Extended anticoagulant therapy in venous thromboembolism: a balanced, fractional factorial, clinical vignette-based study

The need for extended anticoagulant therapy beyond the initial 3 months of anticoagulation for acute venous thromboembolism (VTE) remains a subject of active debate.[1] The ideal duration of extended anticoagulant therapy is unclear, and it is not known how risk factors for recurrence and bleeding influence clinical decisions.[2]

To guide physicians in their decision-making, specialist collectives periodically issue best-practice treatment guidelines. Such guidelines advise certain treatment durations given particular combinations of risk factors. Many physicians around the world consult these guidelines. Recently, however, it has come to light that the best practices outlined in these guidelines are not always followed.[3] Poor guideline adherence has been linked to an increase in the rate of VTE recurrence and all-cause and bleeding-related hospital admissions.[3]

The objective of this study was to shed light on how physicians decide on a particular VTE recurrence prevention plan: how do they weigh recurrence and bleeding risk factors, and when do they decide to extend or to stop treatment? Do physicians make different treatment choices based on their own characteristics? What drives the variability among physicians when it comes to treatment duration? To answer these questions, we conducted a vignette-based study that mimics the clinical setting in which the physician decision-making process surrounding these issues occurs.

Previously, we conducted interviews with senior-level thrombosis experts to identify relevant risk factors for recurrence and bleeding in VTE patients.[4] This yielded an extensive list of risk factors; we decided to include only those that were identified by at least two interviewees.[5] Our final selection comprised 12 factors, each of which we assigned two or more levels (*Online Supplementary Table S1*). A more detailed description of the experimental design, implementation and the recruiting process of specialists has been published.[5] A total of 253 specialists from six continents participated online (Table 1 and *Online Supplementary Table S2*).

To produce the case vignettes, we generated a matrix containing all possible permutations of the combined risk factors. Each of the 27,648 rows in this matrix corresponded to a unique patient profile. To constrain the number of vignettes, we used a Fedorov exchange algorithm to produce a D- and G-efficient balanced fractional factorial design.[5,6] To reduce the burden on the specialists, the vignettes were subsequently distributed across six blocks of 12 vignettes each, to which specialists were randomized.

Each vignette described a patient with VTE who had completed 3 months of initial anticoagulant therapy. For this patient, specialists estimated the risks of recurrent VTE and bleeding on visual analog scales ranging from 0 to 100 and chose one of five therapeutic options: continue anticoagulation for 3 months, continue anticoagulation for 9 months, continue anticoagulation indefinitely, stop treatment, or switch to aspirin. All fields had to be completed before submission, preventing missing values.

Using simulations, the required sample size was determined to be $100 \leq n \leq 250$.[5] Mixed-effects linear quantile regression was used to model the risk estimates for the 10th, 50th and 90th risk percentiles. The choice options relating to treatment duration were set up such that they allowed multinomial as well as binomial classification after grouping, into a 'continue' or 'stop' group. 'Continue' represents the option to continue for 3 months, continue for 9 months, or to continue indefinitely; 'stop' combines the 'stop treatment' and 'switch to aspirin' options. Binomial and multinomial logistic regression analyses were used to model these respective choices. All predictive models were derived from 80% of the data, and evaluated on the remaining and unseen 20% of the data. The predictive ability and fit of the models were evaluated using the area under the receiver operating characteristic curve (AUROC), the predictive accuracy, and using McFadden's pseudo-R^2 (ρ^2).[7] The inclusion of random effects did not improve the fit or the predictive ability of the logistic models; hence, they were omitted from this report. R version 3.3.1 was used for all analyses and plots.

Table 1. Characteristics of the study participants.

Participants' characteristic	Sample size, n (%)
Total number of participants	253 (100)
Male sex	149 (59)
Specialty	
Cardiology	15 (6)
Hematology	76 (30)
Vascular medicine/angiology	68 (27)
Internal medicine	68 (27)
Pulmonology	14 (6)
Other	13 (5)
Age, years	
<30	26 (10)
30-40	95 (38)
41-50	63 (25)
51-60	46 (18)
>60	23 (9)
Duration of practice, years	
0-5	55 (22)
6-10	81 (32)
11-15	41 (16)
16-25	45 (18)
>25	31 (12)
Unique patients seen annually	
<25	69 (27)
25-49	22 (9)
50-99	46 (18)
100-149	41 (16)
>149	75 (30)

The characteristics of the 253 specialists who participated in the study between July 2016 and January 2017 are described in Table 1 and in *Online Supplementary Table S2*.

