Anticoagulant Therapy for Patients with Venous Thromboembolism (VTE): What you need to know in 2016?

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<table>
<thead>
<tr>
<th>Category</th>
<th>Disclosures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, Boehringer-Ingelheim</td>
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<td>Employee</td>
<td>Up-to-Date, Merck Manual</td>
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<td>Consultant</td>
<td>Actelion, AGEN Biomedical, Biotie, Boehringer-Ingelheim, Cytori, Ortho-Janssen, Portola</td>
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<td>No relevant conflicts of interest to declare</td>
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Presentation Objectives

To review recent developments in the management of patients with venous thromboembolism (VTE), addressing the following clinical scenarios:

• What are the anticoagulant options for patients with VTE? *When to use DOACs vs. VKAs vs. LMWH?*

• When should I use thrombolytic or mechanical methods to treat VTE?

• How to decide the duration of anticoagulant therapy, *especially after unprovoked VTE?*
Guideline-based vs. Individualized Management

• Practice guidelines designed for the ‘average’ patient.
• Individualized management considers each patient separately.

• Two approaches complementary: guidelines not applicable to all patients but individualized care should incorporate guidelines.
Individualized, Holistic Patient Management

- Consider each patient unique

“The good physician treats the disease; the great physician treats the patient who has the disease.”
(William Osler)
Holistic Paradigm to Treatment of VTE

**Submassive DVT or PE**

- catheter-associated DVT
- iliofemoral DVT
- isolated calf DVT
- cancer-associated DVT or PE
- splanchnic or cerebral sinus DVT
- massive PE

**Therapy Options**

- VKA or DOAC
- UFH
- LMWH
- Thrombolysis (tPA)
- Mechanical thrombus removal
- Leg elevation and compression stockings
- Lifestyle (activity, diet, smoking)
VTE is a heterogeneous disease...
Case No. 1

• 25 year woman with asthma presents to ER at 8PM with 1-day history of worsening dyspnea not improved with puffers, dizziness and sharp pleuritic chest pain.

• BP = 100/60, HR = 125/min, RR = 25, O_2 sat 90% on R/A
• Diffuse wheezes on auscultation, reduced A/E, FEV_1 <1L
• D-dimer >3000 ng/mL

• Started on new oral contraceptive pill 3 months ago.

• She has a diagnostic test.
Computed Tomography Pulmonary Angiography
What is your initial anticoagulant management?

A. Outpatient LWMH for 4-6 days + VKA
B. Outpatient DOAC (apixaban, dabigatran*, rivaroxaban)
C. Lytic therapy (tPA, 100 mg over 2 hrs) + IV heparin/SC LMWH, then VKA/DOAC
D. In-hospital IV heparin/SC LMWH for 7-10 days, then VKA/DOAC

*Initial treatment with 4-6 days of SC LMWH
<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Recommendations: Anticoagulant Type</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT or PE without cancer</td>
<td>- For initial 3 months, dabigatran, rivaroxaban, apixaban <em>over</em> VKA</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>- If not DOAC-treated, VKA <em>over</em> LMWH</td>
<td>2C</td>
</tr>
<tr>
<td>DVT or PE with cancer</td>
<td>- For initial 3 months, LMWH <em>over</em> VKA, dabigatran, rivaroxaban, apixaban</td>
<td>2C</td>
</tr>
<tr>
<td>DVT or PE on extended (&gt;3 mos) therapy</td>
<td>- No need to change the choice of anticoagulant after first 3 months</td>
<td>2C</td>
</tr>
</tbody>
</table>

DOACs vs. VKA for VTE Treatment

Risk of Recurrent VTE and VTE-Related Death

<table>
<thead>
<tr>
<th>Study</th>
<th>DOAC (n/N)</th>
<th>VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>59/2609 (2.3%)</td>
<td>71/2635 (2.7%)</td>
<td>0.84 (0.60-1.18)</td>
<td>0.84 (0.60-1.18)</td>
<td>0.31</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>36/1731 (2.1%)</td>
<td>51/1718 (3.0%)</td>
<td>0.70 (0.46-1.07)</td>
<td>0.70 (0.46-1.07)</td>
<td>0.10</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>50/2419 (2.1%)</td>
<td>44/2413 (1.8%)</td>
<td>1.13 (0.76-1.69)</td>
<td>1.13 (0.76-1.69)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>66/4118 (1.6%)</td>
<td>80/4122 (1.9%)</td>
<td>0.83 (0.60-1.14)</td>
<td>0.83 (0.60-1.14)</td>
<td>0.25</td>
</tr>
<tr>
<td>RE-COVER</td>
<td>30/1274 (2.4%)</td>
<td>27/1265 (2.1%)</td>
<td>1.10 (0.66-1.84)</td>
<td>1.10 (0.66-1.84)</td>
<td>0.71</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>30/1279 (2.3%)</td>
<td>28/1289 (2.2%)</td>
<td>1.08 (0.65-1.80)</td>
<td>1.08 (0.65-1.80)</td>
<td>0.77</td>
</tr>
<tr>
<td>Combined</td>
<td>271/13430 (2.0%)</td>
<td>301/13442 (2.2%)</td>
<td>0.90 (0.77-1.06)</td>
<td>0.90 (0.77-1.06)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

