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Decision theoretical foundation of clinical practice guidelines: an extension of the ASH thrombophilia guidelines

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Abstract:
Decision analysis can play an essential role in informing practice guidelines. The American Society of Hematology (ASH) thrombophilia guidelines have made a significant step forward in demonstrating how decision modeling integrated within GRADE (Grading of Recommendations Assessment, Developing, and Evaluation) methodology can advance the field of guideline development. Although the ASH model was transparent and understandable, it does, however, suffer from the certain limitations that may have generated potentially wrong recommendations. That is, the panel considered two models separately- after 3-6 months of index venous thromboembolism (VTE), the panel compared Thrombophilia Testing (A) vs. discontinuing anticoagulants (B) and Test (A) vs C (recommending indefinite anticoagulation to all patients) instead of considering all relevant options simultaneously (A vs. B vs. C). Our study aimed to avoid what we refer to as the omitted choice bias by integrating two ASH models into a single unifying threshold decision model. We analyzed 6 ASH panel's recommendations related to testing for thrombophilia in settings of "provoked" vs. "unprovoked" venous thromboembolism (VTE) and low vs. high-bleeding risk (total 12 recommendations). Our model disagreed with the ASH guidelines panels' recommendations in 4 of the 12 recommendations we considered. Considering all three options simultaneously, our model provided results that would have produced sounder recommendations for patient care. By revisiting the ASH guidelines methodology, we have not only improved recommendations for thrombophilia but also provided a method that can be easily applied to other clinical problems and promises to improve the current guidelines' methodology.

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Key points:

- The ASH thrombophilia guidelines modeling was suboptimal.

- The use of appropriate decision methodology leads to more accurate recommendations.

A visual abstract (see Fig)

Illustrates the key findings of our model:

Treatment without testing should be recommended if the probability of VTE recurrence (pVTE) is greater than Prx, test-treatment threshold.

Testing should only be done if P_{tt},test-no treatment threshold <pVTE< P_{rx}, test- treatment threshold.

[The figure shows that in the case of low-bleeding risk, this criterion is met for all 6 ASH thrombophilia panel recommendations (ASH R1 to R6)]

The table compares the ASH Thrombophilia Panel's recommendations with recommendations based on more comprehensive decision modeling.

Abstract

Decision analysis can play an essential role in informing practice guidelines. The American Society of Hematology (ASH) thrombophilia guidelines have made a significant step forward in demonstrating how decision modeling integrated within GRADE (Grading of Recommendations Assessment, Developing, and Evaluation) methodology can advance the field of guideline development. Although the ASH model was transparent and understandable, it does, however, suffer from the certain limitations that may have generated potentially wrong recommendations. That is, the panel considered two models separately- after 3-6 months of index venous thromboembolism (VTE), the panel compared Thrombophilia Testing (A) vs. discontinuing anticoagulants (B) and Test (A) vs C (recommending indefinite anticoagulation to all patients) instead of considering all relevant options simultaneously (A vs. B vs. C). Our study aimed to avoid what we refer to as the omitted choice bias by integrating two ASH models into a single unifying threshold decision model. We analyzed 6 ASH panel's recommendations related to testing for thrombophilia in settings of "provoked" vs. "unprovoked" venous thromboembolism (VTE) and low vs. high-bleeding risk (total 12 recommendations). Our model disagreed with the ASH guidelines panels' recommendations in 4 of the 12 recommendations we considered. Considering all three options simultaneously, our model provided results that would have produced sounder recommendations for patient care. By revisiting the ASH guidelines methodology, we have not only improved recommendations for thrombophilia but also provided a method that can be easily applied to other clinical problems and promises to improve the current guidelines' methodology.

Keywords: clinical practice guidelines, evidence-based medicine, decision analysis, decision curve analysis, medical decision-making

Current evidence-based clinical practice guidelines suffer from several deficiencies [1] including "black-box" operation -- a process with defined inputs and outputs, but without complete understanding of its internal workings [2], and what is referred to as "the integration problem" - lack of a framework for explicit integration of patient preferences, and trade-offs between treatment benefits, and harms. [2] We have previously argued that the solution of the "black-box" and the “integration” problems is only possible within a decision-analytical framework.[1,3-7] Importantly, such a framework enables not only the logical and transparent integration of patient's values and preferences (V&P), and trade-offs between treatment benefits and harms[8,9] but protects against violation of the principles of rational decision-making.[3,4]

Recently, the influential American Society of Hematology (ASH) thrombophilia guidelines[10] has made a significant step forward in demonstrating how decision modeling integrated within GRADE (Grading of Recommendations Assessment, Developing, and Evaluation) [11] methodology can advance the field of guideline development. The panel developed transparent and easily understandable models that are important to end users. [10] However, perhaps in a desire to simplify its presentation, the panel may have chosen a less-than-optimal decision model, leading to what we refer as the "omitted choice bias" [12] that we illustrate below.

Methods

Using the state-of-the-art guidelines methodology GRADE [11], the ASH panel developed 23 recommendations (R) for testing for thrombophilia in the various circumstances leading to "provoked" vs. "unprovoked" venous thromboembolism (VTE). [10] Fig 1 A presents the conceptual thrombophilia model used by the ASH panel.[10] The model represents a truncated version of a decision tree, which we converted into the full decision-analytical model shown in Fig 1B. The panel considered the population of patients who were treated for initial VTE episodes for 3-6 months[13], after which it compared VTE recurrence and major bleeding rates of the following management strategies: perform thrombophilia testing and administer a long-term,

indefinite anticoagulation only to those patients who tested positive vs. do not conduct testing for thrombophilia (Fig 1A) and discontinue treatment for all (as in the case of "provoked" VTE) or continue treatment indefinitely for all (as in the case of unprovoked VTE).

To calculate VTE recurrence and bleeding rates with each strategy, the ASH panel estimated thrombophilia prevalence and the risk ratio for recurrent VTE in patients with thrombophilia vs. patients without thrombophilia (RR_t).[13] The panel relied on the ASH guidelines for the management of venous thromboembolism [13] to estimate the effects (i.e., RR_{rx} and major bleeding risk ratio, RR_{bleed}) of anticoagulant treatment compared with stopping anticoagulant therapy after completion of primary treatment for the initial VTE. For most recommendations, the ASH thrombophilia panel used the following input parameters: the median prevalence (P) of any thrombophilia was 38.0% (minimum 21.6%; maximum 59.5%); RR_t:1.65 (95% CI, 1.28-2.47); RR_{rx} of recurrent VTE of 0.15 (95% CI, 0.10-0.23) [relative risk reduction, $RRR=1-RR$]; RR_{bleed} of major bleeding on indefinite anticoagulant treatment was estimated at 2.17 (95% CI, 1.40-3.35) with the baseline major bleeding rate of 5 per 1000 (0.5%) patients at low risk and 15 per 1000 (1.5%) patients at high risk of bleeding per year.

