Anticoagulation in Kidney Disease: Considerations for Patients with Nephrotic Syndrome

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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?**

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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

Publication Year	Author	N	TE	%TE	Study Type	Notes
Adult						
1975	Bennet *et al.* (11)	21	6	28.6	Prospective	No histology data
1980	Llach *et al.* (22)	151	33	21.9	Prospective	
1980	Andrassy *et al.* (10)	84	29	34.5	Prospective	RVT, DVT, and PE studied
1981	Chugh *et al.* (13)	44	11	25.0	Retrospective	
1981	Kuhlmann *et al.* (18)	17	4	23.5	Prospective	RVT, DVT, and PE studied
1983	Wagoner *et al.*l (27)	27	14	51.9	Prospective	Membranous nephropathy only
1988	Velasquez *et al.* (26)	26	11	42.3	Prospective	
2000	Cherng *et al.* (12)	89	29	32.6	Prospective	V·Q evidence of PE
2008	Wysokinski *et al.* (28)	218	44	20.2	Retrospective	RVT and DVT
TOTAL		677	181	26.7		

Kerlin, B. A., Ayoob, R., & Smoyer, W. E. (2012). Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *CJASN*, *7*(3), 513–520. http://doi.org/10.2215/CJN.10131011

Observed VTE

Risk of thromboembolism by type of nephropathies.							
	Total (n=298)	MG (n=72)	MCD (n=49)	FSGS (n=36)	MPGN (n=26)	DN (n=32)	NOS (n=83)
VTE							
Event, n	29	10	4	5	5	1	4
Obs period, y	2857	716	645	362	378	171	585
Annual incidence	1.02	1.40	0.62	1.38	1.32	0.58	0.68
95% CI	0.68 - 1.46	0.67 - 2.57	0.17 - 1.59	0.45 - 3.22	0.43 - 3.09	0.01 - 3.26	0.19 - 1.75

- 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)

Mahmoodi, et al., Circulation 2008; 117: 224-30.

VTE risk varies by disease type

	Overall, *N* = 1313	FSGS, *N* = 370	IgAN, *N* = 548	MN, *N* = 395	*p*-value
Patients with VTE (N, (%))	44 (3.4)	11 (3.0)	2 (0.4)	31 (7.9)	<0.0001
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)	272 (0,1080)	1094 (401,1604)	453 (363,542)	151 (0,447)	0.07

- 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

Barbour SJ, et al. Kidney Int. 2012 Jan;81(2):190-5. doi: 10.1038/ki.2011.312.

Clinical measures associated with VTE risk

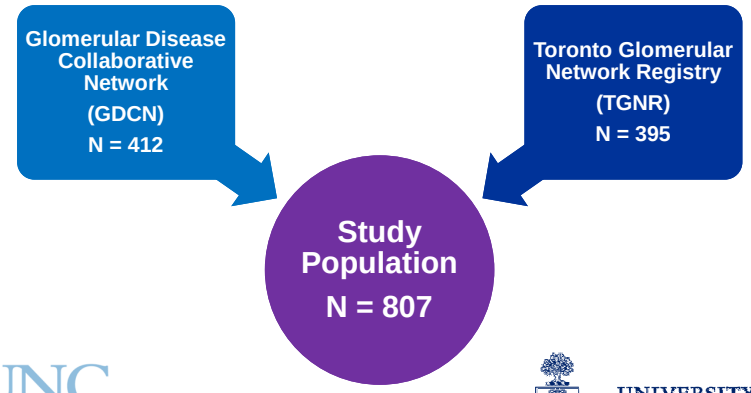
Variable	no. patients/ no. studied	HR (95% CI)	P value
Proteinuria, g/d			0.08
3.5 - 4.8	92/272	1.0, reference	
4.9 - 8.1	91/272	3.1 (0.6 - 15.0)	
≥ 8.2	89/272	5.2 (1.1 - 23.0)	
eGFR, ml/min/1.73m²			0.96
≥ 60	127/251	1.0, reference	
30 - 59	85/251	0.9 (0.3 - 2.6)	
≤ 29	39/251	1.0 (0.2 - 4.9)	
Serum albumin, g/dl			0.41
≥ 3.4	50/184	1.0, reference	
3.3 -2.5	67/184	1.6 (0.3 - 8.2)	
≤ 2.4	67/184	2.6 (0.5 - 12.4)	
P/A ratio	157/298	5.6 (1.2 - 26.2)	0.03

