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Residual venous thrombosis as predictive factor for recurrent venous thromboembolism in patients with proximal deep vein thrombosis: a systematic review

M. Tan, I. C. M. Mos, F.A. Klok, M.V. Huisman

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ABSTRACT

The potential role of the detection of residual thrombosis after deep vein thrombosis (DVT) in the differentiation of patients at risk for recurrent venous thromboembolism (VTE) has not yet been fully established and includes different definitions. We performed a systematic review in order to determine the role of residual thrombosis in predicting recurrent VTE after acute proximal DVT. Databases were searched until June 2010.

Randomized, controlled trials or prospective cohort studies were eligible for inclusion if they included patients with objectively diagnosed proximal DVT, measured thrombus diameter after at least 3 months and reported recurrent VTE during follow-up. Two authors independently reviewed articles and extracted data. Data from 11 studies were used for the current analysis; in total 3203 patients were included. Residual thrombosis was positively correlated with recurrent VTE. Large heterogeneity was present, due to differences in study population, timing and the differences in methods of measuring residual thrombosis. The effect was more pronounced in patients with malignancy or was dependent on the criteria used. This systematic review shows a positive relationship between residual thrombosis and recurrent VTE during follow-up.

Assessing residual thrombosis could be useful in individual recurrence risk estimation.

INTRODUCTION

The optimal duration of anticoagulant therapy in patients with a first unprovoked proximal deep vein thrombosis (DVT) remains a dilemma. Current guidelines suggest treating these patients for at least 3 months, followed by an individual recurrence risk evaluation.[1]However it is unclear how to implement this into an individual evaluation. In spite of these recommendations, these patients have been shown to be at high risk for recurrent venous thromboembolism (VTE) with a cumulative recurrence incidence of 21.5% in the 5 years after a first DVT.[2] Therefore, it is of high clinical importance to distinguish patients with a high recurrent VTE risk from those with a lower risk. Patients with a high recurrence risk are potential candidates for prolonged duration of anticoagulant therapy, whereas in patients with a low risk treatment may well be limited to 3 months. This could minimize the risk for bleeding in patients with a low risk and could protect high risk patients for a recurrent VTE.

Several parameters have been evaluated and proven to be predictors for a higher recurrent VTE risk, e.g. male gender, high Factor VIII and D-dimer levels.[3-5] An additional prognostic factor could be the presence of residual thrombosis after the initial treatment period but data are conflicting. Several studies have indeed identified residual thrombosis as a risk factor for recurrent VTE,[6,7] while other more recent studies have not confirmed this finding.[8-10] Two commonly used definitions of residual thrombosis are the criteria of Prandoni[7] and criteria firstly described by Piovella.[6] The criteria of Prandoni consider residual venous thrombosis present if more than 2.0 mm in diameter on a single compression ultrasonography (CUS) or more than 3.0 mm in diameter in two consecutive tests. The criteria of Piovella consider residual thrombosis present if the ratio of vein diameter during compression x 100, divided by the vein diameter before compression is more than 40%. Although both criteria are now used in studies, there is a lack of one clear uniform definition that is widely accepted.

Factors contributing to the discrepancy in effect of residual thrombosis as a risk factor for recurrent VTE might be explained by the lack of agreement for the definition residual thrombosis or differences in study design. Given this uncertainty of findings, we performed a systematic review to determine the role of residual thrombosis in predicting recurrent VTE after acute deep vein thrombosis.

METHODS

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[11] All parts of the systematic

review were performed independently in a standardized manner by two reviewers; any disagreements were resolved by an additional reviewer.

Data sources and searches

A literature search was performed to identify all published randomized controlled or prospective cohort studies on residual thrombosis in patients initially diagnosed with DVT and which assessed recurrent venous thromboembolism [DVT and pulmonary embolism (PE)] in the follow-up. MEDLINE, EMBASE, Web of Science, the Cochrane dataset, Science Direct, CINAHL and Academic Search Premier were searched using pre-defined search terms. Search criteria included 'deep vein thrombosis' or 'venous thromboembolism' and 'residual venous thrombosis' and 'recurrence', a complete overview of the search criteria has been attached (Appendix SI). Full articles, letters and abstracts published from January 1980 until June 2010 were eligible for this analysis. Papers were not limited to the English language. Also, by searching the reference lists of all established studies and contact experts, the researchers aimed to identify additional relevant papers.

