8. Copyright 2013, with permission from Elsevier
Question 5

Could this have been prevented?

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INCIDENCE AND PREDICTORS OF VTE

Among ambulatory high-risk cancer patients undergoing chemotherapy in the United States

A large, contemporary, real-world analysis

N=17,284 and an age/sex-matched, non cancer control cohort were evaluated
Cancers: bladder, colorectal, lung, ovary, pancreas, or gastric cancers

<table>
<thead>
<tr>
<th></th>
<th>Cancer cohort n=2170</th>
<th>Controls n=237</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE over 12 months after the initiation of chemotherapy</td>
<td>12.6%</td>
<td>1.4%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Incidence range: from 8.2% for bladder cancer to 19.2% for pancreatic cancer

INCIDENCE OF VTE IN AMBULATORY CANCER PATIENTS UNDERGOING CHEMOTHERAPY

<table>
<thead>
<tr>
<th>VTE / 2.4 months</th>
<th>VTE/month</th>
<th>VTE /cycle</th>
<th>Cumulative rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.93%</td>
<td>0.8%</td>
<td>0.7%</td>
<td>2.2% (1.7, 2.8)</td>
</tr>
</tbody>
</table>

# CHEMOTHERAPY INDUCED THROMBOSIS

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Contribution to the risk</th>
<th>VTE events rate or RR/Incidence</th>
</tr>
</thead>
</table>
| Cisplatin/platinum based      | - Elevated von Willebrand factor (vWF) levels  
- Release of procoagulant endothelial microparticles                                                                                                                                                                      | ↑ Events 18.1%                  |
| L-asparaginase (lymphoblastic leukaemia) | - Depletion of key proteins in the regulation of the coagulation pathway  
- Synthesis of plasminogen and antithrombin (AT) is markedly impaired with asparaginase-based therapy                                                                                                             | ↑ Incidence 4.2%                |
| 5-Fluorouracil (5FU)           | - Depletion of protein C and increased thrombin activity  
- Endothelial cell damage with the potential to promote thrombus formation                                                                                                                                              | ↑ Incidence (15%) – if combined with hematopoietic G-SFE (29%) |
| Tamoxifen and Aromatase Inhibitors |                                                                                                                                                                                                                     | ↑ Risk 2.8% – if Tamo+chemo RR 15.5 |

PATIENTS WITH VTE DURING CHEMOTHERAPY HAD SIGNIFICANTLY WORSE PFS AND OS

227 patients
Locally advanced or metastatic pancreatic cancer

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>2.6 mo</td>
<td>5.1 mo</td>
</tr>
<tr>
<td>HR</td>
<td>3.04 (95% CI 2.12, 4.36; P&lt;0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>4.4 mo</td>
<td>9.9 mo</td>
</tr>
<tr>
<td>HR</td>
<td>1.95 (95% CI 1.32, 2.87; P=0.0008)</td>
<td></td>
</tr>
</tbody>
</table>

OBSERVATIONAL STUDY

Greater rates of VTE than reported in clinical trials

The United States IMPACT health care claims database

**27479 patients on chemotherapy**

The risk of VTE increases progressively

No plateau or reduction in VTE within 12 months of starting chemotherapy

Lyman GH, et al., Oncologist 2013;18(2):1321–9. Reproduced with permission of JOHN WILEY & SONS JOURNALS in the format Use in an e-coursepack via Copyright Clearance Center
VTE PROPHYLAXIS FOR AMBULATORY CANCER PATIENTS

- Surgical oncology patient:
  - Out of hospital primary VTE prophylaxis is recommended for up to 4 weeks post operation for high risk abdominal or pelvic cancer surgery patients.

- Medical oncology patient:
  - Multiple myeloma patients (high and low risk)
  - Other patients, no routine VTE prophylaxis recommended outside of a clinical trial setting (consider patient conversation about risks and benefits of VTE prophylaxis in the Khorana score ≥3 patient population).

