Anticoagulation in Kidney Disease: Considerations for Patients with Nephrotic Syndrome

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Glomerular Disease Collaborative Network
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Disclosures

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- Clinical Trial Participation as site PI:
  - Retrophin
  - Mallinkrodt

- No disclosures relevant to this presentation.
Outline

- Venous thromboembolic events (VTE)
  - Who is at risk of thromboembolic events?
- Pathophysiology
  - Why are patients with nephrotic syndrome at higher risk of VTE?
- Prophylactic anticoagulation
  - Who should receive prophylactic anticoagulation?
- What prophylactic anticoagulation?
  - Warfarin or others?

Case 1

- 44 yo AAM – presented to his physician with heavy proteinuria detected on routine physical.
- UPC 4.2, Albumin of 3.3 g/dl, Creatinine of 1.33 mg/dl.
- Renal Bx demonstrates FSGS (with ?collapsing lesion).
- Started on Prednisone 1mg/kg ; cyclosporine 100mg bid.
- Seen in follow up 6 wks later and UPC 1.1.
- He reads on the internet that nephrotic syndrome places him at high risk for a blood clot and wants to know if he should be on anticoagulation. What do you tell him?
Case 2

- **51 yo WM** – prior hx of HTN, recently with more difficult to control hypertension and worsening hyperlipidemia.
- Developed LE that worsened over weeks – found to have extensive L LE DVT extending into the IVC. On Chest CT also found to have bilateral PE.
- Received “lytic” therapy and discharged on **apixaban 2.5mg bid**.
- In follow up 2 months later, has recurrent LE edema - repeat venography demonstrates **recurrent DVT with IVC extension**.
- Placed on fondaparinux and referred to UNC Hematology.
  - Noted by hematologist to have heavy proteinuria (UPC >13)
- Receives thrombolytic therapy again and discharged on **apixaban 5mg bid**.
- Renal biopsy deferred due to anticoagulation and thrombolysis
  - **PLA2r Ab testing - 424 RU/mL**

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*How common is venous thromboembolism in patients with nephrotic syndrome?*
What is the risk of VTE in the nephrotic syndrome?

- Overall incidence of venous thromboembolism (VTE) reported to be ~25% in patients with nephrotic syndrome (NS).
- Varies among forms of NS.
- Varies by intensity and method of screening.
  - Clinically observed vs prospectively “investigated”

Epidemiology of VTE in NS

<table>
<thead>
<tr>
<th>Publication Year</th>
<th>Author</th>
<th>N</th>
<th>TE</th>
<th>% TE</th>
<th>Study Type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>Bennet et al. (11)</td>
<td>21</td>
<td>6</td>
<td>28.6</td>
<td>Prospective</td>
<td>No histology data</td>
</tr>
<tr>
<td>1980</td>
<td>Llach et al. (22)</td>
<td>151</td>
<td>33</td>
<td>21.9</td>
<td>Prospective</td>
<td></td>
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<td>1980</td>
<td>Andrassy et al. (10)</td>
<td>84</td>
<td>29</td>
<td>34.5</td>
<td>Prospective</td>
<td>RVT, DVT, and PE studied</td>
</tr>
<tr>
<td>1981</td>
<td>Chugh et al. (13)</td>
<td>44</td>
<td>11</td>
<td>25.0</td>
<td>Retrospective</td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>Kuhlmann et al. (18)</td>
<td>17</td>
<td>4</td>
<td>23.5</td>
<td>Prospective</td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>Wagoner et al. (27)</td>
<td>27</td>
<td>14</td>
<td>51.9</td>
<td>Prospective</td>
<td>Membranous nephropathy only</td>
</tr>
<tr>
<td>1988</td>
<td>Velasquez et al. (26)</td>
<td>26</td>
<td>11</td>
<td>42.5</td>
<td>Prospective</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Cherven et al. (12)</td>
<td>89</td>
<td>29</td>
<td>32.6</td>
<td>Prospective</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Wysokinski et al. (28)</td>
<td>218</td>
<td>44</td>
<td>20.2</td>
<td>Retrospective</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>677</td>
<td>181</td>
<td>26.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Observed VTE

