Received: 15 December 2017 | Accepted: 20 May 2018

DOI: 10.1111/jth.14534

FORUM

Predicting the risk of recurrent venous thrombosis: What the future might bring

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Funding information
Supported by the Netherlands Heart Foundation (grant NHS2010B167).

Abstract

An important clinical problem in the management of venous thrombosis is to determine whether a patient can safely cease anticoagulant therapy. In this *Forum* article, we summarize the predictive performance of several prediction models for recurrent thrombosis, as well as for bleeding while using anticoagulants. Patients with provoked first thrombosis (considered "low risk") are now denied long-term treatment, although a strong gradient in risk can be found in this group. We furthermore discuss the problem of an unclear definition of "(un)provoked" and show that this affects the yield of currently available prediction scores plus the limitations of a "one-size-fits-all" strategy. Better prediction tools are urgently needed. We propose a strategy for future studies for which the following should be considered: (a) reporting of absolute risks next to C-statistics, (b) model applicable to all patients, (c) no discontinuation of anticoagulation for measurement of predictors.

KEYWORDS

epidemiology, expert testimony, prognosis, risk, secondary prevention, venous thrombosis

1 | INTRODUCTION

One of the most important clinical problems in venous thrombotic disease is to determine whether a patient can safely cease oral anticoagulant therapy. Considering that an individual's venous thrombosis and bleeding risks do not decrease much over time, the decision on treatment duration has strong lifelong implications, as the cumulative risks will become high over a person's lifetime.[1]

The current guidelines advise to classify all patients in two groups, with either high or low risk of recurrence.[2,3] This classification is based on one determinant (i.e., whether the index event was provoked by a transient risk factor or whether it was unprovoked). Roughly speaking, the high-risk group is advised to continue treatment indefinitely and the low risk group is advised to stop after 3 months. There are several problems with this approach: first, the definition of "(un)provoked" is unclear and varies between centers and over time[4]; second, it disregards the strong individual differences between patients; and third, a validated tool to determine the bleeding risk is not included. This situation is unsatisfactory for both patients and doctors.

In this article, we discuss these problems in more detail and propose a strategy to arrive at better prediction tools.

2 | DEFINITION OF "UNPROVOKED" EVENTS

Currently, six prediction models for recurrent venous thrombosis have been published.[5–10] As shown in Table 1, the predictive variables that are included differ per study, as does the definition of "unprovoked" first events. Of the studies included in Table 1, only the

Manuscript handled by: James Douketis
Final decision: Pieter Reitsma, 20 May 2018

TABLE 1 Characteristics of current prediction models for recurrent venous thrombosis

	PROLONG	HERDOO2	Vienna	DASH	DAMOVES	Worcester VTE[a]
Reference	5	6	7	8	9	10
Predictive variables						
High D-dimer	x	x	x	x	x	
Thrombophilia					x	
Older age		x		x	x	
Male sex		x	x	x	x	
Obesity			x			
Postthrombotic signs	x			x		
Proximal DVT			x			
Hormone therapy				x		
Previous malignancy						x
Thrombophlebitis						x
IVC filter						x
Previous surgery						x
Study characteristics						
Enrolled patients, n	608	646	929	1818	398	2889
Maximum follow-up, years	1.5	4	10	5	9	3
Percentage of patients at high risk	37%	65%	NA	48%	NA	NA
Annualized risk of recurrence	11%	14%	NA	9%	NA	NA
Advice on continuation of OAC	Continue	Continue	NA	Unknown	NA	NA
Percentage of patients at low risk	63%	35%	NA	52%	NA	NA
Annualized risk of recurrence	4%	2%	NA	4%	NA	NA
Advice on continuation of OAC	NA	Discontinue	NA	Discontinue	NA	NA
Original C-statistic	NA	NA	0.65	0.71	0.91	0.62
Unprovoked VT						
Absence of						
Cancer	x	x	x	x	x	x
Trauma		x	x	x	x	x
Plaster cast	x	x				x
Surgery	x	x	x	x	x	x
Hospitalization		x		x	x	x
Immobilization	x	x		x	x	
Pregnancy/puerperium	x		x	x	x	x
Estrogen use			x		x	
Antithrombin deficiency	x		x	x	x	
Protein C deficiency			x		x	
Protein S deficiency			x		x	
Homozygous factor V Leiden					x	
Homozygous prothrombin G20210A					x	
Lupus anticoagulant	x	x	x		x	
Anticardiolipin antibodies positive					x	
Antiphospholipid syndrome				x		

Abbreviations: OAC, oral anticoagulant; NA, not available; VT, venous thrombosis.

[a]Also included patients with active malignancy and provoked venous thrombosis, all other studies only included unprovoked venous thrombosis patients in their study.

Worcester venous thromboembolism (VTE) study included patients with both a provoked and unprovoked first venous thrombosis,[10] whereas the other studies were all restricted to patients with unprovoked events. In the Multiple Environment and Genetic Assessment (MEGA) follow-up study, the results of the external validation of three prediction models (Vienna, HERDOO2, and DASH) showed lower C-statistics when we followed our own definition of unprovoked venous thrombosis than when we followed the definitions of the original studies.[11] This reinforces that the definition of "unprovoked venous thrombosis" is unclear and that the performance of the models will be poorer when a clinician uses his or her own definition of "unprovoked" venous thrombosis.

