Thromboembolic Complications in HIV-Infected Patients

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### Disclosures: Alex C. Spyropoulos, MD

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<tr>
<td>Employment</td>
<td>No conflict of interest to disclose</td>
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<td>Research support</td>
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<td>Scientific advisory board</td>
<td>Bayer, Janssen, Pfizer, Daiichi-Sankyo, Boehringer Ingelheim, Sanofi</td>
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<td>Major stockholder</td>
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<td>Travel support</td>
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<td>Other</td>
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This presentation includes no discussion of off-label use of a drug or medical device.
Case Question: HIV and Thrombosis

- 56-year-old male with HIV disease on HAART and CD4 count of 190/mm$^3$ presents with LLE swelling/pain.
- Doppler CUS confirms LLE femoropopliteal DVT.
- Therapy started with treatment dose LMWH and dose-adjusted coumadin, target INR 2.5.
- One month later patient presents with new LLE swelling/pain.
- F/U Doppler CUS confirms extension of index DVT. INR 2.1.

**Question**: How would you treat this patient now?
HIV and VTE: Overview

- Epidemiology
- Hypercoagulable states in HIV-infected patients
- Management and treatment issues in HIV and thrombosis
- Future directions
Epidemiology of HIV and Thrombosis
Epidemiology of HIV and Thrombosis

- Thrombotic events are 10 times more prevalent in the HIV-infected population than general population.
- Autopsy studies reveal high rates of undiagnosed thromboembolism among AIDS patients.
- Common comorbidities include dyslipidemia, malignancy (KS), and tobacco abuse.
- HAART regimens, especially with protease inhibitors, are associated with thrombosis.

Saber AA et al Am Surg 2001; 67:645-47
Wolf K et al J Infect Dis 2002; 185:456-62
Epidemiology of HIV and Thrombosis (cont’d)

- HIV-infected patients with CD4 cell counts < 200/mm³ have a greater thrombotic risk.
- Lower-extremity DVT and pulmonary embolism account for 66% of all thrombotic events.
- The incidence of thrombosis in HIV-infected patients is 2.6 per 1000 person-years.

Hypercoagulable States in HIV-Infected Patients
Virchow’s Triad and Thrombosis: HIV Contributes Multiple Risk Factors

Venous Stasis
Comorbidities, including tobacco abuse
Prolonged bed rest
Hypotension

Vascular Injury
Endothelial cell dysfunction
Central catheters
Platelet aggregation
Surgery
Dyslipidemia

Hypercoagulability
HAART regimens
Malignancy/opportunistic infections
Acquired PS, PC, AT deficiency
Antiphospholipid syndrome
VWF and P-selectin
TNF-α release

Rudolph Virchow
Adapted from Joist JH Semin Thromb Hemost 1990; 16:151-57.
Mechanisms of Hypercoagulability with HIV and Thrombosis

- Acquired protein C and protein S deficiency
- Decrease in antithrombin III levels
- Elevated plasma homocysteine levels
- Elevated factor VIII
- Release of proinflammatory cytokine TNF-α
- von Willebrand factor and P-selectin expression with platelet aggregation

Mechanisms of Hypercoagulability with HIV and Thrombosis

- Transient production of antiphospholipid antibodies
  - Associated with viral infections
  - May be associated with thrombosis
  - As many as one-fourth of HIV-infected patients

Abuaf N et al Thromb Haemost 1997; 77:856-61
HAART Regimens with HIV and Thrombosis

- HAART regimens, especially protease inhibitors, have been associated with increased thrombotic risk
  - Possible alterations in lipid, PAI-1, and fibrinogen levels

Hadigan C et al J Clin Endocrinol Metab 2001; 86:939-43
Anticoagulant Management of HIV and Thrombosis
VTE Treatment in HIV Disease

Options for Acute Management

Acute Phase (≥ 4 days)
- Inferior vena cava filter
- Thrombolysis and IV heparin
- Inpatient IV heparin
- Inpatient SC LMWH/fondaparinux
- Outpatient SC LMWH/fondaparinux

Chronic Phase (≥ 3 months)
- Vitamin K antagonist (VKA)

Outpatient SC LMWH/fondaparinux
Timeline for VTE Treatment: 9th ACCP 2012 Recommendations