Study selection

Studies were included that measured residual thrombosis by CUS at least 3 months after a first episode of proximal DVT with or without additional PE and determined objectively recurrent VTE during follow-up. Objective criteria for DVT were positive findings on CUS or contrast venography. Objective criteria for PE were positive computerized tomography (CT) findings, high probability ventilation perfusion (VQ) scan or positive pulmonary angiography. Further criteria were a prospective design, predefined endpoints, clear description of inclusion and exclusion criteria, standardized treatment for at least 3 months and a follow-up period of at least 12 months.

Exclusion criteria were: impossibility to create two by two tables of residual thrombosis and recurrent VTE, and the use of thrombolytic therapy and/or thrombectomies in the study population. In case of suspected overlapping patient populations, the authors were contacted for clarification.

Data extraction

Information was extracted from each included study on: (i) study characteristics (design, study inclusion and exclusion criteria), (ii) patient characteristics (number, age, gender, history of VTE, presence of malignancy, diagnosis of DVT and therapy), (iii) measurement of residual thrombosis (timing after initial thrombosis, modality used to detect residual thrombosis, criteria used for residual thrombosis) and (iv) outcome measure (duration of follow-up, criteria used to define VTE and the amount of patients with objectively confirmed recurrent VTE during follow-up). If any of this data was missing, the relevant data was requested from the authors. In studies that randomly assigned patients to

continue or stop anticoagulant therapy, patients who continued anticoagulant therapy for the analysis were excluded.

Quality assessment

Individual study quality was assessed by the following items: patient enrollment, outcome assessment, duration of follow-up of at least 12 months, lost-to-follow-up and funding source.

Data synthesis and analysis

Patients who received anticoagulants for reasons other than VTE and patients who were lost to follow-up were excluded from the analysis. We identified the reported numbers of objectively confirmed recurrent VTE in all included studies. Odds ratios (ORs) were calculated to assess the relationship between presence of residual thrombosis and clinical outcome. Furthermore subgroup analyses were performed e.g. the method of determination of residual thrombosis, timing of measurement, initial provoked versus unprovoked DVT and patients with or without malignancy. For statistical analysis the Statistical Package for the Social Sciences (SPSS) version 16.0 was used. Data were entered in Review Manager Version 5.0 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008. Cochran's chi-square test and the I2 test for heterogeneity were used to assess inter study heterogeneity. Proportions and confidence intervals represent fixed effects model calculated proportion. The chi-square test assesses whether observed differences in results are compatible with chance alone. I2 describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error.[12] Statistically significant heterogeneity was considered present at chi-square $P < 0.10$ and $I^2 > 50\%$. Pooling was not executed, in case of identified heterogeneity.

RESULTS

Study selection

The literature search revealed 1227 studies of which 818 studies were unique; 803 studies were excluded after review of title and abstract and 14 studies were identified for more detailed evaluation. After full review, four additional studies were excluded because predefined endpoints (recurrent VTE) were not reported, due to missing measurement of residual thrombosis, a retrospective design and the use of thromboectomies as therapeutic strategy. One additional article was added by expert knowledge.[10] Finally, 11 studies [including two abstracts[13,14] and two letters[9,15] were left for inclusion in this systematic review (figure 1).[6-10;13-18] The funnel plot of included studies was not indicative of publication bias (funnel plot not shown).

