Evaluation of Venous Thromboembolism Recurrence Scores in an Unprovoked Pulmonary Embolism Population: a post-hoc analysis of the PADIS-PE trial

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Full Title:

Evaluation of Venous Thromboembolism Recurrence Scores in an Unprovoked Pulmonary Embolism Population: a post-hoc analysis of the PADIS-PE trial.

Short Title:

Predictors of recurrence after pulmonary embolism

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Take home message

After unprovoked pulmonary embolism, venous thromboembolism recurrence prediction models have a moderate ability to predict the risk of recurrence; residual pulmonary vascular obstruction has the potential to improve accuracy of clinical venous thromboembolism recurrence prediction models.

Abstract (200 words)

Introduction: We aimed to validate the HERDOO2, DASH and Updated Vienna recurrent venous thromboembolism prediction models in a population composed entirely of first unprovoked pulmonary embolism and analyzed the impact of the addition of pulmonary vascular obstruction index (PVOI) on score accuracy.

Methods: Analyses were based on the double-blind randomized "PADIS-PE" trial including 371 unprovoked pulmonary embolism patients initially treated during 6 months, successively randomized to receive an additional 18-months of warfarin or placebo, and subsequently followed-up for two years.

Results: The HERDOO2, DASH and Updated Vienna scores displayed c-statistics of 0.61 (95%CI 0.54-0.68), 0.60 (95%CI 0.53-0.66) and 0.58 (95%CI 0.51-0.66) respectively. Only the HERDOO2 score identified low recurrence risk patients (<3%/year) after stopping anticoagulation. When added to either of the prediction models, PVOI measured at pulmonary embolism diagnosis and/or after 6 months of anticoagulation improved scores' c-statistics between +0.06 and +0.11 points and consistently led to identifying at least 50% of patients who experienced recurrence but in whom the scores would have indicated against extended anticoagulation.

Conclusions: In patients with a first unprovoked pulmonary embolism, the HERDOO2 score is able to identify patients with a low recurrence risk after treatment discontinuation. Addition of PVOI improves accuracy of all scores.

Clinical Trials Registration: URL: http://www.controlled-trials.com. Unique identifier: NCT00740883.

Keywords (4)

Unprovoked pulmonary embolism, recurrent venous thromboembolism, risk factors, randomized trial

Clinical significance

Patients with a first episode of unprovoked pulmonary embolism have a high risk of recurrence. If indefinite anticoagulation is recommended, however, identifying sub-groups of patients where anticoagulation should not be extended remains a major issue.

After unprovoked pulmonary embolism, previously published predictive recurrence scores have a moderate ability to predict the risk of recurrence in this specific population.

Conversely, residual pulmonary vascular obstruction has the potential to implement clinical predictive recurrence scores.

Introduction

Venous thromboembolism includes deep vein thrombosis and pulmonary embolism. Patients with a first episode of unprovoked venous thromboembolism remain at a life-long high risk of recurrence which is reduced with extended and maintained treatment.[1-11] Nonetheless, prolonging anticoagulation indefinitely exposes around two thirds of patients, who will not experience recurrence after stopping treatment, to an unjustified risk of potentially fatal hemorrhage.[12-15]

Therefore, several scores have been derived to identify first-time unprovoked venous thromboembolism patients at low risk of recurrence in whom anticoagulation can be discontinued after 3 to 6 consecutive months. These include the Men Continue and HERDOO2 (HERDOO2) score, the D-dimer, Age, Sex, Hormonal therapy (DASH) score and the Updated Vienna Prediction Model. However, these three scores were derived in populations including both pulmonary embolism and deep vein thrombosis cases and it remains unknown whether they perform well in populations exclusively including pulmonary embolism patients.[16-18] Indeed,

while pulmonary embolism and deep vein thrombosis patients present similar risks of recurrence, the risk is more often fatal in the former group.[19,20] Therefore, addressing optimal anticoagulation management in this population specifically is crucial.

With respect to this, attention has recently been drawn to the role of residual pulmonary vascular obstruction as a predictor of venous thromboembolism recurrence in pulmonary embolism patients.[21-25] Importantly, the most notable finding of our previous sub-analysis of the "Prolonged Anticoagulation During eighteen months versus placebo after Initial Six-month treatment for a first episode of idiopathic Pulmonary Embolism" (PADIS-PE) randomized trial, was the outstanding ability of the pulmonary vascular obstruction index (PVOI), measured at pulmonary embolism diagnosis and/or after 6 months of uninterrupted anticoagulant therapy, to predict venous thromboembolism recurrence in patients with a first unprovoked pulmonary embolism.[21]

In this analysis we first externally validated the HERDOO2 score, the DASH score and the Updated Vienna Prediction Model on our "PADIS-PE" population to determine their predictive ability in patients with a first unprovoked pulmonary embolism. We subsequently used a hypothesis-driven approach to evaluate the impact of the combination of pulmonary vascular obstruction with risk classification by these scores on the predictive ability of venous thromboembolism recurrence.