- **SC LMWH, IV UH, SC UFH, or SC fondaparinux (Grade 1B)**
- **Target INR 2.0-3.0**
- **Warfarin Monitor INR daily**
- **Pt. education**
- **5-day overlap**
- **5 to 7 days**
- **Duration for prox DVT or PE**

* LMWH is recommended as an OP if possible (Grade 1B)

Hadigan C et al J Clin Endocrinol Metab 2001; 86:939-43
Kearon C et al Chest 2012; 141:e419s-94s
### Randomized Controlled Trials of Outpatient Treatment of DVT Using LMWH

<table>
<thead>
<tr>
<th></th>
<th>Koopman et al</th>
<th>Levine et al</th>
<th>Columbus Invest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nadroparin (N=202)</strong></td>
<td>6.9*</td>
<td>5.3*</td>
<td>4.9*</td>
</tr>
<tr>
<td>Recurrence (%)</td>
<td>8.6*</td>
<td>6.7*</td>
<td>5.3*</td>
</tr>
<tr>
<td><strong>UFH (N=198)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding (%)</td>
<td>0.5*</td>
<td>1.2*</td>
<td>3.1*</td>
</tr>
<tr>
<td><strong>Enoxaparin (N=247)</strong></td>
<td></td>
<td>2.0*</td>
<td>2.3*</td>
</tr>
<tr>
<td>Death (%)</td>
<td>6.9*</td>
<td>8.1*</td>
<td>7.6*</td>
</tr>
<tr>
<td><strong>UFH (N=253)</strong></td>
<td></td>
<td>4.5*</td>
<td></td>
</tr>
<tr>
<td>LOS (days)</td>
<td>2.7</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td><strong>Reviparin (N=510)</strong></td>
<td></td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Bleeding (%)</td>
<td>0.5*</td>
<td>1.2*</td>
<td></td>
</tr>
<tr>
<td><strong>UFH (N=511)</strong></td>
<td></td>
<td>3.1*</td>
<td></td>
</tr>
</tbody>
</table>

*P=NS.

Koopman et al NEJM 1996; 334:681-87
Levine et al NEJM 1996; 334:677-81
Columbus Investigators. NEJM 1997;337:657-62
Outpatient VTE Protocol
Clinical Exclusionary Criteria*

**Absolute**
- Active bleeding or positive stool guiac
- Thrombocytopenia <100K
- Major surgery/trauma or CVA <2 weeks
- Phlegmasia
- Symptomatic PE
- Severe renal dysfunction
- Recent GI bleeding
- Hypertensive emergency
- History of heparin sensitivity or heparin-induced thrombocytopenia
- Active or major comorbid illness

**Relative**
- History of familial bleeding disorder
- Morbid obesity
- Iliofemoral DVT
- Pregnancy
- Underlying liver disorder
- Age > 75 yrs
- Acquired or congenital hypercoagulable state

*Based on compendium of RCTs and observational studies, ~60-80% of patients are OP-eligible.

Spyropoulos AC AJMC 2000; 6:1034S-44S
Current Treatment of VTE

- Considerations of UFH or LMWH
  - Once- or twice-daily injection
  - Possibility of HIT
  - Potential osteopenic risk
- Considerations of fondaparinux
  - Daily injection
  - Long half-life (17-21 hrs)

Parenteral anticoagulant and VKA (INR 2.0-3.0)

Bridging therapy

Initial treatment
  - 0 to ~7 days

VKAs (INR 2.0-3.0) or parenteral anticoagulant
  - ~7 days to ~3 months

Long-term treatment
  - ~3 months to indefinite

VKAs (INR 2.0-3.0) or parenteral anticoagulant

Extended treatment

Spyropoulos AC, Turpie AGG CMRO 2013; 29:783-90
Warfarin Failure Syndromes in HIV and Thrombosis

- Achieving optimal VKA-based anticoagulation is challenging in HIV-infected patients
  - Only 28.6% TTR in HIV patients on VKA
  - Only 25% response rate, especially with HAART
  - High rates of warfarin failure syndromes
LMWHs, Coagulation Cascade, and Tumor Biology

- TF: Tissue factor
- PARs: Protease activated receptors
- TFPI: Tissue factor pathway inhibitor
- tPA: Tissue plasminogen activator
- vWF: Von Willebrand factor

Clotting-dependent:
- TF → Thrombin → Fibrin
- LMWH: Inhibition of thrombin generation