Table 5 | Multivariable analysis of risk of venous thromboembolism

	HR	95% CI	*P*-value
Male sex	2.4	1.1–5.3	0.02
Cancer history	2.4	0.9–6.3	0.07
Albumin at presentation			0.02
>38 g/l	Reference		
29–38 g/l	2.7	0.3–23.9	0.4
<29 g/l	9.6	1.2–76.4	0.03
Proteinuria at presentation			0.7
<1 g/day	Reference		
1–3.5 g/day	1.6	0.2–13.9	0.6
3.6–8 g/day	1.9	0.2–14.9	0.5
>8 g/day	2.6	0.3–20.2	0.4
Underlying disease			0.006
IgAN	Reference		
FSGS	5.9	1.3–27.9	0.02
MN	10.8	2.4–49.4	0.002

Mahmoodi, B. K. et al. (2008). *Circulation*, *117*(2), 224–230. http://doi.org/10.1161/CIRCULATIONAHA.107.716951
Barbour SJ, et al. Kidney Int. 2012 Jan;81(2):190-5. doi: 10.1038/ki.2011.312.

Patients with Membranous Nephropathy



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/1.73m^2

Lionaki S et al. CJASN 2012

Hypoalbuminemia and VTE in MN

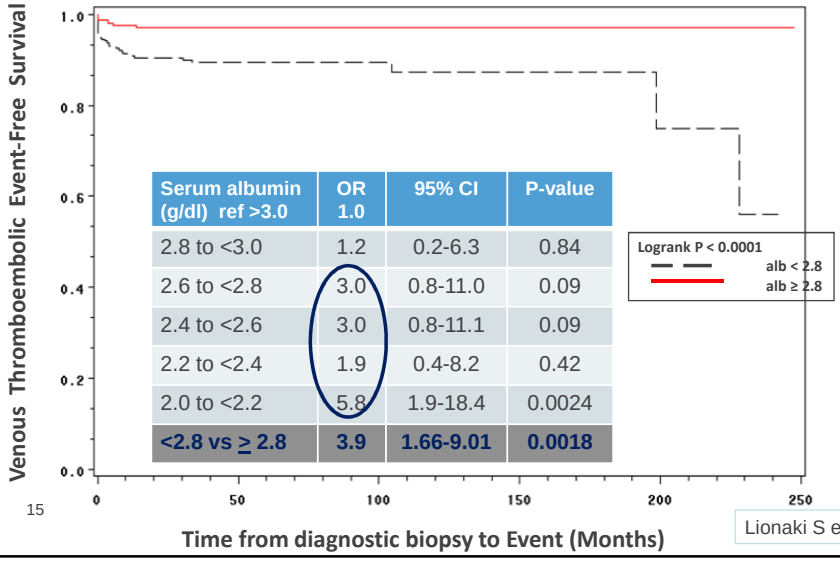
Table 3. Multivariate analysis to identify predictors of VTE

Variable	Adjusted Odds Ratio	95% Confidence Interval	*P* Value[a]
Age at diagnostic biopsy (yr)	0.99	0.97, 1.01	0.39
Sex (M/F)	2.13	1.02, 4.44	0.04
24-hour proteinuria (g/d)	0.98	0.93, 1.04	0.59
Immunosuppressive therapy, any	1.72	0.85, 3.47	0.13
Site of registry (GDCN/TGRN)	0.67	0.36, 1.24	0.20
Serum albumin (g/dl)[b]	2.13	1.32, 3.46	0.002

[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.

Lionaki, S. et al. (2012). Venous thromboembolism in patients with membranous nephropathy. *CJASN*, *7*(1), 43–51. http://doi.org/10.2215/CJN.04250511

Venous thromboembolic event-free survival by serum albumin level



Serum albumin (g/dl) ref >3.0	OR 1.0	95% CI	P-value
2.8 to <3.0	1.2	0.2-6.3	0.84
2.6 to <2.8	3.0	0.8-11.0	0.09
2.4 to <2.6	3.0	0.8-11.1	0.09
2.2 to <2.4	1.9	0.4-8.2	0.42
2.0 to <2.2	5.8	1.9-18.4	0.0024
<2.8 vs ≥ 2.8	**3.9**	**1.66-9.01**	**0.0018**

