Cancer Associated Thrombosis
Review and Update

GPO Case Study Day
November 18th 2016
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Erica Peterson
Disclosures

- Raziya Mia
  - No conflicts of interest to declare

- Erica Peterson
  - Participates in clinical research investigating the use of apixaban and edoxaban in the prevention and treatment of cancer-associated thrombosis
Learning Objectives

At the end of this session participants will be able to

- Determine the unique challenges in management of cancer-associated thrombosis
- Identify patients at high risk for cancer-associated thrombosis
- Recognize which cancer patients require thromboprophylaxis
Cancer-Associated VTE (CAT)

- ~20% of all VTE cases are associated with cancer
- VTE is associated with higher mortality
  - 2nd leading cause of death in cancer patients
- Significant burden on the health care community
  - Increased hospitalization
  - Health care costs and resource utilization
- Can cause treatment discontinuation/delays that impact cancer therapy

Case 1: Mr. P.C.

- 64 year old male
- New diagnosis of pancreatic cancer
- Candidate for curative therapy and admitted for a Whipple’s procedure

Should he receive thromboprophylaxis? If so what agent and how long?
VTE Risk and Cancer Surgery

- Cancer patients have a higher risk of post-op VTE than non-cancer patients
  - 2-fold risk for DVT/non-fatal PE
  - 3-fold risk for fatal PE

- Cancer patients undergoing general, gyne or urologic surgery
  - **Symptomatic VTE** rate 2.1%
  - 40% of VTE events **after POD+21**
  - Death rate 1.72%
  - 46.3% deaths due to VTE (#1 cause of death)

VTE Risk and Cancer Surgery

- Cancer patients undergoing general, gyne or urologic surgery
- **Risk factors for post-op VTE**: age > 60, prior VTE, advanced cancer, anesthesia > 2hrs, bed rest > 3 days

- Because of the prolonged VTE risk after cancer surgery, studies looking at extending prophylaxis to 4 weeks have been performed

Extended prophylaxis was associated with a significant reduction in ALL VTE (NNT=39) and proximal DVT (NNT=71)
Bleeding Rates with Extended Prophylaxis

Extended prophylaxis was **not associated** with an increase in major bleeding or mortality
Who Should Get Post-op Prophylaxis

**ASCO Guidelines**

- Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days.

- Extending postoperative prophylaxis up to 4 weeks should be considered in those undergoing major abdominal or pelvic surgery with high-risk features.
  - E.g. decreased mobility, prior VTE, obesity

Case 1: Mr. P.C.

- Mr. P.C is referred to a medical oncologist and adjuvant chemotherapy is planned.

Should he receive thromboprophylaxis during outpatient chemotherapy?
Outpatient Primary Prophylaxis?

- Many RCTs have studied VTE prophylaxis in cancer outpatients receiving chemotherapy

  - **Multiple sites/advanced disease**: SAVE-ONCO, PROTECHT
  - **Single sites/advanced disease**: TOPIC 1 (breast), TOPIC 2 (lung), PRODIGE (glioma), FRAGEM (pancreas), CONKO-004 (pancreas)
Prophylaxis in Oncology Outpatients

- **VTE rates**

![Graph showing VTE rates for various studies.](image)

Prophylaxis in Oncology Outpatients

▶ VTE rates

Prophylaxis in Oncology Outpatients

VTE rates

- SAVE-ONCO
- PROTECH
- TOPIC-1
- TOPIC-2
- PRODIGE
- FRAGEM
- KONKO-004

Pancreatic CA

LMWH/ultra LMWH
Placebo

Prophylaxis in Oncology Outpatients

Bleeding rates

- LMWH/ultra LMWH
- Placebo

Who Should Get Primary Prophylaxis

- Cochrane meta-analysis of primary prophylaxis RCTs
  - Significant reduction in VTE (RR 0.62, NNT=60)
  - Non-significant increase in major bleeding (RR 1.57)

- ASCO Guidelines: routine primary prophylaxis not indicated in outpatients

- BUT...
  - LMWH should be considered “case-by-case basis in highly selected outpatients” with solid tumours receiving chemo
  - A validated score should be used to identify high risk patients

Risk Stratification in CAT

- **Khorana risk model**
  - 5-independent risk factors identified

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Score</th>
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<tbody>
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<td>Site of cancer</td>
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<td>Very high risk (stomach, pancreas)</td>
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Low risk = 0
Moderate Risk = 1-2
High Risk ≥ 3

Khorana A. et al Blood 2008
Risk Stratification in CAT

- **Khorana risk model**
  - 5-independent risk factors identified

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VTE rates during 2.5 month follow-up

- **Low risk** 0.3%
- **Moderate Risk** 2.0%
- **High Risk** 6.7%

Risk Stratification in CAT

- Khorana risk model

Risk Stratification in CAT

- Khorana model also validated in
  - Outpatients receiving chemotherapy (SAVE-ONCO)
  - Advanced cancer patients treated in phase 1 clinical trials
  - Patients receiving cisplatin based chemotherapy

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Low Risk (0)</th>
<th>Intermediate Risk (1-2)</th>
<th>High Risk (&gt;=3)</th>
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<tbody>
<tr>
<td>Vienna CAT</td>
<td>6 mo</td>
<td>1.5%</td>
<td>3.8-9.6%</td>
</tr>
<tr>
<td>SAVE-ONCO</td>
<td>3.5 mo</td>
<td>1.3%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>---</td>
<td>13%</td>
<td>17.1%</td>
</tr>
<tr>
<td>Phase 1</td>
<td>2 mo</td>
<td>1.5%</td>
<td>4.8%</td>
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Targeted Primary Prophylaxis?