Risk of thromboembolism by type of nephropathies.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=298)</th>
<th>MG (n=72)</th>
<th>MCD (n=49)</th>
<th>FSGS (n=36)</th>
<th>MPGN (n=26)</th>
<th>DN (n=32)</th>
<th>NOS (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE Event, n</td>
<td>29</td>
<td>10</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Obs period, y</td>
<td>2857</td>
<td>716</td>
<td>645</td>
<td>362</td>
<td>378</td>
<td>171</td>
<td>585</td>
</tr>
<tr>
<td>Annual incidence</td>
<td>1.02</td>
<td>1.40</td>
<td>0.62</td>
<td>1.38</td>
<td>1.32</td>
<td>0.58</td>
<td>0.68</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.68 - 1.46</td>
<td>0.67 - 2.57</td>
<td>0.17 - 1.59</td>
<td>0.45 - 3.22</td>
<td>0.43 - 3.09</td>
<td>0.01 - 3.26</td>
<td>0.19 - 1.75</td>
</tr>
</tbody>
</table>

- Median time to VTE was 0.9 years.
- Pulmonary embolism (38%), DVT (34%), combined PE and DVT (10%), combined PE and renal vein thrombosis (10%), renal vein thrombosis (3%), mesenteric vein thrombosis (3%).
- Over first 6 mos – annual incidence 9.85% (95%CI, 5.38-16.52)


VTE risk varies by disease type

<table>
<thead>
<tr>
<th></th>
<th>Overall, N = 1313</th>
<th>FSGS, N = 370</th>
<th>IgAN, N = 548</th>
<th>MN, N = 395</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with VTE (N, %)</td>
<td>44 (3.4)</td>
<td>11 (3.0)</td>
<td>2 (0.4)</td>
<td>31 (7.9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Number of VTE by type

- DVT: 10, 4, 1, 5
- PE: 20, 8, 1, 11
- RVT: 19, 2, 0, 17
- Other: 4, 0, 0, 4

Days to first VTE (med, IQR)

- MN demonstrated the highest risk of VTE
- MN -> 10-fold increase in likelihood of VTE compared to IgA
  - Nearly a two-fold increase when compared to FSGS patients

Clinical measures associated with VTE risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>no. patients/</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin, g/dL</td>
<td>92/272</td>
<td>1.0, reference</td>
<td>0.08</td>
</tr>
<tr>
<td>36 - 48</td>
<td>92/272</td>
<td>1.0, reference</td>
<td>0.08</td>
</tr>
<tr>
<td>46 - 61</td>
<td>91/272</td>
<td>3.1 (1.6 - 5.5)</td>
<td></td>
</tr>
<tr>
<td>≥ 82</td>
<td>89/272</td>
<td>6.2 (1.1 - 23.6)</td>
<td></td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>≥ 60</td>
<td>1.0, reference</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>127/251</td>
<td>1.0, reference</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>85/251</td>
<td>0.9 (0.5 - 1.6)</td>
<td></td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>≥ 2.4</td>
<td>1.0, reference</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>50/184</td>
<td>1.0, reference</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>87/184</td>
<td>1.6 (0.3 - 8.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 2.4</td>
<td>1.6 (0.3 - 8.2)</td>
<td></td>
</tr>
<tr>
<td>F a ratio</td>
<td>157/291</td>
<td>5.6 (1.3 - 28.2)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 5: Multivariable analysis of risk of venous thromboembolism

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2.4</td>
<td>1.1 - 5.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Cancer history</td>
<td>2.4</td>
<td>0.8 - 6.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Albumin at presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 38 g/l</td>
<td>2.7</td>
<td>0.3 - 2.9</td>
<td>0.4</td>
</tr>
<tr>
<td>29-38 g/l</td>
<td>2.7</td>
<td>0.3 - 2.9</td>
<td>0.4</td>
</tr>
<tr>
<td>&lt; 29 g/l</td>
<td>9.6</td>
<td>1.2 - 76.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Proteinuria at presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1g/day</td>
<td>1.6</td>
<td>0.2 - 13.9</td>
<td>0.6</td>
</tr>
<tr>
<td>1-3.5 g/day</td>
<td>1.6</td>
<td>0.2 - 13.9</td>
<td>0.6</td>
</tr>
<tr>
<td>3.6-8 g/day</td>
<td>1.9</td>
<td>0.2 - 14.9</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt; 8 g/day</td>
<td>2.6</td>
<td>0.3 - 20.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Underlying disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>0.0005</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgAN</td>
<td>5.9</td>
</tr>
<tr>
<td>FSGS</td>
<td>10.9</td>
</tr>
<tr>
<td>MN</td>
<td></td>
</tr>
</tbody>
</table>


