JIM Original Article

doi: 10.1111/joim.12969

D-dimer levels and risk of recurrence following provoked venous thromboembolism: findings from the RIETE registry

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Background

- Patients with venous thromboembolism (VTE) secondary to transient risk factors may develop VTE recurrences after discontinuing anticoagulation.
- Identifying at-risk patients could help to guide the duration of therapy.

AIM of the study

- To assess the prognostic value of d-dimer testing after discontinuing anticoagulation to identify patients at increased risk for recurrences.

Methods

- Consecutive patients with objectively documented VTE (either proximal or distal deep vein thrombosis or pulmonary embolism) from the multicentre RIETE database.
- Transient risk factors were classified as major (postoperative) or minor (pregnancy, oestrogen use, immobilization or recent travel).
- D-dimer levels were measured between 30 and 120 days after discontinuing anticoagulant therapy.
- Cancer patients were excluded.

Results

- 1655 VTE patients.
- Amongst patients with major risk factors (N=460), the recurrence rate was 5.74 (95% CI: 3.19–9.57) events per 100 patient-years in those with raised d-dimer levels and 2.68 (95% CI: 1.45– 4.56) in those with normal levels.
- Amongst patients with minor risk factors (N= 1195), the rates were 7.79 (95% CI: 5.71–10.4) and 3.34 (95% CI: 2.39–4.53), respectively.
- Patients with minor risk factors and raised d-dimer levels had a higher rate of recurrences (HR: 2.34; 95% CI: 1.51–3.63) than those with normal levels.
- On multivariate analysis, raised d-dimers (HR: 1.74; 95% CI: 1.09–2.77) were associated with an increased risk for recurrences in patients with minor risk factors, not in those with major risk factors.

Table 1. *Baseline patient characteristics and d-dimer levels, according to the presence of major (surgery) or minor transient risk factors (pregnancy, oestrogen use, recent immobility or recent travel >4 h)*

	Major risk factors	Minor risk factors	Total
Patients, N	460	1195	1655
Clinical characteristics			
Sex (male)	229 (50%)	457 (38%)***	686 (41%)
Age (years, mean ± SD)	57 ± 17	54 ± 20**	55 ± 20
Transient provoking factor (*N*,%)			
Recent surgery	460 (100%)	0	460 (28%)
Pregnancy	2 (0.43%)	47 (3.9%)***	49 (3.0%)
Oestrogen use	23 (5.0%)	335 (28%)***	358 (22%)
Recent immobilization	0	758 (63%)***	758 (46%)
Recent travel	5 (1.1%)	144 (12%)***	149 (9.0%)
Duration of follow-up after therapy			
Days, mean ± SD	620 ± 614	584 ± 584	594 ± 592
Days, median and interquartile range	473 (140–932)	445 (119–883)	455 (123–902)
Time from completion of therapy to d-dimer measurement			
Days, mean ± SD	104 ± 169	89 ± 146	93 ± 153
Days, median and interquartile range	45 (30–104)	43 (30–95)	44 (30–98)
Time ≤ 30 days	129 (28%)	337 (28%)	466 (28%)
Time from completion of therapy to recurrent VTE			
Days, mean ± SD	844 ± 10 371	837 ± 724	839 ± 806
Days, median and interquartile range	417 (145–1167)	615 (344–1135)	600 (237–1138)
VTE at presentation (*N*,%)			
Proximal DVT	146 (70%)	550 (80%)**	696 (78%)
Distal DVT	42 (20%)	94 (14%)*	136 (15%)
Pulmonary embolism	252 (55%)	511 (43%)***	763 (46%)
D-dimer levels after anticoagulant therapy (*N*,%)			
Raised	171 (37%)	382 (32%)*	553 (33%)

Table 3. *Rates of recurrent VTE or death in patients with raised vs. normal d-dimer levels after discontinuing treatment for VTE provoked by a transient risk factor*

	Raised d-dimers		Normal d-dimers			
	N	*N* per 100 patient-years	*N*	*N* per 100 patient-years	Hazard ratio (95% CI)	*P* value
Major transient risk factors, *N*	171		289			
Duration of therapy						
Mean days ± SD	484 ± 499		565 ± 594			0.133
Median days (IQR)	308 (78–858)		367 (91–892)			0.277
Outcomes						
VTE overall	13	5.74 (3.19–9.57)	12	2.68 (1.45–4.56)	2.14 (0.96–4.79)	0.062
Deep vein thrombosis	7	3.09 (1.35–6.11)	7	1.57 (0.68–3.10)	1.97 (0.66–5.88)	0.215
Pulmonary embolism	6	2.65 (1.07–5.51)	5	1.12 (0.41–2.48)	2.37 (0.69–8.43)	0.167
Death	3	1.32 (0.34–3.60)	2	0.45 (0.07–1.48)	2.96 (0.44–24.9)	0.261
In patients with d-dimer levels measured ≤ 30 days after discontinuing therapy (*N* = 129)						
VTE overall	2	3.04 (0.51–10.1)	4	3.42 (1.09–8.24)	0.89 (0.11–5.02)	0.929
Deep vein thrombosis	2	3.04 (0.51–10.1)	3	2.56 (0.65–6.97)	1.19 (0.14–7.98)	0.840
Pulmonary embolism	0	–	1	0.85 (0.04–4.21)	–	0.640
In patients with d-dimer levels measured > 30 days after discontinuing therapy (*N* = 331)						
VTE overall	11	6.84 (3.60–11.9)	8	2.42 (1.13–4.60)	2.82 (1.12–7.36)	0.027
Deep vein thrombosis	5	3.11 (1.14–6.89)	4	1.21 (0.38–2.92)	2.57 (0.65–10.7)	0.175
Pulmonary embolism	6	3.73 (1.51–7.76)	4	1.21 (0.38–2.92)	3.08 (0.84–12.4)	0.088

