Case Study:
Patient with VTE

Stephan Moll, MD
UNC Chapel Hill, NC

ISTH Advanced Training Course
Atlanta, Nov 2nd, 2016
## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Conflicts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>No</td>
</tr>
<tr>
<td>Employee</td>
<td>No</td>
</tr>
<tr>
<td>Consultant</td>
<td>Boehringer-Ingelheim, Janssen Pharmaceuticals</td>
</tr>
<tr>
<td>Major Stockholder</td>
<td>No</td>
</tr>
<tr>
<td>Speakers Bureau</td>
<td>No</td>
</tr>
<tr>
<td>Honoraria</td>
<td>No</td>
</tr>
<tr>
<td>Scientific Advisory Board</td>
<td>No</td>
</tr>
</tbody>
</table>

Off-label use of a drug or medical device: None
28 year old woman
1 week of increasing L leg pain + swelling
3 d mild SOB + CP

VTE: Left leg proximal DVT, B subsegmental PE

VTE risk factors: (a) OCP, (b) BMI 32.7 kg/m², (c) Fam h/o (father unprovoked VTE @ 42 yrs)
Q1:
Outpatient or inpatient?

- Diagnosis
- few days later
- 3 mo
- any time
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hemodynamically unstable?</td>
</tr>
<tr>
<td>2.</td>
<td>Thrombolysis or embolectomy necessary?</td>
</tr>
<tr>
<td>3.</td>
<td>Active bleeding or high risk of bleeding?</td>
</tr>
<tr>
<td>4.</td>
<td>Oxygen needed to keep $O_2$ sat &gt; 90% for &gt; 24 hrs?</td>
</tr>
<tr>
<td>5.</td>
<td>PE dx’d during anticoagulant therapy?</td>
</tr>
<tr>
<td>6.</td>
<td>iv pain medication for &gt; 24 hrs?</td>
</tr>
<tr>
<td>7.</td>
<td>Medical or social reason for admission?</td>
</tr>
<tr>
<td>8.</td>
<td>GFR &lt; 30 ml/min?</td>
</tr>
<tr>
<td>9.</td>
<td>Severe liver impairment?</td>
</tr>
<tr>
<td>10.</td>
<td>Pregnant?</td>
</tr>
<tr>
<td>11.</td>
<td>Documented h/o HIT?</td>
</tr>
</tbody>
</table>

Outpatient vs. Inpatient

- **DVT**: Patient can walk into clinic/ED ➔ pt can walk out of it.
- **PE**: Suitable for, may be, 50% of pts.
Q1: Outpatient or inpatient?

Q2: Thrombolytics?
CaVenT study
  • 209 patients with proximal DVT
  • Randomized, controlled trial
  • Catheter-directed thrombolysis decreased PTS, at expense of major bleeding

ATTRACT trial
  • Enrollment completed (n = 692) Dec 2014
  • Follow-up 2 years

# PE: Indicators of Bad Outcome

## ESC criteria (based on consensus; lack of validation)

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Cardiovascular shock or persistent ↓ BP</td>
<td>&gt; 30 %</td>
</tr>
<tr>
<td>“massive PE”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Lab (troponin, BNP) ↑ or RV dysfunction</td>
<td>1-30 %</td>
</tr>
<tr>
<td>“sub-massive PE”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>nl labs (troponin, BNP); nl RV function</td>
<td>&lt; 1 %</td>
</tr>
<tr>
<td>“low-risk PE”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Ref 1: Torbicki A et al. Eur Heart J 2008;2276-315]
[Ref 2: Meyer G et al. NEJM 2014;370:1402-11]
PE: Thrombolysis?

