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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]

[1]UNC Kidney Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2]Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, Korea

[3]Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[4]Laiko Hospital, Athens, Greece

[5]Division of Nephrology, Department of Medicine, University of Toronto, and Toronto Glomerulonephritis Registry, Toronto, Ontario, Canada

[6]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Abstract

Primary membranous nephropathy is associated with increased risk of venous thromboembolic events, which are inversely correlated with serum albumin levels. To evaluate the potential benefit of prophylactic anticoagulation (venous thromboembolic events prevented) relative to the risk (major bleeds), we constructed a Markov decision model. The venous thromboembolic event risk according to serum albumin was obtained from an inception cohort of 898 patients with primary membranous nephropathy. Risk estimates of hemorrhage were obtained from a systematic

Correspondence: Heather N. Reich, Division of Nephrology, Department of Medicine, University of Toronto, and Toronto Glomerulonephritis Registry, 8N-849 200 Elizabeth St, University Health Network, Toronto, Ontario, Canada M5G 2C4. heather.reich@uhn.ca or Patrick H. Nachman, 7004 Burnett-Womack CB No. 7155, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7155, USA. Patrick_nachman@med.unc.edu.

[7]These authors contributed equally to this work.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Appendix 1. Study diagram to calculate the incidence rate of VTE in a pooled inception cohort of membranous nephropathy.
Appendix 2. Search strategy of a systematic review for the incidence rate of VTE.
Appendix 3. Study diagram of a systematic review for the incidence rate of VTE.
Appendix 4. Study diagram of systematic review for the incidence rate of major bleeding from warfarin anticoagulation in the setting of nephrotic syndrome.
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Appendix 7. Characteristics of 11 studies selected in the systematic literature search for the incidence rate of major bleeding.
Appendix 8. Decision model input data for the different clinical approaches: prophylactic anticoagulation vs. observation.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

literature review. Benefit-to-risk ratios were predicted according to bleeding risk and serum albumin. This ratio increased with worsening hypoalbuminemia from 4.5:1 for an albumin under 3 g/dl to 13.1:1 for an albumin under 2 g/dl in patients at low bleeding risk. Patients at intermediate bleeding risk with an albumin under 2 g/dl have a moderately favorable benefit-to-risk ratio (under 5:1). Patients at high bleeding risk are unlikely to benefit from prophylactic anticoagulation regardless of albuminemia. Probabilistic sensitivity analysis, to account for uncertainty in risk estimates, confirmed these trends. From these data, we constructed a tool to estimate the likelihood of benefit based on an individual's bleeding risk profile, serum albumin level, and acceptable benefit-to-risk ratio (http://www.gntools.com). This tool provides an approach to the decision of prophylactic anticoagulation personalized to the individual's needs and adaptable to dynamic changes in health status and risk profile.

Keywords

anticoagulation; membranous nephropathy; thrombosis

The nephrotic syndrome, characterized by proteinuria, edema, hyperlipidemia, and hypoalbuminemia,[1] is associated with an increased risk of venous thromboembolic events (VTEs) such as deep vein or renal vein thrombosis, and pulmonary embolism.[2–6] The risk of VTEs is particularly high in patients with primary membranous nephropathy when compared with other nephrotic diseases.[7,8] Among patients with primary membranous nephropathy, hypoalbuminemia is the most important independent risk factor for VTEs. On the basis of the largest cohort of patients with membranous nephropathy studied to date, we have recently demonstrated that the risk of VTEs increases incrementally when serum albumin levels fall below 2.8 g/dl.[9] Proteinuria was not an independent risk factor of VTEs. The risk of VTEs varies over time, in parallel with changes in serum albumin.

These findings beg the important question of the utility of prophylactic anticoagulation in patients with membranous nephropathy. There is currently no evidence-based guide for the use of prophylactic anticoagulation tailored to an individual's risks of VTEs and bleeding from anticoagulation.

We developed a tool that aids in deciding whether to use prophylactic anticoagulation in patients with primary membranous nephropathy. We generated a user-friendly computer program that provides the likelihood of benefit from prophylactic anticoagulation based on an individual patient's risk of VTEs, bleeding risk profile, and the physician's and patient's threshold of tolerance to trade-off the risk of major bleeding to prevent a VTE. Our model incorporates new data on risk estimates of clinically apparent VTEs based on levels of hypoalbuminemia (the most powerful predictor risk of VTEs[9]) as well as data regarding the graded risk of major bleeding from warfarin anticoagulation. The risk estimates of VTEs were derived from longitudinal clinical data on 539 patients from an inception cohort of 898 patients with biopsy-proven primary membranous nephropathy.[9] As there are no published data regarding bleeding in patients with the nephrotic syndrome treated with warfarin, the graded risk of bleeding was derived from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, a large population-based cohort study of warfarin prophylactic

anticoagulation, with target international normalized ratio (INR) of 2–3.[10] We verified that the incidence of major bleeds among warfarin-treated patients with glomerulonephritis and hypoalbuminemia from our own registries was within the range reported by the ATRIA study. After calculating base benefit-to-risk ratios, we performed probabilistic sensitivity analysis to account for variability surrounding model inputs.

Our analysis suggests that the benefit-to-risk ratio favors prophylactic anticoagulation in patients at low risk of bleeding, but not in those at high risk of bleeding. Our study uses new real-world clinical data to establish a personalized, easily applicable clinical tool to inform decisions regarding prophylactic anticoagulation in primary membranous nephropathy.

RESULTS

Model construction

We constructed a hybrid Markov decision tree model to predict the benefit-to-risk ratio associated with prophylactic anticoagulation (VTEs prevented:major bleed incurred). The decision model, including major decision and end point nodes, is illustrated in Figure 1.

To construct this model, we used actual observed VTE rates derived from a large patient cohort. No patient received prophylactic anticoagulation. Table 1 summarizes the characteristics of the cohort from which risk estimates of clinically apparent VTEs were derived. For each threshold of serum albumin, the incidence of VTEs was calculated by the number of events during the total period at risk. The period at risk was defined as the time spent at or below the corresponding level of serum albumin.

