

Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis

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Background

- For patients with unprovoked venous thromboembolism (VTE) the optimal duration of anticoagulant treatment is uncertain.
- After 3-6 months of anticoagulation, current guidelines suggest extended (ie, indefinite) anticoagulation in patients who have a non high bleeding risk. This is, however, a weak (grade 2B) recommendation.
- Thus, deciding whether patients with a first episode of unprovoked VTE should receive indefinite anticoagulation or can stop treatment after the initial three to six months, remains an important challenge.

Aim of the study

- To determine the rate of a first recurrent venous thromboembolism (VTE) event after discontinuation of anticoagulant treatment in patients with a first episode of unprovoked VTE, and the cumulative incidence for recurrent VTE up to 10 years.

Methods

- Systematic review and meta-analysis of randomised controlled trials and prospective cohort studies reporting symptomatic recurrent VTE after discontinuation of anticoagulant treatment in patients with a first unprovoked VTE event who had completed at least three months of treatment

Results (i)

- 18 studies involving 7515 patients were included in the analysis.
- The pooled rate of recurrent VTE per 100 person years after discontinuation of anticoagulant treatment was 10.3 events (95% confidence interval 8.6 to 12.1) in the first year, 6.3 (5.1 to 7.7) in the second year, 3.8 events/year (95% confidence interval 3.2 to 4.5) in years 3-5, and 3.1 events/year (1.7 to 4.9) in years 6-10.

Results (ii)

- Compared to patients with isolated pulmonary embolism, the rate of recurrent VTE was higher in patients with proximal deep vein thrombosis (rate ratio 1.4, 95% confidence interval 1.1 to 1.7) and in patients with pulmonary embolism plus deep vein thrombosis (1.5, 1.1 to 1.9).
- In patients with distal deep vein thrombosis, the pooled rate of recurrent VTE per 100 person years was 1.9 events (95% confidence interval 0.5 to 4.3) in the first year after anticoagulation had stopped.
- The risk of recurrence was significantly higher in men than in women
- The case fatality rate for recurrent VTE was 4% (95% confidence interval 2% to 6%).

Table 2 | Risk of recurrent venous thromboembolism (VTE) after discontinuation of anticoagulation in patients with a first unprovoked VTE event

Interval after anticoagulation	Person years of follow-up	Recurrent events					Event rate per 100 person years*				
		VTE	DVT	PE	PE+DVT	Fatal PE	VTE	DVT	PE	PE+DVT	Fatal PE
1st year	6678.0	644	350	194	20	28	10.3 (8.6 to 12.1); 81, <0.001	6.2 (4.8 to 7.7); 79, <0.001	3.3 (2.4 to 4.2); 68, <0.001	0.3 (0.1 to 0.5); 44, 0.008	0.4 (0.2 to 0.7); 57, <0.001
2nd year	3906.0	262	151	82	7	12	6.3 (5.1 to 7.7); 56, 0.002	3.7 (2.8 to 4.7); 55, 0.003	2.0 (1.4 to 2.6); 36, 0.07	0.2 (0.1 to 0.4); 0, 0.63	0.3 (0.2 to 0.6); 10, 0.34
2 year cumulative incidence, % (95% CI)							16.0 (13.3 to 18.8)	9.7 (7.5 to 12.0)	5.2 (3.7 to 6.7)	0.5 (0.2 to 0.9)	0.7 (0.4 to 1.3)
Years 3-5	4772.0	182	116	54	5	6	3.8 (3.2 to 4.5); 24, 0.27	2.5 (2.0 to 2.9); 0, 0.59	1.0 (0.4 to 1.8); 83, <0.001	0.1 (0.0 to 0.3); 71, 0.02	0.1 (0.0 to 0.3); 53, 0.09
5 year cumulative incidence, % (95% CI)							25.2 (21.3 to 29.3)	16.3 (12.9 to 19.5)	8.0 (4.0 to 11.6)	0.8 (0.2 to 1.8)	1.0 (0.4 to 2.2)
Years 6-10	3023.4	99	67	27	0	3	3.1 (1.7 to 4.9); 84, <0.001	2.2 (1.0 to 3.8); 86, <0.001	0.7 (0.2 to 1.6); 79, 0.009	0.0 (0.0 to 0.1); 0, 1.00	0.1 (0.0 to 0.3); 0, 0.37
10 year cumulative incidence, % (95% CI)							36.1 (27.8 to 45.0)	25.1 (17.2 to 33.7)	11.2 (5.9 to 18.4)	0.8 (0.2 to 2.3)	1.5 (0.4 to 3.6)

DVT=deep vein thrombosis; PE=pulmonary embolism.

