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Clinical predictors of confirmed venous thromboembolism in patients with a suspected recurrent venous thromboembolism

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Submitted

ABSTRACT

Clinical decision rules (CDR) have been established for patients with suspected first venous thromboembolism (VTE). However given that pre-test probability, laboratory testing and diagnostic imaging tests perform differently in patients with suspected recurrent VTE, a separate diagnostic management approach may be required. Our objective was to examine the possibility of using different clinical predictors for the diagnosis of recurrent VTE in patients with suspected recurrent VTE. The REVERSE I study enrolled patients with a first unprovoked major VTE. All suspected recurrent VTE events during the follow-up of 646 patients were adjudicated. Potential clinical predictors of recurrent VTE were collected at the baseline visit and at the time of the suspected recurrent VTE. In total 376 patients with suspected recurrent VTE were enrolled. In patients with suspected recurrent VTE (DVT and/or PE), male gender and a positive D-dimer result at the time of suspected recurrent VTE, as well as symptoms starting less than 7 days prior to time of presentation and DVT as previous event were predictors of recurrent VTE. In patients with suspected recurrent DVT, male gender, the presence of leg swelling, warmth and an elevated D-dimer at the time of suspected recurrent DVT were predictors of recurrent DVT. In patients with suspected recurrent PE, male gender was a predictor for recurrent PE. This study showed that predictors for the diagnosis of recurrent VTE may be different than predictors for the diagnosis of a first VTE. This supports the hypothesis that a separate CDR and diagnostic management strategy may be needed in this group of patients.

INTRODUCTION

Venous thromboembolism (VTE) – which consists of deep vein thrombosis in the leg (DVT) and pulmonary embolism (PE) - is common, potentially lethal yet treatable. The accurate management of recurrent VTE is of high clinical importance. Concluding that recurrent VTE is absent while it is not, exposes the patient to the risk of (fatal) pulmonary embolism, while falsely determining that recurrent VTE is present, unnecessarily commits patients to indefinite anticoagulant therapy with an associated risk of –potential – fatal bleeding.[1] Clinicians are often confronted with patients with suspected recurrent VTE, since 20% of all patients with suspected VTE have a history of previous VTE.[2,3]

Clinical decision rules (CDR), such as the Wells models for lower extremity DVT and PE, have been well established for patients with suspected first VTE. However these rules may have limitations for patients with suspected recurrent VTE. First, patients with suspected PE and a history of VTE have their diagnosis more likely confirmed than patients with a suspected PE without a history of VTE (40.3 vs. 20.6%)[4], suggesting a different pre-test probability. Furthermore, patients who had a previous PE often have complaints of chronic dyspnea,[5] which could complicate the risk estimation of recurrent PE. A similar scenario arises for patients who suffered from a DVT, as 30-50% of patients will show signs and symptoms of post-thrombotic syndrome (PTS) following this event.[6] Post-hoc analyses of diagnostic studies have been reassuring in terms of the safety of ruling out VTE on the basis of a non-high pretest probability using the Wells' or Geneva rule in combination with a negative D-Dimer in patients with a previous history of VTE.[4,7] However, the proportion of patients in whom the diagnosis could be ruled out non-invasively was very low: approximately 10%, as compared with 30% among all-comers with suspected VTE.[8] Hence, because of different pre-test probability, the presence of chronic symptoms after the previous VTE and the low diagnostic yield of current existing clinical decision rules a different approach may be needed for effective pre-test estimation of patients with a suspected recurrent VTE. Our objective was to study clinical predictors of a confirmed recurrent VTE diagnosis in patients with a suspected event.