Table 2 provides the decision input data for the two clinical approaches—prophylactic anticoagulation versus observation— including the incidence rates and corresponding probabilities for pertinent clinical outcomes, major bleeds based on risk score categories, and VTEs during periods of hypoalbuminemia below each specified threshold. These thresholds were previously correlated with incremental increases in the risk of VTEs.[9] Major bleeds were defined as involving vital organs or requiring transfusion of ≥2 units of packed red blood cells.[10] For our model, we adopted the low (≤3 points), intermediate (4 points), and high (5–10 points) bleeding risk categories described in the ATRIA study.[10] We also calculated the incidence of major bleed in a cohort of 98 warfarin-treated patients with glomerulonephritis, a median serum albumin 2.1 g/dl (interquartile range 1.7–2.6) and a total warfarin exposure of 207.4 person-years (Table 3). Sixty-five percent had a low, 10% intermediate, and 25% high bleeding score. The annual incidence of bleed was 0.4 events per 100 patient-year of anticoagulation (95% confidence interval: 0.01–2.69), which is in the range reported in the ATRIA study for patients in the low-to-intermediate bleeding risk categories (Table 2).

Predicted benefit-to-risk ratios

The results of the base–case analysis of benefit-to-risk ratio (ratio of the number of VTEs prevented divided by major bleeds incurred) for each category of serum albumin and bleeding risk are provided in Table 4. For patients at low risk of major bleed (ATRIA score ≤3 points) and serum albumin <3.0 g/dl, the base–case model predicts that 4.5 VTEs will be

prevented at the cost of one major bleed during 24 months of prophylactic anticoagulation (benefit-to-risk ratio = 4.5:1). The benefit-to-risk ratio increases incrementally with worsening hypoalbuminemia to 5.2:1 for serum albumin <2.8 g/dl, and to 13.1:1 for serum albumin <2.0 g/dl. For each level of hypoalbuminemia, the benefit-to-risk ratio is lower for patients with intermediate bleeding risk (ATRIA score 4) compared with patients at low risk of bleeding, and increases incrementally from 1.3:1 (for serum albumin <3.0 g/dl) to 3.9:1 (for serum albumin <2.0 g/dl). For patients in the high bleeding-risk category (ATRIA score 5–10), the benefit-to-risk ratio remains below 2:1 even for the most profound hypoalbuminemia level.

Consideration of uncertainty: probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted to evaluate the impact of uncertainty surrounding the risk and event estimates used in the Markov model. The Monte Carlo simulation presents various possible scenarios considering plausible ranges of model inputs. Figure 2 is a graphic representation of the range in benefit-to-risk derived from the Markov model while randomly varying the input estimates. Each simulated plot represents a range of the number of VTEs prevented (horizontal axis) and major bleeding events incurred (vertical axis) according to bleeding risk and the degree of hypoalbuminemia. Reference benefit-to-risk ratios that clinicians and patients may consider as thresholds for decision-making (from upper to lower, 2:1, 5:1, and 10:1, respectively) are provided.

For patients in the high bleeding-risk category (open circles), the density plots aggregate entirely above the 2:1 benefit-to-risk line when the albumin is <3.0 g/dl (Figure 2a), indicating that fewer than two VTEs would be prevented with prophylactic anticoagulation for each major bleed incurred. Indeed in the high bleeding-risk category, the results fall above the 2:1 acceptability threshold line regardless of whether the albumin is <3.0 mg/dl (Figure 2a), <2.5 mg/dl (Figure 2b), or <2.0 mg/dl (Figure 2c), suggesting a uniformly unacceptable benefit-to-risk ratio.

In contrast, for patients in the low bleeding-risk category, (open triangles) the vast majority of simulated results aggregate below and to the right of the 5:1 acceptability threshold when the serum albumin is <2.5 or <2.0 mg/dl (Figure 2b and c). In this setting, five or more VTEs would be prevented for one bleed incurred. Furthermore, for serum albumin level <2.0 g/dl, most of the density plot for the low bleeding-risk category falls to the right and below the 10:1 acceptability threshold (Figure 2c), indicating an even higher benefit-to-risk ratio.

Adaptation for a clinical decision tool

The data from the probabilistic sensitivity analysis were adapted to provide the likelihood of benefit from prophylactic anticoagulation based on each individual's bleeding-risk category, serum albumin, and risk tolerance. For each bleeding-risk category (Figure 3a–c), the benefit-to-risk acceptability curves summarize graphically the probability of clinical benefit from prophylactic anticoagulation compared with observation (y axis) given a physician and patient's willingness to accept the trade-off for the risk of major bleeding to prevent VTEs (x axis). The probability of net benefit varies according to the level of serum albumin

(curves), and can therefore be re-evaluated during the evolving course of a patient's disease. Figure 3a is applicable to patients at low bleeding risk. Accepting a 5:1 benefit-torisk ratio (5 VTEs–prevented for 1 bleed incurred) (x axis), the likelihood of benefit from prophylactic anticoagulation would be 480% with serum albumin <2.5 g/dl(–○–) but <50% with serum albumin <2.8 g/dl (–□–). Applying the more stringent threshold of 10:1, the likelihood of benefit for patients with serum albumin <2.0 g/dl (–◊–) would be 72%. Patients in the intermediate bleeding risk category and a serum albumin <2.0 g/dl would have a likelihood of benefit from prophylactic anticoagulation <15% when accepting a 5:1 benefit-to-risk ratio, but >67% for a 3:1 ratio (Figure 3b). For patients in the high bleeding-risk category, the benefit-to-risk ratio does not favor anticoagulation, with a likelihood of benefit <1% even with serum albumin <2.0 g/dl (Figure 3c).

DISCUSSION

The frequency of VTEs in patients with nephrotic syndrome is higher than in the general population,[11,12] and is higher in patients with membranous nephropathy compared with other proteinuric kidney diseases.[7,8,13] Limited data exist to guide the decision on prophylactic anticoagulation at the individual patient level, balancing the potential benefits and risks, with consideration of evolving disease activity. Several studies have firmly linked the risk of VTEs with the severity of hypoalbuminemia.[9,14] Although no publications specifically address the complication rate of anticoagulation in patients with nephrotic syndrome, several have identified risk factors for bleeding in the setting of prophylactic anticoagulation with warfarin for atrial fibrillation,[10,15,16] and can be reasonably applied to patients with membranous nephropathy. In our study, we have incorporated these new data to weigh the relative benefits and risks of prophylactic warfarin anticoagulation based on individual patients' clinical characteristics.

