Prophylactic Anticoagulation in Nephrotic Syndrome: A Clinical Conundrum

Richard J. Glassock

David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California

ABSTRACT

It has long been recognized that nephrotic syndrome is associated with an increased risk for thromboembolic complications, including deep venous thrombosis, renal vein thrombosis, and pulmonary embolism. This risk varies with the nature of the underlying disease and seems to be greatest for membranous nephropathy. Other factors, including the level of serum albumin, previous thromboembolic episodes, and a genetically determined predisposition to thrombosis, may also be involved. Prevention of thromboembolic events with oral anticoagulants in nephrotic syndrome requires a careful case-by-case analysis of the risks for thromboembolic events balanced by the risks for anticoagulant induced bleeding. Markov-based decision analysis using literature-based assumptions regarding these risks has suggested that prophylactic anticoagulants may be indicated in certain circumstances. Such decisions need to take into account the nature of the underlying disease, the severity of the nephrotic syndrome (as assessed by serum albumin concentration), preexisting thrombophilic states, and the overall likelihood of serious bleeding events consequent to oral anticoagulation (as assessed by the international normalized ratio for prothrombin time). The optimal duration of prophylactic anticoagulation is unknown but very likely extends to the duration of the nephrotic state *per se*.

Uncertainty is integral to the practice of medicine. The current wave of enthusiasm for the practice of "evidence-based" medicine is in large part motivated by a desire to reduce uncertainty in the diagnosis and treatment of patients with a variety of illnesses. In nephrology, the role of prophylactic anticoagulants in the treatment of patients with nephrotic syndrome (especially those with underlying idiopathic membranous nephropathy) is a prime example of the conundrum of uncertainty. A careful analysis of this conundrum requires assessment of the risks for fatal and nonfatal thromboembolic events in nephrotic syndrome and comparison of this risk with the potential benefits and risks of a prophylactic anticoagulation strategy.

Little doubt exists that certain forms of renal disease are associated with an increased risk for thrombosis or embolism ("thrombophilia") compared with the general population.[1,2] Most noteworthy among these disorders are the various forms of primary and secondary nephrotic syndrome,[1,2] systemic lupus erythematosus with "lupus anticoagulant",[3] granulomatous vasculitis (Wegener's granulomatosis),[4] and Behçet syndrome.[5] In the recent past, the greatest attention to thromboembolic risk and its management has been given to the nephrotic syndrome. Among the numerous causes of the nephrotic syndrome, only a relatively few conditions are consistently associated with a decidedly increased risk for thromboembolism; these

include membranous nephropathy (primary and secondary), membranoproliferative glomerulonephritis, minimal-change disease, and perhaps renal amyloidosis.[1,6] However, the reported risk for thromboembolism in these disorders varies widely, depending in part on how the cases were ascertained, how the diagnosis of a thrombotic event was established, or what the severity of the nephrotic state *per se* was. Both venous and systemic or pulmonary arterial thrombosis have been noted to occur with increased frequency in nephrotic syndrome.[1,7] Among the venous thromboses associated with nephrotic syndrome, both acute and chronic renal vein thrombosis (RVT) and deep venous thrombosis (DVT) of the lower extremities may develop (separately or together), both of which may be associated with pulmonary embolism.[1,8–11] DVT is said to develop in approximately 15% of patients with the nephrotic syndrome, either with or without an accompanying RVT.[12] RVT, unilateral or bilateral, has been reported to develop in approximately 25 to 30% of patients with the nephrotic syndrome as a result of primary renal disease, with the greatest risk seen in membranous glomerulonephritis (37%), membranoproliferative glomerulonephritis (26%), and minimal-change disease (24%).[1,8–11] The com-

bined burden of DVT and RVT in patients with membranous nephropathy and the nephrotic syndrome has been estimated to be as high as 45% in some reports.[12] The risk for DVT and/or RVT seems to be higher when the serum albumin concentration is <2.0 to 2.5 g/dl. For example, Bellomo and Atkins[12] found venous thromboembolic events to occur in 40% of patients with membranous nephropathy and nephrotic syndrome with a serum albumin concentration of <2.5 g/dl but only 2.7% in those with a serum albumin concentration of >2.5 g/dl. The reported development of DVT and/or RVT among nephrotic renal diseases varies widely. In cross-sectional studies of membranous nephropathy, the reported risk for RVT has ranged from 1.9 to 60%.[1,8–11,13] To some extent, this extreme variation is the result of differing methods to establish the diagnosis of RVT and gradations in the severity of the underlying disease. In many cases, the RVT is asymptomatic and discovered only upon "routine" screening studies or diagnosed after a thromboembolic event. Ventilation-perfusion lung abnormalities that are suggestive of pulmonary embolism (or *in situ* thrombosis) can be found in 10% of asymptomatic patients without RVT or DVT and in approximately 20% of those with RVT alone accompanying nephrotic syndrome.[8] Higher values for pulmonary embolism (or *in situ* thrombosis in nephrotic syndrome have been reported when pulmonary angiography is used for diagnosis.[14] Thus, general agreement exists that nephrotic syndrome, especially as a result of membranous nephropathy, membranoproliferative glomerulonephritis, and minimal-change disease, is a risk factor for thromboembolic disease, although the precise level of this risk is not fully agreed on. A very low serum albumin level seems to be a surrogate measure of increased risk, but thromboembolism can occur even when serum albumin is only modestly reduced.

