Disclosures

- Bayer
- Boehringer Ingelheim
- Bristol-Myers Squibb
- Eisai
- Leo Pharma
- Pfizer
- Sanofi-Aventis
Objectives

To review evidence and updates in:

• Epidemiology and Pathophysiology
• Risk Assessment Models
• Role of Outpatient Primary Prophylaxis
• Treatment of VTE
Cancer-Associated Thrombosis

- ~20% of all VTE cases are associated with cancer
- higher mortality among patients with VTE than without
- 2nd leading cause of death in cancer patients
- activation of coagulation is important for tumour progression and metastasis
- effective prophylaxis and treatment will reduce morbidity and may decrease overall mortality

Virchow's Triad

Venous stasis
- obesity
- immobility
- chronic heart disease

Vascular injury
- surgery
- chemotherapy
- trauma
- catheterization

Risk factors are cumulative

Hypercoagulability
- malignancy
- hereditary risk factors
- age >40

# Risk Factors for VTE in Cancer

- Risk varies from 1 – 30% depending on:

## Patient-related
- Older age
- Race
- Prior VTE
- Platelet count
- Obesity
- Comorbid conditions

## Cancer-related
- Primary site
- Histology
- Stage
- Grade
- Time interval since diagnosis

## Treatment-related
- Surgery
- Chemotherapy
- Hormonal therapy
- Antiangiogenic agents
- ESA
- Hospitalization
- Catheters

Who Are At Risk for CAT?

• Highest VTE risk in:
  – Older patients
  – Pancreatic, brain, upper GI, lung, ovarian, lymphoma,
  – Metastatic disease
  – First 3 months after cancer diagnosis
  – First month after surgery
  – During systemic chemotherapy (especially cisplatin, anthracyclines, thal/lenalidomide, bevacizumab)

• Important to educate patients regarding signs and symptoms of VTE
Objectives

To review evidence and updates in:

• Epidemiology and Pathophysiology
• Risk Assessment Models
• Role of Outpatient Primary Prophylaxis
• Treatment of VTE
Risk Stratification

Risk of VTE

Cancer-related Risk Factors

Treatment-related Risk Factors

Patient-related Risk Factors
### Khorana Model for Outpatients

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site of Cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, GU excluding prostate)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Pre-chemotherapy platelet count ≥ 350,000/mm$^3$</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Hb &lt; 10g/dL or use of ESA</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Prechemotherapy leukocyte count &gt; 11,000/mm$^3$</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>BMI ≥ 35 kg/m$^2$</strong></td>
<td>1</td>
</tr>
</tbody>
</table>

Khorana Model Validation

- Prospective follow up of 819 patients
- Median observation time/follow-up: 656 days

6-mo cumulative VTE rates:

<table>
<thead>
<tr>
<th>Score</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3</td>
<td>93</td>
<td>17.7%</td>
</tr>
<tr>
<td>2</td>
<td>221</td>
<td>9.6%</td>
</tr>
<tr>
<td>1</td>
<td>229</td>
<td>3.8%</td>
</tr>
<tr>
<td>0</td>
<td>276</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Objectives

To review evidence and updates in:

- Epidemiology
- Risk Assessment Models
- Role of Outpatient Primary Prophylaxis
- Treatment of VTE
LMWH in Solid Tumours

**PROTECHT**  
N=1150

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Nadroprarin</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>VTE</td>
<td>3.9%</td>
<td>2.0%</td>
<td>0.02</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>0%</td>
<td>0.7%</td>
<td>NS</td>
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</table>

**SAVE-ONCO**  
N=3212

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Semuloparin</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>VTE</td>
<td>3.4%</td>
<td>1.2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>1.1%</td>
<td>1.2%</td>
<td>NS</td>
</tr>
</tbody>
</table>

LMWH in Pancreatic Cancer

PROSPECT-CONKO 004

N=312

<table>
<thead>
<tr>
<th>Treatment</th>
<th>VTE</th>
<th>bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>no treatment</td>
<td>9.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>enoxaparin</td>
<td>2.6%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

P<0.01

FRAGEM

N=123

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AVTE</th>
<th>bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>no treatment</td>
<td>23%</td>
<td>3.4%</td>
</tr>
<tr>
<td>dalteparin</td>
<td>3.4%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

P=0.002

Who Should Get Primary Prophylaxis?