RCT of Home vs. Hospital Treatment of PE

PESI <85 (low risk) and **NONE** of:

- \( \text{SaO}_2 < 90\% \)
- \( \text{sBP} < 100 \text{ mmHg} \)
- recent bleed *or* risk of bleeding
- severe chest pain
- PE despite anticoagulant therapy
- >150 kg
- \( \text{CrCl} < 30 \text{ mL/min} \)

<table>
<thead>
<tr>
<th>Screened</th>
<th>1,557</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded</td>
<td>70%</td>
</tr>
<tr>
<td>Declined</td>
<td>6%</td>
</tr>
<tr>
<td>Enrolled</td>
<td>344</td>
</tr>
</tbody>
</table>

age 47 years

\( \geq \text{lobar} \) 49%

cancer 1%

cardiopulmonary disease 5%

### Home vs. Hospital Treatment of PE

<table>
<thead>
<tr>
<th></th>
<th>In hosp (days)</th>
<th>Satisfied (90 days)*</th>
<th>VTE (90 days)*</th>
<th>Major bleed (90 days)*</th>
<th>Death (90 days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home (n=171)</td>
<td>0.5</td>
<td>92%</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hospital (n=168)</td>
<td>3.9</td>
<td>95%</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*only 2 events ≤14 days: both intramuscular hematomas in ‘home’ patients

**Upper 95%CI**

+2.7%  
+4.5%  
+2.1%

Case No. 1...what if?

• Patient has evidence of RV dysfunction (echocardiogram, elevated troponins)?

• Patient is hypotensive despite fluids (systolic BP <90 mmHg) or is in acute respiratory failure?

• Patient’s condition deteriorates despite conventional anticoagulant therapy?
PEITHO-2 Trial: lytic vs. conventional anticoagulant therapy for submassive PE and RV dysfunction

**Stroke:** 12 (2.4%) in lysis group, hemorrhagic in 10, vs. 1 (0.2%), hemorrhagic, in placebo group, P <0.01

**Non-IC major bleeding:** 32 (6.3%) vs. 6 (1.5%), P <0.01

**All-cause mortality:** 12 (2.4%) vs. 16 (3.2%), P = 0.42

ACCP 2016: Patients with Acute PE

- In most patients with PE without hypotension, we recommend against thrombolytic therapy (Grade 1B).

- In patients with PE associated with hypotension (sBP <90 mm Hg) not at high bleed risk, we suggest systemic thrombolytic therapy (tPA) (Grade 2B).

- In patients with PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and are at low bleed risk, we suggest thrombolytic therapy (Grade 2C).

40-year old male with 7 days of progressive right leg swelling

No antecedent DVT risk factors or other medical problems.

No contraindications to anticoagulant therapy.

Venous US shows iliofemoral DVT.
What is your initial anticoagulant management?

A. Outpatient LWMH for 4-6 days + VKA
B. Outpatient DOAC (apixaban, dabigatran*, rivaroxaban)
C. Catheter-directed lysis + IV heparin/SC LMWH, then VKA/DOAC
D. In-hospital IV heparin/SC LMWH for 7-10 days, then VKA/DOAC

*Initial treatment with 4-6 days of SC LMWH
Extent of DVT and Consequences

<table>
<thead>
<tr>
<th>Extent of DVT</th>
<th>Recurrence</th>
<th>Severe PTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliofemoral</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td>Femoral</td>
<td>56%</td>
<td>5%</td>
</tr>
<tr>
<td>Popliteal</td>
<td>39%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Kahn SR (personal communication, 2014)
27 year-old female, acute onset left leg pain

extensive iliofemoral DVT  thrombolysis device  post catheter-directed lysis
Catheter-directed Thrombolysis Trials

CaVenT trial

- **209 patients with iliofemoral DVT**
  - randomized to CDTL + anticoagulation vs. anticoagulation
  - mean age = 51.5 yrs; mean duration symptoms = 6.6 days

- At 24 months:
  - catheter thrombolysis reduced PTS: 41.1% vs. 55.6% (p=0.047)

ATTRACT trial (ongoing)

- 600 patients, 2 year follow-up
- randomized to CDTL + anticoagulation vs. anticoagulation

Patients with ‘Complicated’ Acute DVT

• In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (Grade 2C).