Methods

Study Design and Population:

This is a post-hoc analysis of the PADIS-PE study involving all patients included in the original trial. Eligible subjects were over 18 years and had suffered a first episode of proven

symptomatic unprovoked pulmonary embolism treated with vitamin K antagonists for six consecutive months.[8] Unprovoked pulmonary embolism occurred in the absence of any major reversible risk factors within 3 months prior to diagnosis (i.e. surgery with locoregional or general anaesthesia >30 minutes, trauma with or without plaster cast of the lower limbs, and bed-rest >72 hours) and in the absence of active cancer or cancer resolved under 2 years prior to diagnosis.[8] Patients were included and randomized to the warfarin or placebo arm and pursued their assigned treatment for 18 months.[8] All subjects were subsequently followed-up for an additional median 24-month period.[8] Fourteen French hospitals participated between July 13th, 2007 and March 15th, 2012.[8]

Intervention:

All patients included in the PADIS-PE study had received an initial 6 months of uninterrupted anticoagulation with vitamin K antagonist.[8] At inclusion (i.e., after the initial 6 months of anticoagulation) and before randomization, all patients underwent centralized frozen blood samples, leg vein ultrasound, ventilation-perfusion lung scan, and trans-thoracic echocardiography.[8] All V/Q lung scans (at inclusion and at pulmonary embolism diagnosis) and computerized tomography pulmonary angiography (at pulmonary embolism diagnosis) were centrally reinterpreted by 2 independent readers, blinded from study treatment allocation, results of other imaging tests and patient characteristics.[8]

Outcome Measures:

The primary outcome was symptomatic recurrent venous thromboembolism, including objectively confirmed non-fatal symptomatic pulmonary embolism or proximal deep vein

thrombosis or fatal venous thromboembolism during follow-up.[8,21,26,27] All outcomes were adjudicated blindly by an independent central Clinical Events Committee.[8]

Recurrent Venous Thromboembolism Prediction Scores

The HERDOO2 score, the DASH score and the Updated Vienna prediction model were calculated based on available clinical variables (post-thrombotic signs, age and sex) at inclusion. For the HERDOO2 score, D-dimer levels were measured under anticoagulation at inclusion in the placebo group and at 18 months in the warfarin group; for the two other scores, D-dimer concentrations were measured in the absence of anticoagulation (at 1 month in the placebo group and 19 months in the warfarin group). Patients for whom data was not available for risk classification according to one or more of the three scores were excluded from the analysis.

Imaging Parameters:

PVOI at pulmonary embolism diagnosis was measured using ventilation perfusion lung scanning or computerized tomography pulmonary angiography in 108 and 199 patients respectively. PVOI at inclusion was measured using ventilation perfusion lung scanning in all patients.[27] PVOI measured on ventilation perfusion lung scan or through computerized tomography pulmonary angiography was scored according to the validated methods of Meyer *et al.* and Qanadli *et al*. respectively (*see* supplement).[27-29]

Laboratory Assays:

D-dimer levels were measured from frozen plasma samples taken at inclusion and at 1 and 19 months in all patients to obtain values both under and in the absence of anticoagulant

therapy without requiring unblinding. All D-dimer levels were measured using high sensitivity VIDAS D-dimer test (bioMérieux).

Statistical Methods:

The primary outcome of this analysis was measured in all included patients during the follow-up period after stopping anticoagulation.[8]

Sensitivity, specificity, positive and negative predictive values and Harrell's c-statistics with respective 95% confidence intervals (95%CI) were calculated for each score validated on the PADIS-PE population.

In univariable analysis, time-to-event outcome was estimated, for each venous thromboembolism recurrence prediction model presented as a dichotomized variable according to its recurrence risk prediction (low or high), using a Cox proportional hazard regression model with adjustment on study treatment allocation, which provided hazard ratios (HR) and corresponding 95%CI. In multivariable analysis, hypothesis-driven multivariable prediction models included each venous thromboembolism recurrence prediction model (presented as a dichotomized variable), to which, in turn, were added each threshold of pulmonary vascular obstruction defined in our previous sub-analysis (PVOI ≥40% at pulmonary embolism diagnosis, PVOI ≥5% at inclusion, PVOI ≥40% at pulmonary embolism diagnosis and/or PVOI ≥5% at inclusion). Harrell's c-statistics were calculated to assess each model's predictive ability on the PADIS-PE study population.

Cumulative risks of recurrent venous thromboembolism over the entire-study period were calculated for each recurrence risk class (based on scores alone and on the combination of scores

and PVOI) and corresponding annual incidence rates of recurrent venous thromboembolism were estimated during the 24-month follow-up period after anticoagulant discontinuation.