• Routine primary prophylaxis is not indicated in ambulatory patients

• Should be considered in patients with multiple risk factors:
  – Previous history of thrombosis
  – Advanced pancreatic cancer on chemotherapy
  – High Khorana Score

• Prophylaxis with LMWH effective in reducing VTE

• Important to educate patient regarding signs and symptoms
Who Should Get Primary Prophylaxis?

- ACCP 2012 recommendation: Grade 2B
  - In outpatients with solid tumours who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic-dose LMWH or LDUH over no prophylaxis
  - Additional risk factors: previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide

Objectives

To review evidence and updates in:

- Epidemiology
- Risk Assessment Models
- Role of Outpatient Primary Prophylaxis
- Treatment of VTE
Treatment of CAT

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

- Recommendations are based on results of 3 open-label, randomized controlled trials
  - CATHANOX study: enoxaparin vs warfarin
  - CLOT study: dalteparin vs warfarin or acenocoumarol
  - LITE study: tinzaparin vs warfarin

Study Design

Control Group

LMWH

Vitamin K antagonist (INR 2.0 to 3.0)

CATHANOX

Enoxaparin 1.5 mg/kg OD

LITE

Tinzaparin 175 U/kg OD

CLOT

Dalteparin 200 IU/kg OD then ~150 IU/kg OD

5 – 7 days

1 month

3 months

6 months
Risk of Recurrent VTE with LMWH

CLOT Trial

- log-rank P = 0.002
- Recurrent VTE
  - VKA, 17%
  - dalteparin, 9%
- risk reduction = 52%
- HR 0.48 (95% CI 0.30, 0.77)

Cochrane Syst Review

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>0.47 (0.32 – 0.71)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.05 (0.53 – 2.10)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.02 (0.60 – 1.74)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>0.96 (0.81 – 1.14)</td>
</tr>
</tbody>
</table>

## Comparison of LMWHs

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
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</thead>
<tbody>
<tr>
<td>Molecular weight (d)</td>
<td>4500</td>
<td>5600</td>
<td>6500</td>
</tr>
<tr>
<td>Anti-Xa:Anti-IIa ratio</td>
<td>4:1</td>
<td>2.5:1</td>
<td>1.9:1</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>CAT indication</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prefilled Syringe sizes</td>
<td>30 mg</td>
<td>5000 U</td>
<td>2,500 U</td>
</tr>
<tr>
<td></td>
<td>40 mg</td>
<td>7500 U</td>
<td>3,500 U</td>
</tr>
<tr>
<td></td>
<td>60 mg</td>
<td>10,000 U</td>
<td>4,500 U</td>
</tr>
<tr>
<td></td>
<td>80 mg</td>
<td>12,500 U</td>
<td>10,000 U</td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td>15,000 U</td>
<td>14,000 U</td>
</tr>
<tr>
<td></td>
<td>120 mg</td>
<td>18,000 U</td>
<td>18,000 U</td>
</tr>
<tr>
<td></td>
<td>150 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDV Concentration</td>
<td>100 mg/mL</td>
<td>25,000 U/mL</td>
<td>20,000 U/mL</td>
</tr>
</tbody>
</table>
Recurrent VTE and Bleeding on VKA

Hazard ratio 3.2
Cancer 21%
No Cancer 7%

Time (months)

Hazard ratio 2.2
Cancer 12%
No Cancer 5%

Time (months)

Unanswered Questions

- Duration of treatment?
- Treatment of recurrent thrombosis?
- Treatment in patients with high risk of bleeding?
- Role of novel anticoagulants?
Duration of Anticoagulation

• No clinical trial evidence on optimal duration

• Decision depends on risk of recurrence versus risk of bleeding
  – incidence of these events not well documented
  – case fatality may differ from non-cancer patients

• Other important considerations:
  – quality of life
  – life expectancy
  – drug cost
  – tolerability and patient preference
Recurrence and Bleeding

- Risk factors for recurrent VTE
  - younger age (less than 65 y)
  - metastatic disease
  - tumour type: pancreas, lung (adenocarcinoma), adenocarcinoma of unknown primary

