Disclosures

• Financial conflicts of interest:
  – I have received funding from Bayer (speaker honoraria), Sanofi (advisory boards), Thrombosis Canada (speaker honoraria and funding related to quality improvement projects), and UpToDate (royalties)

• Intellectual conflicts of interest:
  – I am a site investigator for a study funded by Bayer
  – I am a site investigator for an upcoming study funded by Boehringer Ingelheim

• I will discuss off-label usage of pharmaceuticals in this talk
FICTION: Thrombosis is 100% “straightforward”
FACT: Thrombosis is 99% “straightforward”
Objectives

• Learn about current controversies in thrombosis and vascular medicine
  – How long do we treat VTE?
  – When do we thrombolyze PEs?
  – When do we thrombolyze DVTs?
  – Should we use IVC filters?
  – Do we care about weird clots?
    • calf vein thrombosis
    • subsegmental PE
    • portal vein clots
<table>
<thead>
<tr>
<th>Treating unprovoked VTE</th>
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<td>Thrombolysis for PE</td>
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<td>5</td>
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</table>
## The party line: Duration of Therapy

<table>
<thead>
<tr>
<th>Categories of VTE</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated distal DVT, DVT or PE provoked by a transient risk factor</td>
<td>3 months</td>
</tr>
<tr>
<td>First unprovoked VTE</td>
<td>Minimum of 3 months and then reassess. For patients with no or only minor risk factors for bleeding, long-term therapy with annual review can be <strong>offered</strong>. Decision to continue anticoagulation should consider patient’s values and preferences.</td>
</tr>
<tr>
<td>Second unprovoked VTE</td>
<td>Minimum of 3 months and then reassess. For patients with no or only minor risk factors for bleeding, long-term therapy with annual review should be <strong>encouraged</strong>. Decision to continue anticoagulation should consider patient’s values and preferences.</td>
</tr>
<tr>
<td>Cancer-associated VTE</td>
<td>Minimum of 3 months and then reassess. Continue if active cancer (overt evidence of cancer) or continuing to receive anti-cancer therapy</td>
</tr>
</tbody>
</table>

Kearon C et al, Chest. 2012;141(2 Suppl):e419S.
# Systematic Review:
*Recurrent VTE in First 3 Months on Anticoagulants*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pts with any VTE*</th>
<th>Pts with DVT</th>
<th>Pts with PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>19 027</td>
<td>10 050</td>
<td>3 422</td>
</tr>
<tr>
<td>Recurrent fatal VTE (95% confidence interval (CI)), %</td>
<td>0.4 (0.3 – 0.6)</td>
<td>0.3 (0.2 – 0.5)</td>
<td>1.3 (0.9 – 1.7)</td>
</tr>
<tr>
<td>Recurrent PE (95% confidence interval), %</td>
<td>1.6 (1.3 – 2.0)</td>
<td>1.3 (1.0 – 1.7)</td>
<td>3.0 (2.5 – 3.7)</td>
</tr>
<tr>
<td>Recurrent VTE (95% confidence interval), %</td>
<td>3.4 (2.9 – 4.0)</td>
<td>3.2 (2.4 – 4.1)</td>
<td>3.6 (2.3 – 5.0)</td>
</tr>
</tbody>
</table>

*Patients presenting with DVT, PE or both or patients whose initial presentation was not specified in original study reports*

Systematic Review:  
*Bleeding in First 3 Months on Anticoagulants*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients with any VTE+</th>
<th>Patients with DVT</th>
<th>Patients with PE</th>
</tr>
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<tbody>
<tr>
<td>Patients, n</td>
<td>19 027</td>
<td>10 050</td>
<td>3 422</td>
</tr>
<tr>
<td>Fatal major bleeding event (95% CI), %</td>
<td>0.2 (0.1 – 0.3)</td>
<td>0.2 (0.1 – 0.3)</td>
<td>0.2 (0.1 – 0.4)</td>
</tr>
<tr>
<td>Major bleeding event (95% CI), %</td>
<td>1.6 (1.3 – 2.0)</td>
<td>1.6 (1.2 – 2.1)</td>
<td>1.8 (1.1 – 2.6)</td>
</tr>
</tbody>
</table>