• No recommendation for CDT, except if venous gangrene

• Patients who are most likely to benefit from CDT
  - iliofemoral DVT
  - symptoms for <14 days
  - good functional status
  - life expectancy >1 year
  - low risk of bleeding

Case No. 2...what if?

• Patient had ‘uncomplicated’ DVT involving the popliteal vein.

• Has completed 3 months of anticoagulant therapy and feels well.

• Do you continue or stop anticoagulants?
Patients with Unprovoked VTE: what determines recurrence risk?

**Determinants of Recurrent VTE**

- Stopping estrogens
- Male sex
- Elevated D-dimer
- Thrombophilia
- Patient age
- Pro-BNP, CRP, troponin
- Extent of DVT or PE
- Residual vein occlusion (for DVT)
- Initial presentation as DVT or PE
Risk for recurrent VTE depends on circumstances (data from study-level meta-analysis)

<table>
<thead>
<tr>
<th></th>
<th>Recurrence Risk/yr</th>
<th>Risk Ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>0.7%</td>
<td>1.0</td>
</tr>
<tr>
<td>Non-surgical*</td>
<td>4.2%</td>
<td>3.0 (1.1-8.1)</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>7.4%</td>
<td>10.6 (3.4-32.5)</td>
</tr>
</tbody>
</table>

*medical illness, travel, hormone therapy

(1)...**D-dimer** to predict recurrent VTE?

**Principal findings:**
- post-VKA D-dimer (-ve or +ve) can distinguish risk for recurrent VTE over 5-yr period: HR = 2.4 (1.8-3.2)
- risk for recurrence if D-dimer -ve 10-20% after 3-5 yrs *(likelihood of NO recurrence is 80-90% after 3-5 yrs)*

**Secondary findings:**
- timing of post-VKA D-dimer (<3, 3-5, or >5 weeks) and patient age (<65, 65-75, or >75 yrs) do not affect predictive value of D-dimer

(2)...*thrombophilia* to predict recurrent VTE?

![Graph showing time (months) vs. relapse free, %](image)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No thrombophilia, DD-</td>
<td>795 483 104 37 17</td>
</tr>
<tr>
<td>No thrombophilia, DD+</td>
<td>586 332 105 37 16</td>
</tr>
<tr>
<td>Thrombophilia, DD-</td>
<td>219 147 42 14 5</td>
</tr>
<tr>
<td>Thrombophilia, DD+</td>
<td>253 144 62 23 12</td>
</tr>
</tbody>
</table>
(3) ...**male sex, estrogen use** to predict recurrent VTE?

- **unprovoked VTE (women + men)**  
  - men vs. all women (estrogen users + non-users) ... 2.2 (1.7-2.8)  
  - men vs. women (estrogen users excluded) ............ 1.8 (1.4-2.5)

- **women only**  
  - estrogen users vs. non-users ........................................... 0.5 (0.3-0.8)

(4) ...presentation (DVT vs. PE) and recurrence risk

1. Optimal duration of anticoagulation trials

2. California database..... RR = 1.1 (0.9-1.3)

3. Minnesota database... RR = 1.2 (0.89-1.5)

4. Meta-analysis.............. RR = 0.85 (0.66-1.1)

---

1. Kearon C (unpublished data)
(1) $D_{+1} A_{+1} S_{+1} H_{-2}$ score to predict recurrent VTE

### DASH Prediction Score Derived From Cox Regression Analysis

<table>
<thead>
<tr>
<th>DASH Predictors</th>
<th>$\beta$ coefficient*</th>
<th>P-value</th>
<th>Recurrence score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. D-dimer abnormal, after stopping AC</td>
<td>0.96</td>
<td>$&lt;0.0001$</td>
<td>+ 2</td>
</tr>
<tr>
<td>2. Age $&lt; 50$ yr</td>
<td>0.43</td>
<td>0.002</td>
<td>+ 1</td>
</tr>
<tr>
<td>3. Sex - male</td>
<td>0.58</td>
<td>$&lt;0.0001$</td>
<td>+ 1</td>
</tr>
<tr>
<td>4. Hormone use at VTE onset</td>
<td>-1.05</td>
<td>0.002</td>
<td>- 2</td>
</tr>
</tbody>
</table>

