Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials

Florent Boutitie, statistical investigator,[1] Laurent Pinede, investigator,[2] Sam Schulman, professor,[3,4] Giancarlo Agnelli, professor,[5] Gary Raskob, professor,[6] Jim Julian, statistical investigator,[7] Jack Hirsh, professor emeritus,[4] Clive Kearon, professor[4]

[1]Hospices Civils de Lyon, Service de Biostatistique, UMR 5558, CHU de Lyon, France

[2]Internal Medicine Department, Infirmerie Protestante, Lyon, France

[3]Haematology, Karolinska Hospital, Stockholm, Sweden

[4]Department of Medicine, McMaster University and Henderson Research Centre, Hamilton, ON, Canada

[5]Medicina Interna e Cardiovascolare—Stroke Unit, Università di Perugia, Perugia, Italy

[6]College of Public Health, University of Oklahoma, Health Sciences Center, Oklahoma City, OK, USA

[7]Department of Oncology, McMaster University and Henderson Research Centre, Hamilton, ON, Canada

Correspondence to: C Kearon, Hamilton Health Sciences, Henderson Division, 711 Concession Street, Hamilton, ON, Canada L8V 1C3 kearonc@mcmaster.ca

ABSTRACT

Objective To determine how length of anticoagulation and clinical presentation of venous thromboembolism influence the risk of recurrence after anticoagulant treatment is stopped and to identify the shortest length of anticoagulation that reduces the risk of recurrence to its lowest level.

Design Pooled analysis of individual participants' data from seven randomised trials.

Setting Outpatient anticoagulant clinics in academic centres.

Population 2925 men or women with a first venous thromboembolism who did not have cancer and received different durations of anticoagulant treatment.

Main outcome measure First recurrent venous thromboembolism after stopping anticoagulant treatment during up to 24 months of follow-up.

Results Recurrence was lower after isolated distal deep vein thrombosis than after proximal deep vein thrombosis (hazard ratio 0.49, 95% confidence interval 0.34 to 0.71), similar after pulmonary embolism and proximal deep vein thrombosis (1.19, 0.87 to 1.63), and lower after thrombosis provoked by a temporary risk factor than after unprovoked thrombosis (0.55, 0.41 to 0.74). Recurrence was higher if anticoagulation was stopped at 1.0 or 1.5 months compared with at 3 months or later (hazard ratio 1.52, 1.14 to 2.02) and similar if treatment was stopped at 3 months compared with at 6 months or later (1.19, 0.86 to 1.65). High rates of recurrence associated with shorter durations of anticoagulation were confined to the first 6 months after stopping treatment.

Conclusion Three months of treatment achieves a similar risk of recurrent venous thromboembolism after stopping anticoagulation to a longer course of treatment. Unprovoked proximal deep vein thrombosis and pulmonary embolism have a high risk of recurrence whenever treatment is stopped.

INTRODUCTION

Venous thromboembolism, which encompasses deep vein thrombosis and pulmonary embolism, is usually treated with a short course of a parenteral heparin, followed by a longer course of oral vitamin K antagonist treatment.[1] The decision to continue anticoagulant treatment beyond the first few months is based on the treating physician's perception of the benefits and harms of continuing treatment and on the patient's preference. The benefits and harms associated with different lengths of vitamin K antagonist treatment have been evaluated in several studies that randomly allocated patients with venous thromboembolism to receive different lengths of treatment. Three clear messages have emerged from the findings of these studies. Firstly, in unselected patients with venous thromboembolism, shortening the length of treatment from three or six months to 1.0 or 1.5 months results in a substantial increase in the frequency of recurrent thromboembolism after anticoagulants are stopped.[2-4] Secondly, vitamin K antagonist treatment targeted to an international normalised ratio of 2.5 is very effective at preventing recurrent venous thromboembolism.[5 6] Thirdly, the risk of recurrent thromboembolism increases after vitamin K antagonist treatment is stopped.[2-4 7-9] However, the results of these individual trials, and meta-analysis of summary data of their findings,[10-14] have failed to answer many important questions relating to the optimal length of vitamin K antagonist treatment for venous thromboembolism.

The most important limitation of individual studies that have evaluated the optimal length of vitamin K antagonist treatment for venous thromboembolism is that they only compared two lengths of treatment. Consequently, although studies could identify which of two lengths of treatment was superior, no study was in a position to determine if the superior length of treatment was also the optimal length of treatment; perhaps a third length of treatment would result in even better clinical outcomes. Another limitation of individual studies is that they included insufficient numbers of patients in subgroups to be able to determine if the main findings of each study applied to all patients. For example, if clinical features identify a sub-

population of patients with venous thromboembolism who have a substantially lower risk of recurrent thrombosis after vitamin K antagonist treatment is stopped, such patients might benefit from a shorter duration of treatment.

By increasing the number of patients studied and the spectrum of lengths of treatment evaluated, and by enabling time to event analyses and adjustment for confounding variables (such as patients' age and sex), meta-analysis of individual patients' data from several trials has the potential to answer questions that individual trials, and meta-analyses of aggregate data from such trials, cannot answer.[15] For this reason, the authors of seven studies that compared various length of vitamin K antagonist treatment for venous thromboembolism pooled individual patients' data from their studies.[3 4 6-9 12] Our primary goal was to identify the shortest length of treatment that reduced the risk of recurrence to its lowest value after stopping treatment, including in subgroups defined according to the location of the initial venous thromboembolism (for example, isolated distal deep vein thrombosis, proximal deep vein thrombosis, pulmonary embolism)[4 9 16 17] and whether thrombosis was provoked by a temporary risk factor or was unprovoked (that is, no temporary risk factor or association with cancer was present).[2-4 9 18]

METHODS
Description of original studies
The seven included studies enrolled adult men or women with objectively confirmed deep vein thrombosis or pulmonary embolism who did not have known cancer at diagnosis (some patients with cancer were included in one study but excluded from this analysis[3]); treated patients with different lengths of vitamin K antagonist treatment adjusted to achieve an international normalised ratio of 2.0 to 3.0[3 6-9 12] or 2.0 to 2.85[4]; prospectively followed patients after anticoagulant treatment was stopped; and used objective testing to diagnose recurrent venous thromboembolism (table 1). All studies included participants who were randomly allocated to one of two lengths of treatment. Two studies included two distinct populations of patients, each with its own randomised treatment options (table 1).[8 9] In addition to the randomised participants, one study included a concurrent cohort who were treated for three months because they had abnormal impedance plethysmography four weeks after diagnosis of deep vein thrombosis.[3] One study contributed patients to this analysis who were not included in the initial publication because they had yet to complete 12 months of follow-up.[8] Another study contributed data on patients who stopped anticoagulants after 27 months that were not included in the original publication.[6]