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Lionaki S et al. CJASN 2012

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"

Table 3 Univariable analyses: risk factors of venous thromboembolism

Risk factors	Odd ratios	95.0 % CI	*P* value
Relapse of NS	4.9	1.25–19.2	<0.05
Male	0.95	0.24–3.77	0.94
D-dimer (mg/dL)	7.47	2.62–21.3	<0.01
ATIII (mg/dL)	0.95	0.82–1.09	0.46
Fibrinogen (mg/L)	0.99	0.99–1.00	0.63
Proteinuria (g/24 h)	0.99	0.86–1.16	0.95
Serum albumin (g/L)	0.93	0.79–1.10	0.41
Hemoglobin (g/L)	1.63	1.23–2.15	<0.01
Hematocrit (%)	1.15	1.06–1.26	<0.01
Blood platelet count (10^9/L)	0.99	0.93–1.07	0.88

Li SJ et al. Risk factors of venous thromboembolism in focal segmental glomerulosclerosis with nephrotic syndrome. Clin Exp Nephrol. 2015 Jul 29.

Why is the Nephrotic Syndrome so prothrombotic?

Coagulation/Anticoagalation

- 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

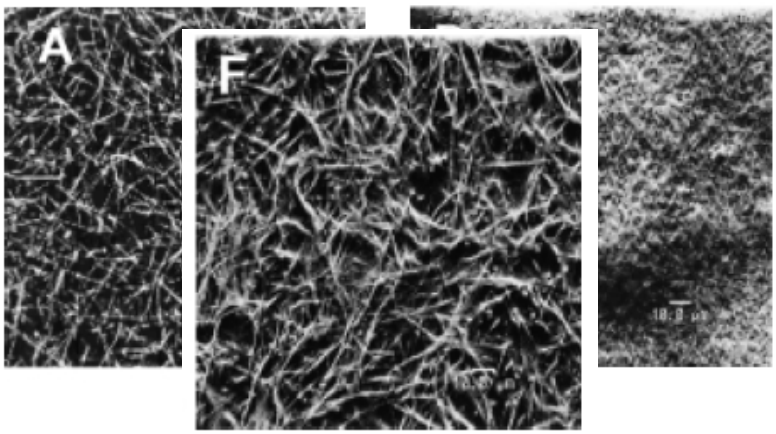
Kerlin, B. A., Ayoob, R., & Smoyer, W. E. (2012). Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *CJASN*, *7*(3), 513–520. http://doi.org/10.2215/CJN.10131011

Imbalance in Hemostasis

	Anti-Thrombotic			Pro-Thrombotic
Procoagulant	N or ↓factor XI (160)[8]	↑, N, or ↓ factor II (69)[8] ↑, N, or ↓ factor VII (50)[8] ↑, N, or ↓ factor IX (56)[8] ↑, N, or ↓ factor X (56)[8] ↓ or ↑ Plt Function[8,48]	N or ↓ factor XII (80)[8,49] ↑Plt Count[8,50,51] ↑vWF (variable)[8]	↑↑fibrinogen (340)[8] ↑↑factor V (330)[8] ↑↑factor VIII (330)[8]
Anticoagulant	↑protein C (62)[8,14,54,55]	↑, N, or ↓ protein S (69)[8,14,54]	↓ protein Z (62)[43,54]	↓ or ↓↓ AT (65)[8,14,54]
Profibrinolytic		↑, N, or ↓ α_2-AP (70)[8]	↓Plasminogen (92)[8] ↓, N, or ↓ tPA (72)[8,55]	
Antifibrinolytic	↓ α_1-AT (54)[8]	↓ or ↑ PAI (52)[8,42]	↑ Lp(a) (~500)[8]	↑↑ α_2-M (725)[8]
Other		*Thrombophilia #APL	↑RBC Aggregation[8] Clot Structure[8,62] Hyperlipidemia[8]	

Kerlin, B. A., Ayoob, R., & Smoyer, W. E. (2012). Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *CJASN*, *7*(3), 513–520. http://doi.org/10.2215/CJN.10131011