All tests were two-sided and a p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS V9.4 software (SAS Institute, Cary, NC, USA).

Results:

A total of 374 patients were enrolled in the PADIS-PE study, three of whom refused inclusion of their data. Therefore, 371 patients remained in the study; 184 randomized to warfarin and 187 to placebo. At inclusion, the median (interquartile range (IQR)) duration of initial anticoagulation on the entire cohort was 6.3 (6.0-6.7) months. After randomization, the median (IQR) length of follow-up was 23.4 (21.5-23.9) months after anticoagulation discontinuation in the warfarin group and 40.9 (29.3-41.3) months in the placebo group. Data for classification according to the DASH score was available for all patients. Missing D-dimer level data resulted in classification of 361 and 267 according to the HERDOO2 score and Updated Vienna prediction model respectively.

Outcome

Symptomatic recurrent venous thromboembolism occurred in 67 patients during follow-up (20.0%; 6.8 events per 100 person-years) presenting as 53 unprovoked events (68.0%): 48 (71.0%) non-fatal and 4 fatal pulmonary embolisms.

Validation of Scores:

When used in our PADIS-PE cohort, the HERDOO2 score classified 279 (77.3%) patients (of which 98 were women) as high risk and 82 (22.7%, all women) as low risk. During the follow-up period, the cumulative risk of recurrent venous thromboembolism was 23.5% (95%CI, 18.5-29.5; 59 events) in the high-risk group and 10.5% (95%CI, 5.4-20.0; 8 events) in the low-risk group, resulting in a significant difference (Hazard ratio [HR] 2.32 [95%CI, 1.11-4.85) (Table 1). The HERDOO2 score showed high sensitivity (88.4% [95%CI, 80.8-96.0]) and high negative predictive value (90.7% [95%CI, 82.8-98.6]) (Table 2). The Harrell's c-statistic of the score on the study population was 0.61 (95%CI, 0.54-0.68) (Table 2).

The DASH score classified 188 (50.7%) patients as high risk and 183 (49.3%) as low risk. The cumulative risk of recurrent venous thromboembolism during follow-up was 24.9% (95%CI, 18.8-32.6; 42 events) in the high-risk group and 14.9% (95%CI, 10.3-21.4; 25 events) in the low risk group, yielding a significant difference (HR 1.71 [95%CI, 1.04-2.80]) (Table 1). The DASH score demonstrated a low sensitivity value (63.3% [95%CI, 51.6-75.0]) and a high negative predictive value (87.3% [95%CI, 81.7-92.9]) (Table 2). The Harrell's c-statistic of the score was 0.60 (95%CI, 0.53-0.66) (Table 2).

The Updated Vienna Prediction Model classified 138 patients (51.7%) as high risk and 129 (48.3%) as low risk. Throughout the follow-up period, the cumulative risk of recurrent venous thromboembolism was 25.8% (95%CI, 18.7-35.0; 32 events) in the high-risk group and 17.8% (95%CI, 11.9-26.2; 21 events) in the low-risk group, resulting in a statistically non-significant difference (HR 1.51 [95%CI, 0.87-2.36]) (Table 1). The Updated Vienna Prediction Model yielded a low sensitivity (60.0 [95%CI, 46.5-73.5]) and a moderate negative predictive value (74.9% [95%CI, 58.9-90.9]) (Table 2). The Harrell's c-statistic of the score was 0.58 (95%CI, 0.51-0.66) (Table 2).

Hypothesis-Driven Analysis:

When combined to each score in the multivariable models, pulmonary vascular obstruction, defined by each of our thresholds, was independently associated with a statistically significant 2 to 5-fold increased risk of recurrent venous thromboembolism (Table 3). In addition, multivariable models combining each dichotomized score with each of our previously defined pulmonary vascular obstruction thresholds consistently displayed increases in c-statistic values between 0.06 to 0.11 points as compared to those of the scores alone (Table 3).

In patients classified at low recurrence risk by the HERDOO2 score alone, the addition of pulmonary vascular obstruction defined as PVOI ≥5% at inclusion, PVOI ≥40% at pulmonary embolism diagnosis or the combination of both PVOI ≥5% at inclusion or PVOI ≥40% at pulmonary embolism diagnosis in our multivariable model, correctly identified respectively 71.4% (5/7), 71.4% (5/7) and 100% (7/7) patients per year at high risk of recurrence in whom the score alone would have given an indication against prolonged anticoagulation (Figure 1, supplementary Table 5).

In patients classified at low risk of recurrence according to the DASH score alone, the addition of the pulmonary vascular obstruction thresholds defined above, to our multivariable model, correctly identified respectively 62.5% (15/24), 62.5% (15/24) and 85.5% (21/24) patients per year at high risk of recurrence for whom use of the score on its own would have provided indication against extended anticoagulation (Figure 1, supplementary Table 5).