- High risk Khorana patients (score >=3) in SAVE-ONCO and PROTECHT studies

<table>
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<th>Low risk</th>
<th>High risk</th>
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<tbody>
<tr>
<td>333</td>
<td>25</td>
</tr>
<tr>
<td>77</td>
<td>15</td>
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Khorana A et al Thromb Res 2014
Mr. P.C is referred to a medical oncologist and adjuvant chemotherapy is planned.

- BMI = 37.5 (Ht. = 179cm/Wt. = 120kg)
- Pre-chemotherapy labs:
  - Hemoglobin 95 g/L
  - WBC 7.1
  - Platelet count 400

Should he receive thromboprophylaxis during outpatient chemotherapy?
Risk Stratification for Mr. P.C.

- BMI = 37.5
- Hemoglobin 95 g/L, WBC 7.1, platelets 400

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High Risk ≥ 3

Should discuss thromboprophylaxis with the patient
Case 1: Mr. P.C.

Would you decision change if Mr. P.C. had the following

- BMI 32.5
- Hemoglobin 105 g/L
- WBC 7.1
- Platelet count 200
Risk Stratification for Mr. P.C.

- BMI = 32.5
- Hemoglobin 105 g/L, WBC 7.1, platelets 200

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High Risk ≥ 3

Should educate patient regarding signs and symptoms of VTE
Additional Questions

- Are there any cancer therapy regimens where thromboprophylaxis is highly recommended?

- Which agent would you recommend?
Who Should Get Primary Prophylaxis

ASCO Guidelines

- Patients with **multiple myeloma** receiving **anti-angiogenesis** agents with chemotherapy and/or **dexamethasone** should receive prophylaxis with either LMWH or low-dose aspirin to prevent VTE.

* thalidomide, lenalidomide and pomalidomide

Lyman G. et al JCO 2015
Who Should Get Primary Prophylaxis

- ASCO Guidelines
  - Routine outpatient primary prophylaxis not indicated
  - LMWH should be considered “case-by-case basis in highly selected outpatients” with solid tumours receiving chemo
  - ASA or LMWH should be given to those with myeloma receiving an imid* with chemo/dex
  - Educate patient regarding signs and symptoms of VTE (particularly in high risk patients)

Lyman G. et al JCO 2015

*thalidomide, lenalidomide and pomalidomide
Prophylaxis Dosing Regimens

- Unfractionated heparin 5000 units SC q8hr
- Dalteparin 5000 units SC daily
- Enoxaparin 40 mg SC daily
- Fondaparinux 2.5 mg SC daily
Case 1: Mr. P.C.

- Following 3 cycles of chemotherapy Mr. P.C. is admitted to hospital with pneumonia.

Should he receive thromboprophylaxis during hospitalization?
Who Should Get In-Hospital Prophylaxis

- ASCO Guidelines
  - Most hospitalized patients with active cancer require thromboprophylaxis throughout hospitalization.
  - Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion.

Lyman G. et al JCO 2015
Case 2: Mr. K.L.M.

- Previously healthy 71 year old male

- Recently diagnosed with free kappa light chain multiple myeloma.
  - Started on CyBorD (cyclophosphamide, bortezomib, dexamethasone)

- Presents for a scheduled pre-cycle 3 evaluation.
Case 2: Mr. K.L.M.

- He tells you that while watching TV last night he began experiencing a little shortness of breath and chest pain with inspiration.

- On examination
  - Patient appears mildly distressed
  - BP 120/70, HR 104/min, RR 20/min, O2 sat 94%
  - Left leg swelling and calf tenderness

What do you do now?
Diagnosis of PE

- Pretest probability
- Diagnostic investigations
  - D-dimer
  - Ventilation/Perfusion (V/Q) scan
  - CT pulmonary angiography
  - Pulmonary angiography
## Diagnosis of PE

### Pretest probability

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs of DVT</td>
<td>3.0</td>
</tr>
<tr>
<td>Other dx more likely</td>
<td>-3.0</td>
</tr>
<tr>
<td>Heart rate &gt; 100</td>
<td>1.5</td>
</tr>
<tr>
<td>Surgery/Immobilization</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td><strong>1.0</strong></td>
</tr>
</tbody>
</table>

**PE likely > 4 (37.1%)**  
**PE unlikely ≤ 4 (12.1%)**

Diagnosis of PE

1. Determine if "PE unlikely" or "PE likely"*

2. PE unlikely
   - D-dimer assay**
     - <500 ng/mL
       - PE excluded
       - No treatment
     - ≥500 ng/mL
       - PE excluded

3. PE likely
   - CT pulmonary angiogram (CT-PA)
     - Negative
       - PE excluded
     - Positive
       - PE confirmed
       - Treatment
     - Inconclusive/ not performed
       - Additional testingΔ
         - PE confirmed
         - PE excluded
         - No treatment
Diagnosis of DVT

- Pretest probability
- Diagnostic Investigations
  - D-dimer
  - Compression US
  - Venography
Diagnosis of DVT

- Pretest probability (2-level Wells Score)

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<tr>
<th>Clinical Feature</th>
<th>Score</th>
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<tbody>
<tr>
<td>Active cancer (or w/in 6 mo)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis/paresis or cast</td>
<td>1</td>
</tr>
<tr>
<td>Surgery or bedridden</td>
<td>1</td>
</tr>
<tr>
<td>Tenderness of deep veins</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling &gt; 3 cm</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema</td>
<td>1</td>
</tr>
<tr>
<td>Collateral veins</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>1</td>
</tr>
<tr>
<td>Alternate diagnosis</td>
<td>-2</td>
</tr>
</tbody>
</table>