- Risk factors for major bleeding
  - recent major bleeding
  - metastatic disease
  - creatinine clearance < 30 ml/min

- No data on biomarkers in predicting recurrence or bleeding

Duration of Anticoagulation

• General expert/guidelines consensus:
  – minimum of 3 – 6 months
  – continue as long as cancer is active or chemotherapy is ongoing
  – discontinue if risk of serious bleeding is high or patient preference

• Consider risk factors for recurrence and bleeding

• Frequently evaluate patients and tailor therapy according to risk, benefits, preference

Treatment of Recurrent VTE

• Experienced-based recommendations:
  – switch to LMWH for “warfarin failures”
  – LMWH dose escalation for “LMWH failures”

• Possible mechanisms for LMWH failure:
  – Accelerated clearance or increased nonspecific binding
  – Massive thrombin generation
  – Acquire AT deficiency
  – Noncompliance

Approach to Recurrent VTE

Symptomatic recurrent VTE

Failure on Warfarin
- Switch to full dose LMWH*
  - Reassess in 5-7 days†
  - No improvement
    - Check peak anti-Xa level
      - Increase LMWH dose accordingly to aim for:
        1.6 – 2.0 U/mL for once daily dosing or
        0.8 – 1.0 U/ml for twice daily dosing
  - Symptomatic improvement
    - Continue same dose
      - Resume usual follow-up

Failure on LMWH
- Increase LMWH by ~25% or back up to full dose*
  - Reassessment should consist of clinical evaluation of symptoms. Radiological imaging is not required except when deterioration is noted and further extension or new thrombosis is suspected.

*full dose refers to the recommended weight-adjusted dose of LMWH for the initial therapy of VTE.
†Reassessment should consist of clinical evaluation of symptoms. Radiological imaging is not required except when deterioration is noted and further extension or new thrombosis is suspected.
Once vs Twice Daily Injections

- Patients with acute DVT/PE (15% had cancer)
- Randomized to UFH, enoxaparin 1.5 mg/kg OD, or enoxaparin 1.0 mg/kg bid

<table>
<thead>
<tr>
<th></th>
<th>All Pts, N</th>
<th>Recurrent VTE</th>
<th>Cancer Pts, n</th>
<th>Recurrent VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH IV</td>
<td>290</td>
<td>12 (4.1%)</td>
<td>45</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>enoxaparin OD</td>
<td>298</td>
<td>13 (4.4%)</td>
<td>49</td>
<td>6 (12.2%)</td>
</tr>
<tr>
<td>enoxaparin bid</td>
<td>312</td>
<td>9 (2.9%)</td>
<td>47</td>
<td>3 (6.4%)</td>
</tr>
</tbody>
</table>

IVC Filters

• Efficacy and safety remain ill-defined after 40 years of usage

• Accepted indication:
  – acute VTE with contraindication to anticoagulation

• Controversial indications:
  – failure of anticoagulation
  – free-floating or iliocaval thrombosis
  – primary prophylaxis in trauma or surgical patients

• Long-term data from single RCT showed no reduction in total VTE or mortality

IVC Filters Complications

• Insertion complications occur in 4 – 11%

• Long-term complications are not infrequent
  – thrombosis (6 – 36%)
  – filter tilt, fracture, migration or embolization (3 – 69%)
  – IVC perforation (3 – 86%)
  – post-thrombotic syndrome (5 – 70%)

• retrievable filters may reduce long-term complications but
  – mixed results regarding long-term safety
  – often become permanent as retrieval rates are low (18 – 60%)
  – PE still happens (2 – 6%)

Filters: FDA Safety Alert

- Between 2005 and 2010, 921 adverse event reports on filters were received by FDA
  - 36% involved device migration
  - 16% involved embolizations
  - 8% involved perforation of the IVC
- May be related to retrievable filters remaining in situ for long periods
- Recommendation: remove filters as soon as protection from PE is no longer needed

Avoid the filter like the plague

FDA Safety Alert Bulletin Aug 2010
Bleeding or Thrombocytopenia

- 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
- No evidence-based guidance on management
Bleeding or Thrombocytopenia

• Treat bleeding source whenever possible

• If active, serious bleeding:
  – hospitalize and withhold anticoagulation
  – insert retrievable filter only if risk of recurrent VTE is very high (within 1 – 4 weeks of diagnosis)
  – start anticoagulation and remove filter when bleeding stops