PATIENTS AND METHODS

REVERSE study

The REVERSE study was a prospective cohort study designed to derive a clinical decision rule to identify patients at low risk for recurrent VTE after completion of 5–7 months of anticoagulant therapy for a first unprovoked VTE.[9] Institutional research ethics board approval was obtained at all participating centers. All consecutive unselected patients seen in clinics by participating physicians for VTE follow-up at 12 tertiary care centers

in four countries were asked to participate if they had:(i) a first episode of unprovoked objectively proven VTE 5–7 months prior to enrollment initially treated with > 5 days of heparin, followed by 5–7 months of oral anticoagulants (target International Normalized Ratio 2–3); and (ii) no recurrent VTE during the treatment period. At the time the REVERSE study was performed, all participating centers treated patients with a first unprovoked VTE for at least 6 months, and none of them used compression ultrasonography (CUS) to decide on treatment duration. A first unprovoked VTE was defined as VTE occurring in the absence of a leg fracture or lower extremity plaster cast, immobilization for more than 3 days, or surgery using a general anesthetic in the 3 months prior to the index VTE event, and without diagnosis of malignancy in the prior 5 years at the time of enrollment. Patients were excluded if they were unable or unwilling to consent, were under the age of 18 years, had already discontinued anticoagulant therapy, required ongoing anticoagulation for reasons other than VTE, were geographically inaccessible for follow-up, or were being treated for a recurrent unprovoked VTE or a previously known high risk thrombophilia, defined as known deficiency of protein S, protein C or antithrombin, known persistently positive anticardiolipin antibodies (> 30 U mL), a known persistently positive lupus anticoagulant or two or more known defects (e.g. homozygous for factor V Leiden (FVL) or prothrombin gene mutation (PGM), or compound heterozygous for FVL and PGM). Thrombophilia testing was not systematically conducted prior to enrollment; patients were only excluded if their high risk thrombophilias were known (i.e. identified prior to enrollment).

Figure 1 shows the order of this study and the moments of enrollment of the patients. The unprovoked VTE event 5-7 months prior to enrollment in the REVERSE study was referred to as 'index event'. The visit for enrollment in the REVERSE study (5-7 months after the index event) was regarded as the 'baseline visit' and patients were enrolled in the current study during the follow up period (i.e. after the baseline visit).

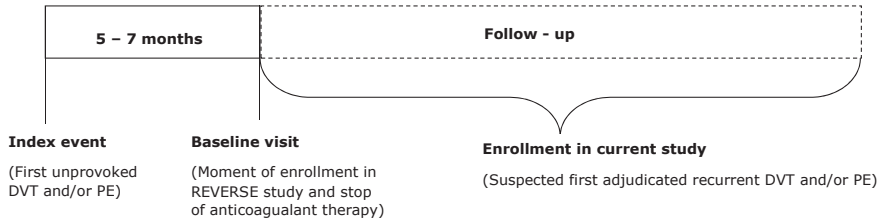

Figure 1. Timeline of study patients

Baseline visit

During the baseline visit (5-7 months after the unprovoked DVT of the legs and/or PE) the patients were interviewed with standardized case report forms. Imaging was per-

formed in all patients, patients who had a DVT as index event received an ultrasonographyand patients with PE received V/Q scans at this visit. Furthermore D-Dimer testing was performed using the Vidas D-dimer reagent on the Vidas Instrument (bioMérieux, Marcy l'Etoile, France). No management decisions were made with the results of the baseline visit.

Follow-up

After baseline imaging was obtained, patients were instructed to discontinue their anticoagulant treatment and to contact study personnel if they developed symptoms of recurrent VTE during follow-up. They were also seen in clinic at least every 6 months and asked about signs and symptoms of recurrent VTE. No systematic imaging screening test for VTE was performed during follow-up. Patients with symptoms suggestive of recurrent VTE underwent a standardized diagnostic strategy that included comparison of imaging tests at the time of suspected recurrent event with imaging conducted at baseline visit as previously described.[10] For the current sub-study, we only included the first adjudicated suspected recurrent VTE during their follow-up to ensure statistical independence of cases. Two of the co-authors (KG and MT), independent of knowledge of final adjudicated outcome, extracted potential clinical predictors of recurrent VTE. These potential clinical predictors were identified through a systematic review of the literature (PROSPERO registration number: CRD42012002356). A case report form was completed for all suspected recurrent VTE during follow-up. All documents related to suspected recurrent VTE (clinical notes, laboratory results and imaging tests) were collected and sent along with the local decision to the coordinating center. All suspected symptomatic VTE events and deaths during follow-up were independently adjudicated by two physicians.