The specialists' perception of recurrent VTE risk and bleeding risk by patients' characteristic are summarized in Figure 1A,B. Figure 1C depicts the decision to continue or to stop treatment based on these risk perceptions. Table 2 provides the impact of individual risk factors and specialists' characteristics on the decision to continue (Table 2) or discontinue (*Online Supplementary Table S5*) treatment. Figure 1D depicts the type of treatment that

specialists selected in relation to the estimated recurrent VTE and bleeding risks. *Online Supplementary Table S7* provides the impact of individual risk factors and specialists' characteristics on each of the treatment options using 'stop treatment' as the reference category.

Our results provide some insight into the decision-making process of thrombosis specialists with regard to the choice for and the duration of extended treatment of VTE. Specifically, there is substantial and clinically important variance with regard to recurrence and bleeding risk perception, especially in low- to moderate-risk patients (*Online Supplementary Tables S3* and *S4*). Variation was also evident in the selection of specific treatment durations, even though the motivating risk factors were strongly comparable (*Online Supplementary Tables S7-S9*). The binary decision to continue anticoagulation *versus* stopping could, however, be predicted with high accuracy (*Online Supplementary Table S6*).

In assessing the risk of VTE recurrence, specialists evidently weighed the presentation and location of VTE the heaviest. As expected, proximal deep vein thrombosis was assigned much more risk than distal deep vein thrombosis. Specialists did not discriminate much between other clinical presentations of VTE in terms of risk of recurrent VTE. This finding suggests that specialists act on a fairly binary distinction between distal deep vein thrombosis and all other locations of VTE. Isolated distal deep vein thrombosis is indeed associated with a lower risk of recurrence and fewer late sequelae than proximal deep vein thrombosis or pulmonary embolism.[8] However, these results demonstrate little appreciation for the substantially higher risk of recurrence associated with the presence of post-thrombotic syndrome.[9]

In line with expectations and guideline recommendations[10,11] on risk assessment, specialists are likely to classify the risk of recurrence as high when the VTE is described as unprovoked. A patient having a personal or family history of VTE also inclines specialists toward prolonging treatment. In addition, male sex has a modest positive impact on the estimated recurrence risk. These are intuitive results that suggest specialists are aware of and act in accordance with the impact of these risk factors on the risk of recurrence as documented in the literature.

Specialists assigned body mass index and thrombophilia comparatively little risk in practice: their perceived impact on VTE recurrence was not large enough to merit a strong influence on treatment decisions. Our interpretation of this result is that, in clinical practice, these risk factors are likely outweighed by others, as is supported

