Prophylactic Anticoagulation in Adult Patients with Nephrotic Syndrome

Judit Gordon-Cappitelli and Michael J. Choi

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Department of Medicine, Division of Nephrology and Hypertension, MedStar Georgetown University Hospital, Washington, DC

Correspondence:
Dr. Michael J. Choi, MedStar Georgetown University Hospital, 3800 Reservoir Road, NW 6 PHC, Washington, DC 20007. Email: michael.choi@gunet.georgetown.edu

Increased thromboembolic risk is a well recognized complication of nephrotic syndrome, with variable reported incidence of deep venous thrombosis (approximately 15%), pulmonary embolus (10%–30%) and renal vein thrombosis (25%–37%) (1). Hypercoagulability is postulated to stem from the imbalance of glomerular loss of anticoagulants (antithrombin III) with increased liver procoagulant synthesis (fibrinogen, factor V, factor VIII), increased platelet activation and aggregability, decreased fibrinolytic activity, and localized clotting activation in the kidney (1). However, it remains unclear which patients with nephrotic syndrome warrant prophylactic anticoagulation.

Certain primary glomerular diseases (membranous nephropathy, minimal change disease, and FSGS) and some secondary glomerular diseases (membranoproliferative GN, membranous lupus nephritis with lupus anticoagulant, amyloidosis, granulomatosis with polyangiitis, Behcet syndrome) have been associated with an increased risk of venous thromboembolic events compared with other glomerular diseases (1). Membranous nephropathy is associated with the highest risk for developing venous thromboembolism (1,2). In 1313 patients with nephrotic syndrome, the adjusted hazard ratio for venous thromboembolism was 10.8 for membranous nephropathy and 5.9 for FSGS compared with IgA nephropathy (2). The reason for this increased thromboembolic risk in membranous nephropathy is unknown with no presently identifiable role for anti–phospholipase A2 receptor antibody. Importantly, the majority of thromboembolic events occur within 6 months of the diagnosis of nephrotic syndrome (2–4). Children with nephrotic syndrome are less likely to have thromboembolism than adults, with few exceptions, and therefore this review will focus on adults with primary nephrotic syndrome.

Nephrotic syndrome is also associated with increased arterial as well as venous thromboembolism. A retrospective study of 298 patients with primary and secondary nephrotic syndrome found the prevalence of both venous and arterial thromboembolism to be eightfold greater than the general population over 10 years (3). The annual incidence was 1.02% for venous thromboembolic events, which was markedly increased in the first 6 months of observation (9.85%). Risk was most strongly correlated with the ratio of proteinuria to serum albumin. The annual risk of arterial thromboembolism was 1.48% over 10 years which was also increased in the first 6 months (5.52%). Diabetes (7.08% versus 0.82% in people without diabetes), sex, age, hypertension, smoking, prior arterial thromboembolism, and eGFR were the best predictors of arterial thromboembolism. Risk was not related to proteinuria, serum albumin, or the ratio of proteinuria to serum albumin. These results contrast with a large study of solely patients with membranous nephropathy which showed a strong association between time-varying severity of nephrotic syndrome and cardiovascular events (5).

Hypoalbuminemia, reflecting severity of nephrotic syndrome, is generally accepted as having the strongest association with venous thromboembolism risk (1,5). In a cohort of 898 patients with membranous nephropathy, a serum albumin level of <2.8 g/dl was associated with a 2.5-fold increased risk of venous thromboembolism compared with patients with a serum albumin ≥ 2.8 g/dl (4). Each 1.0 g/dl decrease in serum albumin resulted in a 2.13-fold increased risk of venous thromboembolism. In some studies, massive proteinuria has been found to be a more significant predictor of venous thromboembolic events than serum albumin (3). Low plasma antithrombin III levels have been demonstrated in patients with nephrotic syndrome, with and without thromboembolic events, making its role in predicting thrombotic risk unclear.

Thromboembolic events are a preventable cause of morbidity and mortality in patients with nephrotic syndrome, yet prophylactic anticoagulation is not universally initiated. Prophylactic anticoagulation was not initiated in patients with membranous nephropathy in either the Glomerular Disease Collaborative Network between 1969 and 2007 ($n=412$) or the Toronto GN Registry between 1974 and 2005 ($n=486$) (4).

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for GN suggested with low-quality evidence (level 2C) that anticoagulation should be considered in membranous nephropathy if serum albumin is <2.0 to 2.5 g/dl with additional risks for thrombosis (proteinuria, >10 g/d; body mass index, >35 kg/m^2; family history of thromboembolism with documented genetic predisposition; New York Heart Association class III or IV congestive heart failure; recent abdominal or orthopedic surgery; or prolonged immobilization) (6). Contraindications to prophylactic anticoagulation included: an uncooperative patient, a bleeding disorder, prior gastrointestinal bleeding,

a central nervous lesion prone to hemorrhage, or a genetic abnormality influencing warfarin metabolism or efficacy. Another risk not mentioned by KDIGO is the development of anticoagulation-related nephropathy. Future KDIGO guidelines may revise these suggestions but there are no prospective randomized trials addressing prophylactic anticoagulation.