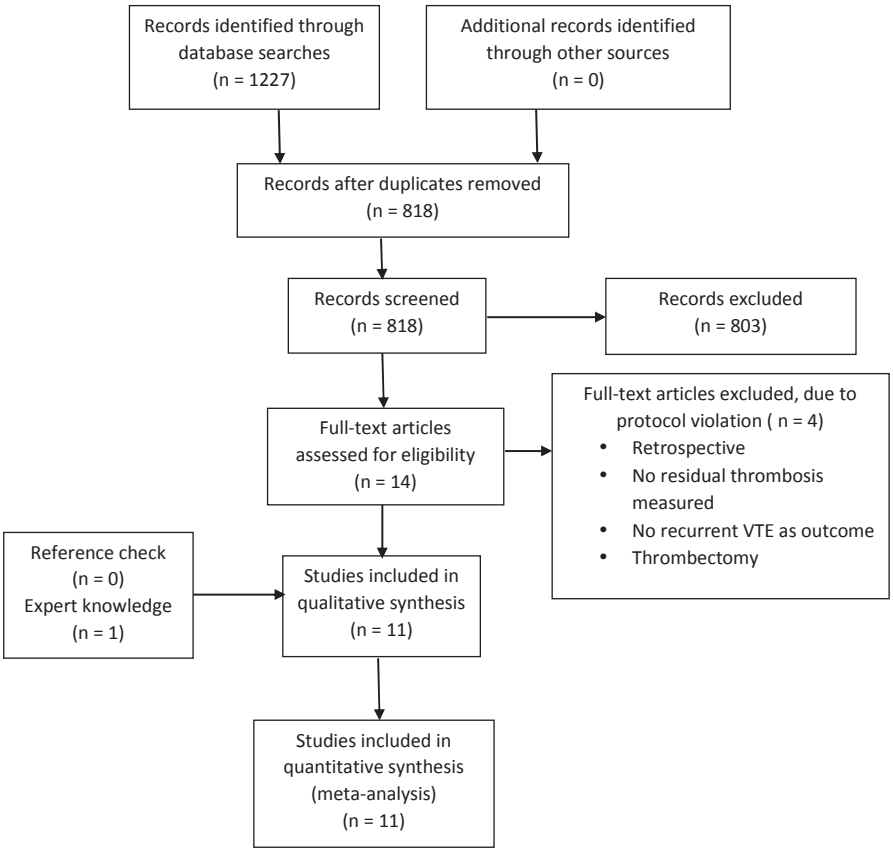

Figure 1. Flow diagram of study selection. VTE, venous thromboembolism

Quality and characteristics of included studies

The quality assessment of the studies is presented in Table 1.

All studies were of prospective design and 9 of 11 studies reported a consecutive patient enrollment. The duration of follow up ranged from a minimum of one to a maximal three years. Only five of the 11 included studies reported lost to follow-up numbers. Studies that included the lost to follow-up rate, reported an acceptable rate with a maximum of 2.2%. Table 2 presents the patient characteristics of the 11 included studies. A total of 3203 patients were included. Mean age varied between 53 and 72 years, and the proportion of male gender ranged from 34% to 59%. The percentage of unprovoked DVT was 77 versus 23 provoked DVT, the latter including 215 (6%) patients with active malignancy. None of the studies included patients with a distal DVT. The criteria for recurrent ipsilateral DVT are described in Table 3. The recurrent VTE rate ranged from 8% to 24%.

Table 1. Study quality assessment.