• If platelet count less than 50x10⁹/L:
  – transfuse platelets if VTE recent (< 30 days)
  – reduce dose of LMWH if VTE established (> 30 days)
Anticoagulant Sites of Action

- **Direct Factor Xa Inhibitors**
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - Betrixaban
  - Darexaban

- **Direct Thrombin (IIa) Inhibitors**
  - Bivalirudin
  - Lepirudin
  - Argatroban
  - Dabigatran

- **Unfractionated Heparin**

- **Low Molecular Weight Heparin**

- **Warfarin**

- **Fibrin Clot**

**Courtesy of Dr. J Ansell.**
## Comparative Pharmacology

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
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</thead>
<tbody>
<tr>
<td>Target</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Action onset</td>
<td>1 – 2 h</td>
<td>2 – 4 h</td>
<td>1 – 3 h</td>
</tr>
<tr>
<td>Half life</td>
<td>12-17 h</td>
<td>5-13 h</td>
<td>12-15 h</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>80%</td>
<td>33% (66%)</td>
<td>25%</td>
</tr>
<tr>
<td>Dosing</td>
<td>BID (OD)</td>
<td>OD (BID)</td>
<td>BID</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-gp</td>
<td>P-gp/CYP3A4</td>
<td>P-gp/CYP3A4</td>
</tr>
<tr>
<td>Lab monitoring</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Antidote</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Drug Interactions

- inhibitors and inducers of P-glycoprotein +/- CYP3A4:

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

**Inducers**
- rifampicin
- phenytoin
- carbamazepine
- phenobarbitone
- dexamethasone
- doxorubicin
- vinblastine
- St. John’s wort
Dabigatran in DVT/PE Treatment
RECOVER I

- 2539 patients with DVT/PE
- All received LMWH x 10 days
- Dabi 150 mg bid vs warfarin
- P<0.001 for non-inferiority in efficacy (2.4% vs 2.1%)
- No difference in major bleeding (1.6% vs 1.9%)

Dabigatran is non-inferior to warfarin for prevention of recurrent or fatal VTE with comparable major bleeding risk

Rivaroxaban in DVT Treatment
EINSTEIN DVT

- 3449 patients with DVT
- Enox/warfarin vs Riva 15mg BID x 3 weeks then 20 mg OD
- No LMWH in rivaroxaban arm
- P<0.001 for non-inferiority in efficacy (2.1% vs 3.0%)
- No difference in major bleeding (0.8% vs 1.2%)

Rivaroxaban is non-inferior to enox/warfarin for prevention of recurrent or fatal VTE with comparable major bleeding risk

Rivaroxaban in PE Treatment

EINSTEIN PE

- 4832 patients with PE
- Enox/warfarin vs Riva 15mg x 3 weeks then 20 mg OD
- No LMWH in rivaroxaban arm
- P<0.001 for non-inferiority in efficacy (2.1% vs 1.8%)
- fewer major bleeding with rivaroxaban (1.1% vs 2.2%; p=0.003)

Rivaroxaban is non-inferior to enox/warfarin for prevention of recurrent or fatal VTE with lower risk of major bleeding

Limitations in Cancer Patients

- Paucity of clinical trial data
- No comparison against long-term LMWH
- Unreliable administration and absorption in patients with N+V+D and mucosal erosion
- Liver and renal dysfunction is common in cancer
- Lack of experience on management for procedures and thrombocytopenia
- Drug interactions may be clinically important
- Lack of measurement (therapeutic range) and antidote
How Should **You** Treat CAT?

- Get over YOUR fear/reluctance of injections
- Have patient do his/her first injection in clinic
- Allow alcohol to dry before injection
- Firm pressure for 2 min after injection to reduce bruising, hematoma and pain – DO NOT RUB
- Rotate sites and use "love handles"
- Insulin syringe offers greater comfort than prefilled syringes
- Round UP on dose to nearest prefilled syringe
- Dose based on body weight without capping
Cancer Associated Thrombosis

- CAT 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 should be discussed with patients at high risk
- LMWH is still the treatment of choice but we need to encourage research using new oral anticoagulants