PEITHO trial

• Patients with submassive PE (R heart strain, + cardiac enzymes)
• Less “hemodynamic compensation”
• No impact on 28 day mortality
• Increased intracranial bleeding

[Meyer G et al. NEJM 2014;370:1402-11]

• Pulmonary HTN (CTEPH)
• Post-PE syndrome

Patients with “moderate” PE (defined by clot burden)

121 pts randomized to tPA vs none

tPA (50 mg as 10 mg bolus + 40 mg over 2 hrs; “safe dose”)

Evaluation at 28 months

Table 2
Primary end points at 28 ± 5 mo of follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>TG (n = 58; 100%)</th>
<th>CG (n = 56; 100%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension*</td>
<td>9 (16%)</td>
<td>32 (57%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary hypertension plus recurrent pulmonary embolism</td>
<td>9 (16%)</td>
<td>35 (63%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Pulmonary artery systolic pressure ≥40 mm Hg.

Table 3
Secondary end points

<table>
<thead>
<tr>
<th>Variable</th>
<th>TG (n = 61; 100%)</th>
<th>CG (n = 60; 100%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent pulmonary embolism</td>
<td>0</td>
<td>3 (5%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1 (1.6%)</td>
<td>3 (5%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Total mortality plus recurrent pulmonary embolism</td>
<td>1 (1.6%)</td>
<td>6 (10%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>2.2 ± 0.5</td>
<td>4.9 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Bleeding | 0 | 0 | — |

Data are presented as mean ± SD or n (%).

PE: Thrombolysis?

Thrombectomy/thrombolytics:

- **DVT**: may be in the young, extensive DVT, low risk for bleeding?
- **PE**:
  - Massive
  - Submassive (R heart strain + pos troponin) in the younger patient at low risk for bleeding?

PEITHO trial

Patients with submassive PE (R heart strain, + cardiac enzymes)

Less "hemodynamic compensation"

No impact on 28 day mortality

Increased intracranial bleeding

[Meyer G et al. NEJM 2014;370:1402-11]
Q1: Outpatient or inpatient?

Q2: Thrombolytics?

Q3: LMWH/warfarin or DOAC?
DOACs and VTE

ACCP 2016: We suggest DOAC over warfarin


In which patient do I consider a DOAC?

a) **Acute DVT or PE**
   - All VTE patients, particularly outpatients
   - Mild to moderate VTE

b) **On long-term warfarin**
   - I discuss it with all patients
   - Fluctuating INRs, high “warfarin hate factor”
DOACs are good treatment choice in many VTE patients – acute or chronic.
Patient Education

Deep Vein Thrombosis and Pulmonary Embolism

ClotConnect.org

Information for Newly Diagnosed Patients

Treatment

The treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) are similar.

The goals of treatment are:
→ To prevent an existing clot from growing in size
→ To prevent the formation of new clots
→ To prevent a DVT from breaking off, traveling through the bloodstream, and becoming a PE
→ To prevent or minimize long-term complications.

a) Blood-Thinning Medications
The primary treatment for blood clots is blood-thinning medication, known as an anticoagulant or "blood-thinner".

These medications increase the time it takes for your blood to clot, reducing the risk of blood clots forming.

Common Questions

1) When will my clot and pain go away?
Blood thinners themselves do not dissolve the clot. The body will slowly break down the clot over the course of several weeks to months. The swelling which accompanied the blood clot gradually improves and disappears.

→ Most patients with DVT or PE recover within several weeks, with minimal or no long-term effects.

Information and Support

Clot Connect is an education and outreach project of the University of North Carolina at Chapel Hill Blood Clot Outreach Program. Clot Connect’s mission is to increase knowledge of blood clots and clotting disorders by providing education and support resources for patients and health care professionals.

Blood clot survivors face many unique challenges including risks associated with anticoagulant use (blood thinners), the development of post-thrombotic disorders and increased risks for future clots. Blood clot survivors and their families need information and support to manage the effects of a blood clot and to prevent future clots.

Health care professionals also need easy access to the latest treatment and scientific research related to the
Q1: Outpatient or inpatient?

Q2: Thrombolytics?

Q3: LMWH/warfarin or DOAC?