The results of our decision analysis indicate that for patients at low bleeding risk (ATRIA risk score 0–3 out of 10), the benefit-to-risk ratio favors prophylactic anticoagulation at low serum albumin levels. For patients at intermediate risk of bleeding (risk score of 4), prophylactic anticoagulation may be favorable with severe hypoalbuminemia (<2 g/dl), while accepting lower benefit-to-risk ratio (<5:1). Thus, for patients at low or intermediate bleeding risk, the threshold serum albumin level below which anticoagulation is favored depends on the patient's and physician's 'trade-off ' acceptability of bleeding risk. In contrast, for patients at high risk of bleeding (risk scores 5–10), the benefit-to-risk ratio does not favor prophylactic anticoagulation even with severe hypoalbuminemia (<2.0 g/dl). We therefore propose that the decision of prophylactic anticoagulation in patients with primary membranous nephropathy should start with an assessment of a patient's bleeding risk (Figure 4). For patients determined to be at low or intermediate risk of bleeding, the next step is to 'look' at the serum albumin concentration and 'choose' the preferred benefit-to-risk ratio. These parameters are then used to determine the probability of benefit of prophylactic anticoagulation.

Our findings offer important advantages over the previous decision analysis.[17] Our study uses the ratio of VTEs prevented to bleeds incurred as the main outcome of interest, thus offering flexibility in choosing the strategy based on an individualized acceptability of

benefit-to-risk ratio. Because we base risk assessment of VTEs on serum albumin level, our approach allows for a dynamic re-evaluation of benefit and risk as the patient's albumin level changes with time or in response to treatment. Likewise, assessment of bleeding risk is also dynamic based on changes in the patient's risk factors (e.g., a decrease in renal function, or development of hypertension). Changes in risks of VTEs and bleeding also can be used to discontinue anticoagulation once the risk of VTEs decreases or that of bleeding increases. The longitudinal data from our large inception cohort allowed us to measure the incidence of VTEs based on the period at risk of each patient for the determined level of hypoalbuminemia, rather than the total time of follow-up. This approach provides a more accurate risk estimate of VTEs than data derived from small cohort studies that did not take into account this period at risk. Likewise, our study uses a stratified risk of bleeding from anticoagulation as described in the ATRIA study. The large size of the ATRIA study cohort provides an accurate estimate of bleeding risk and detailed incidence rates for the various risk categories. This study also provided an easily applicable scoring system for bleeding risk stratification. Importantly, the confidence intervals of the bleeding risks reported in the ATRIA study encompass those reported in other studies of prophylactic anticoagulation for atrial fibrillation (Supplementary Appendix 7 online). Therefore, using the sensitivity analysis, the benefit-to-risk ratios we report for each level of bleeding risk category also reflect those we would have obtained using other bleeding-score models.

Despite differences in demographics and comorbidities between the ATRIA study cohort and ours, the risk factors for major bleeding of warfarin identified by the ATRIA study should also apply to patients with primary membranous nephropathy, as the very large ATRIA cohort (13,559 patients) encompasses the range of age and glomerular filtration rate of our cohort. Further, the bleeding risk in our model is estimated for each patient individually, and is therefore not affected by overall demographic differences between the ATRIA and membranous nephropathy cohorts.

As to the important question of whether patients with hypoalbuminemia have a greater risk of bleeding than reported in the ATRIA study, there are little data published regarding the relationship between serum albumin and risk of anticoagulation with coumadin. Hypoalbuminemia may affect the pharmacokinetics of coumadin[18,19] and increase the risk of overanticoagulation,[20,21] and hypoalbuminemia has been associated with a higher risk of minor but not major hemorrhages in one study.[22] We analyzed data from our own registries regarding 98 warfarin-treated patients with primary glomerulonephritis and coexistent hypoalbuminemia. We found an incidence rate of major bleeding well within the range predicted by ATRIA for patients at low risk of bleeding. Nevertheless, we recognize that the bleeding rates from the ATRIA study should be used cautiously when extrapolating to different populations.

There are limitations to our analysis. Because our VTE incidence is derived retrospectively from clinically apparent events in our cohort, our incidence data may be an underestimation of the true VTE risk. However, a recent large prospective randomized controlled trial in patients with membranous nephropathy reported a frequency of clinically apparent VTEs of 7.5%[23] similar to that observed in our own cohort, thus providing reassurance that we did not underestimate the risk of VTEs. The case fatality rates were drawn from population data,

and extrapolation to patients with idiopathic membranous nephropathy should also be carried out with caution. There are other known risk factors for VTEs that were not incorporated in our original analysis of VTEs for lack of sufficient data (e.g., immobilization, smoking, morbid obesity, heart failure, and genetic propensity). The presence of such additional factors should be taken into account by the treating physician in assessing the benefit-to-risk of prophylactic anticoagulation for an individual patient. Our results have not been prospectively tested, and therefore are not directly clinically validated. Finally, the results of our model are specific to primary membranous nephropathy and the benefit-to-risk ratios for each level of hypoalbuminemia cannot be directly applied to other forms of nephrotic syndrome associated with lower rates of VTEs.[7,8] Adapting our model to other forms of nephrotic syndrome (e.g., focal segmental glomerulosclerosis) will require separate in-depth analysis of VTE incidence by the level of hypoalbuminemia in patients with these diseases. Further study is also required to assess the risk of bleeding in hypoalbuminemic patients using warfarin or newer anticoagulation agents. Finally, future research is needed to prospectively validate our proposed model for prophylactic anticoagulation, ideally through a randomized controlled trial, but more realistically through prospective follow-up of a multicenter registry of patients.

In summary, we propose a practical approach to the decision of prophylactic anticoagulation in patients with primary membranous nephropathy based on an individual patient's bleeding risk, serum albumin concentration, and risk tolerance as reflected by the selected benefit-to risk ratio (Figure 4). This model was adapted to a user-friendly online computerized program (http://www.gntools.com). Our approach allows for a dynamic re-evaluation of the net benefit of anticoagulation with changes in the clinical status of each patient and the risk tolerance of the clinician and patient.

MATERIALS AND METHODS

A detailed description of the methods is available online in the Supplementary Appendix. We built a hybrid Markov decision tree model for our decision analysis (Figure 1). Two alternative therapeutic strategies were compared: (1) prophylactic anticoagulation with warfarin (target INR 2–3) and (2) clinical observation and treatment of symptomatic VTEs. A simulated cohort of 10,000 patients was assumed to enter the model. We used monthly cycles over a 24-month time horizon to assess the relative benefit of anticoagulation compared with clinical observation, balancing the risk of major bleeding against risk of VTEs at various levels of hypoalbuminemia. Input data for the model shown in Table 2 were derived from a large inception cohort of patients and a systematic review of the literature. The analysis was run in two ways: base–case analysis using point estimates of input variables and probabilistic sensitivity analysis with Monte Carlo simulation method.