The underlying mechanisms of the "thrombophilia" of the nephrotic syndrome are multiple but seem to related to an imbalance of prothrombotic factors (*e.g.,* increased fibrinogen levels, in-creased factor VIII levels, increased platelet adhesiveness) and antithrombotic factors (*e.g.,* reduced antithrombin III levels, reduced protein C and S levels or activity) and impaired thrombolytic activity (decreased plasminogen levels, elevated plasminogen activator inhibitor-1 levels or albumin deficiency–related impairment of the interaction of plasminogen-fibrin).[1,15] Volume depletion, diuretic and/or steroid therapy, venous stasis, immobilization, or immune complex activation of the clotting cascade may also participate in the "thrombophilia" of the nephrotic syndrome. It remains a mystery why only certain conditions have such a strong (but variable) association with RVT. The recent discovery of the association of anti-enolase autoantibodies with membranous nephropathy offers a tantalizing clue, because these autoantibodies could interfere with fibrinolysis.[16,17] The coexistence of another "thrombophilic" state, such as hereditary resistance to the activation of protein C (Leiden trait), with nephrotic syndrome could be another factor involved in the generation of thrombotic events in selected patients.[18]

The treatment of *overt* thrombotic or embolic events in patients with nephrotic syndrome is relatively straightforward. Anticoagulation with sequential high or low molecular weight heparin and oral warfarin is the recommended therapy with the greatest experience.[1] The duration of treatment needed to prevent recurrent events is unknown but is probably equal to the duration of the nephrotic state *per se*. "Breakthrough" thrombosis in anticoagulated patients is distinctly uncommon.

Prophylactic oral anticoagulation of asymptomatic patients who have nephrotic syndrome and are believed to be at elevated risk for a thromboembolic event is another matter altogether.[1] The issue of prophylactic anticoagulation in nephrotic syndrome, such as caused by membranous nephropathy, is complicated further by suggestions that asymptomatic patients who are thought to be "at risk" for RVT should be routinely screened for covert RVT, using spiral computed tomography (CT), and then anticoagulated for secondary prophylaxis of a pulmonary embolic event if the test is positive.[8–11] The sensitivity and specificity of CT for the diagnosis of covert RVT is 90 and 100%, respectively, using renal venous angiography as the gold standard.[19] Magnetic resonance angiography may also be useful, but this technique has not been as well studied as CT.[20] Doppler ultrasonography has test characteristics (high false positive [40%] and false negative [15%] rates) that make it less desirable as a screening tool.[21] A major weakness of uncritical advocacy for routine screening for DVT is that a negative test does not predict whether (or when) a negative study is likely to convert to a positive study. Furthermore, the risk for developing an overt pulmonary embolus in an untreated patient with a covert RVT detected by "screening" is not well understood. Some studies have suggested that the risk for a pulmonary embolus is approximately twice as high with the presence of covert chronic RVT (20%) compared with its absence (10%),[1,8] but long-term prospective studies are lacking. Clinical clues (other than an overt thromboembolic episode in the absence of an obvious DVT) for the presence of an occult RVT are relatively few but include ipsilateral renal enlargement, pelvicaliceal abnormalities, and ureteric notching from collateral veins as determined by intravenous urography.[1] A renal biopsy with prominent leukocyte margination (stasis) in the glomerular capillaries and interstitial edema may also suggest RVT.[22] Chronic RVT is most often asymptomatic, whereas acute RVT may produce flank pain and hematuria. Therefore, it remains uncertain whether routine screening for RVT (with CT scanning) is needed in asymptomatic patients with nephrotic syndrome, although a case might be made for this approach in patients who are at high risk, such as patients with membranous glomerulonephritis and severe nephrotic syndrome with a serum albumin level of <2.0 to 2.5 g/dl. A positive study (expected in between 2 and 60% of patients, averaging approximately 30%) would be a possible indication for anticoagulation, depend-

ing on the risks for bleeding or other contraindications to anticoagulation (*e.g.*, a central nervous system lesion). A negative study would be unhelpful with a decision to anticoagulate, because the patient could subsequently develop an asymptomatic RVT or DVT. It is apparent that routine screening for covert RVT is not considered standard of practice because this has not been a requirement for admission to randomized, controlled trials of nephrotic syndrome, including membranous glomerulonephritis.