Statistical analysis

All patients enrolled in the REVERSE study were eligible, if they had a suspected recurrent DVT of the leg(s) and/or PE during follow-up (regardless whether the previous event was a DVT of the leg(s) and/or PE), sought medical attention for the suspected recurrent event, had documentation about their first adjudicated suspected event and if the patients might have died due to a (suspected) recurrent VTE. Univariate analysis was used to determine the strength of association between each predictor and VTE recurrence. The appropriate univariate technique was selected according to the type of data: for nominal data, the chi-square test with continuity correction; for ordinal variables, Mann-Whitney U test; and, for continuous variables, the unpaired 2-tailed t-test, using pooled or separate variance estimates as appropriate. To estimate the clinical strength of an individual predictor, we calculated the odds ratio of the presence of a specific predictor. We stratified our results for patients with suspected recurrent VTE in general,

patients with suspected recurrent DVT and patients with suspected recurrent PE. All statistical analyses were performed with SPSS 20 (IBM).

RESULTS

Between October 2001 and March 2006, 665 patients with a first unprovoked objectively proven VTE were enrolled in the REVERSE study and 646 patients completed follow-up and were analyzed. Figure 2 shows the flow chart of the current study. We screened all 646 patients enrolled in the REVERSE I study. Out of these patients, 402 patients presented with a suspected recurrent VTE during a mean follow-up of 20.2 months (range: 0 – 97 months). After screening, 376 patients were included in our study, 26 patients were excluded because the death event was not related to a suspected recurrent VTE (n=13), no information was available about the adjudication of the recurrent event (n=6), because the suspected recurrent VTE event was related to a suspected thrombosis at another site than the legs/lungs (n=5) and patients who mentioned during a follow-up

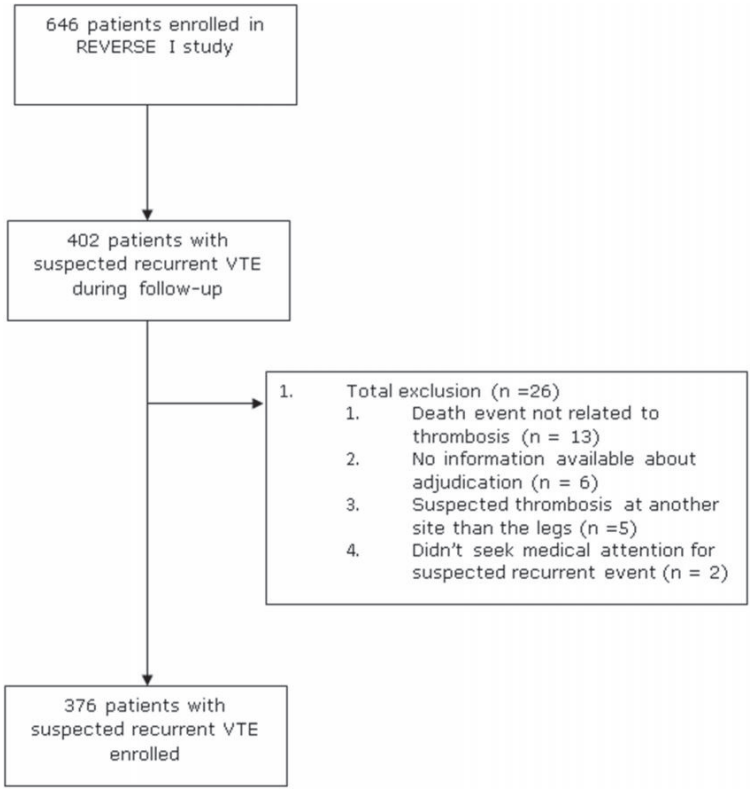

Figure 2. Flow chart enrollment patients

visit that they might have symptoms of a recurrent VTE, but didn't seek objective medical attention (n=2). Table 1 shows the demographic characteristics of the patients. The mean age of participants was 53.1 years (SD ±17.5), 52.7% were men and 97.7% were outpatients when they presented with suspected recurrent VTE. Two-hundred and thirty patients presented with suspected recurrent DVT (61.2%), 105 patients (27.9%) with a suspected recurrent PE and 41 patients (10.9%) with a suspected PE and DVT. Over two third (67.6%) of the patients with a suspected recurrent DVT had a suspected ipsilateral recurrent DVT.

Table 1. Demographic characteristics.