We identify studies by their acronyms as follows: Optimal Duration of Anticoagulation study (ODAC),[3] Duree Optimale du Traitement Anti Vitamines K study (DOTAVK),[9] Duration of Anticoagulation study 1 (DURAC 1),[4] Long-term Anticoagulation for First Idiopathic Thrombosis study (LAFIT),[6] Warfarin Optimal Duration Italian Deep Vein Thrombosis study (WODIT DVT),[7] Warfarin Optimal Duration Italian Pulmonary Embolism study (WODIT PE),[8] and Short term Oral anticoagulation for a First Acute Secondary Thrombosis study (SOFAST)[12] (table 1). We did not seek data from five small trials that compared lengths of anticoagulation (total of 545 participants),[19-22] or from two trials that did not routinely use objective testing to confirm recurrent venous thromboembolism.[2 23]

Definitions of clinical characteristics
We characterised the location of the initial venous thromboembolism as pulmonary embolism, with or without symptomatic deep vein thrombosis; proximal deep vein thrombosis (involvement of the popliteal or more proximal deep veins of the leg) without symptoms of pulmonary embolism; or isolated distal deep vein thrombosis (no involvement of the proximal veins and no symptoms of pulmonary embolism). In distinction to how they were reported in the original publications, patients with pulmonary embolism in DOTAVK and DURAC 1 needed reclassification to

Table 1 | Design of original studies included in pooled analysis

Characteristic	ODAC RCT*[3]	ODAC cohort*[3]	DOTAVK proximal* DVT/PE[9]	DOTAVK isolated distal* DVT[9]	DURAC 1[4]	LAFIT[6]	WODIT DVT[7]	WODIT PE TRF*[8]	WODIT PE no TRF*[8]	SOFAST[12]
Study period	1987-93	1987-93	1993-9	1993-9	1988-93	1994-7	1995-2000	1997-2000	1997-2000	1997-2001
Length of treatment before enrolment (months)	1	1	0	0	0	3	3	3	3	1
Length of treatment after enrolment (months):										
Shorter duration	0	2	3	1.5	1.5	0	0	0	0	0
Longer duration	2	2	6	3	6	24	9	3	9	2
Blinding	Yes	No	No	No	No	Yes	No	No	No	Yes
Follow-up after enrolment (months)†:										
Mean	17.5	17.2	9.5	12.4	20.1	17.3	20.1	22.3	20.0	10.2
Maximum	24.0	24.0	14.3	16.4	24.0	24.0	24.0	24.0	24.0	22.3

PE=pulmonary embolism; RCT=randomised controlled trial; TRF=temporary risk factors.
*Predefined categories of patients with venous thromboembolism from same study are presented in separate columns.
†Analysis and data confined to follow-up after stopping vitamin K antagonist treatment for maximum of 24 months.

Table 2 | Characteristics of participants and rates of recurrent venous thromboembolism after stopping anticoagulant treatment in original studies. Values are numbers (percentages) unless stated otherwise

Characteristic	ODAC RCT[3]	ODAC cohort[3]	DOTAVK proximal DVT/PE[9]	DOTAVK isolated distal DVT[9]	DURAC 1[4]	LAFIT[6]	WODIT DVT[7]	WODIT PE TRF[8]	WODIT PE no TRF[8]	SOFAST[12]	All
No of participants	196	142	539	197	897	162	267	150	210	165	2925
Males	109 (56)	85 (60)	263 (49)	78 (40)	504 (56)	98 (60)	156 (58)	58 (39)	93 (44)	87 (53)	1531 (52)
Mean (SD) age (years)	61.7 (16.1)	60.7 (16.2)	61.6 (16.5)	50.2 (17.8)	60.9 (14.9)	59.2 (16.2)	64.4 (15.6)	55.7 (17.6)	67.0 (12.3)	55.7 (16.3)	60.5 (16.2)
Baseline											
Isolated distal DVT	0 (0)	0 (0)	0 (0)	197 (100)	344 (38)	0 (0)	0 (0)	0 (0)	0 (0)	40 (24)	581 (20)
Proximal DVT	190 (97)	121 (85)	317 (59)	0 (0)	425 (47)	121 (75)	246 (92)	0 (0)	0 (0)	88 (53)	1508 (52)
Pulmonary embolism	6 (3)	21 (15)	222 (41)	0 (0)	128 (14)	41 (25)	21 (8)	150 (100)	210 (100)	37 (22)	836 (29)
No temporary provoking risk factors present*	93 (47)	97 (68)	285 (53)	60 (30)	558 (62)	162 (100)	267 (100)	0 (0)	210 (100)	0 (0)	1732 (59)
Temporary provoking risk factors present*	103 (53)	45 (32)	242 (45)	133 (68)	339 (38)	0 (0)	0 (0)	150 (100)	0 (0)	165 (100)	1177 (40)
Length of treatment											
1 or 1.5 months	86 (44)	1 (1)†	11 (2)†	100 (51)	449 (50)	0 (0)	0 (0)	1 (1)†	0 (0)	89 (54)	737 (25)
3 months	105 (54)	139 (98)	244 (45)	82 (42)	12 (1)†	81 (50)	133 (50)	72 (48)	102 (49)	76 (46)	1046 (36)
6 months	4 (2)†	2 (1)†	245 (46)	3 (2)†	433 (48)	8 (5)†	2 (1)†	77 (51)	2 (1)†	0 (0)	776 (27)
12 or 27 months	1 (1)†	0 (0)	29 (5)†	7 (4)†	0 (0)	73 (45)	132 (49)	0 (0)	106 (50)	0 (0)	348 (12)
Events											
Episodes of VTE/patient years of follow-up after stopping treatment	13/284	20/203	36/415	4/196	144/1481	25/232	36/448	10/279	17/345	7/140	312/4023
Episodes of VTE per 100 patient years after stopping treatment (95% CI)	4.6 (2.7 to 7.9)	9.9 (6.4 to 15.3)	8.7 (6.3 to 12.0)	2.0 (0.8 to 5.4)	9.7 (8.3 to 11.4)	10.8 (7.3 to 15.9)	8.0 (5.8 to 11.1)	3.6 (1.9 to 6.7)	4.9 (3.1 to 7.9)	5.0 (2.4 to 10.5)	7.8 (6.9 to 8.7)

DVT=deep vein thrombosis; PE=pulmonary embolism; RCT=randomised controlled trial; TRF=temporary risk factors; VTE=venous thromboembolism.
*Patients with cancer not included in analysis.
†Patients received length of treatment different from that to which they were allocated.

be consistent with these categories.[4 9 15] Pulmonary embolism and proximal deep vein thrombosis were diagnosed similarly in all studies. Isolated distal deep vein thrombosis was diagnosed by venogram in ODAC,[3] DURAC 1,[4] and SOFAST,[12] and predominantly by ultrasound in DOTAVK[9] (patients with isolated distal deep vein thrombosis were not included in LAFIT,[6] WODIT DVT,[7] and WODIT PE[8]).