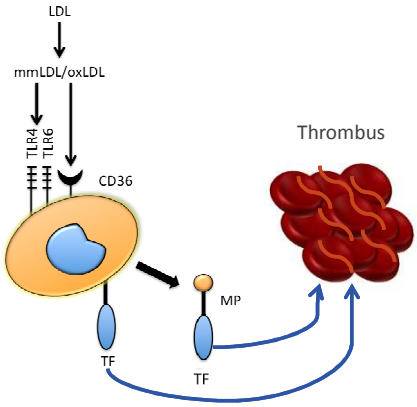
Altered Clot Structure

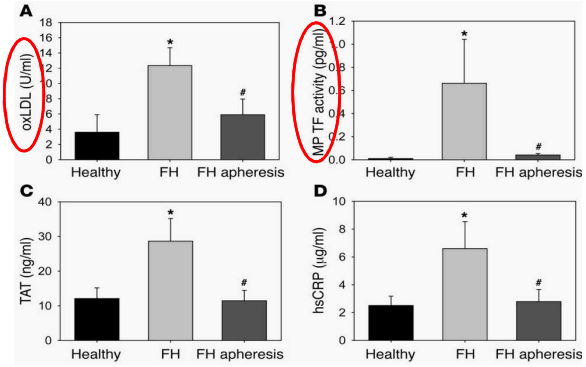


Colle JP et al. Thromb Haemost. 1999 Nov;82(5):1482-9.

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

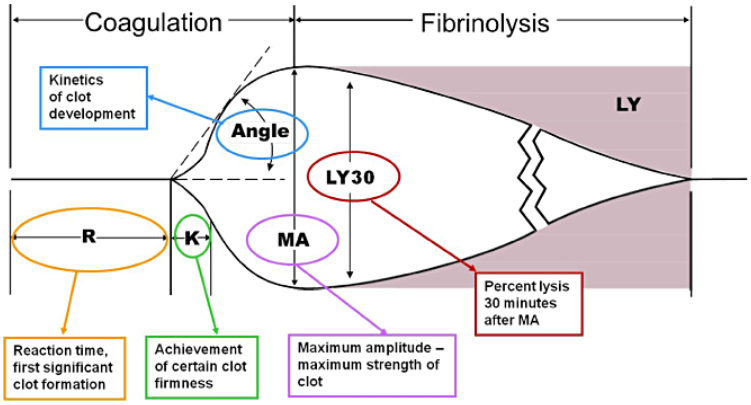




Owens, A. P., III, et al. J Clin Invest. 2012 Feb;122(2):558-68.
Resh M et al. Thromb Res. 2011 May;127(5):395-9.

Global coagulation assays

- Thromboelastography



Transfusion Volume 53, Issue 7, pages 1386-1392, 7 JUN 2012 DOI: 10.1111/j.1537-2995.2012.03728.x

Thromboelastography in NS

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

Huang, M.-J. et al. (2015). Mechanisms of hypercoagulability in nephrotic syndrome associated with membranous nephropathy as assessed by thromboelastography. *Thrombosis Research*, *136*(3), 663–668. http://doi.org/10.1016/j.thromres.2015.06.031

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.**

Huang MJ et al. Hypercoagulable state evaluated by thromboelastography in patients with idiopathic membranous nephropathy. J Thromb Thrombolysis. 2015 Jul 8.

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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

Tkaczyk M, Baj Z. Surface markers of platelet function in idiopathic nephrotic syndrome in children. Pediatr Nephrol. 2002 Aug;17(8):673-7
Kerlin, B. A., Ayoob, R., & Smoyer, W. E. (2012). Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *CJASN*, *7*(3), 513–520.
Gao C et al. Procoagulant activity of erythrocytes and platelets through phosphatidylserine exposure and microparticles release in patients with nephrotic syndrome. Thromb Haemost. 2012 Apr;107(4):681-9. doi: 10.1160/TH11-09-0673.

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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

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

Taewoo Lee[1,2], Andrea K. Biddle[3], Sofia Lionaki[1,4], Vimal K. Derebail[1], Sean J. Barbour[5], Sameer Tannous[1], Michelle A. Hladunewich[5], Yichun Hu[1], Caroline J. Poulton[1], Shannon L. Mahoney[1], J. Charles Jennette[1,6], Susan L. Hogan[1], Ronald J. Falk[1], Daniel C. Cattran[5], Heather N. Reich[5,7] and Patrick H. Nachman[1,7]

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Lee T et al. Kidney Int. 2014 Jun;85(6):1412-20.

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.

Lee T et al. Kidney Int. 2014 Jun;85(6):1412-20.