	All patients, N = 376 **n (%)**
Female	178 (47.3)
Age, years, mean (SD)	53.1 (17.5)
Caucasian ethnicity	347 (92.3)
Index VTE	
DVT	189 (50.3)
PE	111 (29.5)
DVT and PE	76 (20.2)
First suspected VTE	
DVT	230 (61.2)
PE	105 (27.9)
DVT and PE	41 (10.9)
Time from index to first suspected event, months, mean (SD)	26.1 (22.0)
Outpatient	*n = 349* 341 (90.7)
Duration of symptoms before consulting physician, days, mean (SD)	*n = 267* 19.6 (78.1)
Suspected DVT in ipsilateral leg	*n = 204* 138 (54.3)

N: number; SD: standard deviation; VTE: venous thrombo embolism; PE: pulmonary embolism; DVT: deep vein thrombosis

Predictors for VTE in patients with suspected recurrent VTE (DVT and/or PE)

Table 2 shows an overview of the results. Significant predictors for recurrent VTE (DVT and/or PE) in patients with suspected recurrent VTE (DVT and/or PE) were male gender ($p < 0.01$, OR: 2.7 (95% CI, 1.7-4.3)) and older mean age ($p<0.05$). Furthermore if the index event was a DVT, patients were more likely to have suspected recurrent VTE confirmed ($p<0.01$). The time between the index event and the suspected recurrence did not have any significant influence. Concerning potential predictors from the baseline study visit, a high BMI (above 26 kg/m2) was predictive for a confirmed diagnosis. The presence of

Table 2. Statistical analysis of individual predictors for VTE in patients with suspected recurrent VTE (DVT and/or PE).

	Number of patients with predictor available	Prevalence of predictor (n,%)	Percentage or Mean of Predictor Variable			
			All suspected recurrent VTE patients N = 376			
Predictors, n = present			No VTE recurrence n = 262	VTE recurrence n = 114	Odds ratio	P value
Demographics						
Male Gender	376	198 (52.7%)	45.4%	69.3%	2.7 (1.7-4.3)	0.000†
Mean age (years)	376		51.9	56.0		0.034*
Older than 65 years	376	96 (25.5%)	23.7%	29.80%	1.4 (0.8-2.2)	0.208
Index						
Mean time between index event and suspected VTE (months)	376		25.5	27.4		0.448
Type of index event	376					0.014*
1. DVT		189 (50.3%)	115 (43.9%)	75 (65.8%)		
2. PE		111 (29.5%)	100 (38.2%)	17 (14.9%)		
3. Both (DVT and PE)		76 (20.2%)	47 (17.9%)	22 (19.3%)		
Baseline[1]						
BMI > 26 kg/m^2	375	243 (64.8%)	61.5%	72.6%	1.7 (1.0 - 2.7)	0.039*
Abnormal baseline imaging	371	232 (65.2%)	59.7%	69%	1.5 (0.94 – 2.4)	0.09
Mean D-dimer at baseline	366		288.9	377.9		0.088
Elevated baseline D-dimer (cut-off: 250)	267	136 (37.2%)	33.9%	44.6%	1.6 (1-2.48)	0.049*
Change in D-dimer test result compared to baseline	178	66 (37.1%)	30.5%	50.8%	2.4 (1.23-4.49)	0.009†
Acute suspected recurrence						
Symptoms 7 days and shorter	267	186 (69.7%)	65%	80%	2.1 (1.2-3.9)	0.015*
Elevated D-dimer at time of suspected recurrence	181	101 (55.8%)	44.4%	80.7%	5.2 (2.5 – 11.08)	0.000†
Symptoms of both PE and DVT	376	41 (10.9%)	7.3%	19.3%	3.1 (1.6 – 5.9)	0.001†

VTE: venous thrombo embolism; DVT: deep veen thrombosis; PE: pulmonary embolism; n: number; BMI: body mass index; [1] Baseline consist of the first visit for all RE-VERSE patients, which occurs after 5-7 after the index event; *p < 0.05; †p < 0.01

residual thrombi on ultrasonography or V/Q during baseline imaging was not predictive of having the recurrent VTE diagnosed at the time of suspected recurrent VTE. However an elevated D-dimer test result at moment of suspected recurrence, an elevated baseline D-dimer test prior to discontinuing anticoagulant therapy (cut-off > 250 µg/dl) and change in D-dimer test result compared to baseline D-dimer test result were all related to having recurrent VTE confirmed. Finally patients who presented within 7 days after their symptoms onset were more likely to have the diagnosis confirmed ($p< 0.05$, OR: 2.1 (95% CI, 1.2-3.9) than patients with longer term symptoms.

