Venous Thrombo-Embolism
overview

- The statistics
- Pathogenesis
- Prophylaxis
- Treatment
  - Agent
  - Duration
  - Incidental VTE
- Recurrence of VTE
- IVC filters
- CVC related thrombosis
- Thrombocytopenia
- DOACs
Of all cases of VTE:
- About 20% occur in cancer patients
- Annual incidence of VTE in cancer patients ≈ 1/250

Of all cancer patients:
- 15% will have symptomatic VTE
- As many as 50% have VTE at autopsy

Compared to patients without cancer:
- Higher risk of first and recurrent VTE
- Higher risk of bleeding on anticoagulants
- Higher risk of dying as a result of VTE
- Overall survival lower if VTE in Cancer: 12% 1 year survival vs >20%, Sorensen et al, NEJM 2000; 343.

- The risk of VTE in cancer patients undergoing surgery is 3-5 x higher than those without cancer

- Up to 50% of cancer patients may have evidence of asymptomatic DVT/PE

- Cancer patients with symptomatic DVT exhibit a high risk for recurrent DVT/PE that persists for many years
- VTE has significant negative impact on quality of life

- VTE may be the presenting sign of occult malignancy
  - Up to 10% with idiopathic VTE develop cancer within 2 years
Screening for underlying cancer

- NICE
- psychological burden
- cost of screening
- Small randomized trial: no statistically significant difference in cancer related mortality.
- Recommend extensive screening in patients who present with idiopathic VTE?
Pathogenesis
Risk Factors for VTE in Cancer

Risk varies from 1 – 30% depending on:

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

**Cancer-related**
- Primary site*
- Histology
- Metastatic disease
- Time interval since diagnosis

**Treatment-related**
- Surgery
- Chemotherapy
- Hormonal therapy
- Anti-angiogenic therapy
- ESA/EPO
- Hospitalization
- CVCs

* Pancreas, prostate, colon, brain, lung, breast, ovary

**Stasis**
- Prolonged bed rest
- Extrinsic compression of blood vessels

**Vascular Injury**
- Direct invasion by tumor
- Prolonged use of central venous catheters
- Endothelial damage by chemotherapy drugs
- Effect of tumor cytokines on vascular endothelium

**Hypercoagulability**
- Tumor-associated pro-coagulants and cytokines (tissue factor, CP, TNFα, IL-1β, VEGF, etc.)
- Impaired endothelial cell defense mechanisms (APC resistance; deficiencies of AT, Protein C and S)
- Enhanced selectin/integrin-mediated, adhesive interactions between tumor cells, vascular endothelial cells, platelets and host macrophages
Prophylaxis
Contra-indications (relative)

- Recent CNS bleed, intracranial or spinal lesion at high risk for bleeding
- Active bleeding (major): more than 2 units transfused in 24 hours
- Chronic, clinically significant measurable bleeding > 48 hours
- Thrombocytopenia (platelets < 50,000/mcL).
- Recent major operation at high risk for bleeding
- Underlying coagulopathy
- Clotting factor abnormalities
- Planned spinal anesthesia/lumbar puncture
- Patient specific factors (falls, ...)

Prophylaxis

- ‘Medical’ inpatients
- Surgery
- Radiotherapy
- Central Venous Catheters
Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?

“Hospitalized patients with cancer should be considered candidates for VTE prophylaxis in the absence of bleeding or other contraindications to anticoagulation”

Prophylaxis Studies in Medical Patients

Rate of VTE (%)

- Placebo Enoxaparin (MEDENOX Trial): Relative risk reduction 63%
- Placebo Dalteparin (PREVENT): Relative risk reduction 44%
- Placebo Fondaparinux (ARTEMIS): Relative risk reduction 47%

Francis, NEJM, 2007
Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?

“Routine prophylaxis is not recommended.”

“Patients receiving IMIDs (thalidomide, lenalidomide) with chemotherapy or dexamethasone are at high risk for thrombosis and warrant prophylaxis.”