Study	Publication type	Study design	Patient enrollment	Outcome assessment	Duration of follow-up (years)	Lost to follow-up (n, %)	Funding source
Cosmi, 2010 [10]	Full article	Post hoc RCT Multi center	Prospective Consecutive	Blinded central adjudication committee	1.8	1 (0.2)	Italian Federation of Anticoagulation Clinics, Department of Angiology & Blood Coagulation of the University Hospital S. Orsola-Malpighi of Bolgna. The Instrumentation Laboratory company (D-dimer kits)
Prandoni, 2009 [16]	Full article	Multi center RCT	Prospective consecutive	Blinded independent adjudication committee	2.75	8 (1.5)	No external source of funding
Siragusa, 2008 [17]	Full article	Multi center RCT	Prospective	Blinded central adjudication committee	2.0	0 (0)	NR
Cosmi, 2005 [11]	Full article	Single center Cohort study	Prospective consecutive	Blinded repeating CUS, Adjudication of events by 2 blinded investigators	1.8	NR	Grant University of Bologna and of Fondazione "Marino Golinelli"
Cosmi, 2005 [15]	Letter	Single center Cohort study	Prospective consecutive	Adjudicated 2 blinded investigators	2.0	0 (0)	Grant University of Bologna
Prandoni, 2002 [6]	Full article	Single center Cohort study	Prospective consecutive	Fatal PE opinion of independent physician	2.0	NR	NR
Piovella ,2002 [7]	Full article	Cohort study	Prospective consecutive	NR	1.0	NR	Grant Italian National Research Council and Telethon Italy
Poli, 2008 [8]	Letter	Single center cohort study	Prospective consecutive	NR	2.1	NR	NR
Rodger, 2008 [9]	Full article	Multi center cohort study	Prospective consecutive	Independently adjudicated by blinded physicians	1.5	14 (2.2)	Canadian Institute of Health Research and BioMérieux
Siragusa, 2009 [13]	Abstract	Multi center RCT	Prospective	NR	1.1	NR	NR
Siragusa, 2008 [14]	Abstract	Cohort	Consecutive Prospective	NR	3.0	NR	NR

N: number; RCT: randomized controlled trial; NR: not reported; CUS: compression ultrasonography; PE: pulmonary embolism

Table 2. Patient characteristics of included studies.

Study	Total study population (included in analysis) (n)	Age (year)	Male (n, %)	History of VTE (n, %)	Cancer (n, %)	Initial diagnosis of DVT			
						Modality	Distal / proximal (n/n)	Idiopathic / risk factor (n/n)	Duration of treatment (month)
Cosmi, 2010 [10]	619 (397)	62.9	263 (55)	0 (0)	0 (0)	CUS	0/478†	478/0†	at least 3
Prandoni, 2009 [16]	538 (268)	64	135 (50)	0 (0)	0 (0)	CUS	0/268	151/117	unprovoked 6 provoked 3
Siragusa, 2008 [17]	258 (170)	58	91 (54)	0 (0)	0 (0)	CUS	0/170	100/70	3
Cosmi, 2005 [11]	400 (399)	72	236 (59)	0 (0)	0 (0)	CUS	0/400	400/0	6 (median); 7.6 (mean)
Cosmi, 2005 [15]	88 (88)	71	35 (40)	0 (0)	88 (100)	CUS	0/88	0/88	6 (median); 8.8 (mean)
Prandoni, 2002 [6]	313 (313)	59.5	146 (47)	0 (0)	0 (0)	CUS	0/313	124/109‡	4
Piovella ,2002 [7]	283 (251)	64.9	97 (34)	0 (0)	38 (16)	CUS	0/283†	141/142†	3, 6, ≥ 9*
Poli, 2008 [8]	295 (258)	62	157 (53)	0 (0)	NR	CUS	NR	183/112†	9
Rodger, 2008 [9]	646 (452)	53	332 (51)	0 (0)	0 (0)	CUS	0/452	452/0	5-7
Siragusa, 2009 [13]	134 (89)	60.9	46 (52)	0 (0)	89 (100)	CUS	NR	0/89	6
Siragusa, 2008 [14]	518 (518)	NR	NR	0 (0)	0 (0)	CUS	NR	518/0	RVT absent: 3 RVT present: 6

VTE: Venous thromboembolism; DVT: deep vein thrombosis; INR: international normalized ratio; NR: not reported; RVT: residual venous thrombosis; *depending on patient characteristics (provoked/unprovoked/malignancy); †of the original study population; ‡information about presence of a risk factor available in only 233 patients

Table 3. Outcome of included studies.