Predictors for DVT in patients with suspected DVT with a history of any VTE (DVT/and or PE)

Table 3 shows an overview of the results. For patients with suspected DVT with a history of VTE male gender was also predictive ($p < 0.01$; OR: 2.2 (95% CI, 1.2-4.0)), while age was not predictive. Patients who had a DVT as index event were more likely to have recurrent DVT confirmed ($P < 0.01$) than patients with index PE in patients with suspected recurrent DVT. Concerning baseline information, both D-dimer testing and residual thrombosis on baseline imaging (ultrasonography and V/Q scan) had no predictive value for having a recurrent DVT confirmed. Furthermore an elevated BMI (above 26 kg/m2) at baseline was not predictive. The presence of the post-thrombotic syndrome (Villalta score >4) at baseline was also not predictive of having the diagnosis DVT confirmed. For the typical symptoms of recurrent DVT, leg swelling ($p<0.01$) and warmth of the leg ($p<0.01$) were more likely present in patients with a confirmed DVT. If the symptoms are in the ipsilateral leg, the diagnosis seems to be less likely to be confirmed, although this trend is not significant.

Predictors for PE in patients with suspected PE with a history of VTE (DVT and/or PE)

Table 4 shows an overview of the results. Male gender seems to be predictive to have the diagnosis confirmed ($p<0.05$; OR: 2.5 (1.0-6.2)). Age was not predictive, although more patients who had the diagnosis confirmed were older than 65 years old. The timing after the index event or the type of index event didn't influence the likelihood of a confirmed diagnosis. No potential clinical predictors at baseline were predictive for a confirmed PE diagnosis. Typical symptoms of PE such as shortness of breath, chest pain and hemoptysis are not significant related to having the diagnosis confirmed. However, patients who have a PE confirmed have a lower mean saturation ($p< 0.05$). The average heart rate and the presence of diaphoresis are not significantly related to the diagnosis of recurrent PE.

Table 3. Statistical analysis of individual predictors for DVT in patients with suspected DVT with a history of any VTE (DVT/and or PE).

	Number of patients with predictor available	Prevalence of predictor (n, %)	Percentage or Mean of Predictor Variable			
			All suspected recurrent DVT patients N = 230			
			No DVT recurrence n = 164	DVT recurrence n = 66	Odds ratio	P value
Demographics						
Male gender	230	122 (53%)	47.6%	66.7%	2.2 (1.2-4.0)	0.009†
Mean age	230		52.5	55.2		0.294
Older than 65 years	230		25.6	25.8	1 (0.5 -1.9)	0.981
Index						
Mean time between index and suspected recurrent VTE	230		20.6	22.7		0.53
Type of index event	230					0.001†
1. DVT		155 (67.4%)	60.4%	84.8%		
2. PE		35 (15.2%)	20%	3%		
3. Both		40 (17.4%)	19.5%	12%		
Baseline[1]						
BMI > 26 kg/m^2	229	147 (64.2%)	61.6%	70.8%	1.5 (0.8 – 2.8)	0.191
Abnormal baseline imaging	228	135 (59.2%)	56.4%	66.1%	1.5 (0.83 – 2.7)	0.178
Abnormal compression ultrasound at baseline	188	109 (58%)	55.1%	63.9%	1.4 (0.7-2.6)	0.252
Mean D-dimer test at baseline	223		283	440.8		0.158
Elevated baseline D-dimer test (cut-off = 250)	223	87 (39%)	36.5%	45.3%	1.4 (0.8 -2.6)	0.22
Change in D-dimer result between baseline and acute recurrent event	101	41 (40.6%)	35.7%	51.6%	1.9	0.13
Baseline presence of post-thrombotic syndrome in affected leg (Vilalta > 4)	182	182 (34%)	35.7%	30.4%	0.8 (0.4 – 1.5)	0.482
Acute suspected recurrence						
Mean duration of symptoms (days)	153		30.3	10.6		0.269

