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

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doi:10.3324/haematol.2018.209924

Supplemental appendix

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S1: Vignette risk factors and levels

Risk factor	Level 1 (reference)	Level 2	Level 3	Level 4	Level 5	Level 6
Sex	Female	Male				
Age	<65 years	≥65 years				
BMI	Normal	Low	High			
Unprovoked VTE	No	Yes				
Presentation and site of VTE	Distal DVT	Distal DVT with signs of PTS	Proximal DVT	Proximal DVT with signs of PTS	Non-massive PE*	Massive PE
Previous VTE	No	Yes (within 2 years)				
Family history of VTE	No	Yes				
History of major bleeding	No	Yes				
Thrombophilia	None	Acquired	Hereditary			
Renal function	Normal	Impaired (CrCl<50 mL/min)				
Alcohol or substance abuse	No	Yes				
Absolute indication for aspirin	No	Yes				

** I.e., hemodynamically stable PE.*
Abbreviations: BMI, body mass index; CrCl, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE: venous thromboembolism.

S2: Region and country of practice of the study participants

Region and country of practice	Sample size, n (%)
Total number of participants	253 (100)
Western Europe	100 (40)
Austria	5 (5)
Belgium	5 (5)
Denmark	3 (3)
France	16 (16)
Germany	14 (14)
Italy	12 (12)
Netherlands	17 (17)
Norway	2 (2)
Spain	9 (9)
Sweden	2 (2)
Switzerland	12 (12)
United Kingdom	3 (3)
Eastern Europe	33 (13)
Croatia	1 (3)
Czech Republic	6 (18)
Estonia	1 (3)
Hungary	10 (30)
Poland	2 (6)
Russia	13 (39)
Turkey	3 (1)
Turkey	3 (100)
Israel	22 (9)
Israel	22 (100)
North America	25 (10)
United States	10 (40)
Canada	15 (60)
South America	15 (6)
Argentina	1 (7)
Brazil	11 (73)
Mexico	3 (20)
East Asia	10 (4)
China	11 (100)
South East Asia	7 (3)
Philippines	2 (29)
Thailand	2 (29)
Vietnam	3 (43)
Oceania	30 (12)
Australia	20 (67)
New Zealand	10 (33)
Africa	8 (3)
Ghana	3 (38)
South Africa	5 (63)

S3: Standard deviations of the included random effects: risk of recurrent VTE

Standard deviations random effects: risk of recurrent VTE				
Percentile	Intercept	Previous VTE	Family history of VTE	Aspirin indication
10^{th}	7.9	8.7	0.0	0.0
50^{th}	8.5	7.4	2.6	5.5
90^{th}	6.2	0.0	0.0	0.0

Interpretation:

The standard deviations of the random effects reflect the degree of variability in risk estimates between physicians with respect to the variables shown. The intercept reflects the baseline difference in risk assessment: two physicians may assess the thrombotic risk of the same patient differently, even when they otherwise agree on the impact of a given risk factor. The remaining standard deviations indicate the variability between physicians with respect to the coefficients of the shown variables. For instance, this means that there is considerable variation between how physicians assess the impact of a previous VTE in low to moderate risk patients, while there is virtually no disagreement between physicians in assessing this same risk in high risk patients. In high risk patients, only the baseline risk estimates vary.

S4: Standard deviations of the included random effects: risk of bleeding

Standard deviations random effects: bleeding risk				
Percentile	Intercept	History major bleeding	Aspirin indication	Substance abuse
10^{th}	7.2	9.8	5.6	4.9
50^{th}	8.5	10.7	3.8	3.9
90^{th}	6.6	0.0	0.0	0.0