In patients classified at low recurrence risk by the Updated Vienna Prediction Model alone, the presence of pulmonary vascular obstruction, defined according to the previously stated thresholds, in our multivariable model, correctly identified respectively 52.4% (11/21), 63.2%

(12/19) and 84.2% (16/19) of patients per year at high risk of recurrence in whom the score would have advised against prolonging anticoagulant therapy (Figure 1, supplementary Table 5).

Discussion

In this post-hoc analysis of the multicentre randomized, double-blind PADIS-PE study, we found that, amongst the currently externally validated venous thromboembolism recurrence prediction models including the HERDOO2, the DASH and the Updated Vienna scores, the HERDOO2 score was the most accurate when used in patients with a first unprovoked symptomatic pulmonary embolism and was unique in its ability to identify patients with a recurrence risk below 3% per year after anticoagulant discontinuation in this population.

We also demonstrated that the combination, in a multivariable model, of PVOI measured at pulmonary embolism diagnosis and/or after 6 months of uninterrupted anticoagulant treatment, with each recurrence score presented as a dichotomized variable according to risk prediction, led to consistently increased c-statistics as compared to the scores alone (Table 3). Importantly, in our multivariable models, pulmonary vascular obstruction showed a stronger association to recurrence risk than any of the currently available prediction scores. Furthermore, the addition of pulmonary vascular obstruction to recurrence score risk classification in the multivariable model identified at least 50% of patients who experienced recurrence but would not have received extended anticoagulation based on the scores alone (Figure 1). This latter finding suggests that, PVOI as defined by the thresholds used in our analysis, may enhance the ability of current scores to discriminate between low and high recurrence risk pulmonary embolism patients.

The three presently discussed prediction models, were derived using data of both pulmonary embolism and deep vein thrombosis patients. Therefore, certain predictors such as

first presentation of venous thromboembolism in the Updated Vienna Prediction Model or post-thrombotic syndrome in the HERDOO2 score may be of lesser value in populations of symptomatic pulmonary embolism patients only.[16-18]

To this effect and in accordance with the results of our previous sub-analysis, our findings highlight the role of both initial and residual pulmonary vascular obstruction as strong and independent predictors of venous thromboembolism recurrence in patients with a first unprovoked pulmonary embolism.[21] Consistent with our results, Meneveau et al. found that pulmonary vascular obstruction ≥35% measured during hospitalization for an acute episode of pulmonary embolism was a strong predictor of death and recurrent venous thromboembolism at 6 months of discharge.[30] Pesavento et al. demonstrated a significant association between degree of PVOI measured at six months of the index pulmonary embolism event and venous thromboembolism recurrence risk. Wan et al. observed similar results between 5 and 7 months following a first unprovoked pulmonary embolism.[23,31] Planquette et al. likewise found PVOI >10% measured at the end of the anticoagulant treatment period to be an independent predictor of venous thromboembolism recurrence following a first episode of pulmonary embolism.[22] Importantly, our results are concordant with the recent findings of Becattini et al. whose meta-analysis highlights residual pulmonary vascular obstruction as a predictor of recurrent VTE when assessed by perfusion lung scanning, in agreement with our methods.[25] However, despite the extensive work on the topic, this is, to our knowledge the first analysis to examine the effects of adding pulmonary vascular obstruction to validated venous thromboembolism recurrence scores using a hypothesis-driven approach.

Our results may have important clinical implications. While we acknowledge that ventilation perfusion lung scan is costly, entails additional radiation exposure and is not currently

available in all hospital facilities, our study nonetheless provides additional evidence that residual pulmonary vascular obstruction is an important predictor of recurrent venous thromboembolism and that its impact is complementary to that of validated recurrence prediction models, warranting further cost-benefit analysis of this imaging modality. However, we also confirmed that initial pulmonary vascular obstruction, measured at pulmonary embolism diagnosis using computerized tomography pulmonary angiography or ventilation perfusion lung scan, is similarly an independent predictor of recurrence, also complementary to validated predictive models. Conveniently, this early imaging information is available in all patients with pulmonary embolism diagnosed through thoracic imaging. Nevertheless, whether computerized tomography pulmonary angiography or ventilation perfusion lung scan should be systematically performed when acute symptomatic pulmonary embolism is diagnosed based on clinical suspicion and non-compression ultrasound of a proximal vein remains uncertain. Lastly, whether our results would be similar using other recently derived but not yet prospectively validated scores such as the Leiden Thrombosis Recurrence Risk Prediction model, requires investigation.[32]

Our study has several limitations. First, the small sample size and the post-hoc nature of our analysis decrease the power of our results. Second, given the study design of the PADIS-PE randomized trial comparing two durations of anticoagulation, we cannot exclude potential treatment effect on the outcomes. However, systematic adjustment on study treatment allocation has been performed and sensitivity analysis on the placebo group showed similar results (supplementary Table 6). Lastly, our patients were all treated using vitamin K antagonist and we cannot guarantee similar results with direct oral anticoagulant therapy.