Table 3. Statistical analysis of individual predictors for DVT in patients with suspected DVT with a history of any VTE (DVT/and or PE). (Continued)

	Number of patients with predictor available	Prevalence of predictor (n, %)	Percentage or Mean of Predictor Variable			
			All suspected recurrent DVT patients N = 230			
			No DVT recurrence n = 164	DVT recurrence n = 66	Odds ratio	P value
Symptoms 7 days and shorter	153	103 (67.3%)	65%	73%	1.5 (0.7-3.2)	0.3
Suspected ipsilateral DVT	176	117 (66.5%)	70.7%	58.3%	0.6 (0.3 – 1.1)	0.100
Leg pain	204	189 (97%)	92.4	93.3%	1.2 (0.4-3.8)	0.808
Leg swelling	193	145 (75%)	67.9	91.5	5.1 (1.9 – 13.7)	0.000†
Tenderness along the venous system	113	81 (71.7%)	67.5%	81.8%	2.2 (0.8-5.9)	0.125
Warmth	94	39 (41.5%)	32.3%	62.1%	3.4 (1.4-8.5)	0.007†
Calf pain	103	85 (82.5%)	79.4%	88.6%	2 (0.6-6.6)	0.25
Calf diameter difference (≥ 3cm)	75	14 (18.7%)	17.9%	21.1%	1.2 (0.3-4.5)	0.757
Elevated D-dimer test at suspected recurrent event	94	48 (51.1%)	43%	77.8%	5.2 (1.9 -14.5)	0.001†

VTE: venous thrombo embolism; DVT: deep veen thrombosis; PE: pulmonary embolism; n: number; BMI: body mass index; [1]Baseline consist of the first visit for all REVERSE patients, which occurs after 5-7 after the index event; *p < 0.05; †p < 0.01

Table 4. Statistical analysis of individual predictors for PE in patients with suspected PE with a history of VTE (DVT and/or PE).

	Prevalence of predictor (n, %)	Number of patients with predictor available	Percentage or Mean of Predictor Variable			
			All suspected recurrent PE patients N = 105			
			No PE recurrence n = 79	PE recurrence n = 26	Odds ratio	P-value
Demographics						
Male gender	47 (44.8%)	105	39.2%	61.5%	2.5 (1.0-6.2)	0.047*
Mean age		105	51.8	59.4		0.064
Older than 65 year		105	22.8%	42.3%	2.5 (1.0 – 6.4)	0.053
Index						
Mean time between index and suspected recurrent VTE		105	17.8	20.3		0.49
Type of index event		105				
· DVT	19 (18%)		18%	26.9%		0.33
· PE	68 (64.8%)		68%	53.8%		
· Both	17% (17.1%)		16.5%	19.2%		
Baseline[1]						
BMI > 26 kg/m^2	68 (64.8%)	105	60.8%	76.9%	2.2 (0.8 – 6.0)	0.135
Abnormal baseline imaging	66 (64.7%)	102	64.4%	65.4%	1.0 (0.4 – 2.7)	0.93
Abnormal ventilation-perfusion scan at baseline[1=]	53 (62.4%)	85	60.9%	66.7%	1.3 (0.5 – 3.3)	0.638
Mean D-dimer test result at baseline		102	301.8	279.4		0.78
Elevated baseline D-dimer (cut-off = 250)	33 (32.3%)	102	27.6%	46.2%	2.2 (0.9 -5.6)	0.081
Change in D-dimer result between baseline and acute recurrent event	17 (32.7%)	52	28.2%	46.2%	2.2 (0.6-8.0	0.23
Acute suspected recurrence						
Mean duration of symptoms		80	17.1	9.6		0.368
Symptoms 7 days and shorter	55 (68.8%)	80	65%	80%	2.2 (0.6 – 7.3)	0.21

Table 4. Statistical analysis of individual predictors for PE in patients with suspected PE with a history of VTE (DVT and/or PE). (Continued)