S5: Discontinuing treatment

Risk factor	Odds ratio (95% CI)
Male sex	0.77 (0.61 to 0.98)*
Idiopathic	0.40 (0.31 to 0.51)#
Distal DVT with signs of PTS	0.59 (0.42 to 0.82) **
Proximal DVT	0.04 (0.03 to 0.07)#
Proximal DVT with signs of PTS	0.13 (0.09 to 0.19)#
Non-massive PE	0.19 (0.13 to 0.27)#
Massive PE	0.11 (0.08 to 0.17)#
Previous VTE (2 years ago)	0.30 (0.24 to 0.38)#
Family history of VTE	0.74 (0.59 to 0.93)*
History of major bleeding	1.33 (1.06 to 1.67)*
Acquired thrombophilia	0.90 (0.68 to 1.19)
Hereditary thrombophilia	1.31 (0.99 to 1.74)
Renal insufficiency (CrCl<50mL/min)	0.74 (0.59 to 0.93) *
Substance abuse	1.33 (1.06 to 1.68)*
Absolute indication for aspirin	1.83 (1.45 to 2.31)#
Specialist characteristic	**Odds ratio (95% CI)**
Patients seen annually	
25-49	0.97 (0.63 to 1.48)
50-99	1.38 (0.93 to 2.04)
100-149	1.98 (1.34 to 2.94)#
≥150	1.64 (1.15 to 2.36)**
Region of practice	
Eastern Europe	0.23 (0.14 to 0.35)#
Israel	0.36 (0.22 to 0.56)#
North America	0.87 (0.58 to 1.29)
South America	0.31 (0.17 to 0.53)#
East Asia	0.27 (0.13 to 0.53)#
South East Asia	0.56 (0.27 to 1.11)
Africa	0.90 (0.46 to 1.73)
Turkey	0.39 (0.08 to 1.43)
Oceania	1.34 (0.95 to 1.90)

** p<0.05; ** p<0.001; # p<0.0001. Abbreviations: CI, confidence interval; CrCl, creatinine clearance; DVT, deep vein thrombosis; OR, odds ratio; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.*

S6: Predictive metrics and fit: Continuing anticoagulation

AUROC	Predictive accuracy on test set	McFadden's ρ^2
0.83	80.25%	0.24

Abbreviations: AUROC, area under the receiver operating characteristic curve.

Interpretation:

The AUROC indicates the discriminatory ability of the predictive model. An AUROC of 0.50 indicates no predictive ability, while a model with an AUROC of 1.00 can perfectly discriminate between (and thus predict) two options. A McFadden's ρ^2 of 0.20 or more indicates good model fit.

S7: Treatment choices, compared to treatment cessation

	Treat 6 months	Treat 12 months	Treat indefinitely	Switch to aspirin
Risk factor	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Male Sex	1.06 (0.76-1.46)	1.21 (0.83-1.74)	1.70 (1.23-2.36)	1.07 (0.74-1.54)
Unprovoked VTE	2.06 (1.47-2.89)	2.62 (1.78-3.86)	5.08 (3.59-7.19)	1.63 (1.11-2.38)
Distal DVT (reference)	1.00	1.00	1.00	1.00
Distal DVT, signs of PTS	1.79 (1.13-2.83)	1.56 (0.85-2.86)	1.97 (1.21-3.21)	1.41 (0.88-2.26)
Proximal DVT	14.19 (6.54-30.78)	51.19 (22.30-117.50)	99.47 (45.89-215.58)	3.64 (1.53-8.64)
Proximal DVT, signs of PTS	6.73 (3.80-11.91)	11.23 (5.82-21.66)	16.18 (9.11-28.75)	1.98 (1.05-3.71)
Non-massive PE	4.31 (2.58-7.23)	5.31 (2.84-9.95)	10.02 (5.90-17.02)	1.41 (0.77-2.55)
Massive PE	9.79 (5.56-17.24)	16.71 (8.67-32.21)	17.97 (9.95-32.45)	2.40 (1.25-4.61)
Previous VTE (within 2 years)	1.97 (1.38-2.83)	4.58 (3.06-6.85)	15.77 (10.89-22.82)	2.49 (1.68-3.70)
Family history of VTE	1.07 (0.78-1.47)	1.75 (1.21-2.53)	1.62 (1.17-2.23)	1.03 (0.72-1.48)
History of major bleeding	0.89 (0.64-1.24)	0.81 (0.56-1.18)	0.55 (0.40-0.77)	0.96 (0.66-1.39)
No thrombophilia (reference)	1.00	1.00	1.00	1.00
Acquired thrombophilia	1.09 (0.72-1.63)	0.76 (0.48-1.20)	1.17 (0.79-1.75)	0.93 (0.59-1.46)
Hereditary thrombophilia	0.89 (0.59-1.33)	0.50 (0.31-0.78)	0.44 (0.29-0.66)	0.68 (0.43-1.07)
Substance abuse	0.88 (0.63-1.23)	0.70 (0.48-1.02)	0.54 (0.39-0.76)	0.84 (0.58-1.23)
Absolute aspirin indication	1.28 (0.92-1.78)	0.98 (0.67-1.43)	0.98 (0.70-1.37)	4.85 (3.28-7.17)
Specialist characteristic	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Patients seen annually				
<25 (reference)	1.00	1.00	1.00	1.00
25-49	1.27 (0.70-2.28)	1.48 (0.76-2.90)	1.00 (0.55-1.85)	1.36 (0.69-2.69)
50-99	0.62 (0.37-1.05)	0.91 (0.49-1.66)	0.43 (0.25-0.74)	0.59 (0.31-1.11)
100-149	0.37 (0.21-0.63)	0.46 (0.25-0.87)	0.46 (0.27-0.80)	0.68 (0.37-1.26)
≥150	0.48 (0.29-0.79)	1.20 (0.67-2.14)	0.56 (0.34-0.94)	0.95 (0.54-4.04)
Region of practice				
Western Europe (reference)	1.00	1.00	1.00	1.00
Eastern Europe	3.76 (2.09-6.74)	12.67 (6.78-23.49)	2.44 (1.33-4.49)	0.95 (0.44-2.07)
Israel	4.26 (1.90-9.56)	15.60 (6.75-36.08)	8.71 (3.94-19.22)	5.15 (2.25-11.77)
North America	1.30 (0.72-2.35)	1.05 (0.50-2.23)	1.59 (0.91-2.79)	1.53 (0.82-2.84)
South America	2.38 (1.23-4.60)	5.01 (2.38-10.53)	1.65 (0.81-3.36)	0.45 (0.16-1.28)
East Asia	6.48 (2.29-18.34)	15.90 (5.22-48.48)	2.78 (0.91-8.54)	2.91 (0.91-9.26)
South East Asia	2.41 (0.86-6.76)	6.02 (1.94-18.64)	1.68 (0.57-4.95)	1.94 (0.62-6.04)
Africa	2.03 (0.87-4.75)	2.00 (0.69-5.86)	0.50 (0.19-1.36)	1.47 (0.54-4.04)
Turkey	1.44 (0.23-8.82)	7.53 (1.18-48.15)	2.06 (0.34-12.49)	0.68 (0.06-8.06)
Oceania	0.84 (0.52-1.37)	0.42 (0.20-0.88)	0.95 (0.60-1.52)	1.29 (0.78-2.14)