We categorised initial venous thromboembolism as either provoked by a temporary risk factor or unprovoked (that is, not provoked by a temporary risk factor, but the patient could have a chronic medical condition other than cancer). The definition of a temporary risk factor differed across studies, but in all studies this category included recent surgery, plaster cast immobilisation of the leg, or admission to hospital. All participants had a first venous thromboembolism with symptoms, except for 5% of patients in LAFIT who had had a previous provoked thrombosis with symptoms,[6] 9% in ODAC who had a second thrombosis with symptoms,[3] and 9% in SOFAST who had a first asymptomatic deep vein thrombosis detected by screening after high risk surgery.[12]

Length of treatment, follow-up, and diagnosis of recurrent venous thromboembolism after treatment stopped

Lengths of treatment included 1.0, 1.5, 3, 6, 12, and 27 months before anticoagulation was stopped and follow-up for this analysis started (table 1). All recurrences were confirmed by each study's independent

outcome adjudication committee, and, except for a small number of recurrent episodes of deep vein thrombosis detected by routine impedance plethysmography and confirmed by venography in ODAC,[3] all recurrences were associated with symptoms. We limited follow-up to 24 months after anticoagulant treatment was stopped for this analysis.

Statistical analysis

We divided length of anticoagulation before treatment was stopped into the four categories of 1.0 or 1.5 months, 3 months, 6 months, and 12 or 27 months. Follow-up for this analysis started the day that anticoagulant treatment stopped and was censored once participants had a confirmed episode of recurrent venous thromboembolism, died, stopped follow-up in the original study, or had been followed for 24 months. We analysed time since stopping anticoagulant treatment as total follow-up (that is, 0-24 months), subdivided into 0-6 month and 7-24 month periods. We calculated rate of recurrence as the number of events divided by the total number of patient years of follow-up (that is, events per 100 patient years).

We used Cox proportional hazard regression modelling, stratified so as to preserve clustering of participants in the original studies, to assess the relation between baseline factors and the rate of recurrent venous thromboembolism.[15] Risk factors of interest were length of anticoagulation before stopping

Table 3 | Crude rates of recurrent VTE after stopping anticoagulant treatment according to location of initial VTE, length of treatment, and months of follow-up after stopping treatment—all participants

Length of treatment (months)	Months after stopping treatment	Recurrent episodes of VTE per 100 patient years (95% CI) (events/patient years)			
		Pulmonary embolism	Proximal DVT	Isolated distal DVT	All participants
1 or 1.5	≤6	43.0 (25.9 to 71.4) (15/35)	21.9 (15.6 to 30.6) (34/155)	10.0 (5.9 to 16.9) (14/140)	19.1 (14.9 to 24.4) (63/330)
	7-24	8.6 (3.9 to 19.1) (6/70)	7.2 (4.9 to 10.7) (25/345)	3.4 (1.9 to 6.4) (10/291)	5.8 (4.3 to 7.9) (41/706)
	0-24	20.1 (13.1 to 30.8) (21/105)	11.8 (9.1 to 15.2) (59/500)	5.6 (3.7 to 8.3) (24/431)	10.0 (8.3 to 12.2) (104/1036)
3	≤6	10.8 (6.8 to 17.1) (18/167)	11.3 (7.9 to 16.0) (31/275)	4.2 (1.1 to 16.8) (2/48)	10.4 (7.9 to 13.7) (51/490)
	7-24	2.9 (1.5 to 5.3) (10/347)	6.4 (4.5 to 9.0) (33/516)	2.2 (0.3 to 15.81) (1/45)	4.8 (3.6 to 6.5) (44/908)
	0-24	5.4 (3.8 to 7.9) (28/514)	8.1 (6.3 to 10.3) (64/791)	3.2 (1.0 to 10.1) (3/93)	6.8 (5.6 to 8.3) (95/1398)
6	≤6	9.5 (5.3 to 17.2) (11/115)	10.2 (6.4 to 16.2) (18/176)	5.1 (1.9 to 13.5) (4/79)	8.9 (6.3 to 12.5) (33/370)
	7-24	5.2 (2.9 to 9.3) (11/213)	8.1 (5.5 to 12.0) (26/319)	3.7 (1.8 to 7.3) (8/219)	6.0 (4.5 to 8.0) (45/751)
	0-24	6.7 (4.4 to 10.2) (22/328)	8.9 (6.6 to 11.9) (44/495)	4.0 (2.3 to 7.1) (12/298)	7.0 (5.6 to 8.7) (78/1121)
12 or 27	≤6	11.4 (5.4 to 23.8) (7/62)	10.7 (5.6 to 20.5) (9/84)	0.0 (0/1.1)	10.9 (6.7 to 17.8) (16/147)
	7-24	2.9 (1.1 to 7.8) (4/136)	8.1 (4.9 to 13.4) (15/185)	NA	5.9 (3.8 to 9.3) (19/321)
	0-24	5.6 (3.1 to 10.0) (11/198)	8.9 (6.0 to 13.3) (24/269)	0.0 (0/1.1)	7.5 (5.4 to 10.4) (35/468)
All	≤6	13.5 (10.2 to 17.7) (51/379)	13.3 (10.9 to 16.3) (92/691)	7.5 (4.8 to 11.6) (20/267)	12.2 (10.5 to 14.2) (163/1337)
	7-24	4.0 (2.8 to 5.8) (31/766)	7.3 (6.0 to 8.8) (99/1365)	3.4 (2.2 to 5.4) (19/555)	5.5 (4.7 to 6.5) (149/2686)
	0-24	7.2 (5.8 to 8.9) (82/1145)	9.3 (8.1 to 10.7) (191/2056)	4.7 (3.5 to 6.5) (39/822)	7.8 (6.9 to 8.7) (312/4023)

DVT=deep vein thrombosis; NA=not applicable; VTE=venous thromboembolism.

treatment, location of the index venous thromboembolism, and whether the index venous thromboembolism was provoked by a temporary risk factor. We entered age and sex in the model to control for potential confounding effects. We assessed the association between baseline variables and recurrent venous thromboembolism for each of the 0-6 month and 7-24 month periods of follow-up in the Cox proportional hazards modelling as a secondary analysis. We derived adjusted cumulative probabilities of recurrent venous thromboembolism from the multivariable Cox proportional hazard model and plotted them at the mean value of all included covariates.