To illustrate our approach, we focused on the first six thrombophilia panel recommendations in patients with low vs. high risk of major bleeding (12 total recommendations). To address the superiority of a given strategy, the panel needed to estimate the overall risk of VTE recurrence without treatment (here denoted as p, not to be confused with P, the prevalence of thrombophilia shown in Fig 1A;) after unprovoked VTE (R1), provoked after surgery (R2) , provoked after a nonsurgical major transient risk factor, pregnancy, or associated with the use of oral contraceptives (R3-R5) or not-specified as provoked or unprovoked VTE (R6). The ASH panel estimated the overall risk (probability) of VTE recurrence without treatment (p) to range from an average of 100 cases per 1000 patients (10%) (scenario R1); 10 cases per 1000 patients (1%) (R2); 50 cases per 1000 patients (5%) (R3-R5); and 75 cases per 1000 patients (7.5%) (R6).

After 3-6 months of index VTE, the panel modeled a comparison of Thrombophilia Testing (A) vs. Treat None (discontinuing anticoagulants) (B) and Testing (A) vs. C (Treat all-recommend indefinite anticoagulation to all patients). The panel has considered two models: Test (A) vs. Treat None (B) and Test (A) vs. C (Treat all) *separately* instead of considering all relevant options *simultaneously* (A vs. B vs. C) in the single model. However, considering the comparisons separately instead of simultaneously can lead to what can be referred as the "omitted choice bias,"[1] named after the well-known "omitted variable bias" [12] when not considering a relevant option can skew the results and lead to incorrect conclusions.
Although the authors presented an explicit model structure (Fig 1A), they did not leverage the entire apparatus of decision analysis[3,14] to generate recommendations. Instead, the panel relied on intuitive judgment, presumably informed by their model, to determine the optimal management approach for each clinical situation. Specifically, the panel stated [10]: "The following *thresholds* were used to judge the reduction in VTE (first-time or recurrence): trivial: ≤5 events per 1000 patient-years; small: 5 to 20 per 1000; moderate: 20 to 50 per 1000". The management strategy resulting in VTE recurrence below these thresholds was considered superior and thus recommended. However, how the panel weighed the trade-offs between VTE and major bleeding rates is unclear.

We converted two ASH models into a coherent single decision tree (Fig 1B). Many theoretical frameworks exist for solving a decision tree[15], but most decision analyses employ expected utility theory (EUT) [3], as in this paper. EUT is the only theory of choice that satisfies all mathematical axioms of rational decision-making, ensuring that the choices are consistent with the deciders' values and preferences and trade-offs between treatment benefits and harms.[3]

[1] A reader is reminded not to confuse omission choice bias we are referring to with tendency of decision makers to prefer non-action [omission] to action, which is also sometimes referred as “omission choice bias”

When choosing between different options, the most rational choice is that with the highest expected utility, regardless of statistical significance. [16]

From a decision-making perspective, the task is to determine *the probability of* VTE recurrence *(threshold, P_t) above which* we should commit to treatment. [By "treatment," we refer to a commitment to a course of action that may include management consisting of treatment or diagnostic testing.] We are indifferent between acting in favor of one management strategy over another when the net benefits and harms and decision-makers' values and preferences (V&P) between these two strategies are identical [6,15,17-19]. Importantly, threshold (P_t) depends only on benefits and harms (and decision-makers' V&P).[14,15,19] When considering only strategies for administering or stopping treatment, the threshold serves in the following way: if *the probability* of VTE recurrence > P_t we should give treatment (i.e., anticoagulants in our case); if *the probability* of VTE recurrence < P_t, we should not give treatment. [14,15,19] When considering three possible strategies - continuing the treatment, administering the test, and acting according to the results of the test, or stopping the treatment- we have two additional thresholds: the testing threshold P_{tt} and the treatment threshold P_{rx}. So, in total we consider 5 possible management choices.

Using the threshold decision-analytical model[3], we can define these three thresholds (see Appendix 1 for complete derivations of the threshold equations):

$$P_t = \frac{RV \cdot (RR_{bleed} - 1) \cdot H_{norx}}{1 - RR_{rx}}$$	(1)
$$P_{tt} = \frac{RR_t \cdot T_p + (1 - T_p)}{RR_t} \cdot \frac{RV \cdot (RR_{bleed} - 1) \cdot H_{norx}}{1 - RR_{rx}}$$	(2)
$$P_{rx} = \left(RR_t \cdot T_p + (1 - T_p)\right) \cdot \frac{RV \cdot (RR_{bleed} - 1) \cdot H_{norx}}{1 - RR_{rx}}$$	(3)

where H_{norx} refers to harms (i.e., adverse events such as bleeding) observed in the "no treatment" arm; $T_p = P(T+)$ denotes the probability of (thrombophilia) positive test results and $P(T-) = 1 - T_p$ the probability of negative test results; $RR_t, RR_{bleed}\ and\ RR_{rx}$ represent variables as defined above. RV refers to the patient's V&P; when $RV < 1$, the patient values avoiding outcomes of VTE more than avoiding harms of bleeding; if $RV > 1$, the patient places more importance on avoiding the harms of treatment than on the consequences of the disease; when the patient is indifferent between treatment harms and the consequences of the disease outcome, RV =1. When RV=1, the thresholds are solely determined by empirical evidence. ASH panel has compiled data on patients' V&P regarding VTE and bleeding, but their calculations relied only on empirical evidence. It is unclear how the panel considered integrating V&P in formulating their recommendations.

P_{tt} (test-no treatment threshold) refers to the *pre-test (prior)* probability of VTE recurrence at which we are indifferent between no treatment and testing. [3,14,19] P_{rx} (test-treatment threshold) refers to the *pre-test (prior)* probability of VTE recurrence at which we are indifferent between testing and treatment. [3,14,19] If the *prior* probability of VTE recurrence < P_{tt}, this *guarantees that the post-test probability of* VTE recurrence will always be <treatment threshold, P_t, regardless of the test results. [3,14,19] Hence, we should not test and should withhold treatment under these circumstances. If the *prior* probability of VTE recurrence > P_{rx}, this *guarantees that the post-test probability of* VTE recurrence will always be >treatment threshold, P_t,regardless of the test results. [3,14,19] If this relationship holds, we can give treatment without further testing.

Note how formal threshold equations 1-3 effectively capture everyday clinical intuition (Table 1). Thus, in the case of thrombophilia recommendations, we contrast the overall risk (probability) of VTE recurrences (p) against these thresholds. According to our model, *the thrombophilia testing should only be done for* $P_{tt<}\ p < P_{rx}$. No testing/no treatment should be recommended for $p <\ P_{tt}$. Treatment with anticoagulants should be recommended for $p > P_{rx}$.