Clotting-independent:
- TF → PARs
- VIIa → PARs
- Xa → PARs
- LMWH: Inhibition of factor VIIa generation and formation of TF:VII complex
- LMWH: Prevention of conversion of fibrinogen to fibrin
- LMWH: Release of mediators from endothelial cells (TFPI, tPA, vWF)

Angiogenesis, Tumor Growth, and Metastasis

References:
- Fernandez PM et al. Sem Hem Thromb 2004; 30:31
- Ruf W J Thromb Haemost 2007; 5:1584
LMWH vs. OAC for Secondary Thromboprophylaxis in VTE

- Meta-analysis of 1,379 patients receiving secondary thromboprophylaxis for VTE for at least 3 months with LMWH or oral anticoagulant (OAC)
  - VTE recurrence (OR, 0.66; 95% CI, 0.41-1.07) favoring LMWH
  - Bleeding (OR, 0.45; 95% CI, 0.18 -1.11) favoring LMWH
LMWH vs. VKA for Long-Term Treatment of VTE

56-year-old male with HIV disease on HAART and CD4 count of 190/mm$^3$ presents with LLE swelling/pain.

Doppler CUS confirms LLE femoropopliteal DVT.

Therapy started with treatment dose LMWH and dose-adjusted coumadin, target INR 2.5.

One month later patient presents with new LLE swelling/pain.

F/U Doppler CUS confirms extension of index DVT. INR 2.1.

**Question:** How would you treat this patient now?

**Answer:** Long-term Lovenox 1.5 mg/kg SQ daily
Future Directions in the Management of HIV and Thrombosis
SITES OF ACTION OF NEW ANTICOAGULANTS

**Steps in Coagulation**

**Initiation**
- TF/FVIIa
- FVIIai
- NAPc2
- TFPI

**Propagation**
- VIIIa
- Va
- Xa
- IXa
- IX
- X
- II
- IIa

**Thrombin activity**
- Fibrinogen
- Fibrin

**Drug Sites of Action**

- **Indirect:**
  - Idraparinux
  - Idraparinux biotinylated
  - SNAC/Heparin

- **Direct:**
  - DX-9065a
  - Razaxaban
  - Apixaban
  - Ximelagatran
  - Dabigatran
  - TGN-167

The Demise of Warfarin

Ecstatic or Dead?
## Target-Specific OAC Pharmacologic Properties

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Betrixaban</th>
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<tbody>
<tr>
<td><strong>Target Activity</strong></td>
<td>Factor Xa</td>
<td>Factor IIa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Tablet</td>
<td>Capsule</td>
<td>Tablet</td>
<td>Tablet</td>
<td>Tablet</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>QD or BID</td>
<td>QD or BID</td>
<td>BID</td>
<td>QD</td>
<td>QD</td>
</tr>
<tr>
<td><strong>T ½</strong></td>
<td>~9-12 hours</td>
<td>~15 hours</td>
<td>~12 hours</td>
<td>~10 hours</td>
<td>~20 hours</td>
</tr>
<tr>
<td><strong>Cmax</strong></td>
<td>~3 hours</td>
<td>~2 hours</td>
<td>~3 hours</td>
<td>~2 hours</td>
<td>~3 hours</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>~35% biliary, 65% renal</td>
<td>~20% biliary, ~80% renal</td>
<td>~75% biliary, ~25% renal</td>
<td>~65% biliary, ~35% renal</td>
<td>~95% biliary, &lt;5% renal</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Molecular Weight</strong></td>
<td>436 daltons</td>
<td>628 daltons (prodrug)</td>
<td>471 daltons (active)</td>
<td>460 daltons</td>
<td>~500 daltons</td>
</tr>
<tr>
<td><strong>CYP450 Metabolism</strong></td>
<td>Minimal</td>
<td>None</td>
<td>Minimal</td>
<td>Minimal</td>
<td>None</td>
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<tr>
<td><strong>Food Interaction</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>Drug-Drug Interactions</strong></td>
<td>Interacts with some agents metabolized by CYP3A4 (e.g., ketoconazole)*</td>
<td>P-glycoprotein inhibitors may potentiate antithrombotic effect of dabigatran, while P-glycoprotein inducers may attenuate its effect; does not appear to interact with agents metabolized by CYP3A4</td>
<td>No significant interactions disclosed thus far; may interact with agents metabolized by CYP3A4 pathway</td>
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* From draft US label: Not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (eg, azole-antimycotic detoconazole, ritonavir).
Objective confirmation of VTE