Strengths of this analysis rest in the pre-defined and carefully characterized population randomized according to a double-blind design, blind review and validation of all outcomes by independent centralized adjudication committees, central assessment of PVOI by independent physicians blinded from study treatment allocation, results of other imaging tests and patient characteristics as well as the exhaustive collection of PVOI at inclusion. We nonetheless maintain that our results are not intended to contradict any of the current prediction models but rather aim to complement these scores for use in a specific high-risk venous thromboembolism population.

Conclusion:

In patients with a first unprovoked pulmonary embolism, the HERDOO2 score is able to identify patients at a risk of recurrence below 3% per year after anticoagulation discontinuation. When added to any of the HERDOO2, DASH or Updated Vienna prediction models, pulmonary vascular obstruction, measured at pulmonary embolism diagnosis and/or after 6 months of uninterrupted anticoagulation demonstrates a strong and independent association to venous thromboembolism recurrence and increases the ability of the three prediction models to correctly identify patients who are potential candidates for prolonged anticoagulation.

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Figure 1. Incidence of Venous Thromboembolism Recurrence according to Classification of the HERDOO2 (Figure 1A), DASH (Figure 1B) and Updated Vienna (Figure 1C) Prediction Models with the Addition of Pulmonary Vascular Obstruction

Figure 1A. 24-month Annual Incidence of Venous Thromboembolism Recurrence according to Classification of the HERDOO2 Score and Pulmonary Vascular Obstruction Thresholds