+Patients presenting with DVT, PE or both or patients whose initial presentation was not specified in original study reports

Several factors have been associated with recurrence of unprovoked VTE

• “After a first unprovoked VTE, you have a 5-15% percent risk of VTE recurrence within the first year after discontinuing anticoagulation, and a 30% to 50% risk of VTE recurrence within the following 5 to 10 years.”

• What drives up the risk of VTE recurrence?
  – Absence of a temporary risk factor
  – Pulmonary embolism or proximal DVT
  – More than two thrombotic events
  – Male sex
  – Residual vein thrombosis
  – Presence of a vena cava filter
  – Continued estrogen use
  – Diabetes mellitus, neurologic disease with paresis, IBD
  – Malignancy
  – eGFR <30 mL/min
  – Residual venous obstruction
  – D-dimer levels after cessation of anticoagulation
  – Thrombin generation
Risk assessment models may be useful

HERDOO2
- HER on either leg
- Obesity - BMI > 30
- Older than 65 yo

DASH
- Age < 50
- Hormones not used (for women)

Male sex
- Elevated D-dimer

Vienna
- Location of VTE
Duration of therapy in unprovoked VTE is not black and white

• Ongoing trial: **DULCIS** (NCT00954395)
  – Test predictive value of D-dimer and residual vein obstruction (RVO) at 30 days after cessation of anticoagulation

• Ongoing study: **BLEEDING RISK**
  – Derive prediction rule assessing major bleeding risk after the first 3 months of OAC, focusing on patients on any anticoagulant for at least 3 months for treatment of DVT/PE, with plans to continue for at least 3 more months

• In the real world, patient values and preferences drive decision-making

http://clinicaltrials.gov/show/NCT00954395
What about acetylsalicylic acid (ASA) for long-term therapy?

- Two studies compared 100 mg ASA to placebo in patients with first unprovoked DVT who completed 6-18 months of anticoagulation
- Pooled analysis showed that patients on ASA had:
  - 32% reduction in VTE recurrence (p=0.007)
  - 34% reduction in other major vascular events (e.g., ACS, stroke) (p=0.002)
  - No significant increase in major or clinically significant bleeding
- ASA should not be used for initial treatment of DVT
- ASA likely provides less benefit than continued anticoagulation for extended treatment!

Treating unprovoked VTE

Thrombolysis for PE

Thrombolysis for DVT

Using IVC filters

Weird clots
Thrombolysis is recommended for massive or high risk PE

- Patients with acute PE, right ventricular failure and hemodynamic compromise are at increased risk of early mortality

- International guidelines recommend these high risk patients be considered for systemic thrombolysis
  - May reduce mortality
  - May increase risk of major bleeding – including 2% risk of intracranial hemorrhage

The thrombolysis “recipe” is variable

• Various regimens have been used
• Most popular:
  – rt-PA 100 mg IV, with 10 mg given over 10 minutes and remaining 90 mg given over 2 hours
  – Followed by IV heparin infusion with no initial bolus

Evidence is less clear for submassive or intermediate risk PE

- Patients with stable blood pressure require further risk stratification
  - The completely stable patient?
  - The patient with evidence of right ventricular dysfunction on imaging?
  - The patient with evidence of right ventricular dysfunction on laboratory analysis?