We assessed differences in the risk of recurrence after different lengths of anticoagulation as follows. We did a χ^2 test for heterogeneity between the four categories of length of treatment. If heterogeneity was statistically significant, we compared the risk of recurrence in the 1 or 1.5 month group with that in the three longer duration groups combined. We then did a test for heterogeneity between the three longer treatment groups, and, if it was significant, we compared the three month group with the six and 12 or 27 month groups combined. For these comparisons, we assumed that a shorter duration of anticoagulation could be associated with a higher, but not a lower, risk of recurrence.

Statistical tests were two sided, and we considered P values less than 0.05 to be statistically significant. We used SAS version 9.1 for all analyses.

RESULTS

Participants' characteristics

We included a total of 2925 participants with a mean age of 60.5 years; 52% were male (table 2). Venous thromboembolism was isolated distal deep vein thrombosis in 20% of participants, proximal deep vein thrombosis in 52%, and pulmonary embolism in 29% (table 2). Venous thromboembolism was provoked by a temporary risk factor in 40% of participants and was unprovoked in 60%. Length of anticoagulant treatment was 1.0 or 1.5 months in 25% of participants, three months in 36%, six months in 27%, and 12 or 27 months in 12%.

Recurrent venous thromboembolism after anticoagulant treatment stopped

We had 4023 patient years of follow-up, corresponding to a mean follow-up of 1.4 years per patient (table 2). Three hundred and twelve episodes of recurrent venous thromboembolism occurred during this period, corresponding to an overall rate of 7.8 (95% confidence interval 6.9 to 8.7) per 100 patient years (tables 2 and 3). The rate of recurrence was 12.2 (10.5 to 14.2) per 100 patient years in the first six months after anticoagulant treatment was stopped and 5.5 (4.7 to 6.5) per 100 patient years during months 7-24 (table 3).

Length of anticoagulant treatment and risk of recurrence

In an analysis that included all participants (table 3), the risk of recurrent venous thromboembolism during the 24 month period after anticoagulant treatment was stopped differed among the four treatment duration groups (P=0.02 for heterogeneity in the multivariable model). The risk of recurrent venous thromboembolism during the 24 month period was higher in the 1.0 or 1.5 month group compared with patients who were treated for longer (hazard ratio 1.52, 95% confidence interval 1.14 to 2.02; P=0.004) (fig 1). The risk of recurrence during the 24 month period was similar in the three month, six month, and 12 or 27 month groups (P=0.86 for heterogeneity), with no convincing evidence that it was higher in the three month group compared with those treated for six months or longer (hazard ratio 1.19, 0.86 to 1.65; P=0.29). The higher rate of recurrence in the 1.0 or 1.5 month group

Table 4 | Predictors of recurrent venous thromboembolism after stopping anticoagulant treatment, from multivariable Cox regression analysis*

Variable	Hazard ratio (95% CI)	P value
Length of treatment:		
1 or 1.5 months†	1.28 (0.82 to 2.01)	0.28
3 months	1.0 (reference)	
6 months	0.80 (0.51 to 1.25)	0.33
12 or 27 months	0.88 (0.57 to 1.36)	0.56
Location of initial VTE:		
Proximal DVT	1.0 (reference)	
Pulmonary embolism†	1.19 (0.87 to 1.63)	0.27
Isolated distal DVT	0.49 (0.34 to 0.71)	‹0.001
Provoking risk factors *v* unprovoked	0.55 (0.41 to 0.74)	‹0.001

DVT=deep vein thrombosis; VTE=venous thromboembolism.
*Model included age, sex, and trial as potential confounders.
†In a separate multivariable model that distinguished between 0-6 and 7-24 month intervals of follow-up, a statistically significant difference between these two time intervals was found for this variable (see text).

compared with participants who were treated for three months or longer was limited to the first six months after anticoagulant treatment was stopped (hazard ratio 2.12, 1.43 to 3.15; P<0.001), with no apparent difference between these two groups during the 7-24 month follow-up period (1.05, 0.69 to 1.59; P=0.83). Table 4 summarises the risk of recurrence in the 1.0 or 1.5 month group, six month group, and 12 or 27 month group, compared with the three month group.

In participants with provoked venous thromboembolism (table 5), the risk of recurrent venous thromboembolism during the 24 month period was not statistically significantly different among the three treatment duration groups (no participants were treated for 12 or 27 months) (P=0.21 for heterogeneity). However, during the first six months after anticoagulant treatment was stopped, the risk of recurrent venous thromboembolism differed significantly among the three treatment groups (P=0.03 for heterogeneity). In the first six months, the risk of recurrent venous thromboembolism was higher in the 1.0 or 1.5 month group compared with patients treated for three months or longer (hazard ratio 2.89, 1.25 to 6.69; P=0.013), with no suggestion that the risk of recurrence was higher in participants who were treated for three months compared with six months (0.34, 0.10 to 1.12). The risk of recurrence was similar in the three treatment duration groups during the 7-24 month period after anticoagulant treatment was stopped (P=0.94 for heterogeneity), with no suggestion that the risk of recurrence was higher in the 1.0 or 1.5 month group compared with those treated for longer during this period (hazard ratio 0.97, 0.43 to 2.17; P=0.94).