Results

Reproducing the ASH thrombophilia results

The ASH panel presented its results as VTE and bleeding rates, counted separately. As explained below, such an approach introduces bias. Nevertheless, sometimes, we may wish to count events descriptively. If so, our model can be easily used to this effect.

Appendix 3, Table 1 illustrates using our model based on the data from the ASH report [10] to reproduce the panel's calculations for recommendation #1 (an identical approach can be used to reproduce the calculations for other recommendations).

Fig 2a) displays these results graphically, comparing all management strategies (for R1). Figs 2b-d show the results of VTE and major bleeding rates for the remaining recommendations (R2, R3-R5, and R6) in low-risk bleeding settings. Fig 3a-d shows the same results assuming high-risk bleeding. Notably, even though the ASH report referred to the threshold in issuing its recommendations[10], it is impossible to derive the VTE threshold from the method used by the ASH panel. The thresholds for the prevalence of VTE recurrence are zero, and the thresholds for the bleeding rates are undefined (see App 2 for proof).

Comparison of the ASH thrombophilia recommendations with the threshold decision model

Table 2 displays calculations of the decision thresholds based on the equations 1-3. These default calculations reflect the ASH thrombophilia evidence report and assume RV=1 i.e., that patients are equally concerned by the burden of VTE vs. major bleeding. We explore this issue in detail below.

As explained above, to determine whether we should recommend thrombophilia testing, we contrast the probability of VTE recurrence (p) against the decision thresholds. The ASH panel estimated the probability of VTE recurrence (p) of 0.01 (1%) in the scenario guiding derivation of R2, 0.05 (5%) (for R3-R5), 0.075 (7.5%) (to develop R6) and 0.1 (10%) in clinical scenario

resulting in R1. Fig 4 shows the results. Table 3 shows the ASH panel's R1-R6 thrombophilia recommendations compared with the recommendations according to our threshold model. For R1, the probability of VTE recurrence (*p*) of 10%>$P_{rx} = 0.85\%$ (low bleeding risk) and >2.57% (high bleeding risk), which means that the patients should be offered long-term treatment with anticoagulation without thrombophilia testing. This agrees with the ASH R1 recommendation.

For R2, in patients at low bleeding risk *p* of 1% >$P_{rx} = 0.85\%$. However, in the high bleeding risk, *p* of 1% is lower than $P_{rx} = 2.57\%$ and P_{tt}=1.56%. Thus, no thrombophilia testing should be offered in the low-risk bleeding scenario, but extended anticoagulant treatment should be recommended (Fig 4a). In the high bleeding risk scenario *p* = 1% <P_{tt} =1.56%, and no treatment nor thrombophilia testing should be offered to these patients. Thus, our analysis agrees with the ASH R2 recommendation only in the case of high-bleeding risk (Fig 4b).

For R3-R5, *p* = 5% >P_{rx} =0.85% (low bleeding risk) and > $P_{rx} = 2.57\%$ (high bleeding risk), meaning the patients should be offered long-term treatment with anticoagulation without thrombophilia testing. This result does not agree with the ASH R3-R5 recommendations, which recommend thrombophilia testing and administering indefinite anticoagulation only to those patients who tested positive for thrombophilia (Table 3).

Finally, for R6, the probability of VTE recurrence (*p*) = 7.5% >$P_{rx} = 0.85\%$ (low bleeding risk) and >P_{rx} =2.57% (high bleeding risk), indicating that the patients should be recommended long-term treatment with anticoagulation without thrombophilia testing. This conclusion also agrees with the ASH R6 recommendation (Table 3).

The analysis above assumed $RV = 1$. When sensitivity analysis for RV was performed (i.e., when RV ≠ 1) , the results may differ. Table 4 shows the effect of RV on thrombophilia recommendations. For example, if we assume that the patient places twice as much importance

on avoiding major bleeding than VTE recurrence ($RV = 2$), then recommendation #2 is consistent with the ASH panel's recommendation#2 ("Do not test for thrombophilia")[10] (Table 3). Interestingly, in the high bleeding risk scenarios, the same conclusion (“Don’t test/Don’t treat”) holds for RV≥0.64 while testing and treatment strategy are recommended for the patients’ with RV < 0.641 and RV<0.388, respectively; that is if the patient prefers avoiding VTE 1.5 (=1/0.641) and 2.5 (=1/0.388) times over bleeding. The ASH panel reports that the patients generally prefer avoiding VTE recurrence over bleeding. [10] In the low-risk bleeding scenario we found that RV, in most cases, is unrealistically high (and never below 1 for all recommendations) to affect our default recommendations for $RV = 1$. Nevertheless, it is conceivable that some patients fear the consequences of bleeding far more than they do VTE. For instance, in case of R3-R5, in low and high-risk bleeding scenarios, patients might prefer to avoid major bleeding 5.8 to 9.6 times and 1.9 to 3.2 times more often than avoiding VTE, respectively. Under these conditions, our model aligns with the ASH recommendations. (see Discussion).

Discussion

In this paper, we re-analyzed 6x2 recommendations made by the ASH thrombophilia panel[10] for various "provoked" vs. "unprovoked" VTE clinical scenarios used as an example to illustrate the need to improve the broader field of decision-making and guideline development. By incorporating decision modeling within GRADE methods, the ASH thrombophilia panel has taken a substantial stride in advancing the guidelines development methodology and tackling "black-box" operation and "integration” challenges.[2] While we believe that the application of decision modeling is the only logical and transparent method to facilitate the integration of all relevant ingredients required to make recommendations[15], it is also essential to choose the correct model. The thrombophilia testing model developed by the ASH panel[10] generated 4/12 recommendations that proved inaccurate when judged against using a fully developed threshold

model (Table 3).[15] Unlike the ASH panel, our model, assuming that patients placed equal value on avoiding VTE and bleeding, generated recommendations against thrombophilia testing in all scenarios considered.

The discrepancy occurred because of the omitted choice bias[12]: the panel considered two models separately instead of considering all relevant options simultaneously. This resulted in rationally incoherent recommendations when judged against an appropriate decision model. Nevertheless, because the certainty of evidence was judged to be very low, the panel issued conditional (weak) recommendations, meaning that "most individuals in this situation would want the suggested course of action, but many would not." [10] Thus, on the surface, the ASH panel's judgment appears consistent with its recommendations, even if it disagreed with its model. Unfortunately, the panel never explained its deviation from the proposed model that apparently guided all the panel's recommendations. Why engage in modeling or develop guidelines if very low certainty of evidence almost always (barring some exceptions[20]) generates uncertain recommendations that may or may not be coherent with the underlying model structure?

