TO THE EDITOR:

Thrombophilia management calculator

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The American Society of Hematology (ASH) has developed evidence-based guidelines for the management of thrombophilia.[1] Unfortunately, even the best evidence-based guidelines currently suffer from the "black-box" and "integration" problems, making it unclear how the panel weighed the trade-offs between the benefits and harms of treatment, testing, and patients' values and preferences (V&P) related to the consequences of disease (such as experiencing venous thromboembolism [VTE]) vs adverse events of treatment (eg, major bleeding rates). The solution to the "black-box" and the "integration" problems is only possible through the explicit formulation of decision ingredients within a decision-analytical framework.[2] We have recently demonstrated how the ASH thrombophilia guidelines could be further improved if the appropriate decision-analytical apparatus were applied.[3] However, given the methodological nature of the paper, we only addressed 12 (6 × 2) recommendations.[3] The panel actually developed 23 recommendations for 7 different clinical settings, which, after taking the subgroups into account, amounted to 69 different management recommendations. Here, we extend the analysis to all 69 thrombophilia management recommendations.

To this end, we developed a calculator to provide both decision-analytic, explicit, and intuitive ASH panel recommendations for all 69 thrombophilia management recommendations. Here is a short description of the application (the EXCEL file includes tabs titled "Introduction" and "Tutorial-examples," which provide further details):

The output of calculations includes (1) display of the number of VTE and major bleeding events, that is, supporting each decision/recommendation, (2) recommendations for action (do not test and do not treat vs test and act accordingly vs do not test and treat) per ASH guidelines and decision-theoretical model(s) (see below), (3) input for relative values (RV) that captures a patient's V&P. The latter allows a user to assess the sensitivity of a decision as a function of the patient's V&P. Note that 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. (Of note, in the case of using contraceptives and hormone replacement therapy, RV > 1 refers not to bleeding events but to unwanted pregnancies and hot flushes, respectively. In addition, we clarify that a decision tree for using anticoagulant as a treatment vs a decision tree for using oral contraceptives as a "treatment" represents a mirror picture of each other (refer to supplemental Appendix for technical details). The user can also select "low" vs "high" bleeding risk for many recommendations.

We believe this calculator will be helpful to all practicing physicians and their patients facing these decisions, as well as to the guideline's panels wishing to develop or update their thrombophilia management recommendations.

The full-text version of this article contains a data supplement.

Finally, we present the output graphically. The first graph shows the results of our main analyses that are based on the expected utility theory (EUT, the only theory of choice that satisfies all mathematical axioms of rational decision-making).[4] All 3 management strategies are shown: no treatment, testing, and treatment-along with 2 thresholds shown as the 2 broken vertical lines (testing threshold and treatment threshold). Because VTE and bleeding are undesirable ("bad") events, the best strategy is one with the lowest expected utility (weighted average of VTE and major bleeding). The vertical blue line indicates the risk for VTE recurrence without treatment for a recommendation (R) under consideration. In the case of all recommendations except for R15 to R20, if the probability of VTE recurrence is greater than the treatment threshold (ie, the vertical blue arrow in the EUT graph calculator is to the right of the treatment threshold), we should prescribe anticoagulants. If the probability of VTE is between 2 thresholds, we should perform thrombophilia testing and act accordingly. Finally, if the probability of VTE is below the testing threshold, we should refrain from testing or treatment. In cases of recommendations R15 to R20 (where "R" denotes the recommendation number), when the "treatments" are oral contraceptives and hormone replacement therapy, we should prescribe it when the risk of VTE recurrence is below the treatment threshold and refrain from the testing or treatment when it is above the testing threshold.

However, as discussed in our article,[3] people, including guideline panels, may violate the EUT gold-standard rationality[5,6] and employ non-EUT decision strategies. One such non-EUT concept is acceptable regret (ARg), a theoretical construct demonstrating that, under some circumstances, potentially incorrect decisions can be tolerated.[7-9] For example, the ASH Guidelines Panel for the management of pulmonary embolism defined upfront that it can tolerate a false negative (FN) rate of ≤2% of missing pulmonary embolism or a combined FN and false-positive rate of ≤5% as acceptable and clinically relevant thresholds.[10,11] Although it is not completely clear, the ASH thrombophilia panel may have relied on a variant of ARg when it, for example, considered ≤VTE 5 events per 1000 patient-years as trivial.[1] Therefore, we also included a second graph in our thrombophilia calculator showing the best management strategies under ARg. Under acceptable regret theory, any strategy that is below ARg line (shown as a horizontal, dark-blue broken line), at the light blue vertical arrow denoting the risk for VTE recurrence without treatment, is an acceptable management strategy. Note that while under EUT, only 1 strategy (outside of thresholds) is the best, under ARg theory, there may be more than 1 strategy that is acceptable to a decision-maker (see also the EXCEL tab "Tutorial-examples").