Risk estimates for VTEs

To apply the VTE risk estimates in various hypoalbuminemia levels to the model, we calculated the incidence rates of VTEs on 539 patients from an inception cohort of 898 patients with biopsyproven primary membranous nephropathy pooled from the University of North Carolina and the University of Toronto (Table 1 and Supplementary Appendix 1

online). Patients with underlying infection, cancer, autoimmune disease (other than membranous nephropathy), prior history of VTEs, or known thrombotic propensity or precipitating event (e.g., catheter) were excluded. The incidence rate of VTEs was calculated as the total of new events divided by the sum of person time at risk: measured as the duration of hypoalbuminemia with thresholds: <2.0, <2.3, <2.5, <2.8, and <3.0 g/dl. Our previous analysis demonstrated an increased risk of VTEs below the threshold serum albumin concentration of 2.8 g/dl.[9]

A systematic search was conducted to compare the incidence rates of VTEs derived from our cohort to those in the published literature using PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases as well as prior reviews[24,25] and decision analysis[17] (Supplementary Appendices 2 and 3 online).

Risk estimates for major bleeding

Risk estimates for major bleeding from warfarin prophylactic anticoagulation would ideally derive from patients with membranous nephropathy or nephrotic syndrome. An exhaustive literature search revealed no published study reporting the risk of bleeding in these populations (Supplementary Appendix 4 online). We therefore referred to the ATRIA study,[10,26,27] a large cohort study of prophylactic anticoagulation using warfarin in patients with atrial fibrillation. That study defined major bleeding as major vital organ hemorrhage including intracranial hemorrhage, retroperitoneal hemorrhage, or hemorrhage requiring transfusion of ≥2 units of blood. The ATRIA risk score for major bleeding was derived by multivariate regression model and based on anemia (hemoglobin 13 g/dl in men and <12 g/dl in women) (3 points), estimated glomerular filtration rate <30 ml/min per 1.73m^2 (3 points),[28] age ≥75 years (2 points), prior hemorrhage (1 point), and diagnosis of hypertension (1 point). For our model, we adopted the three bleeding risk categories described in the ATRIA study and their respective rates of major bleeding per 100 person-years: low (0–3 points) 0.76; intermediate (4 points) 2.62; and high (5–10 points) 5.76.

To compare the ATRIA study's estimated risks for major bleeding to those reported by randomized controlled trials that used warfarin anticoagulation, we conducted a systematic literature review (Supplementary Appendices 5–7 online). The reported incidence rates for major hemorrhage (0.9–4.6 per 100 person-years) reported by other studies were within the ranges used in the ATRIA study (0.7–6.6 per 100 person-years). These incidence rates are therefore reflected in our sensitivity analyses.

To verify whether patients with nephrotic syndrome have a greater risk of hemorrhage with warfarin anticoagulation, we analyzed the incidence of major bleeding in a separate cohort of 98 patients with glomerulonephritis (membranous nephropathy 72%; focal segmental glomerulosclerosis 25%, immunoglobulin A nephropathy 3%), and hypoalbuminemia (<3 g per day). We compared the incidence of bleeding in this cohort to that predicted by the ATRIA study, taking into accounts the bleeding risk score for each patient (Tables 2 and 3).

Input probabilities

Table 2 summarizes input variables and their ranges used in the model. All incidence rates were converted to probabilities using the formula: probability = $1 - e^{(-\text{rate}\times\text{time})}$.[29] For the

probabilities of VTEs at various serum albumin levels, we used our own cohort data. For probabilities of major bleeding, we used the data from the ATRIA study. Case-fatality rates of VTEs and major bleeding were obtained from a systematic review article,[30] as no deaths from these causes occurred in our cohort. The probabilities of death rate from other causes, progression to end-stage renal disease, and recovery from nephrotic syndrome were derived from our inception cohort data.

Incremental benefit-to-risk ratio

The model calculated the number of VTEs that would occur with ($VTE_{on\ AC}$) and without (VTE_{obs}) prophylactic anticoagulation for 24 months. The number of major bleeds ($bleed_{on\ AC}$) was accumulated only for the prophylaxis strategy as the risk of spontaneous severe hemorrhage (requiring blood transfusion) in the absence of anticoagulation is exceedingly low. We presented the ratio of the number of VTEs prevented (incremental benefit, ΔB: $VTE_{on\ AC} - VTE_{obs}$) to the number of major bleeds that would have occurred with prophylaxis (incremental risk, ΔR: $bleed_{on\ AC} - 0$) as a main outcome of interest.[31] The incremental benefit-to-risk ratio calculation was repeated for different levels of bleeding risk and serum albumin concentration (<2.0, <2.3, <2.5, <2.8, and <3.0 g/dl).

Probabilistic sensitivity analysis

A point estimate of the benefit-to-risk ratio is insufficient to draw conclusions about the use of prophylactic anticoagulation. To characterize the effect of the uncertainty of our model inputs, we conducted a probabilistic sensitivity analysis whereby all model inputs are varied simultaneously across appropriately defined distributions (Supplementary Appendix 8 online). Using a Monte Carlo simulation (with 1000 iterations),[29] values of each model input were selected randomly from the assigned distributions and the numbers of VTEs and major bleeding events incurred were calculated for the prophylaxis and observation strategies. The number of VTEs prevented and major bleeding events are displayed in a scatter plot (Figure 2). The Monte Carlo simulation was repeated for each combination of bleeding risk and serum albumin concentration.