The excess "burden" of thrombosis that is seen in nephrotic syndrome (particularly in membranous nephropathy) may contribute to the morbidity and mortality of this condition. For example, Bellomo and Atkins[12] found a yearly mortality rate from thromboembolism of approximately 10% in membranous nephropathy. These events tended to occur "early" (within the 6 mo) after diagnosis.[12] It is noteworthy that a much lower rate of thromboembolism has been observed in randomized therapeutic trials in idiopathic membranous nephropathy. A survey of all such trials reported between 1979 and 2001 revealed an extraordinarily low rate of thromboembolism (one case in >500 randomly assigned patients who were followed for >2000 patient-years).[23–29] Subtle selection forces operating at the enrollment level may have contributed to this finding. Natural history studies of untreated patients have also noted a low prevalence of thromboembolism in membranous nephropathy.[30]

What, then, should be the position of a nephrologist who is confronted with a patient who has nephrotic syndrome with no overt symptoms or signs suggestive of a thromboembolic disorder with respect to the initiation of *prophylactic* oral anticoagulation? Unfortunately, no randomized, controlled trials have been conducted to provide evidence to guide and inform this decision-making process. What does exist are analyses of hypothetical scenarios using Markov modeling and decision analysis, which uses assumptions (estimated from the literature) regarding the risk and benefit of such *prophylactic* oral anticoagulation in

patients with nephrotic syndrome (most often with membranous nephropathy as the underlying disorder). Sarasin and Schifferli[31] reported on such an analysis in 1994. They assumed an incidence of RVT of 0.5% per month of observation. For DVT, they assumed an incidence of 1% per month for acute symptomatic disease. They assumed that a pulmonary embolus would occur in 30% of patients with RVT and in 50% of patients with DVT. These assumptions may be somewhat higher than the true risk, which is not very well known. They are also much higher than the observed rate of pulmonary embolism in patients with membranous nephropathy enrolled in randomized clinical trials of therapy of membranous nephropathy cited previously. The risk for hemorrhagic complications of oral anticoagulation was deemed to range between 0.05 and 1.4% per month depending on the presence of other risk factors, such as advanced age, history of stroke or gastrointestinal bleeding, or other serious comorbidity. These values have been extrapolated from patients who have received oral anticoagulation for nonrenal indications. More recent studies have suggested that the risk for serious bleeding complications from oral (warfarin) anticoagulation has been decreasing but remains higher in the elderly (10.5 events/100 patient-years) compared with younger patients (6.0 events/100 patient-years).[32] Hemorrhagic events are also associated with the intensity of oral anticoagulation (as assessed by the international normalized ratio [INR] for prothrombin time). Hemorrhagic events are infrequent when the INR is well maintained within a recommended "therapeutic" range (4.8/100 patient-years for an INR of 2.0 to 2.9) but increase substantially when the INR increases above the "therapeutic" range (9.5/100 patient-years for an INR of 3.0 to 4.4 and >40/100 patient-years for INR >4.4).[32] A therapeutic target of an INR between 1.8 and 2.0 has been suggested as optimal for prevention of recurrent DVT.[12]

Using these assumptions and a Markov-based decision analysis model incorporating utilities (morbidity and

mortality), Sarasin and Schifferli[31] concluded that a policy of routine *prophylactic* oral anticoagulation of patients with the nephrotic syndrome as a result of idiopathic membranous glomerulonephritis would result in a gain of 2.5 mo of quality-adjusted life expectancy for a 50-yr-old patient who remained on anticoagulation for 2 yr. However, observation without anticoagulation would be preferred if the risk for venous thrombosis were a factor of two times lower than the estimates and/or the risk for bleeding were twice that assumed. Obviously these analyses do not apply to secondary membranous glomerulonephritis (*e.g.*, malignancy related, lupus membranous glomerulonephritis related), to other forms of glomerular disease associated with the nephrotic syndrome, to patients with a history of thromboembolism, or to patients with a genetic disorder that predisposes to thrombosis (*e.g.*, the Leiden trait). Sarasin and Schifferli[31] also noted that patients with nephrotic syndrome other than that as a result of membranous glomerulonephritis have risk levels of thrombosis that yield different results on Markov decision analysis much closer to a "toss up" and much more sensitive to minor changes in the underlying assumptions. A somewhat similar decision analysis was conducted by Bellomo and Atkins[12] in 1993. They assumed that hemorrhagic complications from oral anticoagulation (at INR levels of approximately 2.0) would occur at a rate of approximately 17 per 100 patient-years (approximately three times higher than rates currently observed) and that the combined risk for thromboembolic events was approximately 40%. They further assumed that "breakthrough" thromboembolism would occur in approximately 10% of patients who are anticoagulated. Using these assumptions, they estimated that 54 morbid events would occur per 100 patient-years (40 thromboembolic events requiring therapeutic anticoagulation, 11 hemorrhagic events, and three "breakthrough" thromboembolic events in anticoagulated patients) in a strategy involving *therapeutic* anticoagulation *after* a thromboembolic event had tran-