### DASH Prediction Rule

<table>
<thead>
<tr>
<th>DASH Score</th>
<th>$\leq 1.0$</th>
<th>2.0</th>
<th>$\geq 3.0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized VTE Recurrence Rate (%)</td>
<td>3.1%</td>
<td>6.4%</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

*Cox regression coefficients after backward elimination and optimism correction

(2) HER-DOO-2 score to predict recurrent VTE

- Derived from 646 patient cohort with unprovoked VTE who received 5-7 months OAC and mean follow-up of 3.1 yrs.
- **Risk Score**
  - Hyperpigmentation
  - Edema
  - Redness
  - D-dimer >250 ng/L \(\text{(during)\ anticoagulant\ therapy}\)
  - Obesity (BMI >30)
  - Older age (>65 yrs)

- **High risk**
  - female with score \(\geq 2\) \(14.1\% /\text{yr}\)
  - any male \(13.7\% /\text{yr}\)

- **Low risk**
  - female with score <2 \(1.6\% /\text{yr}\)

HERDOO2 Validation Study Results (Rodger M, et al. ESC 2016)

All men and high-risk women (n = 2,148)

- Continue anticoagulation (n = 1,802)
  - Recurrent VTE: 1.6 per 100 pt-yrs (95% CI: 1.1-2.3)

- STOP anticoagulation (n = 323)
  - Recurrent VTE: 8.1 per 100 pt-yrs (95% CI: 5.2-11.9)

- STOP anticoagulation (n = 31)
  - Recurrent VTE: None

low-risk women (n = 631)

- STOP anticoagulation (n = 591)
  - Recurrent VTE: 3.0 per 100 pt-yrs (95% CI: 1.8-4.8)

Continuous anticoagulation (n = 1,802)
(3) Vienna score to predict recurrent VTE

Vienna Prediction Model for Recurrent VTE

Version 1.0 (Version 2.0 is available here)

Note: This version (1.0) will be disabled by 1 April 2013, and users will then be automatically redirected to version 2.0. The two versions do not differ in functionality.

Sex
- male
- female

Location
- distal DVT
- proximal DVT
- pulmonary embolism

D-Dimer (μg/l)

Cumulative Recurrence Rate (in %)

<table>
<thead>
<tr>
<th>at 12 months</th>
<th>95% confidence interval</th>
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<table>
<thead>
<tr>
<th>at 60 months</th>
<th>95% confidence interval</th>
</tr>
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</table>

Risk Points: -

Submit

This risk calculator is based on "Risk assessment model to predict recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism" by Sabine Eichinger, MD; Georg Heinze, PhD; Lisanne M. Jandec, MSc; Paul A. Kyrle, MD

## Duration of Antithrombotic Therapy (AT): 2016 ACCP

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Recommended Duration of AT</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT (prox/distal) or PE provoked by surgery or transient non-surgical factor</td>
<td>3 months</td>
<td>1B</td>
</tr>
<tr>
<td>DVT (prox/distal) or PE with active cancer</td>
<td>Extended (no scheduled stop date) over 3 months (if bleed risk not high)</td>
<td>1B</td>
</tr>
<tr>
<td>DVT (prox/distal) or PE that is unprovoked</td>
<td>at least 3 months&lt;br&gt;continue anticoagulants indefinitely if non-high bleeding risk&lt;br&gt;patient sex and D-dimer (1 month post-AT) may influence treatment decision.</td>
<td>2B</td>
</tr>
</tbody>
</table>

...back to the Presentation Objectives

• What are the anticoagulant options for patients with VTE? *When to use DOACs vs. VKAs vs. LMWH?*
  – DOACs considered first-line treatment (WEAK recommendation)
  – LMWH-VKA acceptable treatment option
  – LMWHs for cancer-associated VTE

• When should I use thrombolytic or mechanical methods to treat VTE?
  – lytic therapy for massive (hypotension, resp. failure) PE
  – catheter-directed lysis (±mechanical) for massive (iliofem.) DVT

• How to decide the duration of anticoagulant therapy, *especially after unprovoked VTE*?
  – emerging clinical decision rules to help risk-stratify
  – male sex, +ve D-dimer determinants of recurrent VTE