3 | INDIVIDUAL DIFFERENCES BETWEEN PATIENTS

The problem with applying the current guidelines is that it denies all patients with provoked first events (approximately 50% of total) extended treatment. The incidence of recurrence is not negligible in this group (up to 10% in 2 years)[1] and varies greatly over individual patients, depending on their particular risk factors. In our MEGA follow-up study we found that the absolute risk of recurrence in patients with a first provoked event varied depending on the presence of other risk factors.[11] For instance, men with venous thrombosis provoked by something other than surgery and a high D-dimer level had an absolute recurrence risk of 6.0% (95% confidence interval [CI], 3.9-9.2) per year; this risk was virtually similar to that in men who had unprovoked venous thrombosis and a high D-dimer level. In contrast, women with unprovoked first venous thrombosis and a low D-dimer had an absolute risk of only 2.6% (95% CI, 1.5-4.4) per year to develop recurrence.

4 | PREDICTING THE RISK OF MAJOR BLEEDING WHILE BEING ANTICOAGULATED

Currently, one prediction model has been specifically developed for major bleeding during extended anticoagulation for venous thrombosis (i.e., the SAMe-TT_2R_2 score).[12] This score does not predict the long-term bleeding risk in anticoagulated venous thrombosis patients well with a C-statistic of 0.52.[12] Some information on bleeding risks resulting from long-term anticoagulation therapy can be inferred from studies in patients with atrial fibrillation.[13] This is not ideal because patients with atrial fibrillation are, in several respects, different from those with venous thrombosis. In addition, the developed risk scores do not accurately predict major bleeding in patients with atrial fibrillation who require long-term anticoagulant treatment.[14] A model, developed in patients with venous thrombosis (i.e., the VTE-BLEED score),[14] performed well in a subsequent validation study.[15] However, the original study[14] limited follow-up to only 6 months of acute treatment, which information may not be very useful since all patients with venous thrombosis require at least 3-6 months of anticoagulant treatment. Although this issue was addressed in a validation study, where follow-up could now be 12 months,[15] final proof of efficacy in an outcome trial is needed before it may be recommended to be used in daily clinical practice.

5 | WHY SHOULD WE BOTHER ABOUT PREDICTING RECURRENT VENOUS THROMBOSIS RISK?

It could be argued that prediction of recurrent venous thrombosis is no longer necessary, since prolonged anticoagulation with reduced-dose direct-acting anticoagulants (DOACs) should become the standard of care for patients with a first event. This view is based on two trials that concluded that extended duration treatment with reduced-dose DOACs was as efficacious as full-dose treatment in patients after a first venous thrombosis, with a bleeding profile similar to treatment with aspirin or placebo.[16,17] However, we wish to express caution for such a simplified conclusion. First of all, this finding is biologically unlikely: If extended duration treatment with reduced-dose DOAC is equally effective but has a bleeding profile similar to treatment with placebo, then this breaks Åstrup's thrombohemorrhagic balance that states that every anticoagulant has a bleeding profile.[18] A much simpler and likelier explanation is available for these findings (i.e., a type II error). A type II error means that one accepts the null hypothesis when one actually should have rejected it (in other words "failing to reject the null hypothesis"), which is due to low statistical power. Indeed, bleeding outcome events were very rare in both trials (two major bleeding events in AMPLIFY-EXT and zero events in Einstein Choice while using low-dose DOAC versus four and one events in the placebo and aspirin group, respectively). Relative risks of clinically relevant non-major bleeding were higher in the reduced DOAC groups, but not on a statistical level. That statistical significance could not be demonstrated for either major or non-major bleeding is not surprising because the trials were not set up to test if reduced DOAC was as safe as placebo or aspirin use. For this, one needs to design a noninferiority trial that deals with type II errors in its statistical analysis, generally by enforcing investigators to include many more patients than are needed for a superiority trial (the design that was actually used in both AMPLIFY-EXT and Einstein Choice to show superior efficacy of DOAC over aspirin or placebo). Second, the major bleeding rates in both trials were very low, both in patients who used reduced DOAC and full-dose DOAC (<0.5% per year), which is likely to be due to inclusion of patients in these trials that have a low a-priori risk bleeding profile.[19] Indeed, population-based studies have shown that major bleeding rates can be as high as 2%-4% per year in patients who use DOACs.[20] Finally, whether reduced DOACs are as effective as high-dose DOACs could not be determined in both trials because they were not powered to show

the noninferiority of the reduced dose of DOAC to the full-dose treatment regimen, so any conclusion with respect to this issue is speculative.

These studies therefore provide no useful evidence but merely illustrate the importance of risk refinement, as patients with a moderately high recurrence risk and a low bleeding risk may benefit from this strategy of low dosing. However, patients with a high recurrence risk may truly need a standard dose DOAC, unless they have high bleeding risk, in which case they may need low dosing. Finally, those with low recurrence risk should not be exposed to prolonged treatment at all, not even to low-dose DOACs.