Likelihood of net benefit

To present the simulation results in a manner to assist clinical decision-making, we adopted the concept of net-benefit framework[32] and used it to create benefit–risk acceptability curves. For example, a benefit-to-risk trade-off ratio of 10:1 would accept 1 hemorrhage for 10 VTEs prevented. For each trade-off ratio, if the net benefit is >0, then prophylactic anticoagulation offers a greater benefit than observation. For a range of trade-off values, the curves represent the proportion of times that prophylaxis would be beneficial. This probability was calculated for each combination of bleeding risk category and serum albumin level.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Orth SR, Ritz E. The nephrotic syndrome. N Engl J Med. 1998; 338:1202–1211. [PubMed: 9554862]
2. Velasquez Forero F, Garcia Prugue N, Ruiz Morales N. Idiopathic nephrotic syndrome of the adult with asymptomatic thrombosis of the renal vein. Am J Nephrol. 1988; 8:457–462. [PubMed: 3218659]
3. Llach F. Thromboembolic complications in nephrotic syndrome. Coagulation abnormalities, renal vein thrombosis, and other conditions. Postgrad Med. 1984; 76:111–123. [PubMed: 6238292]
4. Wagoner RD, Stanson AW, Holley KE, et al. Renal vein thrombosis in idiopathic membranous glomerulopathy and nephrotic syndrome: incidence and significance. Kidney Int. 1983; 23:368–374. [PubMed: 6842962]
5. Chugh KS, Malik N, Uberoi HS, et al. Renal vein thrombosis in nephrotic syndrome—a prospective study and review. Postgrad Med J. 1981; 57:566–570. [PubMed: 7329894]
6. Llach F, Papper S, Massry SG. The clinical spectrum of renal vein thrombosis: acute and chronic. Am J Med. 1980; 69:819–827. [PubMed: 7446547]
7. Mahmoodi BK, ten Kate MK, Waanders F, et al. High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. Circulation. 2008; 117:224–230. [PubMed: 18158362]
8. Barbour SJ, Greenwald A, Djurdjev O, et al. Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. Kidney Int. 2012; 81:190–195. [PubMed: 21918501]
9. Lionaki S, Derebail VK, Hogan SL, et al. Venous thromboembolism in patients with membranous nephropathy. Clin J Am Soc Nephrol. 2012; 7:43–51. [PubMed: 22076873]
10. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011; 58:395–401. [PubMed: 21757117]
11. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med. 1991; 151:933–938. [PubMed: 2025141]
12. Kayali F, Najjar R, Aswad F, et al. Venous thromboembolism in patients hospitalized with nephrotic syndrome. Am J Med. 2008; 121:226–230. [PubMed: 18328307]
13. Singhal R, Brimble KS. Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. Thromb Res. 2006; 118:397–407. [PubMed: 15990160]
14. Bellomo R, Wood C, Wagner I, et al. Idiopathic membranous nephropathy in an Australian population: the incidence of thromboembolism and its impact on the natural history. Nephron. 1993; 63:240–241. [PubMed: 8450923]
15. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010; 138:1093–1100. [PubMed: 20299623]
16. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006; 151:713–719. [PubMed: 16504638]
17. Sarasin FP, Schifferli JA. Prophylactic oral anticoagulation in nephrotic patients with idiopathic membranous nephropathy. Kidney Int. 1994; 45:578–585. [PubMed: 8164448]

18. Piroli RJ, Passananti GT, Shively CA, et al. Antipyrine and warfarin disposition in a patient with idiopathic hypoalbuminemia. Clin Pharmacol Ther. 1981; 30:810–816. [PubMed: 7307430]
19. Yacobi A, Udall JA, Levy G. Serum protein binding as a determinant of warfarin body clearance and anticoagulant effect. Clin Pharmacol Ther. 1976; 19:552–558. [PubMed: 1277711]
20. Tincani E, Mazzali F, Morini L. Hypoalbuminemia as a risk factor for over-anticoagulation. Am J Med. 2002; 112:247–248. [PubMed: 11893361]
21. Yoshizawa M, Hayashi H, Tashiro Y, et al. Effect of VKORC1 – 1639G>A polymorphism, body weight, age, and serum albumin alterations on warfarin response in Japanese patients. Thromb Res. 2009; 124:161–166. [PubMed: 19135231]
22. Abdelhafiz AH, Myint MP, Tayek JA, et al. Anemia, hypoalbuminemia, and renal impairment as predictors of bleeding complications in patients receiving anticoagulation therapy for nonvalvular atrial fibrillation: a secondary analysis. Clin Ther. 2009; 31:1534–1539. [PubMed: 19695402]
23. Jha V, Ganguli A, Saha TK, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. J Am Soc Nephrol. 2007; 18:1899–1904. [PubMed: 17494881]
24. Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: a clinical conundrum. J Am Soc Nephrol. 2007; 18:2221–2225. [PubMed: 17599972]
25. Radhakrishnan, J. Renal vein thrombosis and hypercoagulable state in nephrotic syndrome. Basow, DS., editor. Waltham, MA USA: 2012. http://www.uptodate.com.libproxy.lib.unc.edu/contents/renal-vein-thrombosis-and-hypercoagulablestate-in-nephroticsyndrome?source=search_result&search=MEMBRANOUS+VENOUS+THROMBOEMBOLISM&selectedTitle=4%7E150.
26. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA. 2003; 290:2685–2692. [PubMed: 14645310]
27. Go AS, Hylek EM, Borowsky LH, et al. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. Ann Intern Med. 1999; 131:927–934. [PubMed: 10610643]
28. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604–612. [PubMed: 19414839]
29. Briggs, AH.; Claxton, K.; Sculpher, MJ. Decision Modelling for Health Economic Evaluation. Oxford, UK: Oxford University Press; 2006.
30. Carrier M, Le Gal G, Wells PS, et al. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med. 2010; 152:578–589. [PubMed: 20439576]
31. Lynd LD, O'Brien BJ. Advances in risk–benefit evaluation using probabilistic simulation methods: an application to the prophylaxis of deep vein thrombosis. J Clin Epidemiol. 2004; 57:795–803. [PubMed: 15485731]
32. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making. 1998; 18:S68–S80. [PubMed: 9566468]

