Rivaroxaban vs Warfarin in High-Risk Patients with Antiphospholipid Syndrome

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Guest Speakers: Vittorio Pengo, MD; David Garcia, MD

Moderators: Tracy Minichiello, MD; Michael Streiff, MD; Diane Wirth, ANP, CACP
Presenters

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Case

34 year old woman presents to the ED with pleuritic chest pain and shortness of breath. She is on no medication and has no known past medical history.

PEX: HR 115 BP 123/78 O2 sat 92%
Anxious appearing; lungs-cta; cor-tachy, reg rhythm, abd- no HSM, extrem-no edema, no varicosities; skin-lacy rash over lower extremities
LABS: WBC 4.9 K/mcl Hgb 13 g/dL PLT 115 K/mcl0.8. LFTS normal
CT PE: multiple bilateral lobar pulmonary emboli; RV/LV ratio normal
The patient is started on rivaroxaban 15 mg BID and admitted to telemetry unit.
Case

The next day the team notices that admission labs are significant for prolonged PTT 45.1 sec. PT 11.1 sec (nml) and INR is 1.0. The team is concerned about possible antiphospholipid antibody syndrome (APS). What is antiphospholipid antibody syndrome?
A. Initial pathogenesis

- Antiphospholipid antibodies are produced by B cells
- Antiphospholipid antibodies bind to open \( \beta_3 \) GPI
- Endothelial cell

B. Continued pathogenesis

- Activation of inflammatory cells and endothelial cells
- Promotion of coagulation
- Interference with trophoblasts and decidual cells

C. Examples of possible proinflammatory and prothrombotic changes induced by antiphospholipid antibodies

- ↑ Complement activity
- ↑ E-selectin
- ↑ Tissue factor
- ↑ Vascular endothelial growth factor
- ↑ NETosis
- ↑ Expression of glycoprotein IIb/IIIa
- ↑ Tissue factor pathway inhibitor activity
- ↓ Protein C activity
- ↓ Fibrinolysis
- ↓ Complement activity
- ↓ Proliferation and syncytiotrophoblast formation
- ↓ Human chorionic gonadotropin
- ↑ Trophoblast apoptosis

D. Through multiple mechanisms, antiphospholipid-antibody activity results in:

- Inflammation
- Vascularopathy
- Thrombosis
- Pregnancy complications
Case

The next day the team notices that admission labs are significant for prolonged PTT of 45.1. PT is normal, 11.1 and INR is 1.0. The team is now concerned about possible APS. In which patients should we consider the diagnosis of APS?
Diagnosing APS?

• Who should we consider this diagnosis in?
  • Thrombosis @ young age, unusual site, recurrent thrombosis, pregnancy complications
  • Thrombosis PLUS livedo, autoimmune disease, prolonged aPTT, thrombocytopenia
• Sapporo Criteria-a guide not rigid formula: thrombosis OR pregnancy complications (late pregnancy loss, recurrent early loss, early or severe preeclampsia, HELLP syndrome) in patient with persistent antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, or anti-β2GPI)
Case

The team obtains additional targeted review of systems and history:

ROS: + oral ulcers many times per year, Raynaud's phenomenon, and lacy recurrent rash on lower extremities
Family history: no DVT/PE/rheumatologic diseases
Surgical history: none
Gyn history: G2P0, 2 spontaneous abortions, @ 10 weeks and @ 14 weeks.

Which laboratory tests should be sent to evaluate for APS?
APS Lab Testing

- Lupus Anticoagulant Testing
  - False + on heparin, warfarin, DOACs
- aPL antibody testing
  - Anticardiolipin IgG and IgM
  - Beta 2 glycoprotein 1 IgG and IgM
- Assessing the aCL profile (risk)
  - High-positive LA +/- mod-high titer aCL
  - Intermediate-neg LA, mod-high titer aCL
  - Low-neg LA, low titer aCL
  - In clinical practice, moderate-to-high titer of aCL or anti-β2GPI is 40 or more GPL or MPL units, and a low titer is 20 to 39 GPL or GPL or MPL units
The team sends ELISA for APS antibodies but does not send lupus anticoagulant as patient is on anticoagulation. Given pregnancy complications, Raynaud’s, livedo, thrombocytopenia, and prolonged aPTT the team has a high suspicion for APS. Test results are pending at time of discharge. **Should this patient be continued on a DOAC?**
APS Therapies

• Venous thrombosis
  • UFH or LMWH → warfarin, INR 2-3

• Arterial thrombosis
  • Warfarin, INR target?
  • Adding ASA? ASA ONLY for CVA?