## KHORANA PREDICTIVE MODEL FOR CHEMOTHERAPY-ASSOCIATED VTE

Data from the Awareness of Neutropenia in Chemotherapy (ANC) Study Group Registry

<table>
<thead>
<tr>
<th>Patient characteristic</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, gynaecologic, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy platelet count $\geq 350 \times 10^9$/L</td>
<td>1</td>
</tr>
<tr>
<td>Haemoglobin level $&lt;100$g/L or use of red cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count $&gt;11 \times 10^9$/L</td>
<td>1</td>
</tr>
<tr>
<td>BMI 35 kg/m² or more</td>
<td>1</td>
</tr>
</tbody>
</table>

0 points = low risk
1–2 points = intermediate risk
≥3 points = high risk

## PROPHYLAXIS IN DIFFERENT CLINICAL SETTINGS

<table>
<thead>
<tr>
<th>Thromboprophylaxis</th>
<th>Decrease in the incidence of all VTEs</th>
<th>Prophylaxis</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative VTE(^1)</td>
<td>5.6% ➔ 2.6%</td>
<td>Extended vs. conventional</td>
<td>40</td>
</tr>
<tr>
<td>Hospitalised patients(^2)</td>
<td>5.0% ➔ 2.8%</td>
<td>LMWH vs. no</td>
<td>45</td>
</tr>
<tr>
<td>Outpatients on therapy(^3)</td>
<td>3.9% ➔ 2.0%</td>
<td>LMWH vs. no</td>
<td>50–60</td>
</tr>
<tr>
<td>Outpatients on therapy at high risk (Khorana ≥3)(^4)</td>
<td>21% ➔ 12%</td>
<td>LMWH vs. no</td>
<td>12–15</td>
</tr>
</tbody>
</table>

## OUTPATIENT PROPHYLAXIS ON CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Patient population</th>
<th>ASCO(^1)</th>
<th>ESMO(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All outpatients</td>
<td>Routine prophylaxis not recommended</td>
<td>Routine prophylaxis not recommended</td>
</tr>
<tr>
<td>Myeloma, receiving IMiD-based regimens</td>
<td>Aspirin or LMWH for low-risk and LMWH for high-risk patients is recommended</td>
<td>Consider LMWH, aspirin, or adjusted-dose warfarin (INR≈1.5)</td>
</tr>
</tbody>
</table>
| High-risk outpatients                                    | **Consider LMWH prophylaxis on a case-by-case basis in highly selected** outpatients with solid tumours on chemotherapy  | **Consider in high-risk ambulatory cancer patients.**  
**Predictive model** may be used to identify patients clinically at high risk for VTE |

---

Routine thromboprophylaxis is not recommended in cancer outpatients

Based on limited RCT data, clinicians may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumours receiving chemotherapy

Consideration of such therapy should be accompanied by a discussion with the patient about the uncertainty concerning benefits and harms as well as dose and duration of prophylaxis in this setting

Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients
SHOULD PATIENTS WITH CANCER RECEIVE ANTICOAGULATION FOR VTE PROPHYLAXIS WHILE HOSPITALISED?

Data from the National Hospital Discharge Survey (US)

(P<0.001)

Change in incidence of VTE over time in hospitalised cancer and non-cancer patients

VTE is associated with nearly a doubling in the risk for death among cancer patients.

Retrospective cohort study conducted using data from over 66,000 adult neutropenic cancer patients (88,000 hospitalisations).

3% to 12% depending on the type of malignancy experienced VTE during their first hospitalisation.