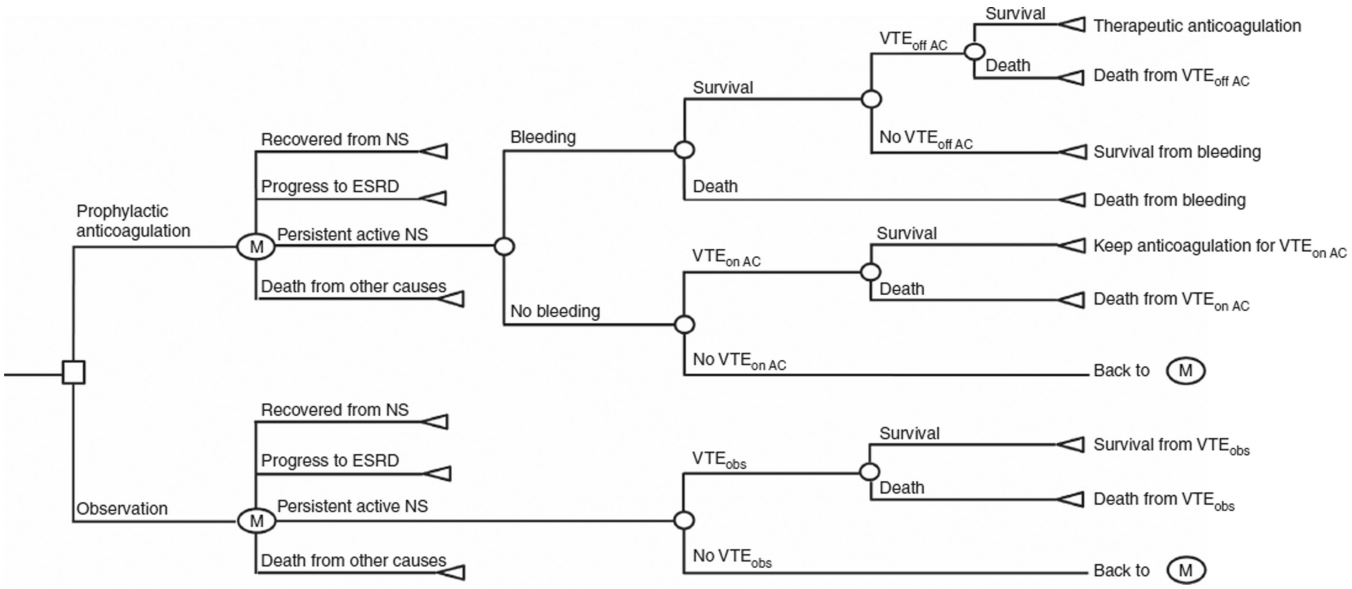

Figure 1. Hybrid Markov decision tree model

The square indicates a decision node in which the clinician may choose from either of two alternatives—prophylactic anticoagulation or observation and treatment of clinically apparent venous thromboembolic events (VTEs). The circles represent chance nodes in which events occur at random (i.e., outside the clinician's control). The letter M in a circle represents a Markov node and the triangles represent terminal nodes or clinical end outcomes. AC, anticoagulation; ESRD, end-stage renal disease; NS, nephrotic syndrome; obs, observation; VTE_{obs}, VTE occurring in the observation strategy; $VTE_{on\ AC}$, VTE occurring while on prophylactic anticoagulation; $VTE_{off\ AC}$, VTE occurring subsequent to a major bleeding event.

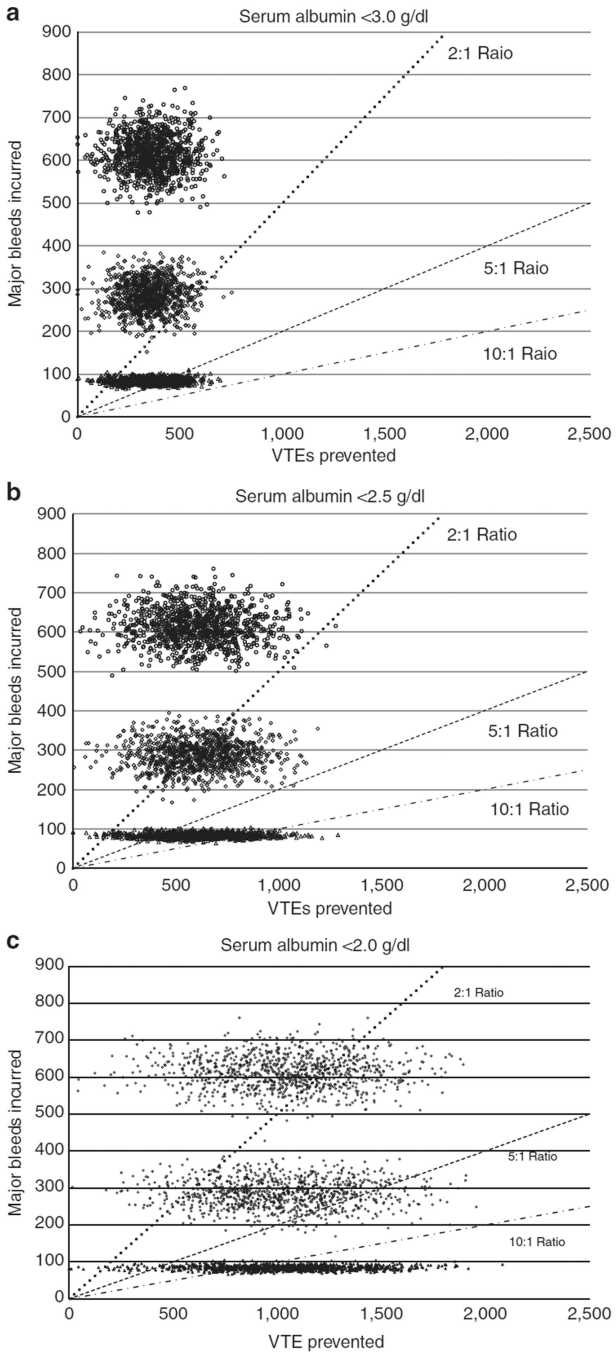

Figure 2. Consideration of uncertainty: probabilistic sensitivity analysis

Monte Carlo simulation plots of benefit and risk at various levels of hypoalbuminemia; plots show the simulation results according to combinations of risk categories of major bleeding in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study[10] and different serum albumin levels: (**a**) <3.0 g/dl, (**b**) <2.5 g/dl, and (**c**) <2.0 g/dl. Each graph includes three density plots representing high risk bleeding risk (upper, open circles), intermediate bleeding risk (middle, open diamonds), and low bleeding risk (lower, open triangles), respectively. Three benefit-to-risk threshold lines are shown for reference (2:1, 5:1, and

10:1). Simulation points lying to the right and below the threshold lines indicate that the benefit-to-risk ratio is larger than the threshold. For example, points lying below and to the right of the ‘10:1 ratio’ line have benefit-to-risk ratios >10:1.