DVT likely > 1 (28%)
DVT unlikely ≤ 1 (6%)

Wells et al. NEJM 2003; 349:1227-35.
# Diagnostic approach to DVT

<table>
<thead>
<tr>
<th>Wells Score</th>
<th>D-Dimer</th>
<th>DUS</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unlikely</strong></td>
<td>Negative highly sensitive D-dimer</td>
<td>Not required</td>
<td>DVT excluded. No further testing required.</td>
</tr>
<tr>
<td></td>
<td>Positive or not done</td>
<td>Proximal DUS or whole leg DUS at presentation</td>
<td>DVT excluded if proximal DUS or whole leg DUS negative. No further testing required.</td>
</tr>
</tbody>
</table>
### Diagnostic approach to DVT

<table>
<thead>
<tr>
<th>Wells Score</th>
<th>D-Dimer</th>
<th>DUS</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely</td>
<td>Negative highly sensitive D-dimer (D-dimer testing not routinely recommended)</td>
<td>Proximal DUS or whole leg DUS at presentation</td>
<td>DVT excluded. No further testing required.</td>
</tr>
<tr>
<td></td>
<td>Positive or not done (D-dimer testing not routinely recommended)</td>
<td>Proximal DUS or whole leg DUS at presentation</td>
<td>DVT excluded if whole leg DUS negative. Patients with a negative proximal DUS should undergo repeat testing at 1 week.</td>
</tr>
</tbody>
</table>

[www.thrombosiscanada.com](http://www.thrombosiscanada.com)
Case 2: Mr. K.L.M.

- Urgent CT angiogram scan shows a saddle PE
- Hemoglobin is 110 g/L
- Platelet count 160
- Creatinine Clearance (CrCl) is 65 ml/min
- Weight 75kg

Would you order any further investigations?
Case 2: Mr. K.L.M.

- When you tell him the diagnosis, Mr. KLM becomes distressed – first the cancer, now a blood clot!

- You try to explain to him that these things happen to cancer patients, but he wants more information than that!!

Can you be more specific in identifying thrombosis risk factors?
Pathogenesis of CAT

- Multifactorial etiology
  - Venous stasis
  - Endothelial dysfunction
  - Hypercoagulability
Pathogenesis of CAT

- Multifactorial etiology
  - Venous stasis
  - Endothelial dysfunction
  - **Hypercoagulability**
    - Genetic mutations in cancer cells
    - Cytokines
    - Adhesion molecules
    - Tissue factor microparticles
Risk Factors for VTE in Cancer

- Divided into 3 main categories
  - Patient-related risk factors
  - Treatment-related risk factors
  - Cancer-related risk factors

- Overall risk is not static and varies over time
  - Acquisition of new risk factors
  - Disease progression
  - Initiation of new therapies
# Risk Factors for VTE in Cancer

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Cancer-related</th>
<th>Treatment-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Primary site</td>
<td>Surgery</td>
</tr>
<tr>
<td>Race</td>
<td>Histology</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Prior VTE</td>
<td>Stage</td>
<td>Hormonal therapy</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Grade</td>
<td>Anti-angiogenic agents</td>
</tr>
<tr>
<td>Obesity</td>
<td>Time interval since diagnosis</td>
<td>ESA</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td>Hospitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Catheters</td>
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Tumour Type and VTE Risk

RR of VTE ranges from 1.02 to 4.34
## Cancer Stage and VTE Risk

<table>
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<th>Risk Ratio</th>
<th>2-year Cumulative Incidence</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Limited Disease (%)</strong></td>
<td><strong>Metastatic Disease (%)</strong></td>
</tr>
<tr>
<td>Pancreas</td>
<td>8.25</td>
<td>3.2</td>
<td>5.4</td>
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<td>4.27</td>
<td>1.5</td>
<td>2.1</td>
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<tr>
<td>Bladder</td>
<td>2.14</td>
<td>0.9</td>
<td>4.3</td>
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<tr>
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<td>1.70</td>
<td>1.0</td>
<td>1.2</td>
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<tr>
<td>Ovary</td>
<td>1.58</td>
<td>0.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1.44</td>
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<td>Breast</td>
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Petterson TM et al Thromb Res 2015; Chew HK Arch Intern Med 2006
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Petterson TM et al Thromb Res 2015; Chew HK Arch Intern Med 2006
Risk of VTE with Age

- Annual incidence of VTE varies with age:
  - Overall $\rightarrow$ 1/1000
  - < 30 y $\rightarrow$ 1/10,000
  - ~ 80 y $\rightarrow$ 1/100

- After age 50
  - Risk doubles with each decade

Silverstein M.D. Arch Intern Med 1998
CAT is Increasing Over Time

Who Are At Risk for CAT?

- Highest VTE risk in:
  - Older patients
  - Pancreatic, brain, upper GI tumours and lymphoma
  - Metastatic disease
  - First 3 months after cancer diagnosis
  - First month after surgery
  - Systemic chemotherapy (especially cisplatin, anthracyclines, thalidomide/lenalidomide/pomalidomide, bevacizumab)

- Can use a validated score (Khorana score) to help estimate individual patient’s risk
Case 2: Mr. K.L.M.