The ASH panel has not performed any sensitivity analyses to assess the uncertainty range at which their recommendations could possibly switch. We have argued that it is precisely in these circumstances that modeling – followed by judicious deliberation of the panel – is most useful as it combines the explicitness and transparency of decision modeling with considered panel's judgments.[1]

Somewhat surprisingly, we also concluded that extended anticoagulation should be offered in patients with low bleeding risk who developed surgery-related VTE. This conclusion disagreed with most current guidelines recommending discontinuing oral anticoagulation after three months of surgery-related VTE. [21] Nonetheless, the UK NICE guidelines state that "in low bleeding risk patients, the benefits of continuing anticoagulation treatment are likely to

outweigh the risks." [22] The reason for this recommendation can be related to the extraordinarily high efficacy (RRR)/Major bleeding [(0.85/0.00585=145.3)] ratio in the low-risk scenarios calculated based on the evidence presented in the ASH thrombophilia guidelines.[10] Such a high benefit/harms ratio generated a low test-treatment threshold $(P_{rx}) = 0.85\%$, which is below 1% probability of VTE recurrence after surgery estimated by the ASH guidelines. [10] According to the EUT, as long as the EU of one strategy is higher than the other- regardless if the differences are trivial or large- we should select that management option. [16] The earlier studies indicated a 0% risk of VTE after surgery [23], but more recent studies suggested a risk of about 3%, noting that after a provoked VTE, the risk may not return to the population baseline of 0.1-0.2 per 100 patients per year.[21,24] Therefore, under the assumed ASH risk of VTE of 1% after three months of anticoagulation for VTE provoked by surgery[10], recommending extended anticoagulation is logically justifiable. Of course, the recommendations depend on the trustworthiness of these estimates. The ASH panel judged that the evidence used in their (and consequently our calculations) is of very low certainty because they were based on calculations with serious indirectness and imprecision of the estimates. [10] Such evidence can be equally right or wrong. [25] It is quite possible that different assumptions would have resulted in different recommendations. However, the panel presented the best evidence on the topic to date, often with a range of estimates. Unfortunately, in the case of the overall risk for VTE recurrence, the panel was able to provide only point estimates (e.g., the risk of unprovoked VTE was 100 per 1000 patients in the first year). [10]

Another disagreement between our models relates to recommendations R3-R5 (Fig 4, Table 3). The reason that the strategy "test and treat only positives" remains inferior to strategy of "treating all" patients according to the threshold model is because the patients with false negative tests would have incorrectly not received treatment.

Our model is based on the well-known threshold model[3], but equations 2 and 3 are novel derivations using the input parameters specified by the ASH thrombophilia panel. [10] The unavailability of these threshold formulas may have been a reason why the ASH thrombophilia panel did not use a full scope of decision modeling as outlined in our paper. If so, we urge the panel to update its recommendations accordingly.

One limitation that affected both our and ASH thrombophilia models is that is based on the "average" data obtained from the literature, including the overall average and estimates of the probability of VTE recurrence. Indeed, individual patients are at different risks of VTE recurrence. As a result, we have called for developing more individualized recommendations by the guidelines panels.[1,27] This can be accomplished by integrating the best evidence from systematic reviews/meta-analyses on the *average* treatment effects with predictive models to estimate *individualized* disease risks or outcomes and *threshold* decision models.[1,27,28] Despite the plethora of models- some better validated than others[29]- the use of predictive models to help individualize the guidelines recommendations has not been widely promoted in the VTE field. Indeed, some experts favor recommendations based on intuitive, holistic assessment over predictive models.[21] The GRADE method refers not only to the benefits and harms of the management and patients' V&P, but also to resource use, feasibility, acceptability, and equity.[11] However, all thrombophilia recommendations, both ASH's and ours, were driven by decision modeling without formally considering these other factors. Clearly considering, articulating, and transparently displaying such issues would be desirable. Indeed, the whole idea of combining decision analysis with the GRADE methodology is to generate recommendations using explicit, easily understood decision models based on the best existing evidence following time-honored cognitive scientists' advice: "to value formal principles of rationality" but then reflect on the appropriateness of further adjustments consistent with our explicit and implicit reasoning.[30-32] Still, the experience from other fields suggests that statistical rules typically outperform experts

who rely on intuitive judgments.[33] Intuitive approaches to integrating complex elements such as synthesis of treatment benefits and harms with patients' V&P often do not agree with EUT models.[4,26] Under these conditions, people may rely on non-EUT decision strategies[4,26], such as anticipating regret of being wrong to drive their decisions.[34-38] This is also true for guidelines panels. For example, we have previously demonstrated that ASH guidelines panel for the management of pulmonary embolism (PE) relied on several decision-theoretical approaches to formulate their recommendations, some of which were based on non-EUT constructs.[4] Which approach to take will largely depend on the type of problem, the consequences and the likelihood of being wrong, contextual issues such as V&Ps, time, available resources, etc. [39] However, there is a general consensus that we should always start with the EUT threshold model based on the best available evidence and further adjust it depending on the other elements considered essential for decision-making.[39] As we showed, our model clearly indicates the importance of consulting the patient's V&P, which may include consideration of costs and other burdens specified within the GRADE system. Nevertheless, it can be argued that " the most optimal decisions may be those that achieve coherence at both the normative and intuitive levels".[31] But, when these two types of knowledge do not agree, maximum efforts should be undertaken to reconcile differences by exploring various theoretical approaches. This may be the most crucial reason why the ASH thrombophilia model should be updated. Providing a transparent and explicit explanation of the reasoning and analytical process through decision modeling—a solution to overcoming the challenges of integration and the 'black-box' issue—when closely integrated with the GRADE methodology, can likely produce more coherent and accurate recommendations than relying solely on either decision models or the GRADE process alone. . Adding the methodology described in this and other papers[1,3-5,15,17,27,28] can bring us to the goal of transparent, trustworthy, easily accessible, understandable, and highly accurate guidelines. The method we described in response to the ASH thrombophilia guidelines can be easily applied to other clinical problems and holds promise to improve the

current guidelines' methods without requiring additional resources that complex decision modeling does.

Contributions

BD developed a conceptual idea and wrote the first draft of the paper; IH solved the model and developed program code; GG revised the paper and improved its intellectual and research content

None of the authors has a relevant conflict of interest.