In participants with unprovoked venous thromboembolism (table 6), the risk of recurrent venous thromboembolism during the 24 month period differed among the four treatment duration groups (P=0.009 for heterogeneity). The risk of recurrent venous thromboembolism during the 24 month period

was higher in the 1.0 or 1.5 month group compared with patients treated for three months or longer (hazard ratio 1.52, 1.09 to 2.12; P=0.014). This difference mainly occurred in the first six months after anticoagulant treatment was stopped (hazard ratio 2.00, 1.27 to 3.17; P=0.003), with little suggestion that the risk of recurrence during the 7-24 month period was higher in the 1.0 or 1.5 month group compared with those treated for longer (1.10, 0.67 to 1.80; P=0.70). We found a trend for a higher risk of recurrent venous thromboembolism during the 24 month period in the three month group compared with those treated for six months or longer (hazard ratio 1.39, 0.96 to 2.01; P=0.08). During the first six months of follow-up, this difference was statistically significant (1.70, 1.02 to 2.82; P=0.041).

Location of initial episode of venous thromboembolism and risk of recurrence

The risk of recurrence during the 24 month period was lower in participants with isolated distal deep vein thrombosis than in those with proximal deep vein thrombosis (hazard ratio 0.49, 0.34 to 0.71; P<0.001) or pulmonary embolism (0.41, 0.27 to 0.63; P<0.001) (table 3 and fig 2). During the 24 month period, the risk of recurrence was similar in participants with pulmonary embolism and proximal deep vein thrombosis (hazard ratio 1.19, 0.87 to 1.63; P=0.27). However, the risk of recurrence in participants with pulmonary
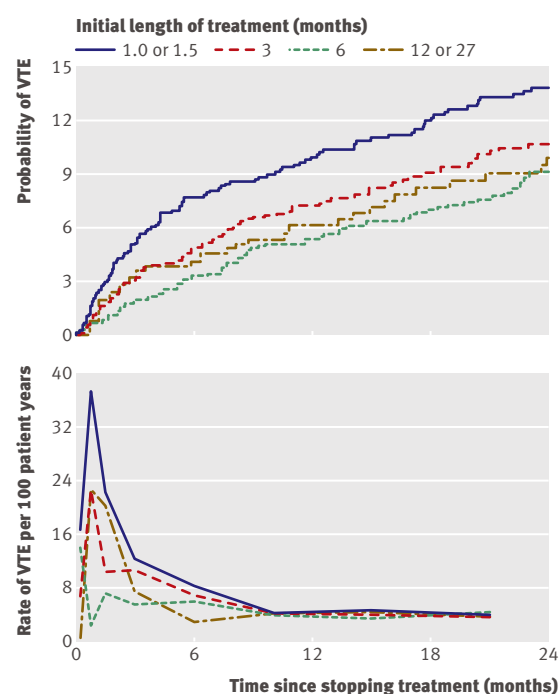

Fig 1 | Cumulative probability (top) and rate (bottom) of recurrent venous thromboembolism (VTE) after stopping treatment according to initial length of treatment (adjusted for age, sex, study, location of initial VTE, and presence of temporary risk factor. Rate of recurrent VTE calculated for 0-0.5, 0.5-1, 1-2, 2-4, 4-8, 8-12, 12-18, and 18-24 month intervals of follow-up

Table 5 | Crude rates of recurrent VTE after stopping anticoagulant treatment according to location of initial VTE, length of treatment, and months of follow-up after stopping—patients with provoked VTE

Length of treatment (months)	Months after stopping treatment	Recurrent episodes of VTE per 100 patient years (95% CI) (events/patient years)			
		Pulmonary embolism	Proximal DVT	Isolated distal DVT	All participants
1 or 1.5	≤6	21.7 (8.1 to 57.8) (4/18)	16.7 (9.7 to 28.7) (13/78)	1.2 (0.2 to 8.5) (1/84)	10.0 (6.3 to 15.9) (18/180)
	7-24	3.0 (0.4 to 21.0) (1/34)	5.6 (2.9 to 10.7) (9/162)	1.3 (0.3 to 5.0) (2/159)	3.4 (1.9 to 6.0) (12/355)
	0-24	9.6 (4.0 to 23.0) (5/52)	9.2 (6.0 to 13.9) (22/240)	1.2 (0.4 to 3.8)(3/243)	5.6 (3.9 to 8.0) (30/535)
3	≤6	5.5 (2.1 to 14.7) (4/72)	0.0 (0/92)	2.9 (0.4 to 20.7) (1/34)	2.5 (1.0 to 6.0) (5/198)
	7-24	1.4 (0.4 to 5.8) (2/139)	5.0 (2.4 to 10.4) (7/141)	0.0 (0/32)	2.9 (1.5 to 5.6) (9/312)
	0-24	2.8 (1.3 to 6.3) (6/211)	3.0 (1.4 to 6.3) (7/233)	1.5 (0.2 to 10.8) (1/66)	2.7 (1.6 to 4.6) (14/510)
6	≤6	7.9 (3.3 to 18.9) (5/64)	7.2 (3.0 to 17.2) (5/70)	5.3 (1.3 to 21.4) (2/37)	7.0 (4.0 to 12.4) (12/171)
	7-24	3.7 (1.5 to 8.8) (5/136)	6.4 (3.1 to 13.5) (7/109)	2.9 (0.9 to 8.8) (3/105)	4.3 (2.6 to 7.1) (15/350)
	0-24	5.0 (2.7 to 9.3) (10/200)	6.7 (3.8 to 11.8) (12/179)	3.5 (1.5 to 8.4) (5/142)	5.2 (3.6 to 7.6) (27/521)
12 or 27	≤6	0.0 (0/2)	0.0	0.0 (0/1)	0.0 (0/2)
	7-24	NA	NA	NA	NA
	0-24	0.0 (0/2)	0.0	0.0 (0/1)	0.0 (0/2)
All	≤6	8.3 (4.8 to 14.4) (13/156)	7.5 (4.7 to 11.9) (18/240)	2.6 (1.0 to 6.8) (4/156)	6.3 (4.6 to 8.8) (35/552)
	7-24	2.6 (1.3 to 5.2) (8/309)	5.6 (3.7 to 8.4) (23/411)	1.7 (0.7 to 4.1) (5/296)	3.5 (2.6 to 4.9) (36/1016)
	0-24	4.5 (2.9 to 6.9) (21/465)	6.3 (4.6 to 8.5) (41/651)	2.0 (1.0 to 3.8) (9/452)	4.5 (3.6 to 5.7) (71/1568)

DVT=deep vein thrombosis; NA=not applicable; VTE=venous thromboembolism.

embolism compared with proximal deep vein thrombosis differed (P=0.012 for interaction) between the 0-6 month (hazard ratio 1.65, 1.12 to 2.43) and 7-24 month (0.74, 0.43 to 1.25) periods (tables 3 and 4). Additional analyses suggested that the higher risk of recurrence during the first six months after stopping treatment in participants with pulmonary embolism mainly occurred in participants who were treated for only 1.0 or 1.5 months (hazard ratio 2.03, 1.12 to 3.69), with less evidence of a difference in those who were treated for three months or longer (1.45, 0.89 to 2.39) (table 3). Other than for this observation, we found no evidence that the location of venous thromboembolism altered the relative risk of recurrence that was associated with different lengths of anticoagulant treatment.