A recent meta-analysis attempted to risk stratify these patients

• 16 trials with 2115 patients
• Major findings (compared to anticoagulation):
  – Thrombolysis associated with lower mortality risk
  – Thrombolysis associated with higher major bleeding risk and intracranial hemorrhage
  – In patients >65 years old, thrombolysis associated with higher major bleeding risk
  – In intermediate risk patients, thrombolysis associated with lower mortality risk and higher major bleeding risk

### Absolute risk of clinically important outcomes

<table>
<thead>
<tr>
<th>Outcome of Interest (No. of Studies Reporting)</th>
<th>No. of Events/No. of Patients, Absolute Event Rate (%)</th>
<th>No. Needed to Treat or Harm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombolytic Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality (16)</td>
<td>23/1061 (2.17)</td>
<td>NNT = 59</td>
<td>.01</td>
</tr>
<tr>
<td>Major bleeding (16)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98/1061 (9.24)</td>
<td>NNH = 18</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ICH (15)</td>
<td>15/1024 (1.46)</td>
<td>NNH = 78</td>
<td>.002</td>
</tr>
<tr>
<td>Recurrent PE (15)</td>
<td>12/1024 (1.17)</td>
<td>NNT = 54</td>
<td>.003</td>
</tr>
<tr>
<td><strong>Anticoagulant Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality (16)</td>
<td>41/1054 (3.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding (16)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36/1054 (3.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH (15)</td>
<td>2/1019 (0.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent PE (15)</td>
<td>31/1019 (3.04)</td>
<td></td>
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</table>

| Age >65 y                                     |                                                        |                            |         |
| All-cause mortality (5)                       | 14/673 (2.08)                                           | NNT = 64                   | .07     |
| Major bleeding (5)<sup>a</sup>                | 87/673 (12.93)                                          | NNH = 11                   | <.001   |

| Age ≤65 y                                     |                                                        |                            |         |
| All-cause mortality (11)                      | 9/388 (2.32)                                            | NNT = 51                   | .09     |
| Major bleeding (11)<sup>a</sup>               | 11/388 (2.84)                                           | NNH = 176                  | .89     |

| Intermediate-risk PE                          |                                                        |                            |         |
| All-cause mortality (8)                       | 12/866 (1.39)                                           | NNT = 65                   | .03     |
| Major bleeding (8)<sup>a</sup>                | 67/866 (7.74)                                           | NNH = 18                   | <.001   |

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Thrombolysis is recommended for massive proximal DVTs

- Options are thrombolytic therapy, surgical thrombectomy or catheter-directed thrombolysis

- 2014 Cochrane review of 17 trials established role of thrombolysis
  - More rapid and complete clot dissolution
  - Less PTS (RR 0.64)
  - More bleeds (RR 2.23)
  - No differences in mortality or pulmonary embolic events.

- Should be considered for patients with acute massive iliofemoral or femoral DVT

Phlegmasia cerulea dolens

Strijkers RHW et al. BMJ 2011;343:d5916
The thrombolysis “recipe” is variable

• Various thrombolytic regimens have been used
• Most popular:
  – rt-PA 100 mg IV, with 10 mg given over 10 minutes and remaining 90 mg given over 2 hours OR whatever the interventional radiologists at SJH tell you to do
  – Followed by IV heparin infusion with no initial bolus

• Ongoing trial: ATTRACT (NCT00790335)
  – Open label randomized multicentre trial of pharmacomechanical catheter-directed thrombolysis with rt-PA in patients with acute proximal DVT
  – Primary outcome: PTS

http://www.clinicaltrials.gov/show/NCT00790335
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<th>Section</th>
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IVC filters are tremendously controversial

• No randomized trial or prospective cohort study has evaluated inferior vena caval filters as sole therapy in patients with DVT!