Single-dummy period
- Warfarin placebo

Double-dummy period
- Dabigatran etexilate 150 mg bid
- Warfarin placebo
- Dabigatran etexilate placebo bid

Initial parenteral therapy

E = enrolment
R = randomization

Until INR ≥ 2.0 at two consecutive measurements (8–11 days)

6 months End of treatment

Primary efficacy outcome: composite of recurrent symptomatic VTE and VTE-related death
Safety outcomes: major bleeding, major/clinically relevant bleeding, any bleeding

n > 2,500 for each trial

E-R

Schulman S et al NEJM 2009; 361:2342-52
Phase 3 EINSTEIN DVT and PE Treatment Trial Designs

Open-label assessor blind event driven noninferiority study for efficacy

Dose: 15 mg bid, days 1-21; 20 mg qd, remainder of study

3449 Patients with DVT
AND
4832 Patients with PE

Randomization *

Rivaroxaban, 3 months
Hep +VKA
VKA only, 3 months

Rivaroxaban, 6 months
Hep +VKA
VKA only, 6 months

Rivaroxaban, 12 months
Hep +VKA
VKA only, 12 months

Observational period 30 days

Primary efficacy outcome: symptomatic recurrent VTE or related death
Primary safety outcome: clinically relevant bleeding

* Duration of rx (3, 6, or 12 months) chosen by investigator based on clinical assessment

EINSTEIN Investigators. NEJM 2010; 363:2499-510
EINSTEIN-PE Investigators. NEJM 2012; 366:1287-97
Apixaban AMPLIFY: Phase III DVT/PE Treatment Study

A safety and efficacy trial evaluating the use of apixaban in the treatment of symptomatic DVT and pulmonary embolism

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Apixaban 10 mg BID for 1 week</th>
<th>Apixaban 5 mg BID for 6 months</th>
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</thead>
<tbody>
<tr>
<td>Enoxaparin 1mg/kg BID until INR ≥2</td>
<td>Warfarin tablets QD to target INR of 2.0-3.0 for 6 months</td>
<td>Apixaban placebo BID for 6 months</td>
</tr>
</tbody>
</table>

5395 patients with acute DVT or PE

Primary efficacy outcome: symptomatic recurrent VTE or any cause death
Safety outcomes: major and clinically relevant nonmajor bleeding

Agnelli G et al NEJM 2013
Hokusai-VTE: Study Design

Randomized, double-blind, event-driven study

N=8,292
439 sites in 37 countries

Objectively confirmed VTE

Stratified randomization:
- DVT / PE
- Dose of edoxaban
- Risk factors

Patients followed for 12-months or until study closure regardless of treatment duration

Edoxaban 60 mg once daily*

Edoxaban
Placebo edoxaban
Warfarin
Placebo warfarin
LMWH / UFH

*Dose was halved to 30 mg QD in patients with CrCl 30–50 mL/min, body weight ≤ 60 kg, or during treatment with potent P-gp inhibitors.

During days 6-12 edoxaban or placebo edoxaban was started once heparin was stopped.

Hokusai-VTE Investigators NEJM 2013
VTE Treatment Paradigms

Monotherapy

Bridge Therapy

Switch Therapy

Begin VTE Tx

End VTE Tx

New oral anticoagulant

IV or subcutaneous anticoagulant

IV or subcutaneous + VKA oral anticoagulant

VKA oral anticoagulant

Spyropoulos AC, Turpie AGG CMRO 2013; 29:783-90

Caveat: Monotherapy or switch therapy approach NOT validated in HIV-infected patients
Conclusion: Management of Thrombosis in HIV-Infected Patients

- The mechanisms of thrombosis in HIV-infected patients are myriad and complex.
  - Include acquired factors as well as intrinsic changes to coagulation system.
  - HIV-infected patients with CD4 cell counts < 200/mm$^3$ have a greater thrombotic risk.

- Conventional anticoagulant therapy with heparin/LMWH followed by warfarin still standard of care.
  - Poorer warfarin control via reduced TTR.
  - Higher incidence of warfarin failure syndrome.
  - Long-term LMWH remains an option.

- Future direction in this patient group include TSOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban in a monotherapy or switch therapy approach.
  - No data in HIV-infected patients.
  - Results of large phase IV registries may be helpful.