

Thrombophilia Management Calculator

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Iztok Hozo (Indiana University Northwest, United States) Benjamin Djulbegovic (Medical University of South Carolina, United States)

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Thrombophilia Management Calculator

Iztok Hozo, PhD¹ & Benjamin Djulbegovic, MD, PhD²

¹Department of Mathematics, Indiana University Northwest, Gary, Indiana, USA

²Medical University of South Carolina, Division of Medical Hematology and Oncology, Department of Medicine, Charleston, SC, USA

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Correspondence:

Benjamin Djulbegovic, MD, PhD
Professor of Medicine
Medical University of South Carolina
39 Sabin Street
MSC 635
Charleston, SC 29425

e-mail: djulbegov@musc.edu

Phone: 843-792-4879

American Society of Hematology 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 VTE) versus adverse events of treatment (e.g., 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 (6x2) recommendations.³ The panel actually developed 23 recommendations for seven 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: a) display of the number of VTE and major bleeding events, i.e., **evidence** supporting each decision/recommendation, b) **recommendations** for action (don't test and don't treat vs. test and act accordingly vs. don't test and treat) per ASH guidelines and decision-theoretical model(s) (see below), c) input for **RV (relative values) 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. [NB: in the case of using contraceptives and hormone replacement therapy, $RV > 1$ refers not to bleeding events but to unwanted pregnancies and hot flashes, respectively. In addition, we clarify that a decision tree for using anticoagulant as a treatment versus a decision tree for using COC as a "treatment" represents a mirror picture of each other; see Appendix for technical details]. The user can also select "low" vs "high" bleeding risk for many recommendations.

Finally, we present 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 three management strategies are shown – no treatment, testing and treatment- along with two thresholds shown as the two 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-R20, if the probability of VTE recurrence is greater than the treatment threshold [i.e., 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 two thresholds, we should perform thrombophilia testing and act accordingly. Finally, if the probability of VTE is below testing threshold, we should refrain from testing or treatment. In cases of recommendations R15-R20, when the treatments are COC and HRT, we should prescribe the treatment 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 paper [<https://doi.org/10.1182/bloodadvances.2024012931>] people, including guidelines 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 (PE) defined up-front that it can tolerate a false negative (FN) rate of $\leq 2\%$ of missing PE, or a combined FN and false positive rate (FP) (FN+FP) rate of $\leq 5\%$ 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 \leq VTE 5 events per 1,000 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 one strategy (outside of thresholds) is the best, under ARg theory, there may be more than one 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 (see Table, 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, one of the goals of the calculator is to highlight the difference between decision analytical vs. the panels’ consensus recommendations as the optimal strategy depends on a given theoretical framework (e.g., EUT, non-EUT, or even acceptance of intuitive decision-making). Nevertheless, when two 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 (e.g., EUT, ARgT or some other analytical approach) that may account for the observed differences.^{4,10}

Authorship

BD conceptualized the paper; IH developed software application.

None of the authors has a relevant conflict of interest.

Thrombophilia Calculator can be accessed at:

https://mathiho.sitehost.iu.edu/ash-threshold_thrombophilia_calculator.xlsx

(depending on the platform, it may be necessary to click on “edit” button, or download the file for full access)

Or, downloaded as a Supplementary EXCEL application.

There are 8 tabs in the EXCEL file: 1) Introduction, 2) Practical tutorial, 3) List of all recommendations (R) (as per ASH Thrombophilia Guidelines), 4) R1-R10 and R21 to R23 recommendations, 5) R15-R20 recommendations, 6) Agreement between decision models and ASH guidelines, 7) Comments regarding some assumptions about input in decision modeling based on the ASH Summary of Findings Tables showing biological implausibility of calculated bleeding risks in recommendations R21-22. Please see the accompanying paper and appendix for further technical details related to the calculator.

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.

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Table					
ASH Thrombophilia Panel Recommendations Agreements with Decision Theoretical Model					
Cases	EUT		ARgT		TOTAL
Total: 69	Agree	Disagree	Agree	Disagree	
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%	

*EUT-expected utility theory; ARgT- Acceptable Regret Theory- acceptable regret theory (assuming RV = 1 and ARg = 5/1000)
(see ms for details)