• Recurrent thrombosis while on warfarin
  • INR overestimating anticoagulation effect
  • INR 3-4 or LMWH
  • Adding ASA
  • Adding hydroxychloroquine, statin
CLINICAL TRIALS AND OBSERVATIONS

Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

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TRAPS-Study Design

• Prospective, randomized, phase 3, open-label, non-inferiority trial

• Inclusion criteria
  • Age 18-75
  • Triple positive aPL (IgG or IgM, > 40 GPL/MPL units or > 99th %ile and LA test)
  • History of thrombosis (venous, arterial or biopsy proven microvascular)

• Exclusion criteria

• Randomization
  • Random block, stratified sex and autoimmune disease
TRAPS-Study Design

• Intervention
  • Rivaroxaban 20 mg QD (15 mg if CrCl 30-50 ml/min) v warfarin (INR 2-3)

• Primary outcome (on treatment and ITT)
  • Cumulative incidence of thromboembolism, major bleeding, vascular death

• Follow up
  • Visits 1 month, 3 months then q 6 months
TRAPS-Statistical Analysis

- Non-inferiority margin-preservation of 50% of warfarin effect
- Sample size- 536 subjects
- Primary outcome analyzed “as treated” and intention to treat (ITT)
## TRAPS-Baseline Characteristics

<table>
<thead>
<tr>
<th>APS laboratory test positivity, n</th>
<th>rivaroxaban</th>
<th>warfarin</th>
</tr>
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<tbody>
<tr>
<td>LA: dRVWT/aPTT/both</td>
<td>16/5/38</td>
<td>14/7/40</td>
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</tbody>
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<thead>
<tr>
<th>Medications at time of randomization, n (%)</th>
<th>rivaroxaban</th>
<th>warfarin</th>
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</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>15 (25)</td>
<td>23 (38)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>11 (19)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Other immunosuppressive drugs</td>
<td>17 (29)</td>
<td>21 (34)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>11 (19)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Statins</td>
<td>7 (12)</td>
<td>10 (16)</td>
</tr>
</tbody>
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<tr>
<th>Previous thrombotic events, n (%)</th>
<th>rivaroxaban</th>
<th>warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial events</td>
<td>11 (19)</td>
<td>14 (23)</td>
</tr>
<tr>
<td>Stroke</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other sites</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Venous events</td>
<td>38 (64)</td>
<td>39 (64)</td>
</tr>
<tr>
<td>Deep vein thrombosis and/or pulmonary embolism</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>Other sites</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Venous and arterial events</td>
<td>10 (17)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Pregnancy morbidity, n (%)†</td>
<td>16 (41)</td>
<td>12 (32)</td>
</tr>
</tbody>
</table>
TRAPS-Results

• Mean follow up 569 days as treated 611 ITT
• Adherence 96% rivaroxaban
• TTR 67% warfarin
• Stopped early after 120 patients randomized due to excess arterial thromboembolic events in rivaroxaban arm
TRAPS-Results

Cumulative incidence of death, thromboembolism, major bleeding

- **rivaroxaban**
- **warfarin**
Rivaroxaban in high risk patients with APS was associated with excess of events compared to warfarin.
Reasons for Rivaroxaban Failure?

• Poor adherence
  • but excellent adherence by pill count

• Suboptimal drug concentration
  • perhaps higher levels needed for arterial circulation

• Mechanism of action
  • warfarin inhibits the intrinsic pathway which is important for thrombin generation
Case

The patient is transitioned to LMWH → warfarin given high suspicion for APS. APS assays return:

B2gp1: IgG 75 GPL
aCL: IgG 59 GPL
Discussion

• How long should she remain on anticoagulation?
• If only one aPL assay was positive would you switch back to DOAC?
• She would like to pursue pregnancy in the future when she has completed acute treatment for VTE. What anticoagulant regimen will you recommend during pregnancy?
• How long would you recommend she stay on anticoagulation if she had only obstetric APS (recurrent loss and positive antibodies)?
ASH 2018 Guidelines:

Heparin-Induced Thrombocytopenia in Patients With VTE and Optimal Management of Anticoagulation Therapy

Guest Speakers: Adam Cuker, MD

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This national conference brings together more than 900 physicians, pharmacists, and nurses for presentations by the leading experts in the field of anticoagulation.

Session Highlights
- Combined Therapy – Afib, Coronary and Peripheral Disease
- Optimizing Anticoagulation Clinics
- Controversies and Challenges in VTE
- Moving the Needle – Creating Change at the National Level
- Improving Safety and Quality in Anticoagulation Care
- What is the Anticoagulation Provider to Do? Real-World Dilemmas

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