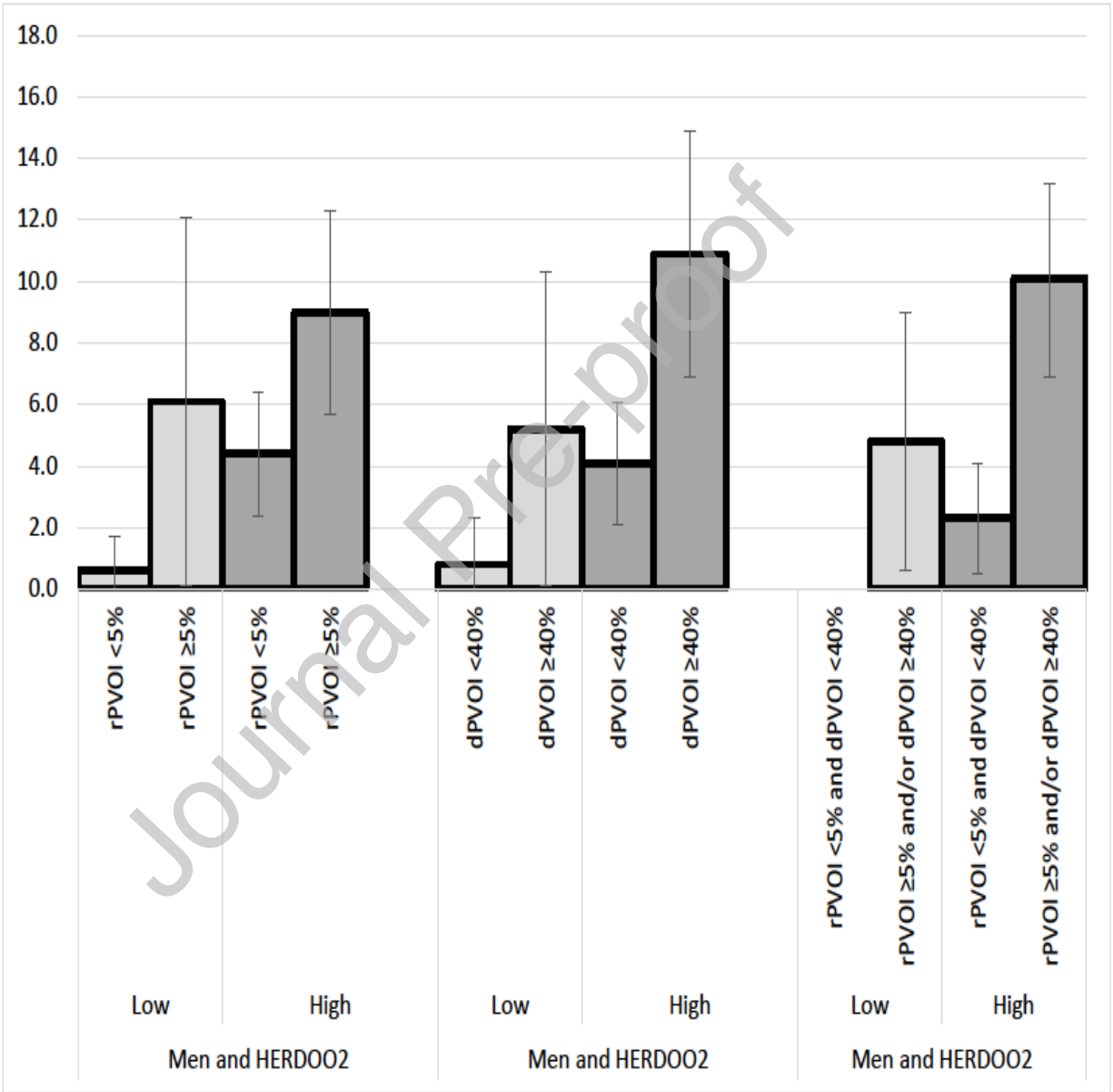

Figure 1B. 24-Month Annual Incidence of Venous Thromboembolism Recurrence according to Classification of the DASH score and Pulmonary Vascular Obstruction Thresholds

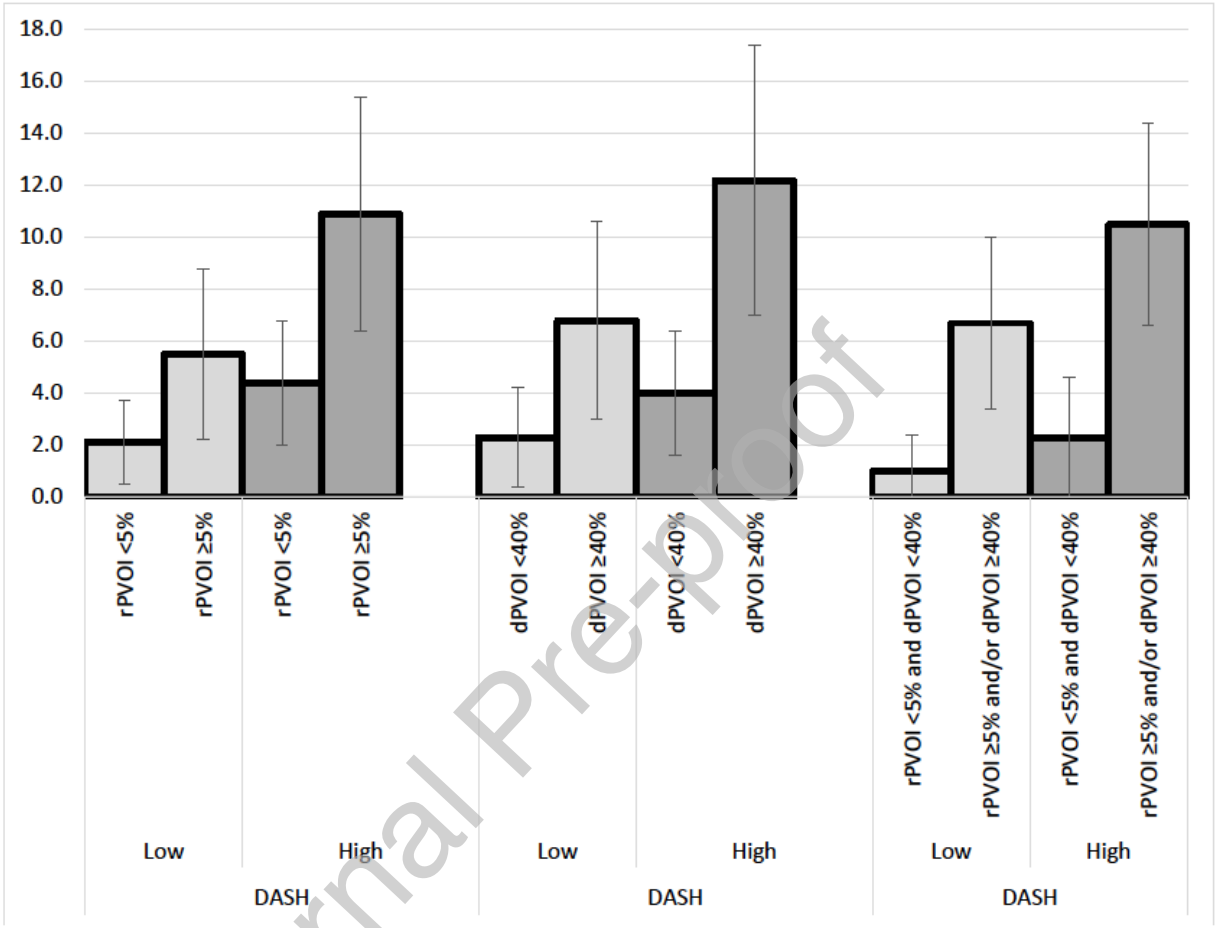

Figure 1C. 24-Month Annual Incidence of Venous Thromboembolism Recurrence according to Classification of the Updated Vienna Prediction Model and Pulmonary Vascular Obstruction Thresholds