Why should we educate patients about CAT?
Effects of VTE Diagnosis

- CAT diagnosis can be very traumatic to patients
- In non-cancer patients VTE diagnosis is associated with
  - Negative psychological impact
  - PTS-like features
- Studies in cancer patients indicate that VTE is associated with
  - Initial shock and distress
  - Perceived limited support

CAT Awareness

- Most cancer patients are unaware of potential risk of VTE
- In a survey of 190 cancer outpatients
  - 100 (53%) were unaware of the VTE risk
  - 161 (86%) were willing to use oral thromboprophylaxis
  - 86 (46%) were willing to use injectable thromboprophylaxis
CAT Awareness

- Qualitative studies also show a lack of awareness of CAT risk amongst patients and physicians
  - Patients unaware of the association between cancer and VTE
  - Patients did not know the red flag signs of VTE (attributed the symptoms to treatment or preexisting conditions)
  - Patients perceived a lack of knowledge about CAT amongst health care provider

Noble S. et al Patient Preference and adherence 2015
Educational Resources

- Thrombosis Canada website
  - www.thrombosiscanada.com

- Website contains information sheets and educational video about cancer-associated thrombosis
Case 2: Mr. K.L.M.

- You tell Mr. KLM that he must start blood thinners. After his initial reaction and your detailed explanation, he accepts this.
- He asks if he can be treated with Warfarin, because he attended the education session when his wife was prescribed this for atrial fibrillation. He knows he has to have blood tests, but doesn’t mind as they can go to the lab together.

What is your recommendation?
Treatment of CAT

- All major consensus guidelines recommend LMWH monotherapy as the preferred treatment for CAT

- Recommendations based on results of 4 open-label RCTs
  - **CANTHANOX** study: enoxaparin vs. warfarin
  - **CLOT** study: dalteparin vs. warfarin/acenocoumarol
  - **LITE** study: tinzaparin vs. warfarin
  - **CATCH** study: tinzaparin vs. warfarin

Risk of Recurrent VTE with LMWH

**Recurrent VTE**

- Dalteparin 200 u/kg x 1 mo then 150 u/kg x 5 mo
- Tinzaparin 175 u/kg (3 mo LITE; 6 mo CATCH)
- Enoxaparin 1.5 mg/kg x 3 mo
- Warfarin to target INR 2.0 to 3.0

**Meta-analysis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>0.56 (0.43 – 0.74)</td>
</tr>
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<td>Major bleeding</td>
<td>1.07 (0.52 – 2.19)</td>
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<tr>
<td>Survival</td>
<td>0.96 (0.66 – 1.73)</td>
</tr>
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Akl E. et al Cochrane Database Syst Rev 2014
Risk of Bleeding with LMWH

Major Bleeding

Dalteparin
Tinzaparin
Enoxaparin
Warfarin to target INR 2.0 to 3.0

Meta-analysis

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</table>

Bleeding rates decrease over time

3.6% in the first month
1.1% for months 2-6
0.7% for months 7-12

Tolerability of LMWH in Cancer

- Qualitative studies indicate that cancer patients
  - Are usually accepting of daily injections
  - Find LMWH convenient and empowering
  - Prefer efficacy and safety over the route of administration
  - Do not want the anticoagulant to interfere with their cancer treatment

ACCP Guidelines

- In patients with proximal DVT or PE we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B).

- In patients with DVT of the leg or PE and cancer as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C) or edoxaban (Grade 2C).

ASCO Guidelines

- LMWH is recommended for the initial 5 to 10 days of treatment of established deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis for at least 6 months

Lyman G. et al JCO 2015
Case 2: Mr. K.L.M.

- Mr. KLM agrees to use LMWH.

What agent and what dose would you recommend?
LMWH Dosing

Treatment of established VTE

Initial

- Unfractionated heparin\textsuperscript{e}  
  80 U/kg IV bolus, then 18 U/kg per hour IV; adjust dose based on aPTT\textsuperscript{h}

- Dalteparin\textsuperscript{e,g,h}  
  100 U/kg once every 12 h; 200 U/kg once daily

- Enoxaparin\textsuperscript{e,g,h,i}  
  1 mg/kg once every 12 h; 1.5 mg/kg once daily

- Tinzaparin\textsuperscript{e,g,h,j}  
  175 U/kg once per day

- Fondaparinux\textsuperscript{e,g}  
  <50 kg, 5.0 mg once daily; 50–100 kg, 7.5 mg once daily; >100 kg, 10 mg once daily

Long term\textsuperscript{k}

- Dalteparin\textsuperscript{h,g}  
  200 U/kg once daily for 1 month, then 150 U/kg once daily

- Enoxaparin\textsuperscript{g,h,i}  
  1.5 mg/kg once daily; 1 mg/kg once every 12 h

- Tinzaparin\textsuperscript{h,j}  
  175 U/kg once daily

- Warfarin  
  Adjust dose to maintain INR 2–3

\textsuperscript{a} Khorana A. et al J Thromb Thrombolysis 2016
Case 2: Mr. K.L.M.

- Mr. KLM agrees to use LMWH.

What agent and what dose would you recommend?

- Weight 75 kg → dalteparin 15,000 units SC daily
  - Need to apply for special authority
  - Round up to nearest pre-filled syringe
Case 2: Mr. K.L.M.

- Would your advice change if
  - The CrCl was 23ml/min?
  - The platelet was 35?
  - Mr. KLM weighs 102kg?
  - Mr. KLM had a high risk of bleeding or had active bleeding?