When we applied decision theory to ASH thrombophilia guidelines, we found that while the EUT disagreed with the ASH thrombophilia panel in 52% of recommendations, the disagreement fell to 29% according to ARg theory (refer to Table 1 and tab "Agreement" in the EXCEL file, which also includes a comparison table for all 69 recommendations). However, this does not mean that the panel's intuitive judgments should automatically be dismissed, particularly when leading experts in the field make them. Indeed, 1 of the goals of the calculator is to highlight the difference between decision-analytical and the panels' consensus recommendations, because the optimal strategy depends on a given theoretical framework (eg, EUT, non-EUT, or even acceptance of intuitive decision-making).

Table 1. ASH thrombophilia panel recommendations agreements with decision-theoretical model

Cases	EUT		ARgT		
Total 69	Agree	Disagree	Agree	Disagree	Total
R1-R10	9	11	11	9	20
R11-R14	5	11	16	0	16
R15-R20	12	9	12	9	21
R21-R23	7	5	10	2	12
n	33	36	49	20	69
%	**47.83**	**52.17**	**71.01**	**28.99**	

Assuming RV = 1 and ARg = 5/1000. Refer to the main text for details. Boldface used to emphasize the summary of the finding.

Nevertheless, when 2 types of judgments—explicit vs intuitive—disagree, every effort should be made to reconcile them.[5,6,12-14]

The first step in this process is to provide a presentation, side-by-side, of both types of judgments—intuitive and explicit—along with the supporting evidence informing these judgments. The second step consists of specifying a theoretical construct (eg, EUT, ARgT, or some other analytical approach) that may account for the observed differences.[4,10]

Contribution: B.D. conceptualized the study; and I.H. developed the software application.

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References

1. Middeldorp S, Nieuwlaat R, Baumann Kreuziger L, et al. American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. *Blood Adv.* 2023;7(22): 7101-7138.

2. Djulbegovic B, Hozo I, Cuker A, Guyatt G. Improving methods of clinical practice guidelines: from guidelines to pathways to fast-and-frugal trees and decision analysis to develop individualised patient care. *J Eval Clin Pract.* 2024;30(3):393-402.

3. Djulbegovic B, Hozo I, Guyatt GH. Decision theoretical foundation of clinical practice guidelines: an extension of the ASH thrombophilia guidelines. *Blood Adv.* Published online 16 April 2024. https://doi.org/10.1182/bloodadvances.2024012931

4. Djulbegovic B, Hozo I. *Threshold Decision-making in Clinical Medicine with Practical Application to Hematology and Oncology. Cancer Treatment and Research.* Springer; 2023.

5. Stanovich KE. *Rationality and the Reflective Mind.* Oxford University Press; 2011.

6. Stanovich KE. How to think rationally about world problems. *J Intell.* 2018;6(2):25.

7. Hozo I, Djulbegovic B. When is diagnostic testing inappropriate or irrational? Acceptable regret approach. *Med Decis Making*. 2008; 28(4):540-553.

8. Hozo I, Djulbegovic B. Clarification and corrections of acceptable regret model. *Medical Decision Making*. 2009;29(3): 323-324.

9. Djulbegovic B, Hozo I. Making decisions when no further diagnostic testing is available (expected regret theory threshold model). *Cancer Treat Res*. 2023;189:39-52.

10. Djulbegovic B, Hozo I, Lizarraga D, Guyatt G. Decomposing clinical practice guidelines panels' deliberation into decision theoretical constructs. *J Eval Clin Pract*. 2023;29(3):459-471.

11. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2(22):3226-3256.

12. Djulbegovic B, Elqayam S. Many faces of rationality: implications of the great rationality debate for clinical decision-making. *J Eval Clin Pract*. 2017;23(5):915-922.

13. Djulbegovic B, Hamm RM, Mayrhofer T, Hozo I, Van den Ende J. Rationality, practice variation and person-centred health policy: a threshold hypothesis. *J Eval Clin Pract*. 2015;21(6):1121-1124.

14. Djulbegovic B, Elqayam S, Dale W. Rational decision making in medicine: implications for overuse and underuse. *J Eval Clin Pract*. 2018;24(3):655-665.