*Data are event rate (95% CI); I² (%), P value unless stated otherwise. P value is for heterogeneity.**Table 3 | Risk of recurrent venous thromboembolism (VTE) after discontinuation of anticoagulation in patients with first unprovoked VTE event according to sex**

Interval after anticoagulation	Person years of follow-up		Recurrent VTE		Event rate per 100 person years*	
	Men	Women	Men	Women	Men	Women
1st year	3273.8	2528.1	377	205	11.9 (9.6 to 14.4); 76, <0.001	8.9 (6.8 to 11.3); 72, <0.001
2nd year	2026.8	1738.1	160	97	7.3 (5.3 to 9.5); 63, <0.001	5.2 (3.6 to 7.0); 57, 0.003
2 year cumulative incidence, % (95% CI)					18.3 (14.4 to 22.5)	13.6 (10.1 to 17.5)
Years 3-5	2880.6	1891.7	125	57	4.4 (3.2 to 5.7); 60, 0.06	3.0 (1.6 to 4.7); 74, 0.01
5 year cumulative incidence, % (95% CI)					28.6 (22.3 to 35.0)	21.2 (14.4 to 28.6)
Years 6-10	1820.6	1202.4	76	23	3.8 (1.6 to 6.9); 89, <0.001	2.0 (1.3 to 2.9); 0, 1.02
10 year cumulative incidence, % (95% CI)					41.2 (28.4 to 55.6)	28.8 (19.8 to 38.4)

*Data are event rate (95% CI); I² (%), P value unless stated otherwise. P value is for heterogeneity.

Table 4 | Risk of recurrent venous thromboembolism (VTE) after discontinuation of anticoagulation in patients with a first unprovoked VTE event according to site of initial event

Interval after anticoagulation	Site of initial VTE			
	Distal DVT	Proximal DVT	Isolated PE	PE+DVT
1st year				
Total person years of follow-up	198.0	2387.4	1200.5	638.9
Total recurrent VTE events	3	233	86	66
Event rate per 100 person years (95% CI); I ² (%), P value*	1.9 (0.5 to 4.3); 0, 0.56	10.6 (8.1 to 13.3); 73, <0.001	7.7 (5.6 to 10.2); 49, 0.02	10.2 (6.7 to 14.2); 59, 0.005
2nd year				
Total person years of follow-up	NA	1417.1	763.5	347.9
Total recurrent VTE events	NA	89	36	25
Event rate per 100 person years (95% CI); I ² (%), P value*	NA	6.5 (5.2 to 7.8); 0, 0.55	4.5 (2.6 to 6.8); 45, 0.07	7.6 (4.7 to 11.2); 23, 0.24
2 year cumulative incidence, % (95% CI)	NA	16.4 (12.9 to 20.1)	11.9 (8.1 to 16.3)	17.0 (11.1 to 23.8)

DVT=deep vein thrombosis; PE=pulmonary embolism; NA=not available.
*P is for heterogeneity.

Table 5 | Comparison of rate of recurrent venous thromboembolism (VTE) after discontinuation of anticoagulation in subgroups of patients with a first unprovoked VTE event

Patient subgroups	Recurrent VTE rate ratio (95% CI)	P value
Men versus women	1.4 (1.3 to 1.6)	<0.001
Distal DVT versus proximal DVT	0.2 (0.04 to 0.5)	<0.001
Distal DVT versus isolated PE	0.2 (0.05 to 0.7)	0.009
Distal DVT versus PE+DVT	0.2 (0.03 to 0.5)	<0.001
Proximal DVT versus isolated PE	1.4 (1.1 to 1.7)	0.004
Proximal DVT versus PE+DVT	0.9 (0.7 to 1.2)	0.47
PE+DVT versus isolated PE	1.5 (1.1 to 1.9)	0.005

DVT=deep vein thrombosis; PE=pulmonary embolism.

Conclusions

- In patients with a first episode of unprovoked VTE who completed at least three months of anticoagulant treatment, the risk of recurrent VTE was substantial and decreased over time
- 4% of recurrent VTE events resulted in death
- These estimates should inform clinical practice guidelines, enhance confidence in counselling patients of their prognosis, and help guide decision making about long term management of unprovoked VTE.