Q4: Compression stockings?
### Stockings? SOX Trial

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Active stockings (n=409)</th>
<th>Placebo stockings (n=394)</th>
<th>Hazard ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of post-thrombotic syndrome events as assessed by Ginsberg's criteria† (cumulative incidence‡)</td>
<td>44 (14.2%)</td>
<td>37 (12.7%)</td>
<td>1.13 (0.73–1.76)</td>
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<tr>
<td>Number of post-thrombotic syndrome events as assessed by Villalta’s criteria§ (cumulative incidence‡)</td>
<td>176 (52.6%)</td>
<td>168 (52.3%)</td>
<td>1.00 (0.81–1.24)</td>
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<table>
<thead>
<tr>
<th>Villalta severity category¶</th>
<th>Active stockings (n=409)</th>
<th>Placebo stockings (n=394)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None (score &lt;5)</td>
<td>185 (51.3%)</td>
<td>178 (51.4%)</td>
<td>..</td>
</tr>
<tr>
<td>Mild (5–9)</td>
<td>119 (33.0%)</td>
<td>111 (32.1%)</td>
<td>..</td>
</tr>
<tr>
<td>Moderate (10–14)</td>
<td>30 (8.3%)</td>
<td>37 (10.7%)</td>
<td>..</td>
</tr>
<tr>
<td>Severe (&gt;14 or ulcer)</td>
<td>27 (7.5%)</td>
<td>20 (5.8%)</td>
<td>..</td>
</tr>
<tr>
<td>Ipsilateral leg ulcer¶¶</td>
<td>17 patients (4.2%); 17 ulcers</td>
<td>16 patients (4.1%); 17 ulcers</td>
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**Conclusion:** Compression stockings did not prevent PTS
Stockings? SOX Trial

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[Note: Kahn S et al. Lancet 2014;383:880-8]

Don’t MAKE patients wear compression stockings, but offer them.
Q1: Outpatient or inpatient?

Q2: Thrombolytics?

Q3: LMWH/warfarin or DOAC?

Q4: Compression stockings?

Q5: D/c anticoag or long-term?
Recurrence Triangle

VTE due to major transient risk factor

Woman with VTE on hormones

Non-major transient risk factor

Woman with unprovoked VTE
  - DVT
  - PE

Man with unprovoked VTE
  - DVT
  - PE

Recurrence Triangle

3 months

VTE due to major transient risk factor

Woman with VTE on hormones
Non-major transient risk factor

Woman with unprovoked VTE
- DVT
- PE

Man with unprovoked VTE
- DVT
- PE

Long-term

Cumulative VTE Recurrence Rate

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE due to major transient risk factor</td>
<td>1 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Woman with VTE on hormones</td>
<td>5 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Woman with unprovoked VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man with unprovoked VTE</td>
<td>10 %</td>
<td>30 %</td>
</tr>
</tbody>
</table>

Hormones and VTE Recurrence

1. [Kyrle P et al. NEJM 2004;350:2558-63]
2. [Christiansen SC et al. JAMA 2005;293:2352-61]

Cumulative VTE Recurrence Rate @ 5 years: 6%
**DODS study**

- Women with **neg. D-dimer** on and off anticoagulation: 0 % VTE recurrence
- Study did not investigate recurrence in women with **pos. DD** who d/c’d anticoag.

Risk of Recurrent VTE with Thrombophilia

1. II20210, hetero: 1.45 (95% CI 0.96-2.21)
   FVL, hetero: 1.56 (95% CI 1.14-2.12)
   [Segal J et al. JAMA 2009; 301:2472-85]

2. FVL, homo: 2.65 (95% CI 1.18-5.97)
   FVL, homo: 1.2 (95% CI 0.5-2.6)
   [Segal J et al. JAMA 2009; 301:2472-85; meta-analysis]
   [Lijfering WM et al. Circulation 2010;121:1706-12]