Study	Total study population (n)	CUS performed* (n, %)	CUS not performd (n)	Time after initial DVT (month)	Modality Residual thrombosis	Criteria residual thrombosis‡	CUS positive for residual thrombosis (n, %)	CUS negative for residual thrombosis (n, %)	Duration of follow-up (year)	Criteria of recurrent ipsilateral DVT	VTE in follow-up (n %)
Cosmi, 2010 [10]	619	478	141 12	At stop VKA, at least 3	CUS	Prandoni	178 (37) 151	300 (63) 246	1.8	Previously compressible venous segment noncompressible or increase of RVT of > 4 mm	51 (11)
Prandoni, 2009 [16]	538	268	NR	3	CUS	Prandoni	79 (29)	189 (71)	2.75	DVT recanalized: Diameter < 2.0 mm in single determination< 3.0 mm in 2 consecutive determinations	46 (17)
Siragusa, 2008 [17]	258	258	0	3	CUS	Piovella	180 (70)	78 (30)	2.0	Previously compressible venous segment noncompressible or increase of RVT of > 4 mm	43 (17)
Cosmi, 2005 [11]	400	399	1	At stop VKA, at least 6	CUS	Prandoni	225 (56)	174 (44)	1.8	Previously compressible venous segment noncompressible or increase of RVT of > 4 mm	67 (17)
Cosmi, 2005 [15]	88	88	0	At stop VKA	CUS	Prandoni	51 (58)	37 (42)	2.0	Previously compressible venous segment noncompressible or increase of RVT of > 4 mm	21 (24)

Table 3. Outcome of included studies. (continued)

Study	Total study population (n)	CUS performed* (n, %)	CUS not performd (n)	Time after initial DVT (month)	Modality Residual thrombosis	Criteria residual thrombosis‡	CUS positive for residual thrombosis (n, %)	CUS negative for residual thrombosis (n, %)	Duration of follow-up (year)	Criteria of recurrent ipsilateral DVT	VTE in follow-up (n %)
Prandoni, 2002 [6]	313	313	0	3/6/12/24/36†	CUS	Prandoni	252 (81)	61 (19)	2.0	By CUS, followed by ascending phlebography in case of indeterminate findings or a strong discrepancy between clinical suspicion and negative CUS result	39 (12)
Piovella ,2002 [7]	283	251	32	1/3/6/12†	CUS	Piovella	129 (51)	122 (49)	1.0	Previously non-occlusive thrombus changed into occlusive thrombus, provided the vein area before compression increased by more than 50%	20 (7)
Poli, 2008 [8]	295	258	37	At stop VKA	CUS	Prandoni / Piovella	105 (41)	153 (59)	2.1	Presence of high clinical likelihood and confirmed by new CUS (criteria n.r)	32 (12)
Rodger, 2008 [9]	646	452	194	5-7	CUS	Prandoni	231 (51)	221 (49)	1.5	Previously compressible venous segment noncompressible or increase of RVT of > 4 mm	91 (14)
Siragusa, 2009 [13]	134	134	0	6	NR	Piovella	92 (69)	42 (31)	1.1	N.R	19 (14)
Siragusa, 2008 [14]	518	518	0	RVT – 3 RVT + 6	CUS	Piovella	312 (60)	206 (40)	3.0	N.R	65 (13)

CUS: Compression ultrasonography; DVT: Deep vein thrombosis; VTE: venous thrombo embolism; PE: pulmonary embolism; RVT: residual vein thrombosis; NR: not reported; *only patients with vitamin K antagonists (VKA) withdrawal; †Only data of 3 months CUS were used in this analysis; ‡Prandoni: residual thrombosis is considered present if vein diameter during compression is more than 2.0 mm in diameter ; Piovella: residual thrombosis is considered present if vein diameter during compression x 100/vein diameter before compression > 40%

Outcome

After pooling the study results as figures 2–4, we identified an overall twofold risk [OR 2.02; 95% confidence interval (CI) 1.62–2.50] of recurrent VTE in patients with proven residual thrombosis. As expected, the heterogeneity between the studies was large, with an I^2 of 77% and chi-square of P < 0.001. This heterogeneity was due to different potential factors, i.e. the use of different criteria for residual thrombosis, differences in timing of residual thrombosis assessment and differences in study population demographics. Therefore, and in accordance with our study protocol, we concluded that it was not meaningful to pool all studies together, but describe the studies separately. It was possible to pool some of the subgroups and these results are described in the following