Input data to the model

- Incidence rate of VTE
- From the pooled inception cohort of GDCN and TGNR

(N= 539)

sAlb < g/dL	Events/100 PY (95% C.I.)
<3.0	3.7 (2.4-5.5)
<2.8	4.3 (2.7-6.4)
<2.5	6.5 (4.0-9.9)
<2.3	8.5 (5.0-13.6)
<2.0	11.4 (5.7-20.4)

- Incidence rate of major bleeding
- From the ATRIA study

(N= 9186)

Risk Category (Point)	Events/100PY (95% CI)
Low (0-3)	0.8 (0.7-0.9)
Interm (4)	2.6 (2.3-3.0)
High (5-10)	5.8 (5.0-6.6)

- Anemia (3)
- Severe renal disease (3)
- Age>75 yo (2)
- Prior bleeding history (1)
- Hypertension (1)

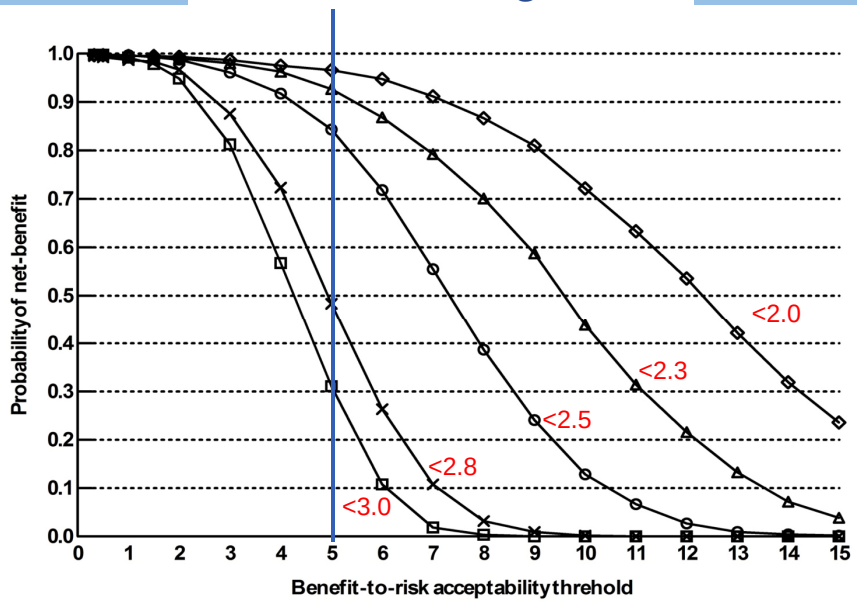
Lee T et al. Kidney Int. 2014 Jun;85(6):1412-20.

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

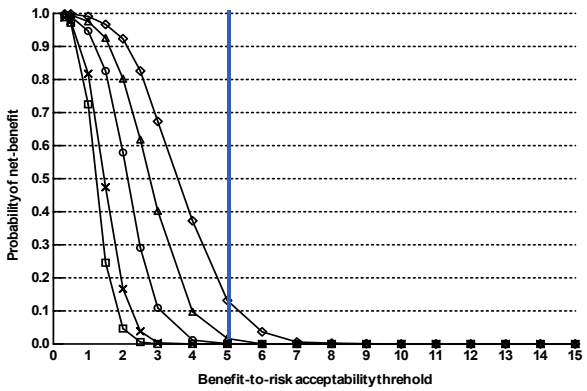
Lee T et al. Kidney Int. 2014 Jun;85(6):1412-20.

Low bleeding risk

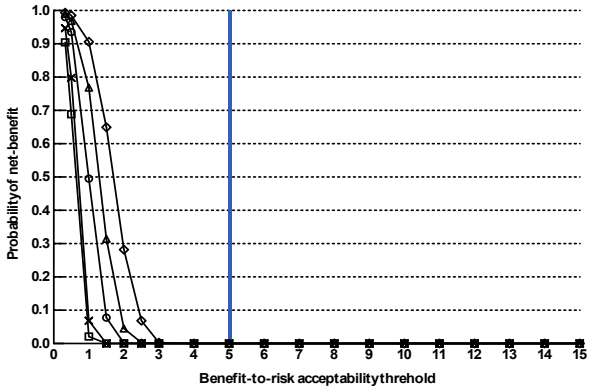


Lee T et al. Kidney Int. 2014 Jun;85(6):1412-20.

