

3° CONVEGNO DI  
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## “ ANTICOAGULAZIONE

Attualità cliniche e di laboratorio.  
Aspetti sociali

”  
BOLOGNA 25-26 GENNAIO 2018  
Savoia Hotel Regency - Via del Pilastro, 2, 40127 Bologna

### Validazione del “DASH score” per il rischio di recidiva di TEV

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## Background

- In patients with unprovoked VTE, the recurrence risk is  $\approx$  10% one year after suspension of anticoagulation <sup>1</sup>
- Prediction model should preferably be based on easily measured parameters, e.g. age, weight, performance status
- Prediction  $\neq$  Causation

1. Nichele et al. *Semin Thromb Hemost*, 2017.

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Model	Men continue HERDOO2	Vienna Prediction Model	DASH Score
Sex	X	X	X
D-Dimer	X	X	X
Age	X	-	X
Site of index VTE	-	X	-
BMI	X	-	-
PTS signs	X	-	-
Hormone therapy	-	-	X

Modified after Kyrle, Haemostaseologie 2013, and Ensor, BMJ 2016

## Prediction models-quality issues

Model	Men continue HERDOO2	Vienna Prediction Model	DASH Score
Selection procedure?	Yes	Yes	Yes
Adjustment for optimism in selection procedure?	No	Yes	Yes
Events per predictor > 10?	No	Yes	Yes
Appropriate type of model?	No	Yes	Yes
Modelled cont. predictors as linear/non-linear?	No	Yes	No
Multiple imputation to handle missing data?	No	No	No
Internal validation?	No	Yes	Yes
External validation?	Yes	Yes	No
Adjustment for optimism in internal validation?	Yes	Yes	Yes
Reported discrimination?	No	Yes	Yes
Reported calibration?	No	Yes	Yes
Final predictor weightings related to regression coefficients?	Yes	Yes	Yes
Risk of bias	High	Moderate	Moderate

## Background (II)

- In the DASH model, the following variables are considered

Variable	Initials	Score
Abnormal D-Dimer in a qualitative test or $\geq 500$ ng/ml in a quantitative test, 3–5 weeks after stopping VKA therapy	D	+2
Age < 50 years	A	+1
Male gender	S	+1
Estroprogestin use at the time of the index event	H	-2

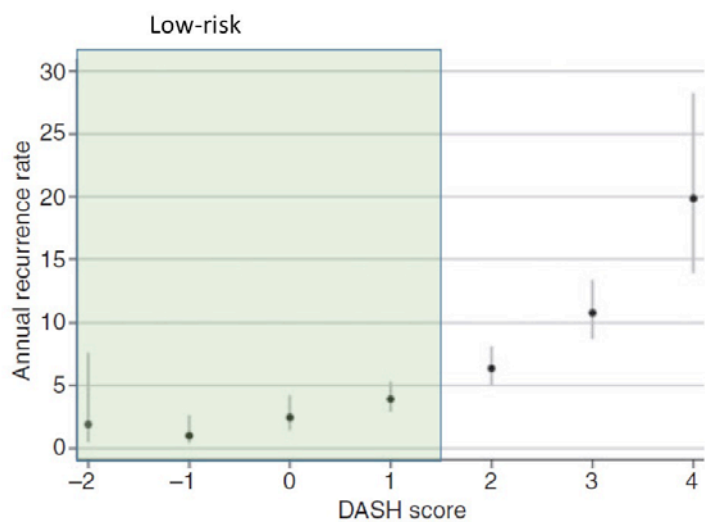
*Tosetto et al. J Thromb Haemost, 2012.*

## Aim of the study

- Validate in an external cohort of patients
  - the calibration of the model (i.e., the accuracy of prediction)
  - its discriminating power (i.e., the number of correctly classified patients)
- As a secondary aim, verify the accuracy of predictions in special patient subgroups
  - Patients with a predicted annual VTE recurrence risk is below 5% <sup>1</sup>
  - Elderly patients <sup>2</sup>

*1. Kearon et al. J Thromb Haemost, 2010.  
2. Tritschler et al. Blood, 2015.*

# Predicted recurrence rates by DASH



*Tosetto et al. J Thromb Haemost, 2012.*

## Study design

- Multicenter, retrospective cohort study
- Time to event analysis
- A number size >600 patients was targeted based on expected recurrence rate and the number of predictors (n=4)

## Eligibility criteria

- VTE which occurred in the absence of an antecedent major clinical VTE risk factor comprising surgery, trauma, active cancer, immobility, or pregnancy and the puerperium
- Index VTE event occurred AFTER January 01, 2007
- Only first events of either proximal vein deep vein thrombosis (DVT) or pulmonary embolism (PE)
- Treatment with VKA or DOAC for at least >3 months
- D-dimer measured after 20-40 days from anticoagulant (VKA or DOAC) treatment suspension
- Having at least three months of complete follow-up after treatment suspension

## Exclusion criteria

- Patients with known antiphospholipid antibodies or antithrombin deficiency
- Patients who were considered by the treating physician as unsuitable for safe interruption of anticoagulant treatment

## Comparison of the learning and validation cohorts

	Learning dataset N=1818	Validation dataset N=827	P overall
Sex:			0.845
Female	48.6%	48.1%	
Male	51.4%	51.9%	
Age	59.0 (17.0)	55.3 (17.5)	<0.001
BMI	28.1 (6.32)	26.3 (5.00)	<0.001
OC use:			0.010
No	65.2%	57.4%	
Yes	34.8%	42.6%	
D-dimer:			<0.001
NEG	54.6%	77.0%	
POS	45.4%	23.0%	
DASH score:			<0.001
Low risk ( $\leq 1$ )	39.9%	65.3%	
High risk ( $>1$ )	60.1%	34.7%	