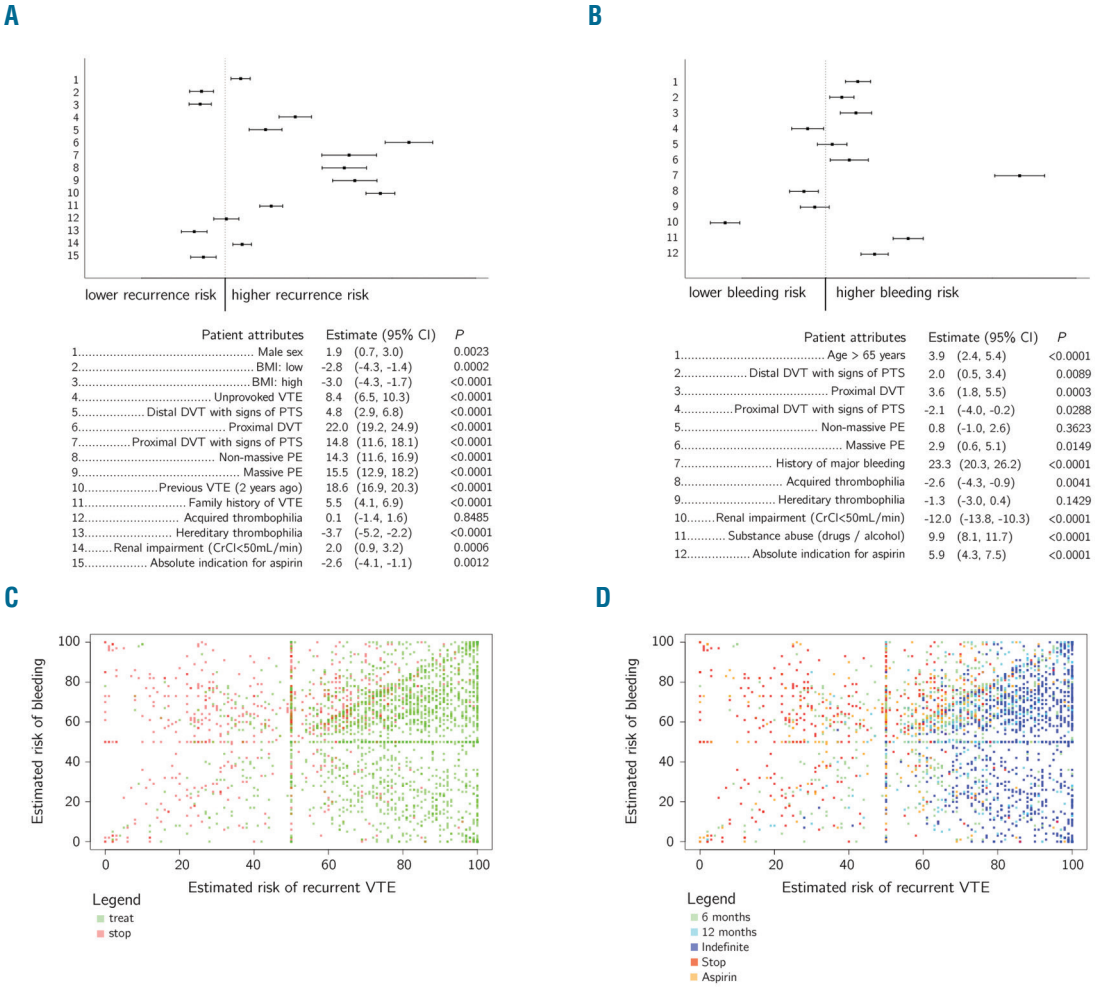

Figure 1. Specialists' risk assessments and treatment decisions. (A) Specialists' perception of risk of recurrent venous thromboembolism by risk factor. (B) Specialists' perception of bleeding risk by risk factor. (C) Decision to continue or to stop treatment, based on risk perception. (D) Treatment duration preference by risk perception.

by research contesting the clinical significance of these risk factors.[12,13]

With regard to bleeding risk factors, specialists were especially careful when treating patients with a history of major bleeding. Other risk factors of particular concern were substance abuse and an absolute indication for aspirin. Substance abuse, which encompasses alcohol and other drug abuse, may be considered a bleeding risk for various reasons: for example, if treated with vitamin K antagonists, it is more difficult to maintain a therapeutic international normalized ratio in such patients, and it is likely that these patients are less compliant with therapy.[4]

Specialists considered renal impairment, defined as a creatinine clearance <50 min/mL, a reason to continue treatment. Indeed, while the bleeding risk of these patients when using vitamin K antagonist therapy is increased, the risk of recurrence in these patients is increased independently of the anticoagulant used.[14]

Due to the study design, we were constrained in the number of covariates that could be included. Hence, we omitted risk factors we deemed of minor importance. This study was, therefore, focused particularly on common, non-transient risk factors; rare risk factors, such as thrombocytopenia for bleeding, were not considered. Cancer was an exception: this risk factor was excluded since its inclusion in the study was not deemed likely to generate novel insights. It is well-known that patients with active malignancy should receive anticoagulation until the cancer is cured or in remission.[15] Furthermore,

Table 2. Odds ratios of continuing anticoagulation according to the presence of risk factors and specialists' characteristics.