Should hospitalized patients with cancer undergoing surgery receive peri-operative VTE prophylaxis?

- All patients should be considered for thromboprophylaxis.
- Procedures greater than 30 minutes should receive pharmacologic prophylaxis.
- Mechanical methods should not be used as monotherapy.
- Prophylaxis should continue for at least 7-10 days post-op. Extended/prolonged prophylaxis should be considered for cancer with high risk features.

Incidence of VTE in Surgical Patients

- Cancer patients have 2 fold risk of post-operative DVT/PE and >3-fold risk of fatal PE despite prophylaxis:

<table>
<thead>
<tr>
<th></th>
<th>No Cancer</th>
<th>Cancer</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=16,954</td>
<td>N=6124</td>
<td></td>
</tr>
<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>

Surgical Cancer Patients

@RISTOS

Prospective cohort
N=2373

symptomatic VTE 2.1%

overall mortality 1.7%

46% due to fatal PE

Extended Prophylaxis in Surgical Patients

ENOXACAN II

- Placebo
  - N=167
- Enoxaparin 40 mg
  - N=165

Incidence of Outcome Event

- VTE (12.0% vs 4.8%, P=0.02)
- Proximal DVT (1.8% vs 0.6%)
- Any Bleeding (3.6% vs 0%)
- Major Bleeding (0% vs 0.4%)

NNT = 14

Bergqvist D, et al. (for the ENOXACAN II investigators) *N Engl J Med* 2012;346:975-980
Should patients with cancer undergoing radiotherapy receive prophylaxis?

- No recommendations from ACCP/ASCO
- No data from randomized trials (RCTs)
- Weak data from observational studies in high risk tumors
Treatment
Anti-thrombotic Therapy: Choices

Pharmacologic (Prophylaxis & Treatment)

- Unfractionated Heparin (UH)
- Low Molecular Weight Heparin (LMWH)

Oral Anticoagulants:
- Warfarin,
- Direct anti-Xa inhibitors,
- Direct anti-IIa inhibitors,
- Fondaparinux
Oral Anticoagulant Therapy in Cancer Patients: Problematic

- Warfarin?
  - Difficulty maintaining tight therapeutic control, due to dietary changes/anorexia, vomiting, drug interactions
  - Frequent interruptions for thrombocytopenia and procedures
  - Difficulty in monitoring: hospital appointments/GP
  - Increased risk of both recurrence and bleeding
CLOT trial: Landmark Cancer/VTE Trial

Primary Endpoints: Recurrent VTE and Bleeding
Secondary Endpoint: Survival

Landmark CLOT Cancer Trial

- Risk reduction = 52%
- HR 0.48 (95% CI 0.30, 0.77)
- Log-rank p = 0.002

Days Post Randomization

Probability of Recurrent VTE, %

- VKA, 17%
- Dalteparin, 9%
CLOT 12-month Mortality
All Patients

Probability of Survival, %

Days Post Randomization

HR 0.94 P-value = 0.40

Standard of care is LMWH at therapeutic doses for a minimum of 3-6 months (ACCP, grade 1A) or 6 months ASCO/NCCN)

Reduced dose after 1 month?

Oral anticoagulant therapy to follow for as long as cancer is active (Grade 1C recommendation—ACCP). Decided on an individual basis.
Initial Phase

5-7 days

LMWH

(GRADE 1A)

Subacute Phase

3 - 6 months

LMWH

(GRADE 1A)

Chronic Phase

Continue anticoagulation (warfarin or LMWH) long-term or until malignancy resolves (GRADE 1C)

Buller HR, et al. Chest 2004; 126 (suppl 3): 401s-428s
Duration

- Usually minimum time of 3-6 months for DVT

- Below knee DVT 3 months

- Consider indefinite anticoagulation if active cancer or persistent risk factors. (ASCO: “After 6 months anticoagulation therapy should be considered for select patients”).
Incidental VTE