Legends

Fig 1
A)ASH Modeling approach for determining the effect of thrombophilia testing. The model starts with the population considered for testing for thrombophilia testing. Thrombophilia testing refers to any type of thrombophilia or a specific type. Intervention: course of action other than "usual care." Depending on the particular question, this means prescribing thromboprophylaxis, withholding thromboprophylaxis, extending thromboprophylaxis, stopping thromboprophylaxis, withholding birth control pills, or withholding hormone replacement therapy. Usual care: typically consisting of short-term (3-6 months) anticoagulation (provoked VTE) or indefinite treatment (unprovoked VTE). P-thrombophilia prevalence (denoted in the paper as T_p); Incidence risks of VTE recurrence: denoted in the paper as p_{t+} and p_{t-} for patients with (thrombophilia) positive results and for patients with negative test results, respectively; ***Association***: risk ratio for recurrent VTE in patients with thrombophilia vs. patients without thrombophilia (RR_t); ***Relative effects of intervention:*** (anticoagulant) on VTE recurrence (RR_{rx}) and bleeding (RR_{bleed})compared with no intervention.

B) A decision tree showing a three-choice clinical dilemma: administer treatment (anticoagulants) vs. performing a diagnostic test (T) (thrombophilia testing) vs. withholding therapy. Each treatment consists of the management strategies "treat all patients", "treat none," and "use thrombophilia test" to decide whether to treat. Abbreviations: *p* - probability of disease/clinical event (VTE- venous thromboembolism); $p_{t+} = \Pr(D + \mid T +)$ refers to the probability of VTE recurrence when the thrombophilia test is positive (T+) . RR_{rx} - risk ratio related to treatment effects; *U1* to *U4*: utilities (outcomes); (see Appendix for details).[By "treatment," we refer to a commitment to a course of action that may include management consisting of treatment or diagnostic testing.]

Figure 2 The impact analysis displaying the total number of VTE and major bleeding incurred for ASH panel recommendation #1(R1) (a), R2(b), R3-R5(c), and R6(d) in the low-bleeding risk scenario. Five decision strategies are shown (from left to right): Treat according to the threshold (Rx threshold, equation 3 in the manuscript), perform testing and act accordingly, test according to thresholds (equation 2 in the manuscript, treat none (give anticoagulants to no patient without testing) and treat all (provide anticoagulants for all patients without testing). Abbreviations: VTE-venous thromboembolism; ASH-American Society of Hematology; R- recommendations.

Figure 3 The impact analysis displaying the total number of VTE and major bleeding incurred for ASH panel recommendation #1(R1) (a), R2(b), R3-R5(c), and R6(d) in the high-bleeding risk scenario. Five decision strategies are shown (from left to right): Treat according to the threshold (Rx threshold, equation 3 in the manuscript), perform testing and act accordingly, test according to thresholds (equation 2 in the manuscript, treat none (give anticoagulants to no patient without testing) and treat all (provide anticoagulants for all patients without testing); Abbreviations: VTE-venous thromboembolism; ASH-American Society of Hematology; R- recommendations.

Figure 4 The results of the threshold decision model analysis in the setting of the low-bleeding risk (a) and high-bleeding risk (b). The vertical lines (ASH R*) refer to the recommendations 1 to 6 by the ASH thrombophilia panel. Theoretical thresholds above or below which treatment vs. thrombophilia testing vs. no anticoagulant treatment should be given are denoted by $P_{tt,}\, P_t, P_{rx}$ (see equations 1-3). Note that because all ASH R lines are to the right side of P_{rx} i.e., larger than the treatment threshold P_{rx} in a low-risk-bleeding scenario, offering indefinite anticoagulant treatment to all patients represents the best management strategy (a). The same holds for ASH R1, R3-5, and R6 in the setting of high-risk bleeding. Because the vertical line ASHR2 is to the left, i.e., lower than P_{tt} (test-no treatment threshold), discontinuing anticoagulation after 3 months of treatment following VTE due to surgery is recommended (see manuscript for details, Table 3). Abbreviations: VTE-venous thromboembolism; ASH-American Society of Hematology; R- recommendations.

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Table 1

Intuitive presentation of the threshold model

Note how the manuscript's formal threshold equations 1-3 effectively capture everyday clinical intuition.

Equation 1 states that the administration of treatment depends on consideration of the benefits and harms of treatment adjusted for the patient's values and preferences (V&P) regarding how they feel about the burden of disease (e.g., venous thromboembolism [VTE]) vs. the adverse events of treatment (e.g., major bleeding). Technically, we refer to the effects of treatment on patient outcomes as "utility".

1) *Treatment threshold* (when tests are not taken into consideration)

Clinically, we are interested in finding out at which probability of disease or outcome we should act ["how high is "high" for us to give treatment; how low is "low" for us not to administer it]. *Intuitively when benefits do not exceed harms, we are uncertain how to proceed*. That is, we are at the treatment "threshold". According to a decision-analytical theory, the threshold is equal to the *expected utility*[2] of administering treatment vs. not administering treatment. From here, we can obtain a simple formula for the treatment threshold[3]:

$$P_t = \frac{Absolute\ risk\ of\ major\ bleeding\ (bleed)}{Relative\ risk\ reduction\ (RRR)}$$

where P_t is the probability of disease or outcome (e.g., recurrence of VTE). Treatment should be given if the benefit of treatment exceeds its harms at the given probability of disease (e.g., VTE recurrence) and patients' V&P. Thus if the probability of VTE (pVTE) > P_t we should administer treatment (e.g., anticoagulants). If P_t < pVTE, we should not give treatment. Importantly, our decisions whether to test [and act according to the test result], or not to test are also contrasted against P_t, which serves as an action threshold against which testing decisions are compared.

2) Testing thresholds

a) test-no treatment threshold (P_{tt})

Equation 2 tells us what every physician intuitively knows - *when the probability of disease is fittingly very small, we can forgo testing and treatment.* It is also self-evident that P_{tt} must be smaller than P_t (i.e., $P_{tt} < P_t$).[4] Generally, we can forgo testing when the pretest probability of disease is so low that even with a positive test result, the posttest probability would have always been below the action threshold P_t.

b) test-treatment threshold (P_{rx})

Equation 3 also agrees with clinicians' intuition – *we don't always need diagnostic confirmation to act*. We can forgo testing when the pretest probability of disease is so high that even with a negative test result, the posttest probability would have always been above the action threshold, *Pt.* Here, too, it is self-evident that P_{rx} must be larger than P_t (i.e., $P_{rx} > P_t$).[5]

These results reflect an old clinical wisdom: "do not order a test that will not change your management".

To decide about thrombophilia testing, we contrast the overall risk (probability) of VTE recurrences ($pVTE$) against these thresholds. According to the threshold model, *the thrombophilia testing should only be done for* $P_{tt} < pVTE < P_{rx}$. No testing/no treatment should be recommended for $pVTE < P_{tt}$. Treatment with anticoagulants should be recommended for $pVTE > P_{rx}$ (see Fig 4 and Visual abstract)

[2] Expected utility is the average of all possible outcomes weighted by their corresponding probabilities,

[3] To simplify exposition, we avoid consideration of V&P; please refer to the main manuscript and Appendix for full technical details. Note that there are many metrics for treatment benefits and harms that may result in different threshold formulas. Here we show a formula pertinent to the treatment of patients at risk of VTE recurrence.