• IVC filters may be useful in patients with acute DVT who cannot be anticoagulated

• Words of warning about IVC filters:
  – They decrease rate of PE, but increase rate of DVT
  – They have no impact on established PE
  – They have local adverse effects
  – They are not always “retrievable”
Common retrievable IVC filter types

Cordis OptEase filter

Günther Tulip Filter
Main complications of IVC filters

<table>
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<tr>
<th>Complication</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to retrieve a “retrievable” filter</td>
<td>0-22</td>
</tr>
<tr>
<td>Complications from insertion</td>
<td>4-11</td>
</tr>
<tr>
<td>Insertion site thrombosis</td>
<td>2-28</td>
</tr>
<tr>
<td>IVC thrombosis</td>
<td>6-30</td>
</tr>
<tr>
<td>Filter migration</td>
<td>3-69</td>
</tr>
<tr>
<td>IVC perforation</td>
<td>9-24</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>5-70</td>
</tr>
</tbody>
</table>

Reported IVC filter related events in a national FDA-sponsored voluntary database over an 11-year period

Treating unprovoked VTE

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Weird clots
Do we care about calf vein thrombosis?

• Don't look for them! (We don't)
• Meta-analysis to explore treatment options found poor quality, small studies
  – Clot propagation is less frequent if you anticoagulate (OR 0.29) - but do we really care?

• Consider several factors when deciding on treatment
  – Severity of symptoms
  – Clot close to proximal veins
  – Other risk factors
  – Bleeding risk

Do we care about calf vein thrombosis?

• Ongoing trial: CACTUS-PTS (NCT00421538)
  – Randomized trial of 6 week course of nadroparine 171 u/kg OD versus placebo for first time symptomatic isolated distal thrombosis
  – Outcomes include proximal DVT, symptomatic PE and PTS

http://clinicaltrials.gov/show/NCT00421538
Do we care about subsegmental PE?

- Multi-row detector CTPA highly sensitive and specific for PE

- 2010 systematic review suggested subsegmental PEs were not that important

- But 2013 prospective cohort study suggested that they were!
  - Compared to patients with no PE, subsegmental PE patients on anticoagulation had more...
    - Symptomatic recurrent venous thromboembolism occurred in (3.6% vs 1.1%)
    - Death (6.5% vs 5.4%)

---

Do we care about subsegmental PE?

• If I am not inclined to treat
  – I do an U/S first
  – And do another one later
• If I am inclined to treat
  – I generally do so if there's an active VTE risk factor
  – I generally do so only if the risk of bleeding is low

• Ongoing trial: SSPE (NCT01455818)
  – Prospective cohort study withholding anticoagulant therapy in patients with subsegmental PE who have negative results by serial ultrasonography for DVT
  – Primary outcome: recurrent VTE

http://clinicaltrials.gov/show/NCT01455818
Do we care about portal vein clots?

The splenic artery is a branch of the celiac trunk. It traverses along the superior margin of the pancreas toward the spleen branching to form up to six major arteries before entering the spleen. The splenic vein joins the superior mesenteric vein to form the portal vein.
Do we care about portal vein clots?

• Where do we see them?
  – Cirrhosis
  – Abdominal infection/inflammation/instrumentation/trauma
  – Oral contraceptives
  – Thrombophilias
  – Myeloproliferative neoplasms

• Why do we care?
  – Acute pyelophlebitis
  – Intestinal ischemia
  – Portal hypertension
  – Varices
  – Portal cholangiopathy
Do we care about portal vein clots?

• Consider several factors when deciding on treatment
  – When the clot occurred
  – Whether we’re dealing with infection or ischemia
  – The risk of recurrent clotting
  – The risk of bleeding
  – Whether there’s an important reason to recanalize the vein
Do we care about portal vein clots?

• 2001 retrospective study observed 136 adults with noncirrhotic PVT - 84 were anticoagulated
  – Anticoagulation reduced risk of clotting
  – Anticoagulation did not increase risk of bleeding

• Liver transplant patients may do better post-op if they receive anticoagulation pre-op

• Surgical shunting may be needed in the acute setting

In Summary

• The “1%” of thrombosis is what...
  – Challenges us clinically
  – Drives the research agenda
  – Keeps us focused on the importance of making decisions *collaboratively* with our patients
Thank you for your attention!