Risk factors	Odds ratio (95% confidence interval)
Male sex	1.29 (1.03-1.63)*
Unprovoked VTE	2.51 (1.98-3.20)#
Distal DVT (reference)	1.00
Distal DVT with signs of PTS	1.70 (1.22-2.37)**
Proximal DVT	22.65 (13.99-37.87)#
Proximal DVT with signs of PTS	7.73 (5.26-11.49)#
Non-massive PE	5.31 (3.71-7.67)#
Massive PE	8.74 (5.96-12.99)#
Previous VTE (within 2 years)	3.31 (2.61-4.21)#
Family history of VTE	1.34 (1.07-1.69)*
History of major bleeding	0.75 (0.60-0.95)*
No thrombophilia (reference)	1.00
Acquired thrombophilia	1.11 (0.84-1.48)
Hereditary thrombophilia	0.76 (0.57-1.01)
Renal impairment (CrCl <50 mL/min)	1.35 (1.07-1.70)*
Substance abuse	0.75 (0.59-0.94)*
Absolute indication for aspirin	0.55 (0.43-0.69)#
Specialists' characteristics	**Odds ratio (95% confidence interval)**
Patients seen annually	
<25 (reference)	1.00
25-49	1.03 (0.68-1.58)
50-99	0.72 (0.49-1.07)
100-149	0.51 (0.34-0.75)#
≥150	0.61 (0.42-0.87)**
Region of practice	
Western Europe (reference)	1.00
Eastern Europe	4.41 (2.86-6.98)#
Israel	2.82 (1.80-4.49)#
North America	1.14 (0.77-1.71)
South America	3.27 (1.90-5.83)#
East Asia	3.75 (1.90-7.84)#
South East Asia	1.77 (0.90-3.68)
Africa	1.11 (0.58-2.19)
Turkey	2.58 (0.70-12.68)
Oceania	0.74 (0.53-1.05)

*P<0.05; **P<0.001; #P<0.0001. Reference categories are shaded; reference categories for dichotomous variables are not shown. CrCl: creatinine clearance; DVT: deep vein thrombosis; OR: odds ratio; PE: pulmonary embolism; PTS: post-thrombotic syndrome; VTE: venous thromboembolism.

we focused exclusively on specialists' decision-making directly following the initial 3 months of acute therapy; later decision time-points, patients' preferences and potential therapy resumption after initially discontinuing anticoagulation (e.g., based on post-hoc evaluation of D-dimer levels) were not evaluated. Lastly, we were unable to account for the type of medication and dosing regimen, instead allowing participants to assume that the anticoagulant of their choice, and at their disposal in real life, would be used.

Generally, VTE specialists appear to act in accordance with guidelines, although some notable misjudgements were made: for instance, the presence of post-thrombotic syndrome did not affect the willingness to continue therapy, and renal impairment was erroneously deemed protective against bleeding. Education could address these misunderstandings, to improve decision-making in these areas.

The mechanism underlying the observation that specialists treating a greater yearly number of patients are less inclined to continue anticoagulant therapy should be investigated further. The geographical differences that were demonstrated by this study should be considered in devising treatment guidelines, as area-specific circumstances may constrain treatment choices.

Vincent ten Cate,[1] Anthonie W.A. Lensing,[2] Jeffrey I. Weitz,[3] Jan Beyer-Westendorf,[4] Philip S. Wells,[5] Patrick Mismetti,[6] Paolo Prandoni,[7] Alexander T. Cohen,[8] Bruce L. Davidson[9] and Martin H. Prins[10]

[1]Department of Epidemiology, Maastricht University Medical Center, Maastricht, the Netherlands; [2]Department of Cardiovascular Sciences, Vascular Medicine Unit, University of Padua, Padua, Italy, and Bayer AG, Wuppertal, Germany; [3]Thrombosis & Atherosclerosis Research Institute and McMaster University, Hamilton, Ontario, Canada; [4]Thrombosis Research Unit, Department of Medicine I, Division Hematology, University Hospital "Carl Gustav Carus" Dresden, Germany; [5]Department of Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; [6]Clinical Research Unit, University Hospital of Saint-Etienne, Saint-Etienne, France; [7]Department of Cardiovascular Sciences, Vascular Medicine Unit, University of Padua, Padua, Italy; [8]Department of Haematological Medicine, King's College Hospital, London, UK; [9]University of Washington School of Medicine, Seattle, WA, USA and [10]Department of Epidemiology, Maastricht University Medical Center, Maastricht, the Netherlands

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Correspondence: VINCENT TEN CATE.
vincent10kd@gmail.com

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