3. FVL + II2010: 4.81 (95% CI 0.50-46.3)
   FVL + II2010: 1.0 (95% CI 0.6-1.9)
   [Segal J et al. JAMA 2009; 301:2472-85; meta-analysis]
   [Lijfering WM et al. Circulation 2010;121:1706-12]

4. II20210, homo: insufficient data
Risk of Recurrent VTE with Thrombophilia

Protein C
Protein S
Antithrombin

2.8 (95 % CI 2.0 – 4.0)

[Liijfering WM et al. Circulation 2010;121:1706-12]

APLA: 1.41 (95 % CI 0.99-2.00)
ACA: 1.53 (95 % CI 0.76-3.11)
LA: 2.83 (95 % CI 0.83-9.64)

10 prospective studies
2,527 patients

Findings:
- After 1\textsuperscript{st} unprovoked DVT, RVO weak overall predictor of recurrent VTE (HR = 1.32, 95% CI: 1.06–1.65)
- Association is stronger if RVO is detected at earlier time (3 months) after thrombosis (HR = 2.17; 95% CI: 1.11–4.25), but non-significant if detected later, i.e. >6 months (HR = 1.19; 95% CI: 0.87–1.61).

Residual Clot as Predictor of Recurrence

- 10 prospective studies
- 2,527 patients
- Findings:
  - After 1\textsuperscript{st} unprovoked DVT, RVO weak overall predictor of recurrent VTE (HR = 1.32, 95\% CI: 1.06–1.65)
  - Association is stronger if RVO is detected at earlier time (3 months) after thrombosis (HR = 2.17; 95\% CI: 1.11–4.25), but non-significant if detected later, i.e. >6 months (HR = 1.19; 95\% CI: 0.87–1.61).


- “Residual Clot” clinically not helpful.
- “However, f/u Doppler ultrasound indicated when stopping anticoagulation, as a new baseline.

[i.e. >6 months (HR = 1.19; 95\% CI: 0.87–1.61)]


How Long to Anticoagulate?

Conglomerate decision of:

1. Risk of recurrent VTE
   (a)…., (b)….., (c) ….

2. Risk for Bleeding
   (a).., (b)..., (c) ...

3. Patient preference

“Warfarin Hate Factor”

Blood Thinner “Hate Factor”
Q1: Outpatient or inpatient?
Q2: Thrombolytics?
Q3: LMWH/warfarin or DOAC?
Q4: Compression stockings?
Q5: D/c anticoag or long-term?
Q6: ASA?
Q7: Major bleed

Diagnosis

few days later

3 mo

any time

Patient
1. **Major Bleeding** on warfarin


2. **Urgent Surgery** on warfarin

DOACs and Major Bleeding

1. Dabigatran

2. Idarucizumab

[Pollack CV et al. NEJM 2015;373(6):511-20]

3. Andexanet


4. PER-977 (aripazine, ciraparantag)

Bleeding on Anticoagulants

**UNC HEALTH CARE GUIDELINE**
Emergent Anticoagulation Reversal

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**Warfarin**

**Anti-Xa Agents**

---

**TABLE 2: MANAGEMENT OF WARFARIN-RELATED BLEEDING EVENTS**

<table>
<thead>
<tr>
<th>INR</th>
<th>Bleeding</th>
<th>Risk Factors</th>
<th>Intervention</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4.0</td>
<td>Yes</td>
<td>None</td>
<td>Oral vitamin K</td>
<td>NHLBI guidelines</td>
</tr>
<tr>
<td>3.5-4.0</td>
<td>Yes</td>
<td>None</td>
<td>Oral vitamin K</td>
<td>NHLBI guidelines</td>
</tr>
<tr>
<td>2.5-3.5</td>
<td>Yes</td>
<td>None</td>
<td>Oral vitamin K</td>
<td>NHLBI guidelines</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>Yes</td>
<td>None</td>
<td>Oral vitamin K</td>
<td>NHLBI guidelines</td>
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<tr>
<td>&gt;2.0</td>
<td>Yes</td>
<td>None</td>
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<td>NHLBI guidelines</td>
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</tbody>
</table>