Lee *et al.* (7) constructed a Markov decision model regarding initiation of prophylactic anticoagulation in 898 patients with membranous nephropathy. The likelihood of benefit from warfarin to prevent venous thromboembolic events based on serum albumin level was compared with the patient's estimated bleeding risk (http://www.med.unc.edu/gntools/gntools-team.html). The bleeding risk of patients was classified into low, intermediate, and high categories based on results from the Anticoagulation and Risk Factors in Atrial Fibrillation Study which incorporated severe kidney disease, prior bleeding, hypertension, older age, and anemia as patient characteristics predicting hemorrhage. Patients at low risk for bleeding had a calculated benefit-to-risk ratio of 4.5:1 and 13.1:1 for serum albumin levels of <3 and <2 g/dl, respectively, which indicated there is benefit for anticoagulation at any serum albumin level <3 g/dl. Patients with an intermediate risk had a moderately favorable benefit-to-risk ratio of 5:1 when there was a serum albumin level of <2 g/dl. Patients with high bleeding risk were not predicted to benefit from anticoagulation, even with serum albumin levels <2 g/dl.

Few studies report on the outcomes for patients with nephrotic syndrome who are treated with prophylactic anticoagulation. Kelddal *et al.* retrospectively examined anticoagulation in 79 (minimal change disease, $n=35$; membranous nephropathy, $n=19$; FSGS, $n=7$) patients with nephrotic syndrome without diabetes. It is the only study comparing outcomes between a group anticoagulated using warfarin or low molecular weight heparin (which was combined with aspirin in those with prior aspirin therapy) with a control group without anticoagulation (8). The two participating centers differed in level of hypoalbuminemia for initiating prophylactic anticoagulation. There were no thrombotic events in 44 patients who had been anticoagulated compared with four events in 35 patients who were not anticoagulated. Those on anticoagulation had a significantly lower serum albumin (1.5 versus 2.0 g/dl), predisposing this group to thromboembolism. The authors suggested possible benefits with anticoagulation, especially in those with serum albumin levels <2 g/dl, while cautioning the use of simultaneous aspirin and anticoagulation.

Medjeral-Thomas *et al.* (9) retrospectively reported on the use of an anticoagulation regimen in 143 patients with either primary membranous nephropathy ($n=58$), minimal change disease ($n=45$), or FSGS ($n=40$) over a 5-year period. Patients were excluded if there was a clinical contraindication to anticoagulation. Patients with serum albumin levels <2.0 mg/dl received prophylactic low molecular weight heparin which could be changed to low-dose warfarin for a target international normalized ratio of 1.5–2.5, and patients with albumin levels between 2.0 and 3.0 g/dl received 75 mg/d aspirin. The patients changed treatment according to the serum albumin level during follow-up. Median baseline serum albumin was 1.5 g/dl. No venous thromboembolic events occurred in patients who were on prophylaxis >1 week, whereas there were three major bleeding events with two patients on aspirin and one on low molecular weight heparin.

The role of aspirin in prophylaxis is unclear. In contrast to the success reported above, 46% of patients with membranous nephropathy reported by Lionaki *et al.* (4) developed venous thromboemboli while on antiplatelet agents at the time of the event. Prophylactic acetylsalicylic acid has been proposed for patients with membranous nephropathy who have a serum albumin of ≥2.5 g/dl and an elevated Framingham risk score (10) due to high rates of cardiovascular events (5). This would include most patients with membranous nephropathy except those with serum albumin levels >3.2 g/dl and young, nonsmoking patients with an eGFR >60 ml/min per 1.73 m^2. Aspirin could also be considered in patients with membranous nephropathy categorized as having both high risk of bleeding as well as high risk of venous thromboembolism (serum albumin <2.5 g/dl). Case reports of direct-acting oral anticoagulants for prophylactic anticoagulation in patients with nephrotic syndrome have been described, but experience at this time is limited.

To summarize, risks for arterial and venous thromboembolic events in nephrotic syndrome are increased with severe hypoalbuminemia and especially in patients with membranous nephropathy. If the risk of bleeding is perceived to be low, it would be reasonable to initiate prophylactic anticoagulation early in diagnosis for patients with membranous nephropathy who have serum albumin levels <2 to 2.5 g/dl. For those at high risk of bleeding, it may be prudent to avoid anticoagulation. In those with intermediate risk of bleeding, prophylaxis for those with serum albumin levels <2 would be considered reasonable. Aspirin may be an alternative in those who have higher albumin levels, and/or if there is a high perceived risk of arterial or venous thromboembolic events with high bleeding risk. One could consider prophylaxis with other high-risk glomerular diseases listed above although thromboembolic events are less likely than with membranous nephropathy. Further increased risk of venous thromboembolic events with immobility, obesity, malignancy, recent surgery, pregnancy, medications, central venous catheters, or genetic predisposition would decrease the threshold to start prophylaxis. Evaluation for continuing anticoagulation would depend on the ongoing severity of hypoalbuminemia as well as the presence of the factors above.

Disclosures

Dr. Choi reports personal fees from the Mid-Atlantic Nephrology Fellows Young Investigators Forum. Dr. Gordon-Cappitelli has nothing to disclose.

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