Intermediate bleeding risk



High bleeding risk



Lee T et al. Kidney Int. 2014 Jun;85(6):1412-20.

Decision Approach

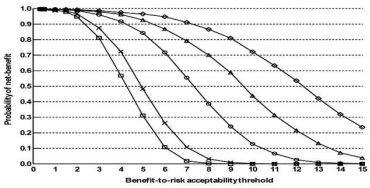
1. Determine the risk of major bleeding

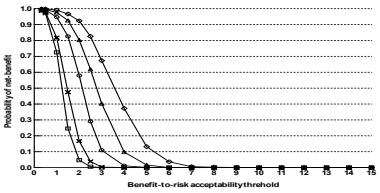
Low → 2. Look at the serum albumin level

Intermediate → 2. Look at the serum albumin level

High → No prophylactic anticoagulation

3. Look at the benefit-to-risk acceptability curve





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Lee T et al. Kidney Int. 2014 Jun;85(6):1412-20.

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Imperial College
Proposed prophylaxis algorithm

Serum albumin <2.0g/dL → Serum albumin 2.0– 3.0g/dL → Serum albumin >3.0g/dL

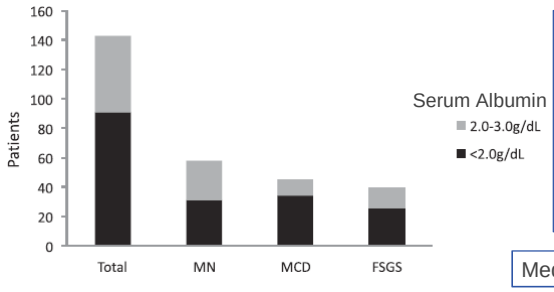
- Serum albumin <2.0g/dL → Prophylactic low molecular weight heparin → Oral coumarin target INR 1.5 -2.5
- Serum albumin 2.0– 3.0g/dL → 75mg aspirin daily
- Serum albumin >3.0g/dL → No VTE prophylaxis

Medjeral-Thomas, N et al. Clin J Am Soc Nephrol 2014; 9: 478–483

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

Characteristic	All (*n*=143)	MN (*n*=58)	MCD (*n*=45)	FSGS (*n*=40)
Median age (range) (yr)	48.7 (20.0–85.5)	54.3 (26.0–85.5)	48.7 (20.0–82.2)	48.1 (24.0–84.5)
Sex, *n* (%)				
Male	76 (53.1)	35 (60.3)	23 (51.1)	18 (45.0)
Female	67 (46.9)	23 (29.7)	22 (48.9)	22 (55.0)
Median follow-up (range) (wk)	154 (30–298)	129 (44–298)	191 (930–285)	159 (30–279)
Median serum creatinine at presentation (range) (mg/dl)	0.94 (0.54–4.43)	0.89 (0.58–2.85)	0.90 (90.54–3.59)	1.52 (0.54–4.43)



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?

Medjeral-Thomas, N et al. Clin J Am Soc Nephrol 2014; 9: 478–483

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

Agent	Renal dose adjustment	Protein binding	Evidence of use in NS	FDA approved for TE prophylaxis
Warfarin	No dose adjustment recommended Frequent INR monitoring may be warranted	High (99%)	Yes	Yes
Heparin	No dose adjustment recommended Adjust based on aPTT or anti-Xa activity	NA	Yes	Yes
Enoxaparin	CrCl <30 mL/min: 30 mg sc daily	Low	Yes	Yes
Dabigatran	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 <30 or hemodialysis: use not recommended	Low (35%)	No	No
Rivaroxaban	CrCl 30-50 mL/min: use with caution CrCl <30 mL/min or hemodialysis: avoid use	High (92-95%)	No	post ortho. surgery
Apixaban	Age ≥80 years, body weight ≤60 kg, or Cr ≥1.5 mg/dL, recommended dose is 2.5 mg twice daily	High (87%)	No	Yes
Clopidogrel	No dose adjustment recommended	High (98%)	No	No

Adapted and modified from Pincus KJ et al. Ann. Pharmacotherapy 2013;47:725-34
Ther Clin Risk Manag. 2015;11:1273-1282

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

Rankin AJ et al. Nephron. 2017;135(1):39-45.

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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).

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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.

*Frost, C., et al., Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. Br J Clin Pharmacol, 2013. 76(5): p. 776-86