What agent and what dose would you recommend?
Anticoagulation with Renal Impairment

- Renal impairment is common in cancer patients

- LMWHs is **renally cleared** and may therefore **accumulate with long term** use in patients with renal impairment (Cr Cl < 30 mL/min)
  - Tinzaparin appears to have the lowest potential to accumulate
  - Enoxaparin shows significant accumulation in renal insufficiency

Lee AY Blood 2013;122:2310
Anticoagulation with Renal Impairment

- If CrCl < 30 mL/min consider anti-Xa monitoring and/or dose reduction
  - Enoxaparin dose for CrCl < 30 mL/min is 1 mg/kg daily
  - Consultation with hematologist recommended

- Anti-Xa monitoring
  - Measure **Peak effect and trough level**
    - Peak BID dosing target 0.6-1.0 units/mL
    - Peak OD dosing target 1.0-2.0 units/mL
    - Trough < 0.5 units/mL

Lee AY Blood 2013;122:2310
If platelet count < 50 management depends on the acuity of the VTE

- Transfuse platelets if VTE recent (< 30 days)
- Reduce dose of LMWH if VTE established (> 30 days)
CAT and Thrombocytopenia

- Acute VTE event
  - Platelet count $\geq 50 \times 10^9$/L
    - Weight-based full dose LMWH
  - Platelet count $< 50 \times 10^9$/L
    - Transfuse to maintain platelet count $\geq 50 \times 10^9$/L
    - Platelet count 20-50 $\times 10^9$/mL
      - Weight-based full dose LMWH
    - Platelet count $< 20 \times 10^9$/mL
      - Half-dose LMWH
  - Unable to maintain platelet count $\geq 50 \times 10^9$/L
    - Platelet count $< 20 \times 10^9$/mL
      - Hold anticoagulation

$\Rightarrow$ VTE within last 30 days

Lee AY Blood 2013;122:2310
CAT and Thrombocytopenia

Subacute/Chronic VTE event

- VTE >30 days

1. Platelet count $\geq 50 \times 10^9/L$
   - Weight-based full dose LMWH

2. Platelet count 20-50 $\times 10^9/L$
   - Half-dose LMWH

3. Platelet count <20 $\times 10^9/L$
   - Hold anticoagulation

Lee AY Blood 2013;122:2310
CAT and Obesity

- LMWH subcutaneously has almost 100% bioavailability
- Distribution – mainly plasma and vascular tissues (not fat)
- Small cohort studies suggest dosing for treatment should be **based on actual body weight** not ideal body weight
  - Do not cap the dose based on weight
  - For very high doses can divide BID (e.g. dalteparin 100 units/kg BID)

Lim et al. J Thromb Thrombolysis 2010
VTE and Bleeding

- Multiple reasons for bleeding in cancer patients
- In patients with bleeding who also require anticoagulation, need to consider:
  - Severity and source of bleed (e.g. epistaxis vs ICH)
  - Whether source can be treated or eliminated
  - How long is the bleeding event likely to last
  - Likelihood of recurrence of bleeding event
  - Indication for anticoagulation
VTE and Bleeding

- No evidence-based guidance on management
  - Treat bleeding source whenever possible
  - Active, serious bleeding:
    - Hospitalize and withhold anticoagulation
    - Insert retrievable filter only if risk of VTE is very high (within first 4 weeks after diagnosis)
    - Start anticoagulation and remove filter when bleeding stops

- When restarting anticoagulation restart prophylactic doses and uptitrate as tolerated
IVC Filters

- Efficacy and safety remain ill-defined after 40 years of use
- Long-term data shows no reduction in total VTE or mortality
- Short and long-term complications are common
  - Thrombosis (6 – 36%)
  - Filter tilt, fracture, migration or embolization (3 – 69%)
  - IVC perforation (3 – 86%)
  - Post-thrombotic syndrome (5 – 70%)

IVC Filter Efficacy

- Limited to ONLY 2 RCTs!

- **PREPIC trial**: Permanent IVC filter + anticoagulation vs. anticoagulation alone
  - Reduced symptomatic PE (6.2 vs. 15.1%, $p=0.0008$)
  - Increased recurrent VTE (35.7% vs. 27.5%, $p=0.042$)
  - No difference in mortality

- **PREPIC2 trial**: Retrievable filter + anticoagulation vs. anticoagulation alone
  - **No effect on recurrent PE** at 3 (3.0% vs. 1.5%) or 6 mo (3.5% vs. 2%)
  - No effect on recurrent DVT, major bleeding or death

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  - No effect on recurrent DVT, major bleeding or death

- No data in patients with contraindication to anticoagulation

IVC Filter Complications
IVC Filter Complications

Embolized filter strut in lung
IVC Filter Complications

Filter is tilted, hook of IVC filter is embedded in the IVC wall AND filter tines have penetrated IVC wall
IVC Filters Summary

- IVC filters should be restricted to patients with acute VTE and a contraindication to anticoagulation

- Anticoagulation should be restarted as soon as the high risk period for PE has passed

- Risk/benefit ratio of the filter should be reassessed at regular intervals
Case 1: Mr. K.L.M.

- At his next follow up visit, Mr. KLM has numerous bruises at anticoagulant injections sites, including around the umbilicus.

Do you have any advice?
Practical Pearls about LMWH ...

- Have patient do his/her first injection in clinic
- Allow alcohol to dry before injection
- Inject SLOWLY (over 5-10 seconds)
- Firm pressure for 2 – 5 min after injection
  - Reduces bruising, hematomas and pain
- **DO NOT RUB**
- Insulin syringe with multi-dose vials offers greater comfort than prefilled syringes
Practical Pearls about LMWH ...

- Rotate sites and use “love handles”
Case 2: Mr. K.L.M.