Provoked versus unprovoked venous thromboembolism and risk of recurrence

The risk of recurrence in participants with an initial event that was provoked by a temporary risk factor was about half of that in participants with unprovoked venous thromboembolism (hazard ratio 0.55, 0.41 to 0.74; P=0.0001) (fig 3 and table 4), with no evidence that this effect was modified by the length of anticoagulant treatment or the location of venous thromboembolism. The lower risk of recurrence in participants with an initial event provoked by a temporary risk factor compared with those with unprovoked venous thromboembolism was similar in the first six month period (hazard ratio 0.49, 0.32 to 0.75; P=0.009) and in the 7-24 month period (0.62, 0.41 to 0.94; P=0.024).

Isolated distal deep vein thrombosis provoked by a temporary risk factor was associated with a low absolute risk of recurrence after stopping anticoagulant treatment (2.0 (95% confidence interval 1.0 to 3.8) per 100 patient years for all such participants) (table 5).

We found no suggestion that this subgroup of participants had a higher risk of recurrence if they were treated for 1.0 or 1.5 months compared with three months or longer (hazard ratio 0.36, 0.09 to 1.54; P=0.17), although only nine recurrent episodes of venous thromboembolism contributed to this comparison. In contrast, participants with unprovoked isolated distal deep vein thrombosis (table 6) had a high absolute risk of recurrence (8.1 (5.7 to 11.6) per 100 patient years), and the risk of recurrence was higher in such participants who were treated for 1.0 or 1.5 months compared with a longer duration of treatment (hazard ratio 2.30, 1.05 to 5.03; P=0.04).

DISCUSSION

This analysis found that three months of anticoagulant treatment resulted in a similar risk of recurrence after treatment was stopped to a longer duration of treatment and that shortening treatment to 1.0 or 1.5 months doubled recurrence rates. Subgroup analyses suggested two possible exceptions to these overall findings. Firstly, patients with isolated distal deep vein thrombosis provoked by a temporary risk factor did not seem to have a higher risk of recurrence if they were treated for only 1.0 or 1.5 months. Secondly, patients with unprovoked venous thromboembolism seemed to have a lower risk of recurrence if they were treated for six months or longer compared with three months. When a shorter course of treatment was associated with a higher rate of recurrence, this increase was confined to the first six months after stopping treatment.

The analysis also confirmed, and more precisely defined, that the risk of recurrence after stopping treatment is about double when venous thromboembolism is unprovoked compared with if it is provoked by a temporary risk factor[2-4 9 18]; that the risk is about half after an isolated distal deep vein thrombosis compared

Table 6 Crude rates of recurrent VTE after stopping anticoagulant treatment according to location of initial VTE, length of treatment, and months of follow-up after stopping—participants with unprovoked VTE

Length of treatment (months)	Months after stopping treatment	Recurrent episodes of VTE per 100 patient years (95% CI) (events/patient years)			
		Pulmonary embolism	Proximal DVT	Isolated distal DVT	All participants
1 or 1.5	≤6	67.0 (37.1 to 120.9) (11/16)	27.1 (17.6 to 41.5) (21/78)	23.0 (13.3 to 39.6) (13/57)	29.9 (22.3 to 40.0) (45/151)
	7-24	13.9 (5.8 to 33.5) (5/36)	8.7 (5.4 to 14.3) (16/183)	6.1 (3.0 to 12.2) (8/131)	8.3 (5.8 to 11.9) (29/350)
	0-24	30.6 (18.7 to 49.9) (16/53)	14.2 (10.3 to 19.6) (37/261)	11.2 (7.3 to 17.1) (21/188)	14.8 (11.8 to 18.6) (74/501)
3	≤6	14.9 (8.8 to 25.2) (14/94)	17.0 (11.9 to 24.1) (31/183)	7.9 (1.1 to 56.0) (1/13)	15.9 (11.9 to 21.2) (46/289)
	7-24	3.8 (1.9 to 7.7) (8/208)	6.9 (4.7 to 10.2) (26/375)	7.9 (1.1 to 56.3) (1/12)	5.9 (4.2 to 8.2) (35/596)
	0-24	7.3 (4.8 to 11.1) (22/302)	10.2 (7.9 to 13.3) (57/558)	7.9 (2.0 to 31.6) (2/25)	9.2 (7.4 to 11.4) (81/885)
6	≤6	11.6 (5.2 to 25.9) (6/52)	12.4 (7.2 to 21.4) (13/104)	4.8 (1.2 to 19.3) (2/41)	10.6 (6.9 to 16.3) (21/197)
	7-24	7.9 (3.5 to 17.5) (6/76)	9.1 (5.8 to 14.2) (19/210)	4.4 (1.8 to 10.6) (5/114)	7.5 (5.2 to 10.7) (30/400)
	0-24	9.4 (5.3 to 16.5) (12/128)	10.2 (7.2 to 14.4) (32/314)	4.5 (2.2 to 9.5) (7/155)	8.5 (6.5 to 11.2) (51/597)
12 or 27	≤6	11.6 (5.5 to 24.4) (7/60)	10.7 (5.6 to 20.6) (9/84)	NA	11.1 (6.8 to 18.1) (16/144)
	7-24	2.9 (1.1 to 7.8) (4/136)	8.1 (4.9 to 13.4) (15/185)	NA	5.9 (3.8 to 9.3) (19/321)
	0-24	5.6 (3.1 to 10.1) (11/196)	8.9 (6.0 to 13.3) (24/269)	NA	7.5 (5.4 to 10.5) (35/465)
All	≤6	17.1 (12.4 to 23.5) (38/222)	16.5 (13.1 to 20.7) (74/449)	14.4 (8.8 to 23.5) (16/111)	16.4 (13.8 to 19.5) (128/782)
	7-24	5.0 (3.3 to 7.6) (23/457)	8.0 (6.4 to 10.0) (76/952)	5.4 (3.2 to 9.2) (14/258)	6.8 (5.6 to 8.2) (113/1667)
	0-24	9.0 (7.0 to 11.6) (61/679)	10.7 (9.1 to 12.6) (150/1401)	8.1 (5.7 to 11.6) (30/369)	9.8 (8.7 to 11.2) (241/2449)