[4] According to the expected utility theory (EUT), most widely used decision-analytical theory and employed in this manuscript.

[5] See footnote #3

Table 2

Calculations of the decision thresholds for thrombophilia testing

A) *Low-bleeding risk (5/1000)*

Treatment threshold:

$$P_t = \frac{RV \cdot (RR_{bleed} - 1) \cdot H_{norx}}{1 - RR_{rx}} = \frac{1 \cdot (2.17 - 1) \cdot 0.005}{1 - 0.15} = .0069 = 0.69\%$$

Test vs. no treatment threshold:

$$P_{tt} = \frac{RR_t \cdot T_p + (1 - T_p)}{RR_t} \cdot \frac{RV \cdot (RR_{bleed} - 1) \cdot H_{norx}}{1 - RR_{rx}}$$

$$= \frac{1.65 \cdot 0.38 + (1 - 0.38)}{1.65} \cdot \frac{1 \cdot (2.17 - 1) \cdot 0.005}{1 - .15} = .0052 = 0.52\%$$

Test vs. treatment threshold:

$$P_{rx} = \left(RR_t \cdot T_p + (1 - T_p)\right) \cdot \frac{RV \cdot (RR_{bleed} - 1) \cdot H_{norx}}{1 - RR_{rx}}$$

$$= \left(1.65 \cdot 0.38 + (1 - 0.38)\right) \cdot \frac{1 \cdot (2.17 - 1) \cdot 0.005}{1 - 0.15} = 0.0085 = 0.85\%$$

B) *High-bleeding risk (15 per 1000)*

Treatment threshold:

$$P_t = \frac{RV \cdot (RR_{bleed} - 1) \cdot H_{norx}}{1 - RR_{rx}} = \frac{1 \cdot (2.17 - 1) \cdot 0.015}{1 - 0.15} = .0206 = 2.06\%$$

Test vs. no treatment threshold:

$$P_{tt} = \frac{RR_t \cdot T_p + (1 - T_p)}{RR_t} \cdot \frac{RV \cdot (RR_{bleed} - 1) \cdot H_{norx}}{1 - RR_{rx}}$$

$$= \frac{1.65 \cdot 0.38 + (1 - 0.38)}{1.65} \cdot \frac{1 \cdot (2.17 - 1) \cdot 0.015}{1 - .15} = .01560417 = 1.56\%$$

Test vs. treatment threshold:

$$P_{rx} = \left(RR_t \cdot T_p + (1 - T_p)\right) \cdot \frac{RV \cdot (RR_{bleed} - 1) \cdot H_{norx}}{1 - RR_{rx}}$$

$$= \left(1.65 \cdot 0.38 + (1 - 0.38)\right) \cdot \frac{1 \cdot (2.17 - 1) \cdot 0.015}{1 - 0.15} = .0257 = 2.57\%$$

Table 3 Comparisons of the ASH Thrombophilia Panel's recommendations with recommendations based on decision modeling

Recommendation (R) numbers	Populations	ASH Considered strategies (after 3-6 months of treatment)	ASH Panel Recommendations	Recommendations based on decision model with all three strategies
R1	Unprovoked VTE	Test vs Treat all	Do not test for thrombophilia; recommend indefinite anticoagulant treatment to all patients	Do not test for thrombophilia; recommend indefinite anticoagulation (regardless of assumed bleeding risk)
R2	VTE provoked by surgery	Test vs. Treat none	Do not test for thrombophilia; **recommend discontinuing anticoagulant treatment**	Do not test for thrombophilia; **recommend extended anticoagulation (low bleeding risk)** Do not test for thrombophilia; **discontinue anticoagulant treatment** (high bleeding risk)
R3	VTE provoked by nonsurgical major transient risk factor	Test vs Treat none	**Test for thrombophilia;** recommend indefinite anticoagulant treatment for patients with thrombophilia with stopping anticoagulant treatment for patients without thrombophilia	**Do not test for thrombophilia;** recommend indefinite anticoagulation (regardless of assumed bleeding risk)
R4	VTE provoked by pregnancy or postpartum	Test vs Treat none	**Test for thrombophilia;** recommend indefinite anticoagulant treatment for patients with thrombophilia with stopping anticoagulant treatment for patients without thrombophilia	**Do not test for thrombophilia;** recommend indefinite anticoagulation (regardless of assumed bleeding risk)
R5	VTE associated with use of COC	Test vs Treat none	**Test for thrombophilia;** recommend indefinite anticoagulant treatment for patients with thrombophilia with stopping anticoagulant treatment for patients without thrombophilia	**Do not test for thrombophilia;** recommend indefinite anticoagulation (regardless of assumed bleeding risk)
R6	An unspecified type of VTE (ie, not specified as provoked or unprovoked VTE)	Test vs Treat all	Do not test for thrombophilia; recommend indefinite anticoagulant treatment to all patients.	Do not test for thrombophilia; recommend indefinite anticoagulation (regardless of assumed bleeding risk)

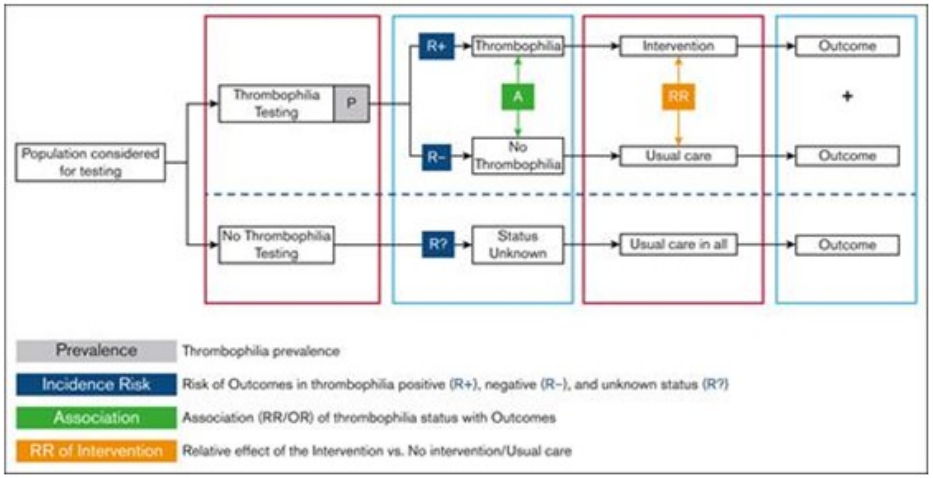
Table 4 Impact of patient's values and preferences on recommendations							
Best strategy for RV range			Best strategy	Probability of VTE recurrence			
				Recommendation 1	Recommendation 2	Recommendations 3-5	Recommendation 6
				0.1	0.01	0.05	0.075
Bleeding Risk	Low-risk	0.005	Treat none	RV ≥ 19.226	RV ≥ 1.923	RV ≥ 9.613	RV ≥ 14.419
			Test	11.652 ≤ RV ≤ 19.226	1.165 ≤ RV ≤ 1.923	5.826 ≤ RV ≤ 9.613	8.739 ≤ RV ≤ 14.419
			Treat all	RV ≤ 11.652	RV ≤ 1.165	RV ≤ 5.826	RV ≤ 8.739
	High-risk	0.015	Treat none	RV ≥ 6.409	RV ≥ 0.641	RV ≥ 3.204	RV ≥ 4.806
			Test	3.884 ≤ RV ≤ 6.409	0.388 ≤ RV ≤ 0.641	1.942 ≤ RV ≤ 3.204	2.913 ≤ RV ≤ 4.806
			Treat all	RV ≤ 3.884	RV ≤ 0.388	RV ≤ 1.942	RV ≤ 2.913