- Two months later he tells you he is tired of giving himself injections, and saw an advertisement about new blood thinner.
- Luckily you just went to a Family Practice conference and lots of things were said about DOACs, so you feel well informed.

Would you recommend these to Mr. KLM?
Direct Oral Anticoagulants (DOACs)

- 3 agents currently approved in Canada for VTE treatment
  - Rivaroxaban (Factor $\text{X}_\text{a}$ inhibitor)
  - Apixaban (Factor $\text{X}_\text{a}$ inhibitor)
  - Dabigatran (thrombin inhibitor)
## DOAC Pharmacology

<table>
<thead>
<tr>
<th>Target</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action onset</td>
<td>1 – 2 h</td>
<td>2 – 4 h</td>
<td>1 – 3 h</td>
<td>4-5 days</td>
</tr>
<tr>
<td>Half life</td>
<td>12-17 h</td>
<td>5-13 h</td>
<td>12-15 h</td>
<td>40 h</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td>Dosing</td>
<td>BID</td>
<td>OD (BID)</td>
<td>BID</td>
<td>OD</td>
</tr>
<tr>
<td>Lab monitoring</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>YES</td>
</tr>
<tr>
<td>Antidote</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>YES</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-gp</td>
<td>P-gp/CYP3A4</td>
<td>P-gp/CYP3A4</td>
<td>MANY</td>
</tr>
</tbody>
</table>
DOAC Drug Interactions

**Inhibitors**
- antifungals
- ritonavir
- amiodarone
- verapamil
- clarithromycin
- quinidine
- tamoxifen
- TKIs
- cyclosporin
- tacrolimus

**Inducers**
- rifampicin
- phenytoin
- carbamazepine
- phenobarbitone
- dexamethasone
- doxorubicin
- vinblastine
- St. John’s wort

Increase Drug Levels
Decrease Drug Levels
DOAC trials for VTE treatment

**Dabigatran: RE-COVER and RE-COVER II**
- UFH/LMWH + Warfarin
- Dabigatran 150 mg BID

**Rivaroxaban: EINSTEIN DVT AND EINSTEIN PE**
- Rivaroxaban 15 mg BID x 21 days then 20 mg OD

**Apixaban: AMPLIFY**
- Apixaban 10mg BID x 1 week then 5 mg BID

---

DOAC trials for VTE treatment

Dabigatran: RE-COVER and RE-COVER II
- UFH/LMWH + Warfarin
- Dabigatran 150 mg BID

9.5% active cancer

Rivaroxaban: EINSTEIN DVT AND EINSTEIN PE
- Rivaroxaban 15 mg BID x 21 days then 20 mg OD
- Enoxaparin + Warfarin

9.2% active cancer

Apixaban: AMPLIFY
- Apixaban 10mg BID x 1 week then 5 mg BID
- Enoxaparin + Warfarin

5.3% active cancer

All cancer patients were highly selected
• Well
• No bleeding
• No significant renal/hepatic dysfunction

DOAC trials for VTE treatment

DOACs = Warfarin
But...LMWH > Warfarin in cancer patients

Cancer Subgroup in DOAC trials

Einstein (Rivaroxaban)  RR (95% CI)
0.64 (0.23, 1.81)

Hokusai (Edoxaban)
0.52 (0.16, 1.72)

RECOVER (Dabigatran)
0.78 (0.35, 1.76)

Amplify (Apixaban)
0.58 (0.11, 2.34)

Overall:
0.66 (0.39-1.11)

# Cancer Subgroup in DOAC trials

<table>
<thead>
<tr>
<th></th>
<th>VTE or VTE death, patients, n/N (%)</th>
<th>Major bleed, patients, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Control</td>
</tr>
<tr>
<td><strong>RECOVER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer status*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>58/2380 (2.4)</td>
<td>50/2392 (2.1)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>10/173 (5.8)</td>
<td>12/162 (7.4)</td>
</tr>
<tr>
<td><strong>EINSTEIN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer status†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>70/3834 (1.8)</td>
<td>75/3850 (1.9)</td>
</tr>
<tr>
<td>Cancer at entry</td>
<td>6/232 (2.6)</td>
<td>8/198 (4.0)</td>
</tr>
<tr>
<td>Cancer diagnosis during study</td>
<td>10/84 (11.9)</td>
<td>12/83 (14.5)</td>
</tr>
<tr>
<td><strong>AMPLIFY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer status‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>56/2528 (2.2)</td>
<td>66/2557 (2.6)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>3/81 (3.7)</td>
<td>5/78 (6.4)</td>
</tr>
<tr>
<td><strong>Hokusai</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer status§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>103/3658 (2.8)</td>
<td>99/3629 (2.7)</td>
</tr>
<tr>
<td>History of cancer</td>
<td>10/269 (3.7)</td>
<td>21/294 (7.1)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>4/109 (3.7)</td>
<td>7/99 (7.1)</td>
</tr>
</tbody>
</table>

Studies looking specifically at DOAC use in cancer patients are currently ongoing.
DOAC Limitations in Cancer Patients

- Unreliable administration and absorption in patients with n/v, diarrhea and mucosal erosion
- Higher risk of GI bleed for dabigatran
- Liver and renal dysfunction is common in cancer
- Drug interactions may be clinically important
- Lack of measurement (therapeutic range) and antidote
- Lack of experience on management for procedures and thrombocytopenia
- No comparison against long-term LMWH for treatment
- Paucity of clinical trial data
**ASCO Guidelines**

- **LMWH** is recommended for the **initial 5 to 10 days** of treatment of established deep vein thrombosis and pulmonary embolism as **well as for long-term secondary prophylaxis** for at least 6 months.

- Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE.

---

Lyman G. et al. JCO 2015
Case 2: Mr. K.L.M.

- A month later, Mr. KLM presents with acute left leg swelling.
- Doppler US ordered and imaging confirms recurrent DVT

Now what?
Recurrent CAT on Anticoagulation

- Important considerations
  - Was patient compliant with anticoagulation?
  - If on LMWH was he on an adequate dose? **Need to confirm weight/dose**
  - If on warfarin was INR therapeutic? **Need to check current and recent INRs**
  - If recurrence occurs shortly after starting LMWH is this due to heparin-associated thrombocytopenia? **Need to check platelet count/exclude HIT**
Recurrent CAT on Anticoagulation

Treatment options

- If on warfarin switch to LMWH (if INR therapeutic)
  - Can also bridge with LMWH (if INR subtherapeutic and patient refuses LMWH)
- If on LMWH need to increase/escalate dose
LMWH Escalation for Recurrent VTE

- 2 small retrospective studies suggest that dose escalation is safe and effective
  - Carrier et al. → 70 patients
    - 8.6% recurrent VTE during 3 month f/u
    - 4.3% bleeding complications during 3 month f/u
  - Ihaddadene et al. → 55 patients
    - 7.3% recurrent VTE during 3 month f/u
    - 5.5% bleeding complications during 3 month f/u

Figure 2: Management algorithm of recurrent venous thromboembolism (VTE) in patients with cancer

- HIT, heparin-induced thrombocytopenia
- VKA, vitamin K antagonist
- LMWH, low-molecular-weight heparin
- UFH, unfractionated heparin
- INR, international normalized ratio
- BID, twice daily dosing
- OD, once daily dosing

1. Recurrent VTE during anticoagulant therapy
2. Exclude HIT and Non-compliance
3. Sub-therapeutic anticoagulation
   - VKA: Switch to full dose LMWH
   - LMWH: Bridge with LMWH or UFH and resume VKA (target INR 2-3)
4. Therapeutic anticoagulation
   - VKA: Increase LMWH by 20-25%
   - LMWH: Shift to full dose of LMWH
5. Reassess in 1 week
   - No Improvement: Peak anti-Xa level
   - Symptomatic improvement: Continue current management
6. Adjust LMWH dose to target peak anti-Xa level
   - OD peak 1.0-2.0 U/mL
   - BID peak 0.8-1.0 U/mL

For personal use only. on August 20, 2016.
In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).

In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C).

Case 2: Mr. K.L.M.

- A month later, Mr. KLM presents with acute left leg swelling.

**Now what?**

Current dalteparin dose 15,000 units daily → therefore increase to 18,000 units daily
Case 2: Mr. K.L.M.

- 2 months after completion of chemotherapy, Mr. KLM has increasing abdominal pain and is found to have a mesenteric mass. This requires a biopsy, either surgically or through diagnostic imaging.

What would you recommend regarding management of anticoagulant therapy in either scenario?
Perioperative anticoagulation Management

- How to manage anticoagulants around surgery depends on 3 factors

<table>
<thead>
<tr>
<th>Indication for Anticoagulation</th>
<th>Surgical Procedure</th>
<th>Type of Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of Thrombosis</td>
<td>Procedural Bleeding risk</td>
<td>Short Acting (DOACs/LMWH) vs. Long Acting (warfarin)</td>
</tr>
</tbody>
</table>
Perioperative anticoagulation Management

- Management should be individualized based on 3 questions
  - Does the anticoagulation need to be stopped?
  - If the anticoagulant needs to be stopped, for how long?
  - How soon after the procedure should anticoagulation be restarted?
Procedural Bleeding Risk

- **High or very high risk procedures**
  - Any surgery or procedure with neuraxial anesthesia
  - Neurosurgery (intracranial or spinal)
  - Cardiac surgery (CABG, heart valve replacement)
  - Major intra-abdominal surgery or intestinal anastomosis
  - Major vascular surgery
  - Major orthopedic surgery (hip or knee replacement)
  - Lung resection surgery
  - Urological surgery (prostatectomy, bladder tumour resection)
  - Extensive cancer surgery (pancreas, liver)
  - Reconstructive plastic surgery
  - Selected procedures (kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)
Procedural Bleeding Risk

- **Standard risk** procedures
  - Other intra-abdominal surgery or general surgery
  - Other intrathoracic surgery
  - Other orthopedic surgery
  - Other vascular surgery
  - Non-cataract ophthalmologic surgery
  - Gastroscopy or colonoscopy with biopsies
  - Selected procedures (e.g. bone marrow/lymph node biopsy, thoracentesis, paracentesis, arthrocentesis)
  - Complex dental procedure (multiple tooth extractions)
Procedural Bleeding Risk

- **Low risk procedures**
  - Cataract surgery
  - Dermatologic procedures (e.g. skin biopsy)
  - Gastroscopy or colonoscopy without biopsies
  - Coronary angiography
  - Permanent pacemaker insertion or internal defibrillator placement
  - Dental extractions (1 or 2 teeth)
  - Endodontic (root canal) procedure
  - Subgingival scaling or other cleaning
Perioperative LMWH Management

-6  -5  -4  -3  -2  -1  0  1  2  3  4  5  6  Days

LMWH

LMWH

* use half therapeutic dose 24 hr pre-op for very high risk (i.e. VTE with 30 days)
# use prophylactic doses POD+1 and +2 for very high risk procedures

Procedure
Case 2: Mr. K.L.M.