Patients with Membranous Nephropathy

Study Population N = 807

Glomerular Disease Collaborative Network (GDCN) N = 412
Toronto Glomerular Network Registry (TGNR) N = 395
Membranous Nephropathy

- Combined cohort from UNC/GDCN + U of Toronto/TGNR
- Total of 807 patients
- 65 events (7.2%), 0.017 per person-year
  - 26 RVT, 21 DVT, 27 PE
- At the time of VTE:
  - Upro 9.9 g/day (1.1, 40.0)
  - Serum albumin of 2.2 ± 0.6 g/dL (0.6, 3.7)
  - Mean eGFR of 70.5 ± 27.8 ml/min/1.73m²


Hypoalbuminemia and VTE in MN

Table 3. Multivariate analysis to identify predictors of VTE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnostic biopsy (yr)</td>
<td>0.99</td>
<td>0.97, 1.01</td>
<td>0.39</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>2.13</td>
<td>1.02, 4.44</td>
<td>0.04</td>
</tr>
<tr>
<td>24-hour proteinuria (g/d)</td>
<td>0.98</td>
<td>0.93, 1.04</td>
<td>0.59</td>
</tr>
<tr>
<td>Immunosuppressive therapy, any</td>
<td>1.72</td>
<td>0.85, 3.47</td>
<td>0.13</td>
</tr>
<tr>
<td>Site of registry (GDCN/TGNR)</td>
<td>0.67</td>
<td>0.26, 1.34</td>
<td>0.20</td>
</tr>
<tr>
<td>Serum albumin (g/dl) (^b)</td>
<td>2.13</td>
<td>1.32, 3.46</td>
<td>0.002</td>
</tr>
</tbody>
</table>

\(^a\) P value was calculated by logistic model evaluating the association of serum albumin while controlling for age at diagnostic biopsy, sex, 24-hour proteinuria, immunosuppressive therapy, and site of registry.

\(^b\) Per each g/dl decrease in serum albumin.

Clinical measures and VTE in FSGS

- Cross-sectional study of 120 Patients with FSGS (all with serum albumin < 3.0 g/dl)
- 10% found to have VTE by some form of imaging
- In univariate analyses, VTE associated with:
  - Relapse of NS
  - D-dimer
  - "Hemoconcentration"

Why is the Nephrotic Syndrome so prothrombotic?

Coagulation/Anticoagulation

- Albumin roughly 66kD in size
- Elevation in larger size procoagulant proteins
  - Fibrinogen, Factor V, Factor VIII (>300 kD)
- Anticoagulant proteins smaller in size thought to be lost in urine
  - Antithrombin (65kD)
    - most consistently demonstrated to be decreased
  - Protein C (62 kD)
  - Protein S (69 kD)
    - about 60-70% bound to C4b-binding protein

