Evaluation of the PADIS score stratifying risk for venous thromboembolism recurrence after a first unprovoked pulmonary embolism: results from the REVERSE study

Received: 25 June 2021
Accepted: 1 Nov 2021

To the Editor:

Current guidelines suggest that most patients presenting with a first episode of an unprovoked venous thromboembolism (VTE) event be considered for indefinite anticoagulation, as long as their bleeding risk remains acceptably low [1, 2]. However, this exposes a considerable number of patients to long term anticoagulation as 70% of patients with a first unprovoked VTE will have no recurrence [3]. In 2010, a guidance from the International Society on Thrombosis and Haemostasis (ISTH) suggested that a 1-year cumulative rate of recurrent VTE after stopping anticoagulation of less than 5%, with a 95% confidence interval (CI) upper limit lower than 8%, is low enough to consider that long-term anticoagulant therapy would not be beneficial [4]. As such, efforts are ongoing to identify risk factors and scoring tools to help discriminate between subsets of patients whose risk/benefit ratio most- or least-strongly favours continued therapy.

In a planned sub-study of the PADIS-PE trial [3], Tromeur *et al.* [5] derived a prediction score aiming at stratifying VTE recurrence risk after a first unprovoked pulmonary embolism (PE). PADIS-PE score consisted of summing-up age category (50–65 years +2; age >65 years +3), presence of pulmonary vascular obstruction index (PVOI) ⩾5% (+2), and presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies +2) measured after 6 months of anticoagulation to classify patients into low- (score of 0), intermediate- (score 2–3), and high-risk (score ⩾4) groups with corresponding recurrence rates of 1.29, 5.32, and 12.86 per 100 person-years, respectively. Patients from the low-risk category may benefit from cessation of anticoagulation; however, to date, this scoring system has never been assessed in an independent cohort.

Herein, we applied this score to patients from the REVERSE study presenting with a first unprovoked PE and report outcomes.

The REVERSE cohort was a cohort of 646 patients with a first major unprovoked VTE event who had received 5–7 months of oral anticoagulation and were followed up for up to 8 years thereafter. Cases of suspected symptomatic VTE recurrence were investigated with reference to baseline imaging and then independently and blindly adjudicated. Full study details have been previously published [6].

We applied the PADIS-PE score to the subset of patients from the REVERSE cohort who were included for a first unprovoked PE. Patients were stratified into low-, intermediate- and high-risk groups according to the derived formula as previously outlined. The primary end-point of this study was recurrence of symptomatic VTE up to 2 years after stopping anticoagulation in the different pre-defined risk categories. The 1-year recurrence rate of VTE was estimated using the Kaplan–Meier method.

Of the 646 patients from the REVERSE study, 307 cases of unprovoked PE (194 isolated PE and 113 PE with deep vein thrombosis) were initially reviewed, and 229 patients had sufficient data available to allow for the application of the derived score (68 PVOI assessments and 14 antiphospholipid antibodies testing were missing). Patients mean±SD age was 50.0±17.2 years, 133 (58.1%) were female, and the mean±SD BMI was 28.5±6.7 kg·m^{-2}. The total observation time was 311.5 patient-years.

Shareable abstract (@ERSpublications)
This study does not support that the PADIS-PE score can safely identify patients who could stop anticoagulation after a first unprovoked PE https://bit.ly/3GOzeEl

Cite this article as: Caiano L, Sharkey R, Rodger MA, *et al*. Evaluation of the PADIS score stratifying risk for venous thromboembolism recurrence after a first unprovoked pulmonary embolism: results from the REVERSE study. *Eur Respir J* 2022; 59: 2101801 [DOI: 10.1183/13993003.01801-2021].

TABLE 1 Rate of recurrent venous thromboembolism by PADIS score risk category

Risk category	Patients	Observation time (patient-years)	1-year cumulative recurrence rate of VTE (%)	Incidence of recurrent VTE over total follow-up (per 100 person-years)
Low	80 (34.9%)	116.25	4.0 (−0.3–8.3)	5.2 (2.4–10.8)
Intermediate	85 (37.1%)	116.8	5.9 (0.8–11.0)	4.3 (1.8–9.6)
High	64 (27.9%)	78.4	9.4 (2.3–16.5)	14.0 (8.0–23.4)

Recurrence rates and incidence values are presented with 95% confidence intervals. VTE: venous thromboembolism.

When applying the score to our sample, 80 patients (34.9%) were classified in the low-, 85 (37.1%) in the intermediate-, and 64 (27.9%) in the high-risk category (table 1). The corresponding observation times were 116.25, 116.8, and 78.4 patient-years respectively.

1 year after stopping anticoagulation, 16 symptomatic VTE recurrences had been observed (1-year cumulative risk 7.3%, 95% CI 3.8–10.8). The breakdown in the low-, intermediate- and high-risk categories was 3, 5 and 8 events, respectively, corresponding to a 1-year cumulative risk of recurrent VTE of 4.0% (95% CI −0.3–8.3%), 5.9% (95% CI 0.8–11.0%), and 9.4% (95% CI 2.3–16.5%) (table 1).

Over the total observation time, 22 symptomatic recurrent VTE events were observed and the VTE recurrence rate was 7.1 (95% CI 4.7–10.5) per 100 person-years. The number of recurrences in the low-, intermediate- and high-risk category were 6, 5 and 11 respectively and the VTE recurrence rates were 5.2 (95% CI 2.4–10.8), 4.3 (95% CI 1.8–9.6) and 14.0 (95% CI 8.0–23.4) per 100 person-years (table 1).