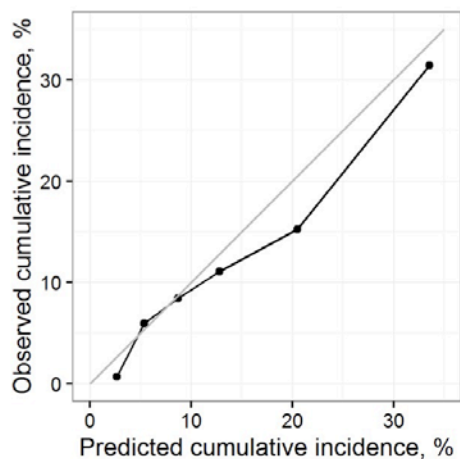
## Predicted rates in Validation vs. Learning cohorts

DASH score	Annualized rate (95% CI)		Cumulative recurrence at 2 years (95% CI)	
	Validation observed	Learning predicted <sup>1</sup>	Validation observed	Learning predicted <sup>1</sup>
$\leq 1$	0.5 (0.4 - 0.6)	1.2 (1.1 - 1.3)	0.7 (0.1 - 2.0)	2.6 (0.3 - 4.9)
0	3.9 (3.6 - 4.2)	2.4 (1.4 - 4.2)	5.9 (0.3 - 11.3)	5.4 (3.1 - 9.3)
1	5.3 (5.1 - 5.4)	3.9 (2.9 - 5.3)	8.4 (4.7 - 12.0)	8.7 (6.3 - 12.0)
2	6.7 (6.5 - 7.0)	6.4 (5.0 - 8.1)	11.1 (5.9 - 16.0)	12.8 (9.9 - 16.4)
3	6.8 (6.5 - 7.2)	10.8 (8.7 - 13.4)	15.2 (6.9 - 22.8)	20.5 (16.4 - 25.5)
4	12.1 (10.9 - 13.3)	19.9 (13.9 - 28.2)	31.4 (10.1 - 55.5)	33.6 (23.3 - 46.8)

Patients having a DASH score  $\leq 1$  had an annualized recurrence rate of 3.5% (95% CI 2.5-4.7), with a cumulative risk of recurrence at one year of 3.6% (95% CI 1.9-5.0).

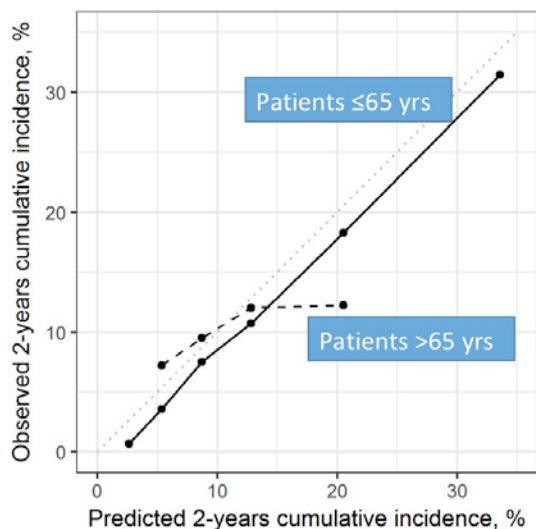
1. Tosetto et al. J Thromb Haemost, 2012.

# Predicted vs. observed recurrence



- The slope of the calibration plot at 2-years was 0.71 (95% CI 0.49-1.45)
- c-statistics overall: 0.65

# Predicted vs. observed recurrence by age



c-statistics

≤65 yrs	>65 yrs
0.72	0.54

# Conclusions

- The DASH model appears to be a reproducible tool to estimate recurrence risk
- Patients having a DASH score  $\leq 1$  had a cumulative risk of recurrence at one year of 3.6% (95% CI 1.9-5.0)
- As expected, calibration plots and c-stat was slightly worse in our validation cohort (over-optimism of prediction models)
- Need for improved models, especially in patients  $>65$  yrs

# The TRIP Investigators

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Characteristics	No VTE Recurrence (n=727)	VTE Recurrence (n=100)
Age (years)	54.7 (17.8)	59.8 (15.2)
Sex		
Females (%)	358 (49.2)	37 (37.0)
Males (%)	369 (50.8)	63 (63.0)
Hormone therapy at the time of index VTE		
No (%)	482 (66.3)	91 (91)
Yes (%)	245 (33.7)	9 (9)
Body-mass index (kg/m <sup>2</sup> )	26.3 (5.15)	26.5 (4.10)
Days from suspension of anticoagulant therapy	34.0 (9.89)	33.7 (9.04)
Duration of anticoagulant treatment (months)	14.0 (11.7)	12.8 (11.9)
Oral anticoagulant drug		
Dabigatran	2 (0.3)	0 (0)
Rivaroxaban	28 (3.9)	5 (5.0)
Warfarin	684 (95.3)	93 (93.0)
Acenocoumarol	12 (1.6)	2 (2.0)
Previous cancer	19 (2.6)	2 (2.0)
Mild thrombophilia	90 (12.5)	22 (22.0)
Severe thrombophilia	12 (1.6)	2 (2.0)