Inconsistent findings among various studies

## Imbalance in Hemostasis

<table>
<thead>
<tr>
<th></th>
<th>Anti-Thrombotic</th>
<th>Pro-Thrombotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procoagulant</strong></td>
<td>N or ↓ factor XI (160)(^5)</td>
<td>N or ↓ factor XII (80)(^{5,49})</td>
</tr>
<tr>
<td></td>
<td>↓ N, or ↓ factor II (69)(^5)</td>
<td>↓ Plt Count(^{3,50,51})</td>
</tr>
<tr>
<td></td>
<td>↓ N, or ↓ factor VII (50)(^5)</td>
<td>↓vWF (variable)(^4)</td>
</tr>
<tr>
<td></td>
<td>↓ N, or ↓ factor IX (58)(^5)</td>
<td>↑ fibrinogen (340)(^5)</td>
</tr>
<tr>
<td></td>
<td>↓ or ↑ Plt Function(^4,48)</td>
<td>↑↑ factor V (330)(^6)</td>
</tr>
<tr>
<td><strong>Anticoagulant</strong></td>
<td>↑ protein C (62)(^{1,14,54,55})</td>
<td>↓ protein Z (62)(^{43,54})</td>
</tr>
<tr>
<td></td>
<td>↓ N, or ↓ protein S (69)(^{1,14,54})</td>
<td>↓ or ↓ AT (65)(^{1,14,54})</td>
</tr>
<tr>
<td><strong>Profibrinolytic</strong></td>
<td>↑ N, or ↓ a(^2)-AP (70)(^6)</td>
<td>↓ Plasminogen (92)(^6)</td>
</tr>
<tr>
<td></td>
<td>↓ N, or ↓ IPA (72)(^5,56)</td>
<td>↓ N, or ↓ IPA (72)(^5,56)</td>
</tr>
<tr>
<td><strong>Antifibrinolytic</strong></td>
<td>↓ a(^2)-AT (54)(^8)</td>
<td>↑ Lp(a) (750)(^8)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>↓ or ↑ t-PAI (52)(^{4,42})</td>
<td>↑↑ a(^2)-M (725)(^8)</td>
</tr>
<tr>
<td></td>
<td>*Thrombophilia</td>
<td>RBC Aggregation(^9)</td>
</tr>
<tr>
<td></td>
<td>*APL</td>
<td>Clot Structure(^9,62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperlipidemia(^8)</td>
</tr>
</tbody>
</table>


## Altered Clot Structure

Hyperlipidemia and Coagulation

- In familial hyperlipidemia, oxidized forms of LDL (oxLDL) are markedly elevated
- Associated with elevations in microparticle Tissue Factor
- Observational data to suggest statins associated with lower VTE risk in NS

Global coagulation assays

- Thromboelastography

Figure captions:
Thromboelastography in NS

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls</th>
<th>MCD, S Alb &lt; 2 g/dl</th>
<th>MN, S Alb &lt; 2 g/dl</th>
<th>MCD, S Alb 2-3 g/dl</th>
<th>MN, S Alb 2-3 g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>R (min)</td>
<td>7.3 ± 1.1</td>
<td>6.7 ± 1.0</td>
<td>5.5 ± 0.8*</td>
<td>7.2 ± 1.5</td>
<td>6.6 ± 1.2*</td>
</tr>
<tr>
<td>α-angle (deg)</td>
<td>57.7 ± 5.6</td>
<td>68.9 ± 5.1*</td>
<td>74.8 ± 3.2*</td>
<td>65.5 ± 6.6*</td>
<td>68.9 ± 6.2*</td>
</tr>
<tr>
<td>MA (mm)</td>
<td>56.6 ± 4.9</td>
<td>71.1 ± 5.4*</td>
<td>73.3 ± 4.8*</td>
<td>68.1 ± 5.0*</td>
<td>70.9 ± 5.4*</td>
</tr>
<tr>
<td>Cl</td>
<td>-1.9 ± 1.7</td>
<td>1.24 ± 1.3*</td>
<td>2.8 ± 1.1*</td>
<td>0.1 ± 1.98*</td>
<td>1.24 ± 1.2*</td>
</tr>
</tbody>
</table>

* p<0.05, vs. control

- Suggests that entire system - activated intrinsic pathway, fibrinogen, platelet function and fibrin-platelet interaction in MN - is accelerated.
- Intrinsic pathway may be more activated in MN when compared to MCD.


Thromboelastography in NS

- In cohort of 235 MN patients, demonstrated similar findings of hypercoagulability in 92 (38%).
- Correlated with low serum albumin.
- Among the hypercoagulable patients, measures of coagulation by TEG were attenuated with statin therapy.

Other hematologic abnormalities

- **Microparticle production**
  - Demonstrated to be increased in children and adults with NS
  - Express phospholipid and other procoagulant molecules
  - In MN and MCD, microparticles increased in number
    - Derived from platelets, RBCs and endothelial cells
    - Correlated with total cholesterol and albumin

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Limits to understanding pathophysiology

- **Cormobidities**
  - Central venous catheter placement
  - Prolonged immobilization/hospitalization
  - Recent surgical intervention
  - Other hypercoaguable states
    - Genetic predisposition (Factor V Leiden, prothrombin gene mutation)
    - Antiphospholipid antibodies, acquired thrombophilia

- **Lack of prospective, systematic studies**
  - Many studies have evaluated one or a few components of coagulation
  - Lack of prospective association with thromboembolic event

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When should we anticoagulate prophylactically (and how)?