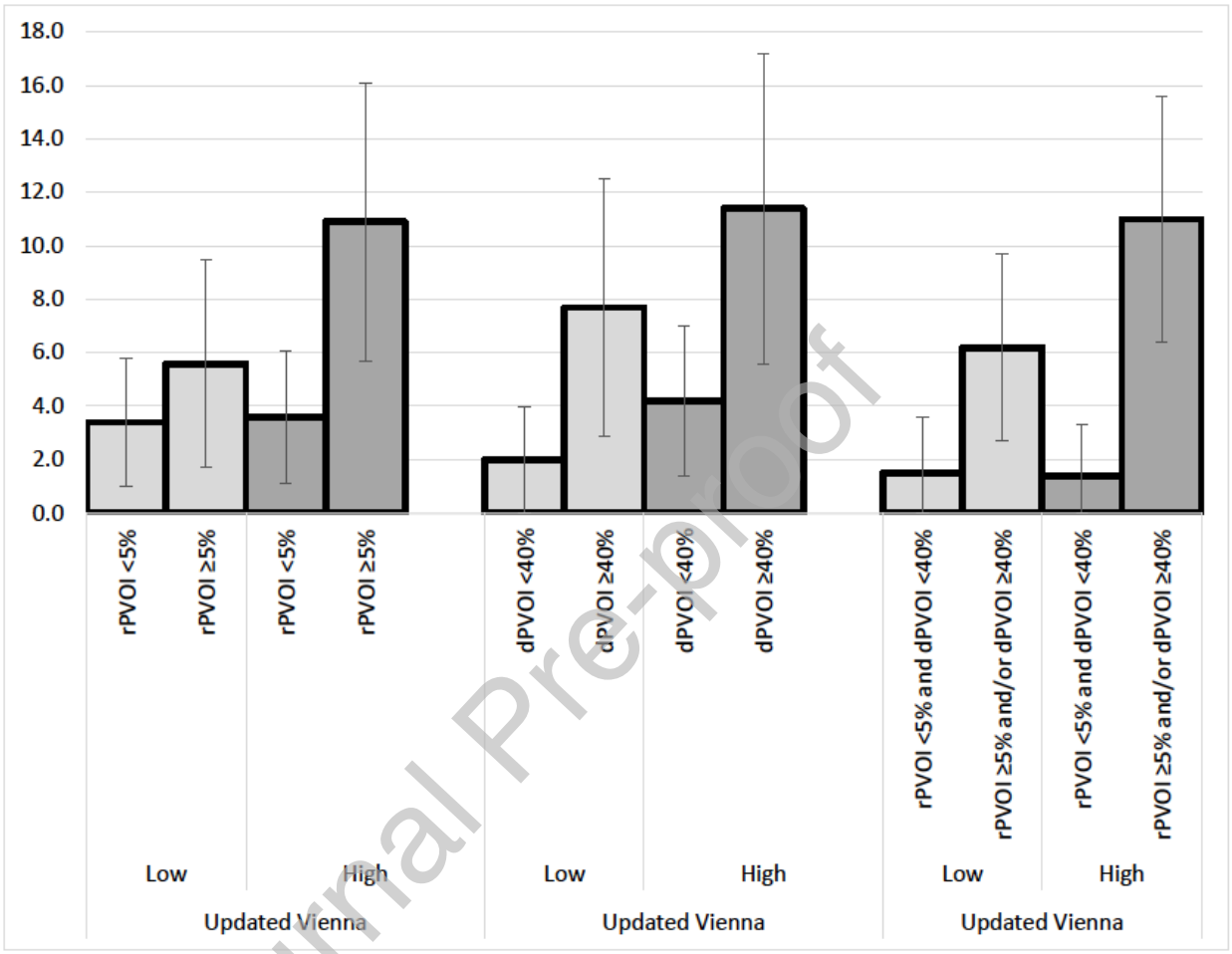

Table 1. Hazard Ratios of the Scores on the PADIS-PE Cohort

	Recurrent VTE*	No Recurrent VTE*	Hazard Ratio (95% CI) †	p-value	24-Month Annual Incidence after stopping anticoagulation %person-year, (95% CI)*
HERDOO2 Score					
Patients at high risk (%)	**59 (88.1)**	**184 (77.6)**	**2.32 (1.11-4.85)**	**0.026**	**6.24 (4.50-7.98)**
Patients at low risk (%)	**8 (11.9)**	**53 (22.4)**	**1.00**		**2.37 (0.47-4.27)**
DASH Score					
Patients at high risk (%)	**42 (62.7)**	**118 (48.0)**	**1.71 (1.04-2.80)**	**0.035**	**6.89 (4.64-9.14)**
Patients at low risk (%)	**25 (37.3)**	**128 (52.0)**	**1.00**		**3.47 (1.90-5.04)**
Updated Vienna Prediction Model					
Patients at high risk (%)	**32 (60.4)**	**89 (49.4)**	**1.51 (0.87-2.63)**	**0.14**	**6.76 (4.15-9.37)**
Patients at low risk (%)	**21 (39.6)**	**91 (50.6)**	**1.00**		**4.08 (2.08-6.08)**