Table 4 Impact of patient's values and preferences on recommendations

RV (relative values) refers to patients' V&P; when $RV < 1$, the patient values avoiding outcomes of disease more than avoiding treatment harms; if $RV > 1$, the patient places more importance on avoiding the harms of treatment than on the consequences of the disease. When the patient is indifferent between treatment harms and the consequences of the disease outcome, RV =1. When RV=1, the thresholds are solely determined by empirical evidence (see text for details).

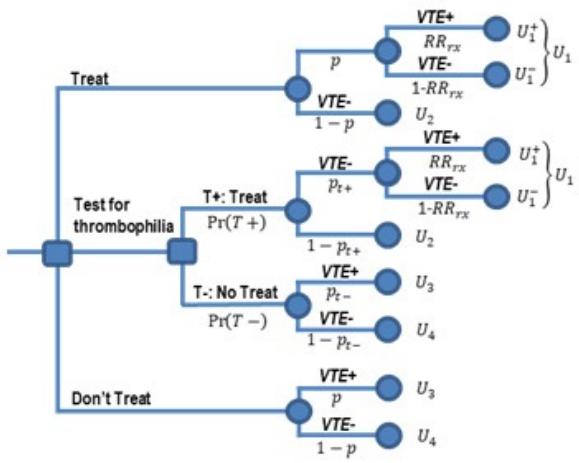
Figure 1

ASH model



a)

Full decision model



b)

Fig 1

Figure 2

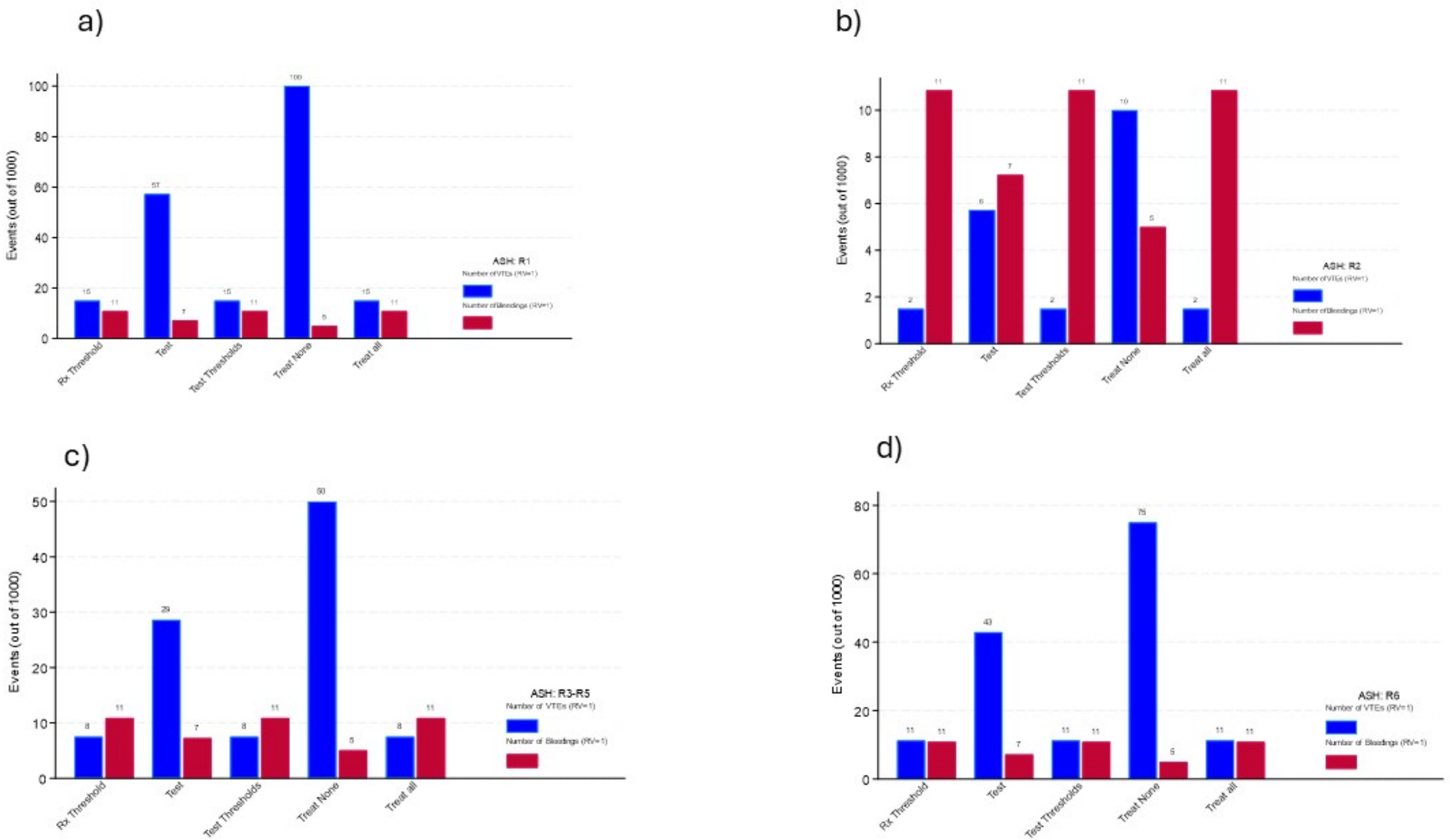


Fig 2 (low bleeding risk)