6 | WHAT THE FUTURE MIGHT BRING

In current practice, risk estimation of recurrent venous thrombosis and bleeding at an individual level is performed only crudely. This implies that a large proportion of patients with a first venous thrombosis is either over- or undertreated with anticoagulants, for a prolonged period, leading to high lifetime risks of both recurrence and bleeding. We propose to individually classify patients with respect to thrombotic and bleeding risk and subsequently determine who will benefit from anticoagulant treatment and who will be unnecessarily exposed to its risks. To achieve this, further studies are needed in which the following issues should be considered:

First, one should not be too focused on results of the C-statistic only. For instance, the assumption that a model only works well if the C-statistic is high (e.g., higher than 0.7) is flawed because the C-statistic only describes how well models can rank order high-risk patients and low-risk patients, but is not a function of the actual predicted probabilities.[21] As an example, consider data from the MEGA follow-up study, in which the C-statistic for a model only including factor VIII was 0.60.[22] This means that the probability is 60% that a patient with recurrence has a higher factor VIII level than a patient who did not develop recurrence. This information does not help in determining if a patient with a high factor VIII has a high absolute risk of recurrent venous thrombosis and therefore might be a candidate to receive long-term anticoagulant treatment. In fact, the absolute risk of recurrent venous thrombosis in patients with a high (i.e., >200 IU/dL) factor VIII was 5.1% per year, whereas the absolute risk in those who had a factor VIII level of ≤100 IU/dL was 1.4% per year (corresponding with a hazard ratio of recurrent venous thrombosis of 3.4; 95% CI, 2.2-5.3)[22]; which is a clinically relevant difference, and this knowledge is therefore more informative than the C-statistic. It is important to mention here that exposure variables for which the relative risk of a disease is ≤3 have little impact on the C-statistic.[23] When studying a disease that is not very prevalent, for example first venous thrombosis, a relative risk of 3 for a high level of a certain biomarker would shift the estimated 5-year risk from 0.5% to only 1.5%; a clinically unimportant difference. This is clearly different when the absolute risks are much higher as is the case for recurrent venous thrombosis. Then the same high biomarker level could alter the estimated 5-year risk of a recurrent venous thrombotic event from 10% to 30%, which could lead to different treatment recommendations. Thus, for risk prediction, the actual or absolute predicted risk, which is not captured by the C-statistic, is of primary clinical interest.

Second, one should develop a model that applies to all patients, and not only to patients with unprovoked venous thrombosis. Although unprovoked venous thrombosis is clearly associated with a higher risk of recurrence than a provoked event,[1–3] the risk of recurrence in those with a provoked event is not negligible and varies greatly among patients, as discussed previously. As was shown in the MEGA follow-up study, within groups that are currently thought to have with a low recurrence risk (provoked first event, women), a high factor VIII level was still predictive for recurrent events.[22] This implies that a more refined risk estimation is possible at an individual level.

Third, biomarkers such as D-dimer and factor VIII levels improve prediction of a recurrent event.[1,5–8,11,22] However, discontinuation of anticoagulation treatment (both vitamin K agonists and DOACs) is needed for reliable measurements. A period between discontinuation for blood sampling and restart of anticoagulation might confer an additional risk period of recurrence. All relevant information for assessing a patient's risk should therefore be determined during anticoagulant treatment. Genetics and clinical variables can be useful for this purpose. D-dimer levels or coagulation factor assays may be feasible, but under strict measurement conditions.[24,25] Fourth, not only recurrence risk should be incorporated in a risk score but also the bleeding risk when extending anticoagulation. Predicting these risks in the elderly may be particularly useful because current predictive scores for recurrence have failed in elderly patients,[26] whereas elderly patients are at increased risk of bleeding while using anticoagulant treatment.[2] Finally, whatever prediction rule is developed, it needs external validation and successful application in practice as tested in appropriately designed clinical trials.

7 | CONCLUSION

The predictive ability of the currently available models is limited and the current guidelines advise to estimate a patient's recurrence risk based only on whether or not the first event was provoked; however, the definition of provoked/unprovoked determines the prediction of the respective associated risks but varies strongly. Furthermore, risks of recurrence vary according to presence of well-described risk factors and a much more refined risk estimation is possible than the current binary stratification. Properly conducted controlled studies into development of new models are needed that take the following into account: (a) reporting of absolute risks next to C-statistic, (b) applicable to all patients, and (c) no discontinuation of anticoagulation necessary. This way, by determining individual risk profiles for both recurrent thrombosis and bleeding risk, personalized treatment is possible, by which occurrence of both conditions will be minimized.

CONFLICT OF INTERESTS

The authors state that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

W.M. Lijfering, J.F. Timp, and S.C. Cannegieter were the main investigators of the manuscript. W.M. Lijfering wrote the first draft of the manuscript and the final version. J.F. Timp and S.C. Cannegieter were responsible for review of the manuscript.

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How to cite this article: Lijfering WM, Timp JF, Cannegieter SC. Predicting the risk of recurrent venous thrombosis: What the future might bring. *J Thromb Haemost*. 2019;17:1522–1526. https://doi.org/10.1111/jth.14534