	RVT present		RVT absent		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Prandoni						
Cosmi (2005a)	41	225	26	174	19.9%	1.27 [0.74, 2.17]
Cosmi (2005b)	16	51	5	37	3.3%	2.93 [0.96, 8.90]
Cosmi (2010)	17	151	32	246	17.9%	0.85 [0.45, 1.59]
Prandoni (2002)	30	252	9	61	10.6%	0.78 [0.35, 1.74]
Prandoni (2009)	19	79	27	189	10.0%	1.90 [0.98, 3.67]
Rodger (2008)	45	231	32	221	21.8%	1.43 [0.87, 2.35]
Subtotal (95% CI)		**989**		**928**	**83.6%**	**1.30 [1.00, 1.68]**
Total events	168		131			
Heterogeneity: Chi2 = 6.80, df = 5 (P = 0.24); I2 = 26% *Test of overall effect: Z = 1.98 (P = 0.05)*						
Piovella						
Piovella (2002)	16	129	4	122	3.0%	4.18 [1.36, 12.87]
Siragusa (2008a)	25	92	1	78	0.7%	28.73 [3.79, 217.76]
Siragusa (2008b)	63	312	2	206	1.6%	25.81 [6.24, 106.75]
Siragusa (2009)	11	47	1	42	0.7%	12.53 [1.54, 101.84]
Subtotal (95% CI)		**580**		**448**	**5.9%**	**13.68 [6.58, 28.44]**
Total events	115		8			
Heterogeneity: Chi2 = 5.56, df = 3 (P = 0.14); I2 = 46% *Test of overall effect: Z = 7.01 (P < 0.00001)*						
Mixed						
Poli (2008)	14	105	18	153	10.5%	1.15 [0.55, 2.44]
Subtotal (95% CI)		**105**		**153**	**10.5%**	**1.15 [0.55, 2.44]**
Total events	14		18			
Heterogeneity: Not applicable *Test for overall effect: Z = 0.38 (P = 0.71)*						
Total (95% CI)		**1674**		**1529**	**100.0%**	**2.02 [1.62, 2.50]**
Total events	297		157			
Heterogeneity: Chi2 = 43.51, df = 10 (P < 0.00001); I2 = 77% *Test of overall effect: Z = 6.35 (P < 0.00001)* *Test for subgroup differences: Chi2 = 31.15, df = 2 (P < 0.00001); I2 = 94%*						

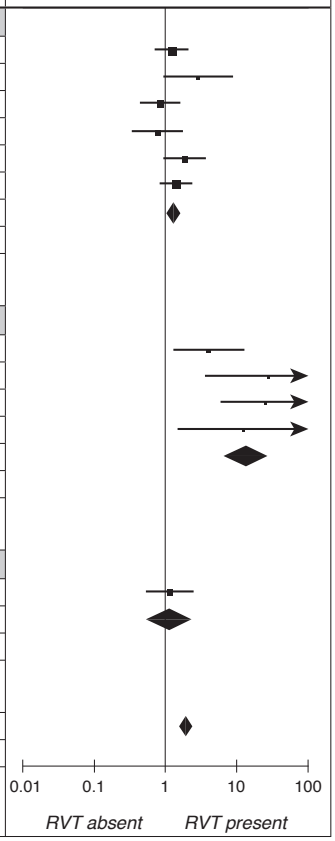

Figure 2. Forest plot of studies with different methods of determination of residual thrombosis. Mantel Haenszel (M-H) methods for combining trials were used for weighting the studies. The squares represent the weighted odds ratio of the single study; the diamonds represent the mean weighted odds ratio of the (sub) totals. RVT, residual venous thrombosis: 95% CI, 95% confidence interval; df, degrees of freedom