Management after a VTE event

“Traditional Approach”

• Typically 3-6 month of anticoagulation and would continue as long as patient remains hypoalbuminemic (opinion)

• Initial therapy with heparin (or LMWH)

• Followed by warfarin anticoagulation for the remainder of therapy
Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy

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Prophylactic use of anticoagulation (in Membranous Nephropathy)

1) Risk for VTE varies in case-by-case (depends on hypoalbuminemia)

2) Balancing the “Benefit” (VTE prevention) and “Risk” (bleeding complications)

The purpose:
Create a practical decision tool tailored to an individualized risk for VTE (hypoalbuminemia) and bleeding.

**Input data to the model**

- Incidence rate of VTE
- From the pooled inception cohort of GDCN and TGNR (N=539)
- Incidence rate of major bleeding
- From the ATRIA study (N=9186)

<table>
<thead>
<tr>
<th>sAlb &lt; g/dL</th>
<th>Events/100 PY (95% C.I.)</th>
<th>Risk Category (Point)</th>
<th>Events/100 PY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.0</td>
<td>3.7 (2.4-5.5)</td>
<td>Low (0-3)</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>&lt;2.8</td>
<td>4.3 (2.7-6.4)</td>
<td>Interm (4)</td>
<td>2.6 (2.3-3.0)</td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>6.5 (4.0-9.9)</td>
<td>High (5-10)</td>
<td>5.8 (5.0-6.6)</td>
</tr>
<tr>
<td>&lt;2.3</td>
<td>8.5 (5.0-13.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>11.4 (5.7-20.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Probabilistic Sensitivity Analysis**

- Factors considered in the sensitivity analysis:
  - Range of incidence rate of VTE
  - Range of incidence rate of bleeding
  - Range of efficacy of anticoagulation
  - Range of fatality rate from VTE or bleed

- “Monte-Carlo Simulation” runs a 1,000 simulations using each time a random sampling of distributed probabilities for each transition state

Imperial College

Proposed prophylaxis algorithm

1. Determine the risk of major bleeding
   - Low
   - Intermediate
   - High
2. Look at the serum albumin level
   - No prophylaxis and anticoagulation
3. Look at the benefit-to-risk acceptability curve

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**Decision Approach**

1. Determine the risk of major bleeding
   - Low
   - Intermediate
   - High
2. Look at the serum albumin level
3. Look at the benefit-to-risk acceptability curve

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Imperial College RETROSPECTIVE Analysis

Table 1. Cohort characteristics at initiation of the prophylaxis regimen, both for the entire cohort and for each type of glomerulopathy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=143)</th>
<th>MN (n=58)</th>
<th>MCD (n=45)</th>
<th>FSGS (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) (yr)</td>
<td>48.7 (20.0–85.5)</td>
<td>54.3 (26.0–85.5)</td>
<td>48.7 (20.0–82.2)</td>
<td>48.1 (24.0–84.5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76 (53.1)</td>
<td>35 (60.3)</td>
<td>23 (51.1)</td>
<td>18 (45.0)</td>
</tr>
<tr>
<td>Female</td>
<td>67 (46.9)</td>
<td>23 (29.7)</td>
<td>22 (48.9)</td>
<td>22 (55.0)</td>
</tr>
<tr>
<td>Median follow-up (range) (wk)</td>
<td>154 (30–289)</td>
<td>129 (44–298)</td>
<td>191 (93–285)</td>
<td>159 (30–279)</td>
</tr>
<tr>
<td>Median serum creatinine at presentation (range) (mg/dl)</td>
<td>0.94 (0.54–4.43)</td>
<td>0.89 (0.38–2.85)</td>
<td>0.90 (0.54–3.59)</td>
<td>1.52 (0.54–4.43)</td>
</tr>
</tbody>
</table>

VTE in 2 patients (1.39%) within the first week after starting prophylaxis.
1 patient (0.69%) had GI bleed requiring hospitalization
2 patients (1.40%) had elective blood transfusions.

Is this more efficacious or safer than warfarin?