Our results must be considered with caution. Firstly, because the ISTH criteria for defining an acceptable recurrence risk to stop anticoagulation were set considering an expected 2.74% annual rate of major bleeding on warfarin [7, 8]. Given significantly lower rates of major bleeding on direct oral anticoagulants, withholding anticoagulation in patients with a recurrence risk up to 5% 1 year after treatment ends is probably not acceptable anymore. Our group previously proposed a more conservative approach with a 1-year recurrence rate threshold set at 3% that appears more reasonable now [9].

Secondly, rates of recurrent VTE in patients classified in the low-risk group were higher than expected from the derivation study (5.2 *versus* 1.29 per 100 patient-years respectively). As a consequence, it raised the recurrence rate of the low-risk group to the same level as the intermediate-risk group (5.2 and 4.3 per 100 patient-years, respectively). Of important note, the proportion of patients classified in the low-risk group in this study was higher than in the derivation cohort (35% *versus* 20%). Patients from REVERSE were younger than those from PADIS-PE (50 *versus* 58 years) and thus were more likely to be classified at low-risk. Differences in anticardiolipin antibodies assays and cut-offs for positivity between both studies can also reasonably explain misclassification of patients. Lastly, although the kappa coefficient for interobserver agreement of PVOI assessment was 0.71 in this cohort, meaning substantial reproducibility, we cannot exclude false-negative interpretation [10].

This study has several limitations. Similar to PADIS-PE, anti-β2-glycoprotein-I antibodies were not measured. This could underestimate factors associated with the risk of recurrence and impact on the predictive accuracy of selected variables. Some patients enrolled in REVERSE did not have a baseline VQ scan and could not be evaluated for this analysis. However, bias is unlikely as it is not expected that not having this imaging test would influence the risk for VTE recurrence. Finally, this study lacks power to allow for definitive conclusions. Larger sample size defined *a priori* could help narrow the 95% confidence intervals and confirm patients classified in the low-risk group have a 1-year risk for recurrent VTE of less than 3%.

In conclusion, this study does not support that the PADIS-PE score can safely identify patients who could stop anticoagulation after a first unprovoked PE. Further adequately powered studies are needed to validate this score.

Lucia Caiano[1,2], Rhys Sharkey[1,3], Marc A. Rodger[4], Michael J. Kovacs[5], Grégoire Le Gal[1] and Aurélien Delluc[1]

[1]Dept of Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ottawa, ON, Canada. [2]Dept of Medicine and Surgery, University of Insubria, Varese, Italy. [3]Dept of Medicine, St. Boniface Hospital, Winnipeg, MB, Canada. [4]Dept of Medicine, Faculty of Medicine, McGill University, Montréal, QC, Canada. [5]Division of Hematology, Dept of Medicine, University of Western Ontario, London, ON, Canada.

Corresponding author: Aurélien Delluc (adelluc@toh.ca)

Acknowledgements: The REVERSE investigators: P.S. Wells and T. Ramsay, Ottawa, ON, Canada; S.R. Kahn, I. Chagnon and S. Solymoss, Montreal, QC, Canada; D.A. Anderson, Halifax, NS, Canada; M. Crowther, Hamilton, ON, Canada; R. White, Sacramento, CA, USA.

Author contributions: L. Caiano, R. Sharkey, G. Le Gal and A. Delluc performed the research, analysed data, performed data analysis and wrote the manuscript; M.J. Kovacs and M.A. Rodger performed the research, interpreted the data, and provided critical review of the manuscript.

Conflict of interest: None declared.

Support statement: This study was funded by the Canadian Institutes of Health Research (grant number MOP 64319) and BioMérieux (through an unrestricted research grant). M.A. Rodger is the McGill University Harry Webster Thorp Professor of Medicine. A. Delluc is the recipient of a University of Ottawa Dept of Medicine Research Salary Award. G. Le Gal is supported by an Early Researcher Award from the Province of Ontario, a Mid-Career Investigator Award from the Heart and Stroke Foundation of Ontario, and a Research Chair on the Diagnosis of Venous Thromboembolism, Department of Medicine, University of Ottawa. All of the authors are members of the CanVECTOR network supported by Canadian Institutes of Health Research (grant number CDT-142654). Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Kearon C, Akl EA, Ornelas J, *et al.* Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; 149: 315–352.
2 Konstantinides SV, Meyer G, Becattini C, *et al.* 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020; 41:543–603.
3 Couturaud F, Sanchez O, Pernod G, *et al.* Six months *vs* extended oral anticoagulation after a first episode of pulmonary embolism: the PADIS-PE randomized clinical trial. *JAMA* 2015; 314: 31–40.
4 Kearon C, Iorio A, Palareti G. Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting. *J Thromb Haemost* 2010; 8: 2313–2315.
5 Tromeur C, Sanchez O, Presles E, *et al.* Risk factors for recurrent venous thromboembolism after unprovoked pulmonary embolism: the PADIS-PE randomised trial. *Eur Respir J* 2018; 51: 1701202.
6 Rodger MA, Kahn SR, Wells PS, *et al.* Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ* 2008; 179: 417–426.
7 Kearon C, Ageno W, Cannegieter SC, *et al.* Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost* 2016; 14: 1480–1483.
8 Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med* 2003; 139: 893–900.
9 Rodger MA, Le Gal G, Anderson DR, *et al.* Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. *BMJ* 2017; 356: j1065.
10 Wan T, Rodger M, Zeng W, *et al.* Residual pulmonary embolism as a predictor for recurrence after a first unprovoked episode: results from the REVERSE cohort study. *Thromb Res* 2018; 162: 104–109.