Figure 3

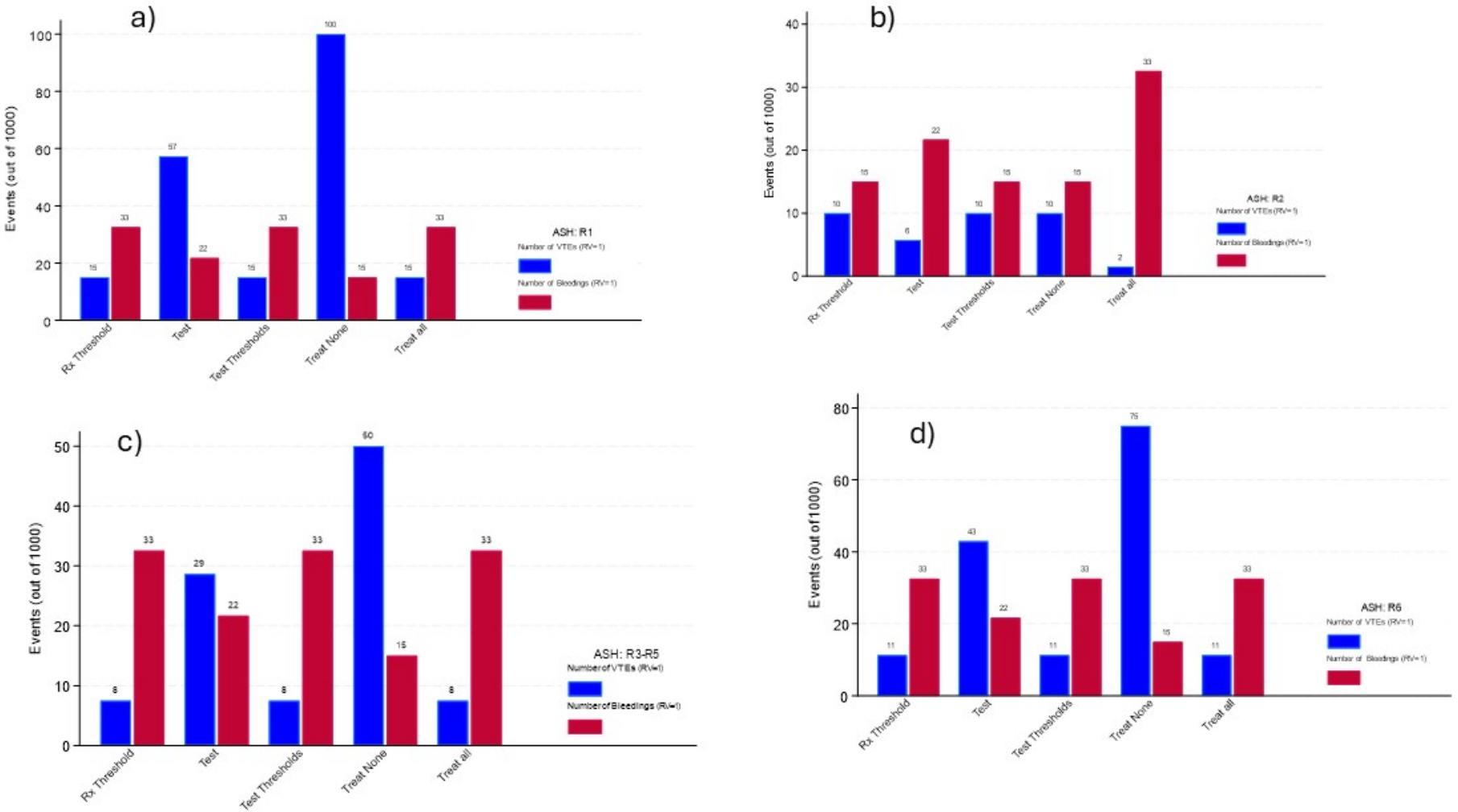


Fig 3 (high-bleeding risk)

Figure 4

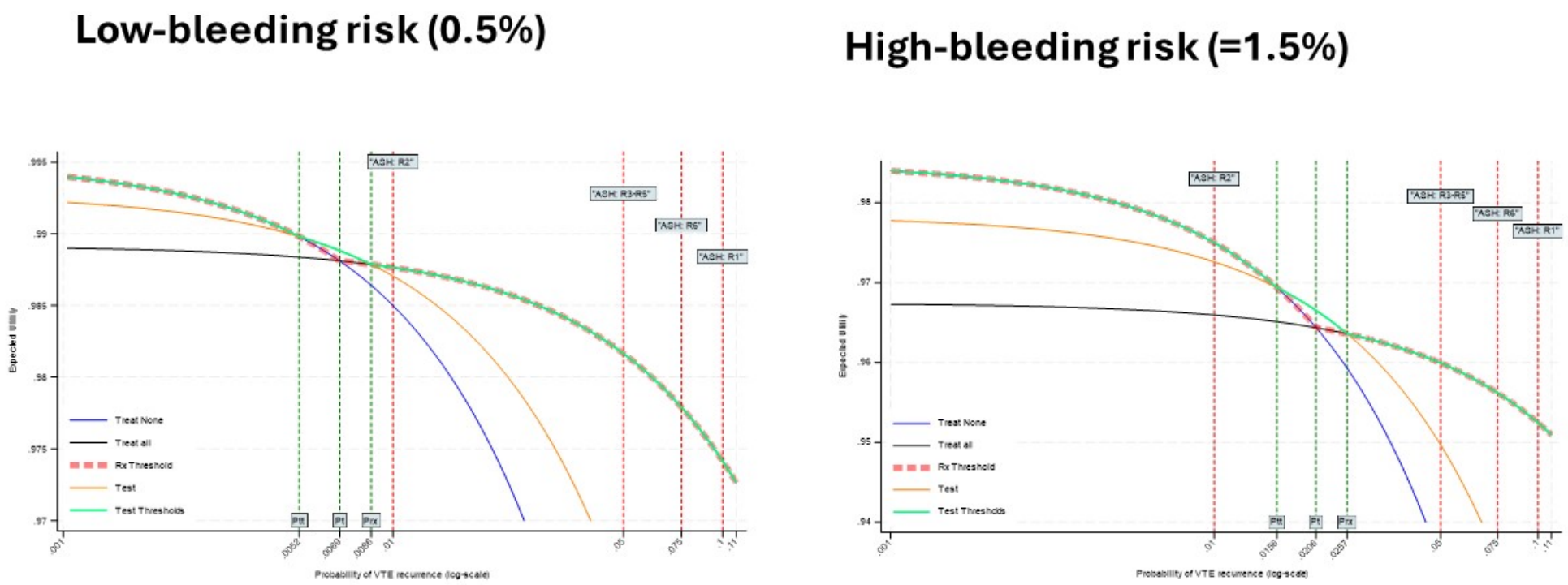


Fig 4