	Prevalence of predictor (n, %)	Number of patients with predictor available	Percentage or Mean of Predictor Variable			
			All suspected recurrent PE patients N = 105			
			No PE recurrence n = 79	PE recurrence n = 26	Odds ratio	P-value
Shortness of breath	71 (80.7%)	88	76.9%	91.3%	3.2 (0.7 -26)	0.133
Chest pain	75 (81.5%)	92	85.7%	68.2%	0.36 (0.1 -1.1)	0.065
Pain with deep breath	46 (69.7%)	66	70%	68.8%	0.9 (0.3 – 3.2)	0.925
Hemoptysis	4 (9.5%)	42	6.9%	15.4%	2.5 (0.3 – 19.7)	0.39
Sweating	5 (16.7%)	30	9.1%	37.5%	6 (0.8 -46.1)	0.065
Mean O_2 saturation at time of suspected recurrence		41	96.4	93.7		0.047*
Mean heart rate		59	90.9	86.00		0.422
Heart rate > 100	13 (22%)	59	25%	13.3%	0.5 (0.1 – 2.4)	0.35

VTE: venous thrombo embolism; DVT: deep veen thrombosis; PE: pulmonary embolism; n: number; BMI: body mass index; [1] Baseline consist of the first visit for all RE-VERSE patients, which occurs after 5-7 after the index event $p < 0.05$; †$p < 0.01$

DISCUSSION

Our study shows that predictors for confirming a venous thrombosis in patients with suspected recurrent VTE might be different than in patients with suspected first VTE. For instance, we showed that potential clinical predictors for suspected recurrent VTE included male gender, a change in D-dimer test result from baseline value, and a previous confirmed DVT. These predictors are not included in current CDRs for DVT or PE. Before commencing this study we performed a systematic review of studies on predictors for the diagnosis of VTE in patients with suspected recurrent VTE (PROSPERO: CRD42012002356). Few research studies have focused specifically on the diagnostic management of patients with suspected recurrent VTE. No study has focused on the clinical predictors of VTE in patients with suspected VTE and a history of VTE. However, being able to identify as many of these patients as possible as having a low pretest probability would be of high clinical relevance. Imaging could be safely withheld in this group, thereby reducing the risk of misdiagnoses (high frequency of residual thrombi that may be mistaken for recurrent thrombi), costs, radiation exposure and simplifying the diagnostic management of these patients. This study is the first study that evaluated potential clinical predictors in patients with suspected recurrent VTE. Previous studies focused on the predictors in patients with suspected first VTE or any suspected recurrent VTE, but no study assessed the predictors for the diagnosis of a recurrent VTE in patients with suspected recurrent VTE specifically. Furthermore we have shown that objective predictors, like gender, oxygen saturation, D-dimer testing and a previous DVT were significantly related with a proven recurrent VTE diagnosis; predictors that are not included in current available CDRs for suspected DVT and PE. Additionally all suspected recurrent VTE events were independently adjudicated by an adjudication committee. This study has a few limitations. It is a post-hoc analysis. However all data were systematically collected with an a priori developed case report form. To minimize information bias, we have only included data that were clearly reported in the clinical charts. If nothing was mentioned about a clinical predictor in a clinical report of a patient, we excluded the patient for the analysis of that specific predictor. Another limitation is that although we have enrolled over 370 patients, the power of the study is limited for the subcategories of suspected VTE, e.g. in patients with suspected PE and a history of VTE. Therefore, predictors that turned out not to be significant in this study, could be significant associated with a recurrent DVT and/or PE in a larger cohort. Furthermore the time between the index event and the suspected recurrence was relatively short (mean 20.2 months), therefore whether these findings would apply to patients with a longer time period between the index event and suspected recurrent event is uncertain. In a meta-analysis examining the predictive values for patients with a suspected first DVT, the presence of a malignancy and a previous DVT were useful for predicting DVT. Our