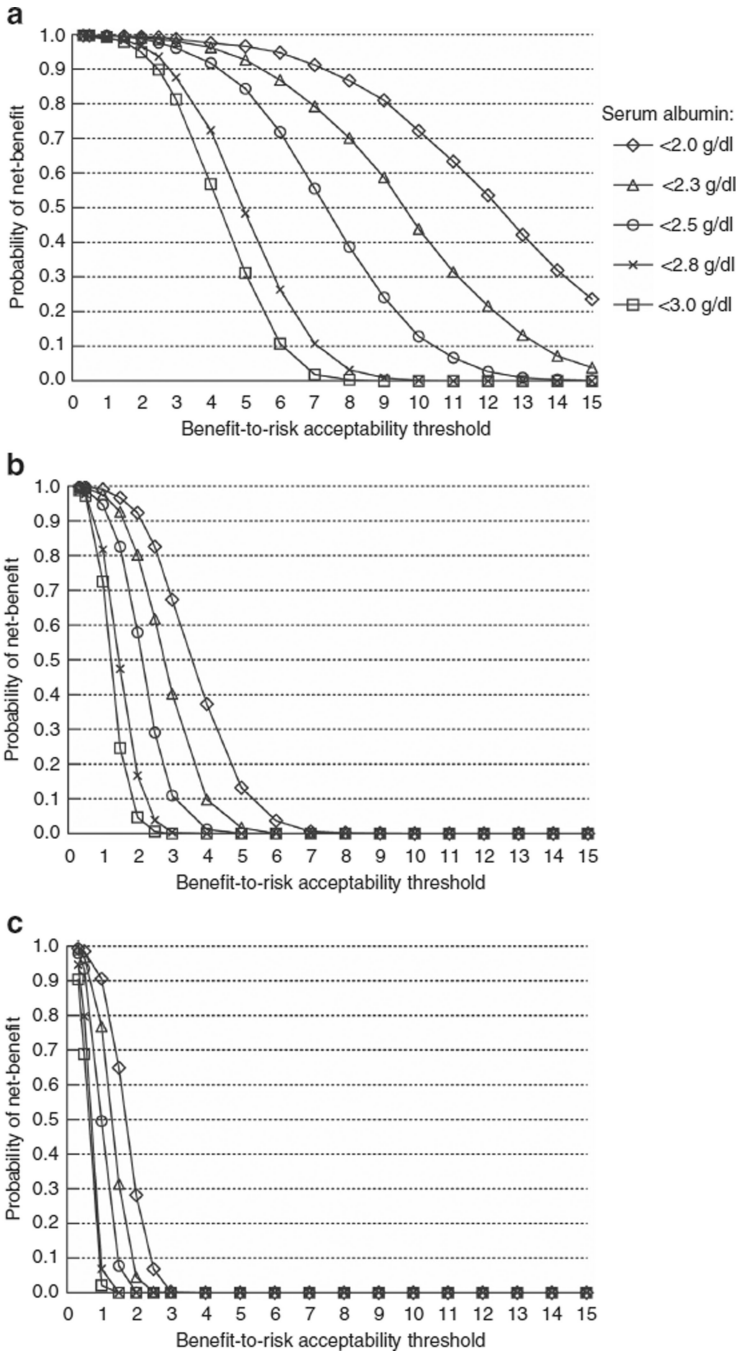

Figure 3. Benefit–risk acceptability curves

Benefit–risk acceptability curves represent the probability (vertical axis) of prophylactic anticoagulation being beneficial at various levels of the benefit-to-risk ratio (horizontal axis). Major bleeding risk categories (low and intermediate) were derived from the ATRIA study.[10] Each curve corresponds to each serum albumin level (from top to bottom,<2.0 to <3.0 g/dl, respectively). (**a**) Low risk of major bleeding, (**b**) intermediate risk of major bleeding, and (**c**) high risk of major bleeding.

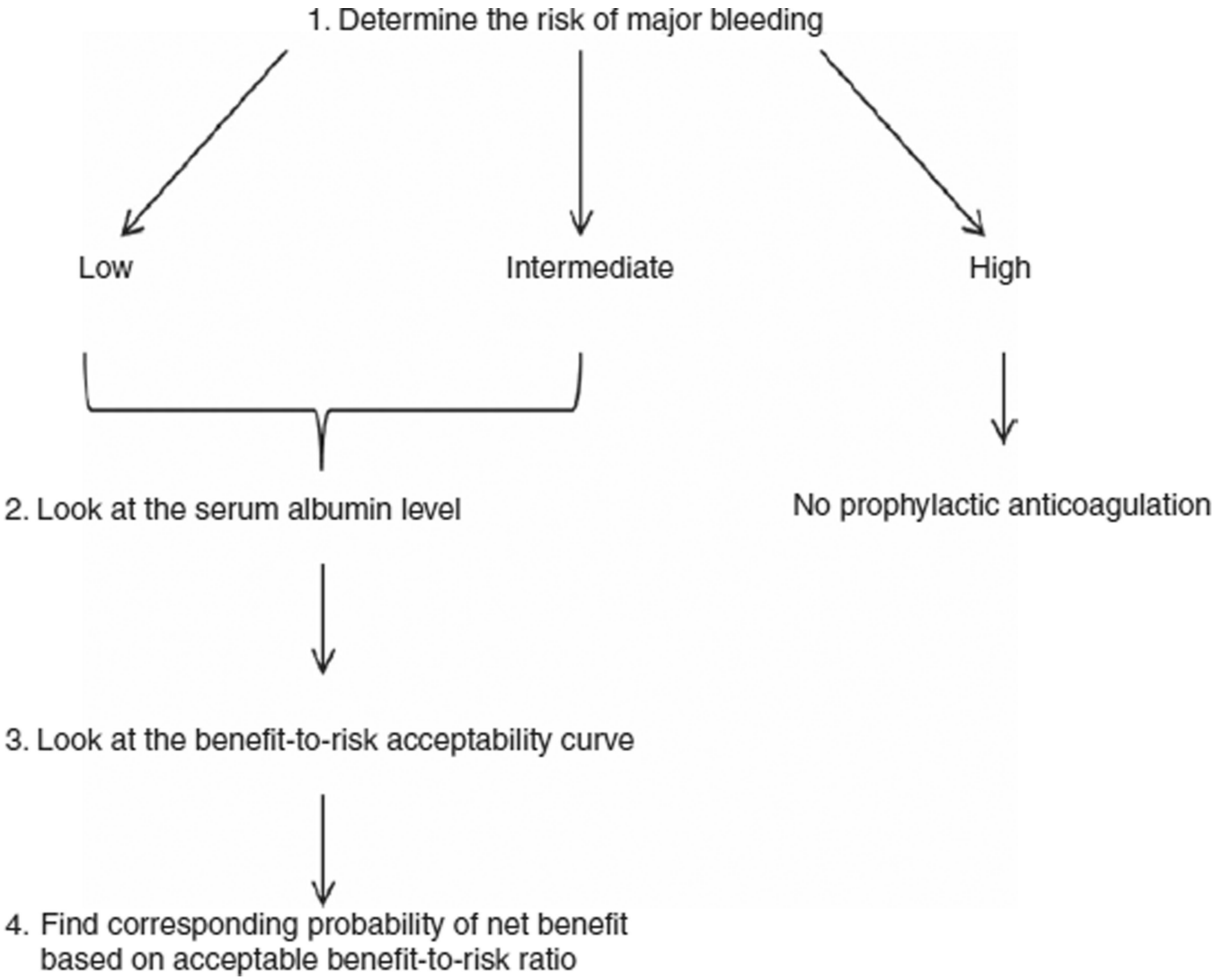

Figure 4.
Decision approach for prophylactic anticoagulation.