DVT=deep vein thrombosis; NA=not applicable; VTE=venous thromboembolism.

with after either a proximal deep vein thrombosis or a pulmonary embolism[4 9 16]; and that the rate of recurrence during the first six months of follow-up is about double the rate during the next 18 months.[24] Patients with venous thromboembolism and cancer, who generally remain on anticoagulant treatment long term because they have a high risk of recurrence, were not included in the analysis.[1]

Strengths and limitations
Strengths of our analysis that increase the precision and validity of its findings are that we included data from a large number of participants, baseline variables were recorded at enrolment rather than retrospectively, the time of stopping anticoagulant treatment was well documented, participants were followed prospectively with very few unexplained losses to follow-up, and recurrent thrombosis was accurately diagnosed by adjudication committees. Limitations are that participants were not consecutive patients with venous thromboembolism, the precision of estimates among subgroups is still limited, only 12% of participants were in the 12 or 27 month group (all had unprovoked proximal deep vein thrombosis or pulmonary embolism), we were unable to assess the influence of thrombophilic states and other laboratory variables on risk of recurrence, and inferences about the influence of different lengths of treatment on risk of recurrence are based on comparisons across studies as well as within studies. In addition, we were unable to differentiate between patients who had venous thromboembolism provoked by minor and major temporary risk factors, a distinction that has been shown to influence the risk of recurrence, with a particularly low risk of recurrence if thrombosis was associated with recent surgery.[25] Another potential limitation is that the analysis included a non-randomised cohort of patients with proximal deep vein thrombosis who were treated

for three months because they had abnormal impedance plethysmography after one month of treatment, and some of the recurrent episodes of deep vein
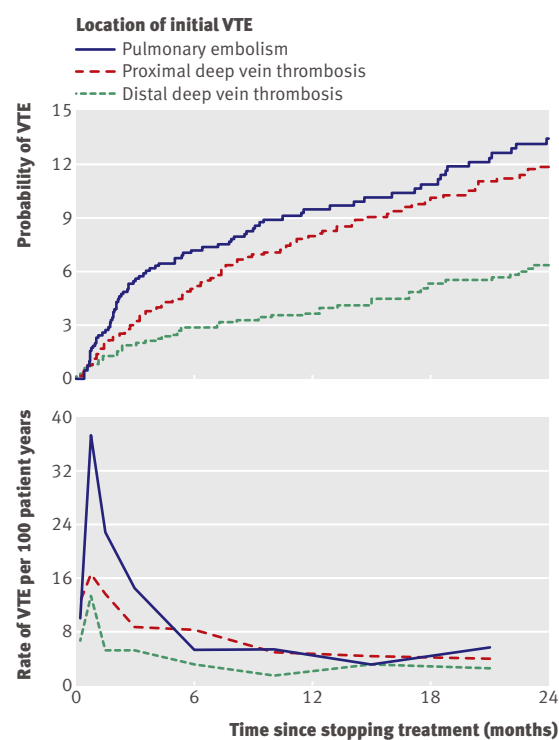

Fig 2| Cumulative probability (top) and rate (bottom) of recurrent venous thromboembolism (VTE) after stopping treatment according to whether VTE was pulmonary embolism, proximal deep vein thrombosis, or isolated distal deep vein thrombosis (adjusted for age, sex, study, length of treatment before stopping anticoagulant, and presence of temporary risk factor). Rate of recurrent VTE calculated for 0-0.5, 0.5-1, 1-2, 2-4, 4-8, 8-12, 12-18, and 18-24 month intervals of follow-up
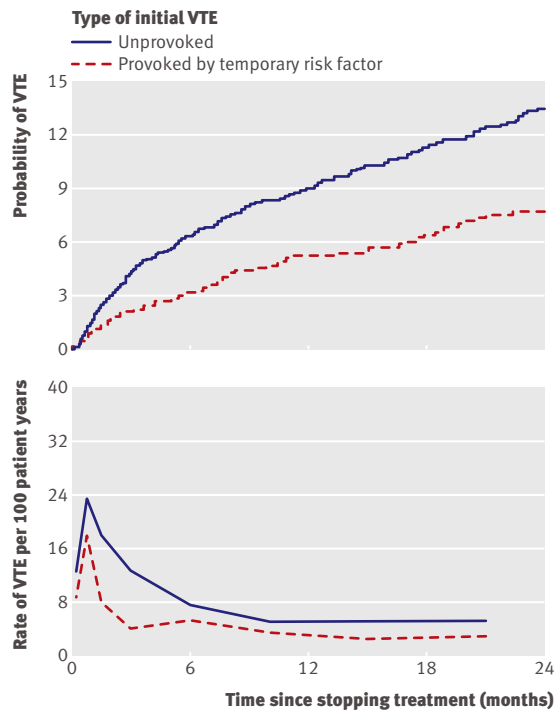
Fig 3 | Cumulative probability (top) and rate (bottom) of recurrent venous thromboembolism (VTE) after stopping treatment according to whether VTE was provoked by a temporary risk factor or was unprovoked (adjusted for age, sex, study, length of treatment before stopping anticoagulant, and location of initial VTE). Rate of recurrent VTE calculated for 0-0.5, 0.5-1, 1-2, 2-4, 4-8, 8-12, 12-18, and 18-24 month intervals of follow-up

thrombosis in the randomised and cohort components of this study were detected by routine impedance plethysmography in the absence of new symptoms.[3] However, a sensitivity analysis that excluded this study resulted in similar findings (data not shown).