VTE, venous thromboembolism; CI, confidence interval.
*Crude proportion of events during the entire study period after randomization in patients who attended the 42-month follow-up visit (see reference 8)
†Time-to-event outcome was estimated (based on event occurring during the entire study period after randomization), for each predefined variable, using a Cox proportional hazard regression model with adjustment on study treatment allocation, which provided hazard ratios (HR) and corresponding 95% confidence intervals.
**For the patients in the placebo group, all events occurring during the 24 months following randomization (i.e.; the initial 18-month study period plus 6-month follow-up period after discontinuation of the study drug) were considered. For the patients randomised to active treatment, only the events that occurred during 24 months after study treatment discontinuation were included.

Table 2. Accuracy of Current Recurrence Prediction Scores on the PADIS-PE Study Population

	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Harrell's c-Statistic (95% CI)
HERDOO2 Score	88.4 (80.8-96.0)	29.2 (11.0-47.4)	24.4 (17.2-31.5)	90.7 (82.8-98.6)	0.61 (0.54-0.68)
DASH Score	63.3 (51.6-75.0)	63.0 (44.7-81.2)	29.9 (17.4-42.3)	87.3 (81.7-92.9)	0.60 (0.53-0.66)
Updated Vienna Prediction Model	60.0 (46.5-73.5)	33.3 (9.4-57.2)	20.1 (11.6-28.5)	74.9 (58.9-90.9)	0.58 (0.51-0.66)

CI, confidence interval.

Table 3. Hypothesis-Driven Multivariable Models Including Current Recurrence Prediction Scores and Pulmonary Vascular Obstruction Thresholds

	Hazard Ratio (95% CI)	P-value	Harrell's c-Statistic (95% CI)
Models Including the HERDOO2 Score and Pulmonary Vascular Obstruction Thresholds			
Model 1			
Patients Classified "at risk" according to the HERDOO2 score	2.29 (1.04-5.05)	0.038	**0.67 (0.60-0.75)**
PVOI ≥5% at inclusion	2.45 (1.47-4.08)	0.0006	
Model 2			
Patients Classified "at risk" according to the HERDOO2 score	2.43 (1.11-5.34)	0.027	**0.68 (0.60-0.75)**
PVOI ≥40% at diagnosis	2.86 (1.69-4.84)	<0.0001	
Model 3			
Patients Classified "at risk" according to the HERDOO2 score	2.32 (1.05-5.10)	0.036	**0.71 (0.64-0.78)**
PVOI ≥40% at diagnosis and/or PVOI ≥5% at inclusion	4.80 (2.28-10.1)	<0.0001	
Models Including the DASH Score and Pulmonary Vascular Obstruction Thresholds			
Model 1			
Patients Classified "at risk" according to the DASH score	1.66 (1.00-2.75)	0.050	**0.67 (0.60-0.74)**
PVOI ≥5% at diagnosis	2.56 (1.54-4.25)	0.0003	
Model 2			
Patients Classified "at risk" according to the DASH score	1.51 (0.91-2.52)	0.112	**0.66 (0.59-0.73)**
PVOI ≥40% at diagnosis	2.92 (1.73-4.95)	<0.0001	
Model 3			
Patients Classified "at risk" according to the DASH score	1.40 (0.84-2.34)	0.195	**0.69 (0.62-0.77)**
PVOI ≥40% at diagnosis and/or PVOI ≥5% at inclusion	4.80 (2.28-10.1)	<0.0001	
Models Including the Updated Vienna Prediction Model and Pulmonary Vascular Obstruction Thresholds			
Model 1			
Patients Classified "at risk" according to the Updated Vienna Model	1.33 (0.76-2.33)	0.323	**0.65 (0.57-0.73)**
PVOI ≥5% at inclusion	2.33 (1.33-4.11)	0.003	
Model 2			
Patients Classified "at risk" according to the Updated Vienna Model	1.50 (0.84-2.67)	0.170	**0.66 (0.58-0.74)**
PVOI ≥40% at diagnosis	2.88 (1.60-5.18)	0.0004	
Model 3			
Patients Classified "at risk" according to the Updated Vienna Model	1.47 (0.82-2.62)	0.191	**0.69 (0.61-0.78)**
PVOI ≥40% at diagnosis and/or PVOI ≥5% at inclusion	5.02 (2.13-11.8)	0.0002	

CI, confidence interval; PVOI, pulmonary vascular obstruction index