- Good news – he turned out to have a benign lipoma! He gradually recovers from all his treatments.
- He maintains a good response to chemotherapy, with normal serum free lights chain level. He wants to know if he can now stop anticoagulation.

What would be your recommendation as to how long he should continue on therapy?
Case 3: Ms. A.C.

- 69 year old female with Stage III B (pT4aN1a – 1/20 lymph nodes positive) moderately differentiated adenocarcinoma of the colon
- Status post laparoscopic sigmoid colectomy. Following discussion
- Right port-a-cath inserted and plan to receive adjuvant chemotherapy with FOLFOX
Case 3: Ms. A.C.

- She presents prior to her 12th and final cycle and reports acute onset of right anterior neck pain and swelling that began the day prior.
- No associated fever.
- On examination you find a tender, swollen mass in the right neck, with no associated redness.

What is your next step?
Case 3: Ms. A.C.

- Ultrasound shows an **occlusive thrombus** in the proximal right internal jugular vein with mild extension into the subclavian vein

- CXR is normal and shows Port-A-Cath tip in the mid SVC

**How will you manage this in comparison to cancer associated VTE?**
Upper Extremity DVT Anatomy

Deep veins of the UE include:
- Internal jugular
- Brachiocephalic
- Subclavian
- Axillary
- Brachial
Epidemiology of Catheter-related Thrombosis

- Upper extremity DVTs account for 10% of DVTs
  - Incidence in cancer patients

- UE DVT complications include
  - PE in 2-9% of patients
  - PTS in 7-47% of affected individuals

- CRT rates are higher with PICC lines (vs. CVCs)
Treatment of CRT

- Due to the risk of PE and PTS, CRT is treated similarly to LE VTE
  - Minimum 3 months of anticoagulation
  - In cancer patients agent of choice is LMWH

- Anticoagulation should continue as long as the catheter remains in situ (if > 3 months)

- If the catheter is removed anticoagulation can be stopped after 3 months
Case 3: Ms. A.C.

What about cycle 12 chemotherapy – delay or proceed?

Can you use the Port-A-Cath for venous access?

What if treatment completion CT scan shows metastatic disease and you need to restart chemotherapy. Can the Port-A-Cath be used or should it be replaced?
Should we Remove the Catheter?

- The CVC should remain in situ if it is still needed and functional
  - Removing and replacing the CVC exposes the patient to procedural and thrombotic complications
Case 4: Mr. N.H.L.

- 59 year old male with diffuse large B cell lymphoma receiving CHOP-R chemotherapy
- At pre-cycle #4 evaluation she reports no chest pain, dyspnea, cough, or hemoptysis.
- Interval CT scan prior to cycle #5 reveals an isolated subsegmental PE.

Should any further investigation be performed?

Should Ms. NHL be fully anticoagulated?
Case 4: Mr. N.H.L.

- What if imaging showed:
  - A segmental right sided pulmonary embolism.
  - A mesenteric vein thrombosis.

Should Ms. NHL be fully anticoagulated?

What is the rate of Incidental Thrombosis on Imaging studies?
Incidental VTE

- Retrospective studies in oncology patients
  - Douma et al: incidental VTE 2.5%, PE/DVT 1.3% and abdominal vein thrombosis 1.1%
  - Cronin et al: incidental VTE 6%, DVT 6.8% and PE 3.3%

- Prospective studies
  - Shah et al: incidental VTE 2%

- Observed rates are increasing over time due
  - Improved imaging techniques
  - More scans

Incidental VTE

Symptomatic VTE

- PE: 74%
- PE + DVT: 8%
- DVT: 8%
- DVT + phlebitis: 5%
- UE DVT: 5%

Incidental VTE

- PE: 26%
- PE + DVT: 13%
- DVT: 35%
- DVT + phlebitis: 10%
- UE DVT: 8%
- Splanchnic/portal: 2%
- Renal: 6%
Incidental VTE

- Indirect evidence suggests that incidental and symptomatic VTE share the same risk factors:

  - older age
  - hospitalization
  - previous VTE
  - elevated WBC
  - cancer
  - recent chemotherapy
  - metastatic disease
  - first 3-6 months after cancer diagnosis

Incidental PE: Clinically Significant?

- Thrombus burden/location of emboli are similar to symptomatic PE

- When compared to matched controls incidental PE patients were more likely to have:
  - Fatigue (54% vs. 20% p=0.0002)
  - SOB (22% vs. 8% p=0.02)

- Incidental and symptomatic PE are both associated with increased mortality

- Patients with incidental PE have similar rates of recurrent VTE, bleeding and mortality compared to those with symptomatic PE

Incidental VTE in Cancer

- Prevalence increasing due to improved imaging and awareness and likely true rise in incidence
- **Must confirm diagnosis**
- Prognosis appears to be similar to symptomatic VTE in terms of VTE recurrence and mortality
- Role of anticoagulation is unclear
  - Currently recommended by ACCP guideline (2B) and 2013 ASCO guideline

Conclusions

- CAT is a **common**, costly and **potentially fatal**
- VTE risk assessment and patients education should be done routinely prior to starting chemotherapy
- Primary prophylaxis is not routinely indicated but should be discussed with patients at high risk
- Incidental VTE should be treated with standard therapy
- LMWH is still the treatment of choice but we need to encourage research using DOACs
RM’s ‘must reads’ for GPO’s


- Cancer and Thrombosis. Thrombosis Canada 2015:1-4
Questions?