VTE Prophylaxis

- **Statins**
  - Potential role for prevention of VTE
  - Pleiotropic effects including enhanced fibrinolysis
  - In hyperlipidemic rat models, statin therapy reduces oxLDL and subsequent tissue factor production
  - A single retrospective cohort study suggesting statin use in NS is associated with a reduced annual incidence of VTE
    - (0.37% [95%CI, 0.12-1.15] vs 0.81% [95%CI, 0.50-1.30]).
    - (Resh M et al. Thromb Res. 2011;127(5):395-9)
Pharmacokinetic Considerations for Potential Prophylactic Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Renal dose adjustment</th>
<th>Protein binding</th>
<th>Evidence of use in NS</th>
<th>FDA approved for TE prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>No dose adjustment recommended</td>
<td>High (99%)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Heparin</td>
<td>No dose adjustment recommended</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>CrCl &lt;30 mL/min: 30 mg sc daily</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>CrCl 30-50 mL/min and concomitant P-gp inhibitor: consider 75 mg bid; CrCl 15-30 mL/min: use 75 mg bid; do not use with P-gp inhibitor; CrCl &lt;30 or hemodialysis: use not recommended</td>
<td>Low (35%)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl 30-50 mL/min: use with caution; CrCl &lt;30 mL/min or hemodialysis: avoid use</td>
<td>High (92-95%)</td>
<td>No</td>
<td>post ortho. surgery</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Age ≥80 years, body weight ≤60 kg, or Cr ≥1.5 mg/dL, recommended dose is 2.5 mg twice daily</td>
<td>High (87%)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>No dose adjustment recommended</td>
<td>High (98%)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>


Summary

- Venous thromboembolism is common in primary nephrotic syndrome.
- Severity of risk depends upon the type of nephrotic syndrome.
  - Membranous nephropathy with highest risk.
- Hypoalbuminemia (and proteinuria) may be best indicator of VTE risk.
  - Consider other risks (e.g. smoking, immobilization, genetic predispositions)
- Pathophysiology is multifactorial.
  - Imbalance of coagulation and anticoagulation.
  - Impaired fibrinolysis, platelet activation and other hematologic changes.
  - May be exacerbated by hyperlipidemia.
Summary

- Prophylactic anticoagulation may be warranted in patients with moderate – severe hypoalbuminemia if their bleeding risk is not high (for membranous nephropathy)
  - ?perhaps also in other forms if additional risk factors?
- Statins may offer some protection
  - Treatment of hyperlipidemia should be addressed in NS
- Can D-dimer be used for screening those at risk? (I don’t know)
- Efficacy and safety of aspirin or anti-platelet agents has not been tested in NS
- Pharmacodynamics, efficacy and safety of Direct Oral Anticoagulants not tested in NS
  - Consider monitoring of drug levels (and/or pharmacokinetic studies)

Limitations in Understanding Prophylactic Anticoagulation in NS

- Scottish Biospy Registry – Adults undergoing kidney bx with primary NS from 2008 – 2013.
- 206 patients with median follow up of 2.9 (IQR 1.6 - 4.6) years.
- 14 (6.8%) with VTE
- Median time to diagnosis 36 days (IQR -22, 178)
- 6 VTE occurred prior to bx and 1 during remission
  - only 7 VTE that could be prevented
- Assume 75% reduction in VTE with prophylactic anticoagulation
  - Need 972 participants to achieve 80% in a clinical trial

Case 1

- **44 yo AAM with FSGS**
  - follow up UPC 1.1 and prior Albumin 3.3.
- **Does he need anticoagulation?**

- **1 week after returning clinic visit, develops L LE edema and diagnosed with acute DVT (following a 4.5 hour drive home from your clinic visit).**

Case 2

- **51 yo WM – probable membranous nephropathy**
  - Recurrent DVT/PE requiring thrombolytic therapy x 2
  - Now on Apixaban 5mg bid
- **Is this the right medication?**
- **Five months later – has screening LE dopplers**
  - Found to have acute on chronic DVT in L femoral vein
  - Apixaban level drawn 4 hrs post dose – 50 ng/ml (mean dose in healthy mean 128.5ng/mL*).
  - Switched back to fondaparinux and has remained on this without issue.