Table 1

Characteristics of the inception cohort of patients with membranous nephropathy

Characteristic	Mean±s.d. median (IQR), or *n* (%)
Total *n*	539
Baseline: at diagnosis	
Age (years)	49.2±16
Sex, *n* (%)	
Male	340 (63.1)
Female	199 (36.9)
Race, *n* (%)	
White	360 (66.8)
Black	66 (12.2)
Others	72 (13.4)
Unknown	41 (7.6)
Serum albumin (g/dl)	2.4±0.6
eGFR (ml/min per 1.73m^2)	73.5±31.6
Proteinuria (g/24 h)	8.5±5.7
Treatment regimen	
No immunosuppression	170 (31.5)
Corticosteroid alone	199 (36.9)
Cyclophosphamide/CNI	170 (31.5)
Follow-up	
Observed incidence of VTE, *n* (%)	24 (100)
DVT of lower extremities	6 (25)
RVT	5 (21)
PE (including combined with DVT or RVT)	11 (46)
Others (subclavian vein and IVC)	2 (8)
Observed incidence of VTE, number of events/person-year at risk[a]	
Serum albumin <3.0 g/dl (*n*=539)	24/656.66
Serum albumin <2.8 g/dl (*n*=483)	23/539.47
Serum albumin <2.5 g/dl (*n*=381)	21/325.24
Serum albumin <2.3 g/dl (*n*=221)	15/176.29
Serum albumin <2.0 g/dl (*n*=169)	11/96.29

Abbreviations: CNI, calcineurin inhibitor; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; IQR, 25th to 75th percentile interquartile range; IVC, inferior vena cava; PE, pulmonary thromboembolism; RVT, renal vein thrombosis; VTE, venous thromboembolism.

[a]Person-year at risk represents the cumulative duration below the specified threshold of hypoalbuminemia.

Table 2

Decision model input data for the different clinical approaches: prophylactic anticoagulation versus observation

Parameters	Annual incidence events/100 PY (95% CI)	Monthly probability (ranges)
Death from other causes in NS	1.38 (0.63–2.62)	0.00115
Progression to ESRD	0.31 (0.04–1.11)	0.00025
Recovery from NS	60.16 (52.41–67.92)	0.0489
Active persistent NS	20.67 (16.12–25.21)	0.94969
Prophylactic anticoagulation		
Major bleeding[a],[10]		
Low risk (score 0–3)	0.76 (0.66–0.87)	0.00063 (0.00055–0.00073)
Intermediate risk (score 4)	2.62 (2.28–3.01)	0.00218 (0.00167–0.00279)
High risk (score 5–10)	5.76 (5.01–6.61)	0.00479 (0.00415–0.00552)
Death from major bleeding[30]		0.113
Hazard ratio of VTE on anticoagulation		0.05 (0.01–0.37)
$VTE_{on\ AC}$[b]		Calculated
Death from $VTE_{on\ AC}$[30]		0.137
$VTE_{off\ AC}$		Same as VTE_{obs}
Death from $VTE_{off\ AC}$[30]		0.137
Observation		
VTE_{obs} serum albumin <3.0 g/dl	3.67 (2.35–5.46)	0.00306 (0.00196–0.00454)
VTE_{obs} serum albumin <2.8 g/dl	4.26 (2.70–6.40)	0.00355 (0.00225–0.00532)
VTE_{obs} serum albumin <2.5 g/dl	6.46 (4.00–9.87)	0.00537 (0.00333–0.00819)
VTE_{obs} serum albumin <2.3 g/dl	8.51 (4.96–13.62)	0.00707 (0.00412–0.01129)
VTE_{obs} serum albumin <2.0 g/dl	11.42 (5.70–20.44)	0.00948 (0.00474–0.01689)
Death from VTE_{obs}[30]		0.137

Abbreviations: AC, anticoagulation; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation study; CI, confidence interval; ESRD, end-stage renal disease; NS, nephrotic syndrome; obs, observation; PY, person-year; VTE, venous thromboembolic event; VTE_{obs}, VTE occurring in the observation strategy; $VTE_{on\ AC}$, VTE occurring while on prophylactic anticoagulation; $VTE_{off\ AC}$, VTE occurring subsequent to a major bleeding event.

[a] Bleeding risk categories as described in the ATRIA study. The ATRIA risk score is calculated based on the presence of the following factors: anemia (3 points), severe renal disease (estimated GFR <30 ml/min per $1.73m^2$) (3 points); age ≥75 years (2 points); any prior hemorrhage (1 point); and diagnosed hypertension (1 point).

[b] Incidence rate of $VTE_{on\ AC}$=incidence rate of VTE_{obs}×hazard ratio of VTE on anticoagulation.

Table 3

Incidence of major bleeding in a cohort of 98 warfarin-treated patients with glomerulonephritis

Characteristic	
Total *n*	98
Underlying disease, n (%)	
MN	71 (72)
FSGS	3 (3)
IgA nephropathy	25 (24)
Serum albumin level, median (IQR) (g/dl)	2.1 (1.7–2.6)
Concomitant drugs, n (%)	
ASA	23 (23)
Steroids	85 (87)
ATRIA score, 0–10	2.5 (0–4)
ATRIA risk criteria, n (% *of total exposure time*)	
Low (0–3)	64 (70)
Intermediate (4)	10 (9)
High (5–10)	24 (21)
Total exposure time on warfarin (years)	207.42
Median time of exposure (IQR) (years)	1.43 (0.75–2.7)
Major bleeding event, *n*	1
Incidence, event/100 person-year (95% CI)	0.48 (0.01–2.69)

Abbreviations: ASA, aminosalicylic acid; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation study; CI, confidence interval; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; IQR, interquartile range; MN, membranous nephropathy.

Table 4

Base–case analysis: the ratio of benefit-to-risk according to risk categories for VTE and major bleeding

	Bleeding risk categories		
Level of serum albumin (g/dl)	**Low benefit-to-risk ratio**	**Intermediate benefit-to-risk ratio**	**High benefit-to-risk ratio**
<3.0	4.5 (378/84)	1.3 (378/286)	0.6 (377/614)
<2.8	5.2 (437/84)	1.5 (436/286)	0.7 (436/614)
<2.5	7.7 (650/84)	2.3 (649/286)	1.1 (648/614)
<2.3	10.0 (842/84)	2.9 (841/286)	1.4 (840/614)
<2.0	13.1 (1103/84)	3.9 (1103/286)	1.8 (1102/614)

Abbreviation: VTE, venous thromboembolic events. Numbers within parenthesis are numbers of VTE prevented/major bleeds incurred. Base–case analysis was conducted by applying point estimates of parameters.