Khorana AA, et al., J Clin Oncol 2006;24:484–90. Reprinted with permission. © 2011 American Society of Clinical Oncology. All rights reserved.
META-ANALYSIS OF VENOUS THROMBOEMBOLISM PROPHYLAXIS
In medically ill patients

12,391 patients (8,357 in placebo-controlled trials) from 9 studies

- Prophylaxis with LMWH, UFH, fondaparinux, and placebo
- DVT rates
  - lower with LMWH/fondaparinux compared with placebo (OR 0.60; 95% CI 0.47, 0.75)
  - similar between LMWH and UFH (OR 0.92; 95% CI 0.56, 1.52)
- No differences in the rate of death or PE between LMWH/fondaparinux, UFH, or placebo
- Major bleeding rates similar across all treatment arms considered
- Minor bleeding rates similar with LMWH and UFH and greater than in placebo-treated patients
- Cancer-specific rates were not provided for either VTE or bleeding

Hospitalised patients with active malignancy with acute medical illness or reduced mobility should receive thromboprophylaxis in the absence of bleeding or other contraindications.

Hospitalised patients with active malignancy without additional risk factors may be considered for pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.

Data inadequate to support or oppose thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion.
Cancer patients have **2-fold risk** of post-operative DVT/PE and
**>3-fold risk** of fatal PE despite prophylaxis
**33% to 53%** of VTE episodes occurring **after hospital discharge**

### INCIDENCE OF VTE IN SURGICAL PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>No Cancer N=16,954</th>
<th>Cancer N=6,124</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-op VTE</td>
<td>0.61%</td>
<td>1.26%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>0.27%</td>
<td>0.54%</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>Autopsy PE</td>
<td>0.11%</td>
<td>0.41%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>0.71%</td>
<td>3.14%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

POSTOPERATIVE VTE IN PATIENTS WITH CANCER

@RISTOS was a prospective observational study

2373 patients who underwent surgery for cancer

The risk of VTE varies by site of the primary tumour

POSTOPERATIVE VTE IN PATIENTS WITH CANCER

Duration of thromboprophylaxis – @RISTOS study

2373 patients who underwent surgery for cancer

- 40% of all VTE occurs in the outpatient setting (>21 days of surgery)
- PE is the most common single cause of death (46%) at 30 days after surgery

**META-ANALYSIS**

Prolonged thromboprophylaxis with LMWH for abdominal or pelvic surgery

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Out-of-hospital LMWH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall VTE</td>
<td>14.3%</td>
<td>6.1%</td>
<td>P&lt;0.0005</td>
</tr>
<tr>
<td></td>
<td>(95% CI 11.2%, 17.8%)</td>
<td>(95% CI 4.0%, 8.7%)</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>3.7%</td>
<td>4.1%</td>
<td>P=0.73</td>
</tr>
<tr>
<td></td>
<td>(95% CI 2.4%, 5.5%)</td>
<td>(95% CI 2.7%, 6.0%)</td>
<td></td>
</tr>
</tbody>
</table>

VENOUS THROMBOEMBOLISM PROPHYLAXIS AND TREATMENT IN PATIENTS WITH CANCER

- All patients with malignant disease undergoing major surgical intervention should be considered for pharmacologic thromboprophylaxis with either UFH or LMWH.

- Extended prophylaxis with LMWH for up to 4 weeks postoperatively should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features.

THROMBOSIS AND CANCER

Answers!

Why did this occur? **CANCER-THROMBOSIS**

What is the influence in patient’s prognosis? **POOR PROGNOSIS**

What is the optimal management of this patient? **LMWH**

Should this patient be managed differently if this were an incidental finding? **NO**

Could this have been prevented? **MAYBE**
CONCLUSIONS

- **Thrombosis in cancer patients** is a common, costly and potentially fatal complication.
- **Patients at highest risk** are those with advanced disease receiving systemic chemotherapy and other additional risk factors.
- **Primary prophylaxis** is not routinely indicated but could be discussed with patients at high risk.
- Selected cancer patients benefit from **extended prophylaxis** up to 4 weeks after surgery.
- **Prophylaxis in hospitalised patients** is a safety priority.
- **LMWH** is the “best” category available for patients with established VTE and PE, for long-term (6 months) secondary prophylaxis.
THANK YOU!