spired. Using similar estimates, they estimated that 37 morbid events per 100 patient-years (26 hemorrhagic events and 10 breakthrough thromboembolic events in anticoagulated patients) in a strategy involving routine prophylactic anticoagulation. Thus, the rate of morbid events is 32% lower with a *prophylactic* rather than a *therapeutic* strategy using these estimates. A "sensitivity" analysis was not conducted to determine what level of assumptions (risk for thrombosis and risk for hemorrhagic complications from anticoagulation) would generate a toss-up decision between the therapeutic and prophylactic strategies, but if the theoretical risk for thromboembolism is half that used in this analysis, then the "benefit" of a *prophylactic* compared with a *therapeutic* strategy is nullified. Despite repeated calls for a randomized clinical trial of prophylactic anticoagulation to validate or deny the conclusions derived from decision analyses, none has yet been conducted. A possible argument against "routine" prophylactic anticoagulants in idiopathic membranous nephropathy is that none of the randomized therapeutic trials in membranous nephropathy reported between 1979 and 2001 required that enrolled patients be routinely treated with prophylactic anticoagulants.[23–29] Because ethical considerations demand that participants in such trials receive standard of care, one would have to conclude that prophylactic anticoagulation of patients with membranous nephropathy (and by inference other patients with nephrotic syndrome) has not yet reached a uniform level of standard of care.

This does not mean that prophylactic anticoagulants are not indicated in management. Patients who have severe nephrotic syndrome, regardless of underlying cause, and a history of a thromboembolic event (a DVT or a pulmonary embolus) should be offered prophylactic anticoagulants if no contraindications exist. Patients with severe nephrotic syndrome (serum albumin <2.0 to 2.5 g/dl) should also be considered candidates for prophylactic anticoagulation if they have other risk factors

for thrombosis (*e.g.*, congestive heart failure; prolonged immobilization; morbid obesity; abdominal, orthopedic, or gynecologic surgery). Patients with a family history of "thrombophilia" (who might have a genetic predisposition to thrombosis) might also be considered for prophylactic therapy. The utility of screening for such genetic causes of thrombophilia has not been tested in a cohort of patients with the nephrotic syndrome. The value of prophylactic aspirin therapy has also not been rigorously tested in nephrotic syndrome.

The decision to screen (with CT) asymptomatic patients with nephrotic syndrome for covert RVT should be undertaken with caution. A clearly positive test will mandate anticoagulation for secondary prophylaxis of a pulmonary embolus, and there are no randomized, controlled trials to suggest that this "screen and treat" strategy is both safe and effective. A negative study is not helpful with respect to the decision to recommend prophylactic anticoagulation. Personally, I find little reason to recommend routine screening for RVT in patients with the nephrotic syndrome. Studying patients with nephrotic syndrome and overt DVT or pulmonary emboli for occult RVT seems to me to be very unnecessary because anticoagulation will be offered to the patient irrespective of the findings. In my inspection of the relevant literature, I can also find no justification for prolonged *prophylactic* anticoagulation for patients with unilateral or bilateral covert chronic RVT discovered by screening to improve the nephrotic syndrome or to slow the rate of progression to ESRD. No evidence exists that anticoagulation has any clear-cut beneficial effects on these parameters.

In summary, a "selective" or individualized rather than a "routine" approach to prophylactic anticoagulation seems justified in nephrotic syndrome. A case can be made for prophylactic anticoagulation in patients with severe nephrotic syndrome (serum albumin concentration <2.0 to 2.5 g/dl) as a result of membranous nephropathy when no contraindication to the use of long-term warfarin anticoagulation exists. It is unclear

whether a "cutoff" of an albumin concentration of <2.0 or 2.5 g/dl is most appropriate. The INR during maintenance therapy should be targeted to 1.8 to 2.0, and the treatment should be continued for as long as the patient is nephrotic (unless, of course, a serious hemorrhagic event ensues). The desirability of prophylactic anticoagulation of an individual patient would be enhanced if a history of a thromboembolic event is obtained or if other factors that favor thrombosis are identified. Screening for genetic causes of thrombophilia might be indicated if a family history of recurrent thrombosis is present, but the value of this approach and its cost-effectiveness have not yet been evaluated in the nephrotic syndrome. However, the clinical conundrum that is the subject of this clinical commentary can be truly resolved only by a properly designed randomized clinical trial. I can only echo the numerous calls for this conundrum-resolving exercise, none of which has been heeded to date.

DISCLOSURES

None.

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