study did not show a significant correlation between a malignancy in the past 5 years and a confirmed diagnosis but we acknowledge that patients with active cancer were excluded from our cohort and hence our cohort had a very low prevalence of patients with a malignancy (2.6%).[11] Additionally this study only enrolled patients who had a first unprovoked event as index event. Therefore we know how the predictors would perform in patients who had a previous provoked VTE. Also we enrolled patients who had a first adjudicated recurrent VTE event to prevent that a patient would be enrolled multiple times in our study, but consequently we do not know whether our results would apply for patients who had multiple suspected recurrences in their past. Our study suggests that a suspected ipsilateral recurrent DVT is associated with a lower rate of recurrent VTE diagnosis. A hypothesis might be that many suspected DVT patients present with symptoms mimicking a recurrent event, while a post-thrombotic syndrome is ultimately diagnosed rather than new DVT, making ipsilateral symptoms a negative predictor. Interestingly, chest pain was a negative predictor for a confirmed recurrent PE diagnosis. A hypothesis could be that patients are told to report chest pain and did so regularly. Not all clinical predictors that are statistically significant are necessarily clinically relevant or useful. Whether a clinical predictor is clinically useful is also dependent on the prevalence of the predictor in the cohort. The classic use of a CDR is to identify patients who are at low risk for a disease and eligible for a non-invasive diagnostic exclusion. To have any clinical relevance, the predictor cannot have a too high prevalence in the cohort, since only a limited proportion could have the diagnosis excluded, minimizing the efficacy of the predictor. The predictors that turned out to be significant in our cohort have a reasonable to low prevalence in our cohort and might therefore be of clinical value.

In conclusion, this is the first study to show that predictors for the diagnosis of a recurrent VTE may be different than predictors for the diagnosis of a first VTE. For instance, our results show that male gender is not only a risk factor for recurrent VTE, but is also an important predictor for confirmed VTE among patients with suspected recurrent VTE. None of the existing CDRs take gender into consideration. The findings of this post-hoc analysis raise the hypothesis that it is likely possible to derive a separate CDR for patients with suspected recurrent VTE, which could increase the diagnostic yield of non-invasive testing in this patient population. Improved diagnostic management in this population would lead to more optimal clinical management and improved safety for these patients.

REFERENCES

1. Guyatt GH, Norris SL, Schulman S, Hirsh J, Eckman MH, Akl EA, Crowther M, Vandvik PO, Eikelboom JW, McDonagh MS, Lewis SZ, Gutterman DD, Cook DJ, Schünemann HJ; American College of Chest Physicians.Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):53S-70S
2. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, Kovacs G, Mitchell M, Lewandowski B, Kovacs MJ. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003;349(13):1227-1235
3. van Belle A, Büller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, Kramer MH, Kruip MJ, Kwakkel-van Erp JM, Leebeek FW, Nijkeuter M, Prins MH, Sohne M, Tick LW; Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 2006;295(2):172-179
4. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Perrier A, Bounameaux H. Value of D-dimer testing for the exclusion of pulmonary embolism in patients with previous venous thromboembolism. Arch Intern Med 2006;166(2):176-180
5. Klok FA, Tijmensen JE, Haeck ML, van Kralingen KW, Huisman MV. Persistent dyspnea complaints at long-term follow-up after an episode of acute pulmonary embolism: results of a questionnaire. Eur J Intern Med 2008;19(8):625-629
6. Kahn SR. Frequency and determinants of the postthrombotic syndrome after venous thromboembolism. Curr Opin Pulm Med 2006;12(5):299-303.
7. Anderson DR, Wells PS, Kovacs MJ, Rodger M, McCarron B, Robinson S. Management of patients with suspected recurrent deep vein thrombosis using clinical probability and D-dimer. Blood 2001;98:1878 (abstract)
8. Carrier M, Righini M, Djurabi RK, Huisman MV, Perrier A, Wells PS, Rodger M, Wuillemin WA, Le Gal G. VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. Thromb Haemost 2009;101(5):886-892
9. Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, Solymoss S, Crowther M, Perrier A, White R, Vickars L, Ramsay T, Betancourt MT, Kovacs MJ. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ 2008;179(5):417-426
10. Le Gal G, Kovacs MJ, Carrier M, Do K, Kahn SR, Wells PS, Anderson DA, Chagnon I, Solymoss S, Crowther M, Righini M, Perrier A, White RH, Vickars L, Rodger M. Validation of a diagnostic approach to exclude recurrent venous thromboembolism. J Thromb Haemost 2009;7(5):752-759.
11. Goodacre S, Sutton AJ, Sampson FC. Meta-analysis: The value of clinical assessment in the diagnosis of deep venous thrombosis. Ann Intern Med 2005;143(2):129-139