- 6% of all cancer patients (staging/restaging scan); 2.6% PE on staging CT chest.
- Incidental vs asymptomatic: 40-70% of patients retrospectively have/had symptoms.
- No RCTs, but two publications* where treatment occurred depending on physicians choice. In both papers anti-coagulated patients had an overall survival benefit.
- ASCO/ACCP: Should be treated

Recurrence of VTE
Treatment of Recurrent VTE

- 6-9% on LMWH (10-17% Warfarin): CLOT trial
- If on Warfarin: switch to LMWH (irrespective of INR)
- LMWH dose escalation is effective in cancer patients with recurrent VTE on anticoagulation
  - If on reduced dose (75% after 1 month): increase to full dose
  - If on full dose: 25% dose escalation and/or 50% dose escalation and split dose (off license)
  - Fewer than 5% experience any bleeding

- **DO NOT INSERT IVC FILTER**

- No evidence for other anticoagulants

IVC filters
IVC filters

- High risk of recurrence (>30%)
- Does not treat hypercoagulability or reduce symptoms
- Complications: Can lead to further thrombosis, venous gangrene, limb loss.
- No data to show reduction in mortality or hospitalization

- Do not use (ASCO, ACCP) unless: Absolute contra-indication to anticoagulation
CVC related thrombosis

(Central Venous Catheter)
Catheter related thrombosis

- No prospective data
- 14-18%
- Low risk of recurrence and low risk of post-thrombotic syndrome
- Complications:
  - Fibrin sheath formation (blocked line)
  - Superficial thrombophlebitis
  - Deep vein thrombosis
Management

- No benefit in routine prophylaxis to prevent thrombosis secondary to central venous catheters, including LMWH (2B) and fixed-dose warfarin (1B). (WARP trial; Young AM et al. Lancet 2009;373:567).

- No need for removal if functional and symptoms manageable (ACCP).

- For catheter associated thrombosis, anti-coagulate as long as catheter is in place and for 3 months (ACCP) or 6-12 weeks (BCSH).
Thrombocytopenia

- >75: Prophylaxis ok
- >50: treatment ok
- <50: transfuse platelets first 4 weeks
- If not possible to maintain:
  - 20-50: half dose LMWH
  - <20: hold off anticoagulation (retrievable filter?)

NOTE: unlicensed, non-evidence based.
DOACs

- Trials: EINSTEIN, RECOVER, AMPLIFY, HOKUSAI, …
- Only small numbers of cancer patients
- Non-inferiority
- Control arms often Warfarin, not LMWH
- No direct comparison with LMWH
- ASCO 2013: not recommended
Conclusions - overview

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- Treatment
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  - Duration
  - Incidental VTE
- Recurrence of VTE
- IVC filters
- Catheter related thrombosis
- Thrombocytopaenia
- DOACs
CLOT 12-month Mortality
All Patients

Probability of Survival, %

Days Post Randomization

HR 0.94 P-value = 0.40

Anti-Tumor Effects of LMWH CLOT 12-month Mortality

Patients Without Metastases (N=150)

Malignant Glioma

- Brain metastases or primary cancer of central nervous system
- Patients with primitive or metastatic intracranial malignancies present an increased risk of both VTE and bleeding. The rate of symptomatic DVT in patients with malignant glioma is 20–30%.
- The new antiangiogenic agent bevacizumab, used in recurrent glioblastoma, is associated with a further increased risk of VTE.
- The risk of intracranial bleeding is reported to be up to 7% and this is the main cause of the reluctance of physicians to use anticoagulants in this setting.
- The risk of intratumoral haemorrhage on therapeutic anticoagulation is estimated to be 2%.
- Historically, physicians have often favoured the insertion of inferior vena cava filters over anticoagulation in patients with malignant glioma and VTE but, more recently, it has been reported a high rate of VTE recurrence with inferior vena cava filters, without improved overall survival or reduced intracranial haemorrhage.