**TABLE 3: MANAGEMENT OF DABIGATRAN-RELATED BLEEDING EVENTS**

**TABLE 4: MANAGEMENT OF FACTOR XA INHIBITOR-RELATED BLEEDING EVENTS**

**Warfarin**

**Dabigatran**

**Anti-Xa Agents**

---

**TABLE 3: MANAGEMENT OF DABIGATRAN-RELATED BLEEDING EVENTS**

<table>
<thead>
<tr>
<th>Bleeding Severity</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>1. Discontinue dabigatran</td>
</tr>
<tr>
<td></td>
<td>2. Oral vitamin K</td>
</tr>
<tr>
<td></td>
<td></td>
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<th>Bleeding Severity</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>1. Discontinue factor Xa inhibitor</td>
</tr>
<tr>
<td></td>
<td>2. Oral vitamin K</td>
</tr>
<tr>
<td></td>
<td>3. Consider any of the following based on bleeding severity:</td>
</tr>
<tr>
<td></td>
<td>• Symptomatic treatment</td>
</tr>
<tr>
<td></td>
<td>• Mechanical compression</td>
</tr>
<tr>
<td></td>
<td>• Surgical intervention</td>
</tr>
<tr>
<td></td>
<td>• Fluid replacement and hemodynamic support</td>
</tr>
<tr>
<td></td>
<td>• Blood product transfusion</td>
</tr>
<tr>
<td></td>
<td>• Oral Anticoagulant Chamber of previous dose ingested within 12 hours: passenger.</td>
</tr>
<tr>
<td></td>
<td>0.5 g PO x 2 doses if reversal is not achieved with the strategies outlined above, proceed to the steps below and obtain a hematology consultation for further recommendations.</td>
</tr>
</tbody>
</table>
Contraceptive Choices

Estrogen combination pill
- 4th generation
- 3rd generation
- 2nd generation

Injectable progestins
- Depot preparation
- Rod

Progestin pill (minipill)

Progestin-releasing IUDs

Non-hormonal methods

Norelgestromin & ethinyl estradiol
Etonogestrel & estradiol ring
Drospirenone & ethinyl estradiol

6. Tepper NK et al. Contraception 2016;May 3. [Epub ahead of print]
Progestin-IUDs safe contraceptive choice.
Family Implications

What’s the absolute VTE risk / year?

- Fam H/o VTE (1st degree relative) 2.6x
- + OCP + obesity + smoking + FVL
- + OCP + obesity + smoking
- + OCP + obesity
- + OCP or obesity or FVL

References:

Family Implications

What’s the absolute VTE risk / year?

- + OCP + obesity + smoking + FVL
- + OCP + obesity + smoking
- + OCP + obesity
- + OCP or obesity or FVL

Fam H/o VTE (1st degree relative)

2.6x

# Which Family Members to Test

<table>
<thead>
<tr>
<th>Proband’s thrombophilia</th>
<th>Male Family Member</th>
<th>Female Family Member</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sons</td>
<td>Brothers</td>
</tr>
<tr>
<td>Hetero FVL or hetero prothrombin 20210</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Homo FVL or homo prothrombin 20210</td>
<td>no</td>
<td>reasonable</td>
</tr>
<tr>
<td>Double hetero</td>
<td>reasonable</td>
<td>reasonable</td>
</tr>
<tr>
<td>C, S, AT</td>
<td>reasonable</td>
<td>reasonable</td>
</tr>
</tbody>
</table>

"**reasonable**" because: consider LMWH with airline travel, cast, non-major surgery; prolonged after major surgeries.

"**yes**" because: advise against estrogen contraceptives/hormone therapy; give ante- and postpartum anticoagulation.
Summary – 3 Key Points

1. Define clot.
2. VTE risk factors: a)…. (b)…. (c) …
3. Duration of anticoagulation: Recurrence triangle
4. “Warfarin/DOAC hate factor.”
Questions?
Comments?
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