Reference categories are shaded; reference categories for dichotomous variables are omitted. Abbreviations: CI, confidence interval; CrCl, creatinine clearance; DVT, deep vein thrombosis; OR, odds ratio; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.

Interpretation: this table shows the results of a multinomial logistic regression model, with treatment cessation as the reference choice. Odds ratios with confidence intervals that contain 1 are not statistically significant.

S8: Predictive metrics and fit: Treatment choices, compared to treatment cessation

Choice	AUROC	Predictive accuracy on test set	McFadden's ρ^2
Combined	0.62	51.26%	0.20
6 months	0.70	78.29%	-
12 months	0.66	84.31%	-
Indefinite	0.81	73.53%	-
Stop	0.85	86.97%	-
Aspirin	0.78	90.19%	-

Interpretation:

This table shows that, while the multinomial model demonstrates adequate fit (and so the coefficient estimates are reliable), its discriminatory ability (ability to predict specific treatment choices) is poor (multiclass AUROC=0.62). It also shows that when individual choices are modeled separately (against all other choices), using binomial logistic regression, the model predicts choices fairly well. In other words, the predicted probabilities for individual choices are reasonably accurate, but the combined (multinomial) model fails to discriminate between separate options, because the predicted probabilities are too close to one another. This result indicates that not enough information was present to differentiate between treatment choices. An alternative explanation is that this decision-making process has a random element to it that eludes prediction altogether.

S9: Confusion matrix of actual versus predicted choices

	Predicted choice					
Actual choice	Stop	6 months	12 months	Indefinite	Aspirin	Sum
Stop	50	25	0	18	9	102
6 months	18	66	10	52	15	161
12 months	9	25	21	47	7	109
Indefinite	11	35	9	209	7	271
Aspirin	15	14	2	20	20	71
Sum	103	165	42	346	58	714

Interpretation:

This table depicts the actual choices that were made (in the test set, i.e., the 20% of data unseen during modelling) versus the choices predicted by the multinomial model. This table, like S8, illustrates how the model fails to adequately predict separate choices; only the 'indefinite anticoagulation' option is predicted correctly in the majority of instances.