Clinical implications and conclusions

The clinical implications of our findings are that if patients with venous thromboembolism do not have an indication for indefinite anticoagulant treatment they generally should stop treatment at three months. As patients with a provoked isolated distal deep vein thrombosis who were treated for 1.0 or 1.5 months had a low risk of recurrence, and as extending treatment to three months did not seem to further lower this risk, our results suggest that the risk of recurrence will not be excessive if such patients need to stop anticoagulants before they have completed three months of treatment. Patients with unprovoked proximal deep vein thrombosis or pulmonary embolism had a high risk of recurrence whenever they stopped treatment; consistent with this observation, several studies suggest that these patients will often benefit from indefinite anticoagulant treatment.[1 26 27] If patients with unprovoked proximal deep vein thrombosis or pulmonary embolism are not treated indefinitely, this analysis suggests that their risk of recurrence may be higher if they are treated for three months rather than six months (recurrent venous thromboembolism during the six months after stopping treatment in participants with unprovoked proximal deep vein thrombosis or pulmonary embolism who were treated for three months compared with six months or longer: hazard ratio 1.57, 95% confidence interval 0.94 to 2.61; P=0.08). However, as the increase in recurrent venous thromboembolism in the three month group was of borderline statistical significance, as we found no suggestion of a comparable increase in participants with provoked proximal deep vein thrombosis or pulmonary embolism who were treated for three months rather than six months, and as this finding was one of many subgroup analyses, we cannot be certain that this was a true increase. Although extending treatment from three months to six months in such patients may reduce the subsequent risk of recurrent venous thromboembolism, this potential benefit needs to be balanced against a higher risk of bleeding with, and the greater cost and inconvenience of, the longer duration of treatment.[1] Elevated D-dimer concentrations during or after anticoagulant treatment seem to be a valuable predictor of recurrence in patients with unprovoked venous thromboembolism.[28-30] This analysis was unable to assess if D-dimer or other laboratory variables were predictors of recurrence. If such factors improve identification of the subgroup of patients with unprovoked venous thromboembolism who can stop anticoagulant treatment because they have a low risk of recurrence, the results of this analysis suggest that treatment can be stopped after three months of anticoagulation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In general, venous thromboembolism should be treated for at least three months, and the risk of recurrence increases when anticoagulant treatment is stopped

Whether treatment of venous thromboembolism for longer than three months reduces the risk of recurrence when anticoagulation is ultimately stopped is uncertain

Whether the minimum length of anticoagulant treatment should be influenced by the initial presentation of venous thromboembolism is also uncertain

WHAT THIS STUDY ADDS

If the risk of recurrent venous thromboembolism is not high enough to justify indefinite anticoagulation, treatment can be stopped after three months in most patients

The risk of recurrence after stopping anticoagulants is doubled if venous thromboembolism was a proximal deep vein thrombosis or pulmonary embolism compared with an isolated distal deep vein thrombosis

The risk is also doubled if thrombosis was unprovoked rather than provoked by a temporary risk factor, and the influence of these two factors on the risk of recurrence is additive

1   Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob G, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: ACCP evidence-based clinical practice guidelines (8th ed). *Chest* 2008;133:454-545S.

2   Research Committee of the British Thoracic Society. Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. *Lancet* 1992;340:873-6.

3   Levine MN, Hirsh J, Gent M, Turpie AG, Weitz J, Ginsberg J, et al. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. *Thromb Haemost* 1995;74:606-11.

4   Schulman S, Rhedin A-S, Lindmarker P, Carlsson A, Lärfars G, Nicol P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995;332:1661-5.

5   Schulman S, Granqvist S, Holmstrom M, Carlsson A, Lindmarker P, Nicol P, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Engl J Med* 1997;336:393-8.

6   Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;340:901-7.

7   Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep vein thrombosis. *N Engl J Med* 2001;345:165-9.

8   Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med* 2003;139:19-25.

9   Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I, et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001;103:2453-60.

10   Pinede L, Duhaut P, Cucherat M, Ninet J, Pasquier J, Boissel JP. Comparison of long versus short duration of anticoagulant therapy after a first episode of venous thromboembolism: a meta-analysis of randomized, controlled trials. *J Intern Med* 2000;247:553-62.

11   Ost D, Tepper J, Mihara H, Lander O, Heinzer R, Fein A. Duration of anticoagulation following venous thromboembolism: a meta-analysis. *JAMA* 2005;294:706-15.

12   Kearon C, Ginsberg JS, Anderson DR, Kovacs MJ, Wells P, Julian JA, et al. Comparison of 1 month with 3 months of anticoagulation for a first episode of venous thromboembolism associated with a transient risk factor. *J Thromb Haemost* 2004;2:743-9.

13   Van Dongen CJ, Vink R, Hutten BA, Buller HR, Prins MH. Recurrent thromboembolism after treatment with vitamin K antagonists. *Arch Intern Med* 2003;163:2793.

14   Hutten BA, Prins MH. Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. *Cochrane Database Syst Rev* 2000;3:CD001367.

15   Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010;340:c221.

16   Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. *Arch Intern Med* 2000;160:769-74.

17   Eichinger S, Weltermann A, Minar E, Stain M, Schonauer V, Schneider B, et al. Symptomatic pulmonary embolism and the risk of recurrent venous thromboembolism. *Arch Intern Med* 2004;164:92-6.

18   Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet* 2003;362:523-6.

19   O'Sullivan EF. Duration of anticoagulant therapy in venous thrombo-embolism. *Med J Aust* 1972;2:1104-7.

20   Fennerty AG, Dolben J, Thomas P, Backhouse AG, Bentley DP, Campbell IA, et al. A comparison of 3 and 6 weeks' anticoagulation in the treatment of venous thromboembolism. *Clin Lab Haematol* 1987;9:17-21.

21   Holmgren KAJ, Andersson G, Fagrell B, Johnsson H, Ljungberg B, Nilsson E, et al. One-month versus six-month therapy with oral anticoagulants after symptomatic deep vein thrombosis. *Acta Med Scand* 1985;218:279-84.

22   Farraj RS. Anticoagulation period in idiopathic venous thromboembolism: how long is enough? *Saudi Med J* 2004;25:848-51.

23   Campbell IA, Bentley DP, Prescott RJ, Routledge PA, Shetty HG, Williamson IJ. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. *BMJ* 2007;334:674-7.

24   Prandoni P, Lensing AWA, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;125:1-7.

25   Iorio A, Kearon C, Filippucci E, Marcucci M, Macura A, Pengo V, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. *Arch Intern Med* 2010;170:1710-6.

26   Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells PS, Julian JA, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;349:631-9.

27   Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, et al. Long-term, low-intensity warfarin therapy for prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;348:1425-34.

28   Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ* 2008;179:417-26.

29   Verhovsek M, Douketis JD, Yi Q, Shrivastava S, Tait RC, Baglin T, et al. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. *Ann Intern Med* 2008;149:481-90,W94.

30   Douketis J, Tosetto A, Marcucci M, Baglin T, Cushman M, Eichinger S, et al. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. *Ann Intern Med* 2010;153:523-31.

Accepted: 30 March 2011