Minor transient risk factors, N	382		813			
Duration of therapy						
Mean days ± SD	530 ± 519		515 ± 536			0.650
Median days (IQR)	381 (99–868)		367 (79–829)			0.537
Outcomes						
VTE overall	43	7.79 (5.71–10.4)	38	3.34 (2.39–4.53)	2.34 (1.51–3.63)	<0.001
Deep vein thrombosis	23	4.16 (2.70–6.15)	21	1.84 (1.17–2.77)	2.26 (1.24–4.12)	0.008
Pulmonary embolism	20	3.61 (2.27–5.48)	17	1.48 (0.89–2.33)	2.44 (1.27–4.72)	0.008
Death	13	2.36 (1.31–3.93)	9	0.79 (0.39–1.45)	2.98 (1.27–7.27)	0.012
In patients with d-dimer levels measured ≤ 30 days after discontinuing therapy (N = 858)						
VTE overall	28	7.28 (4.93–10.4)	26	3.23 (2.16–4.67)	2.25 (1.31–3.87)	0.003
Deep vein thrombosis	16	4.15 (2.46–6.60)	14	1.74 (0.99–2.85)	2.39 (1.15–4.98)	0.019
Pulmonary embolism	12	3.11 (1.68–5.29)	12	1.49 (0.81–2.53)	2.09 (0.92–4.74)	0.077
In patients with d-dimer levels measured > 30 days after discontinuing therapy (N = 337)						
VTE overall	15	8.97 (5.21–14.5)	12	3.58 (1.94–6.09)	2.50 (1.16–5.48)	0.019
Deep vein thrombosis	7	4.19 (1.83–8.28)	7	2.09 (0.91–4.13)	2.00 (0.67–5.97)	0.206
Pulmonary embolism	8	4.78 (2.22–9.08)	5	1.47 (0.54–3.27)	3.24 (1.05–10.9)	0.041

Table 4. *Univariate and multivariate analyses of risk factors for recurrent VTE. Results are expressed as hazard ratio and 95% confidence intervals*

	Major risk factors Univariate analysis	Major risk factors Multivariate analysis	Minor risk factors Univariate analysis	Minor risk factors Multivariate analysis
VTE recurrences, *N*	25		81	
Clinical characteristics				
Male gender	0.91 (0.41–2.01)	–	1.36 (0.88–2.11)	–
Age > 65 years	1.23 (0.53–2.89)	–	2.96 (1.89–4.62)**	1.97 (1.15–3.37)*
Weight > 75 kg	0.44 (0.17–1.19)	–	1.16 (0.75–1.80)	–
Initial VTE presentation				
Pulmonary embolism	0.50 (0.22–1.15)	–	1.02 (0.65–1.59)	–
Concomitant illnesses				
Chronic heart failure	2.47 (0.33–18.50)	–	0.67 (0.09–4.82)	–
Chronic lung disease	1.50 (0.44–5.08)	–	1.63 (0.88–3.03)	–
CrCl levels < 60 mL min^{-1}	2.70 (1.08–6.72)*		2.98 (1.87–4.74)**	
Recent major bleeding	0.05 (0.00–1841.2)	–	0.05 (0.00–191.4)	–
Concomitant medications				
Antiplatelet agents	1.59 (0.53–4.73)	–	1.44 (0.77–2.68)	–
D-dimer testing				
Positive	2.28 (1.03–5.04)*		2.41 (1.55–3.74)**	1.74 (1.09–2.77)*
Measurement ≤ 30 days	1.03 (0.40–2.65)		1.15 (0.72–1.84)	
Vein recanalization				
No	0.91 (0.23–3.57)	–	1.37 (0.62–3.00)	–

CrCl, creatinine clearance levels; VTE, venous thromboembolism.
*$P < 0.05$; **$P < 0.001$.

Conclusions

- Patients with raised d-dimer levels after discontinuing anticoagulant therapy for VTE provoked by a minor transient risk factor were at an increased risk for recurrences.
- These results may have implications for practice suggesting a new tailored approach to anticoagulation even in patients with VTE provoked by a transient risk factor.