Study or Subgroup	RVT present Events	RVT present Total	RVT absent Events	RVT absent Total	Odds Ratio Weight	Odds Ratio M-H, Fixed, 95% CI
3 months						
Prandoni (2009)	19	79	27	189	10.0%	1.90 [0.98, 3.67]
Siragusa (2008a)	25	92	1	78	0.7%	28.73 [3.79, 217.76]
Siragusa (2008b)	63	312	2	206	1.6%	25.81 [6.24, 106.75]
Subtotal (95% CI)		**483**		**473**	**12.3%**	**6.43 [3.90, 10.62]**
Total events	107		30			
Heterogeneity: Chi2 = 19.00, df = 2 (P < 0.0001); I2 = 89%						
Test of overall effect: Z = 7.29 (P < 0.00001)						
6 months						
Rodger (2008)	45	231	32	221	21.8%	1.43 [0.87, 2.35]
Siragusa (2009)	11	47	1	42	0.7%	12.53 [1.54, 101.84]
Subtotal (95% CI)		**278**		**263**	**22.5%**	**1.76 [1.10, 2.81]**
Heterogeneity: Chi2 = 4.05, df = 1 (P = 0.04); I2 = 75%						
Test of overall effect: Z = 2.37 (P = 0.02)						
Mixed						
Cosmi (2005a)	41	225	26	174	19.9%	1.27 [0.74, 2.17]
Cosmi (2005b)	16	51	5	37	3.3%	2.93 [0.96, 8.90]
Cosmi (2010)	17	151	32	246	17.9%	0.85 [0.45, 1.59]
Piovella (2002)	16	129	4	122	3.0%	4.18 [1.36, 12.87]
Poli (2008)	14	105	18	153	10.5%	1.15 [0.55, 2.44]
Prandoni (2002)	30	252	9	61	10.6%	0.78 [0.35, 1.74]
Subtotal (95% CI)		**913**		**793**	**65.2%**	**1.27 [0.95, 1.71]**
Total events	134		94			
Heterogeneity: Chi2 = 9.53, df = 5 (P = 0.09); I2 = 48%						
Test for overall effect: Z = 1.60 (P = 0.11)						
Total (95% CI)		**1674**		**1529**	**100.0%**	**2.02 [1.62, 2.50]**
Total events	297		157			
Heterogeneity: Chi2 = 43.51, df = 10 (P < 0.00001); I2 = 77%						
Test of overall effect: Z = 6.35 (P < 0.00001)						
Test for subgroup differences: Chi2 = 10.93, df = 2 (P = 0.005); I2 = 82%						

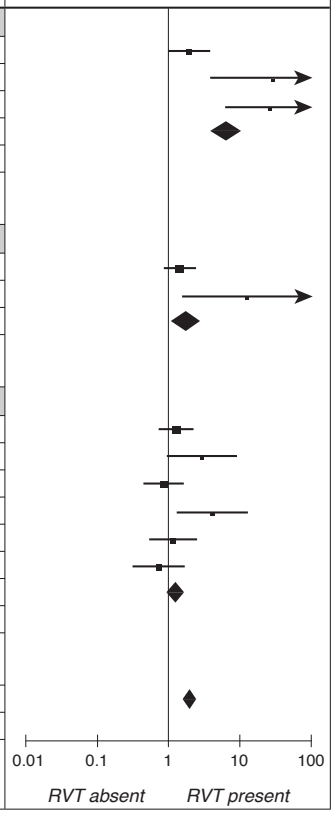

Figure 3. Forest plot of studies with different timing of measurement. Mantel–Haenszel (M–H) methods for combining trials were used for weighting the studies. The squares represent the weighted odds ratio of the single study; the diamonds represent the mean weighted odds ratio of the (sub) totals. RVT, residual venous thrombosis: 95% CI, 95% confidence interval; df, degrees of freedom.

paragraphs. Two main criteria for residual thrombosis are used in the included studies. The criteria of Prandoni were used in six studies.[7,8,10,15-17] and these criteria consider veins to be recanalized if they were 2.0 mm or less in diameter on a single test or 3.0 mm or less in diameter in two consecutive tests. The Piovella criteria uses the following formula to calculate residual thrombosis: vein diameter during compression x 100 divided by the vein diameter before compression; residual thrombosis was considered absent if the figure was 40% or less of the vein diameter; this criterion was used in four studies.[6,13,14,18] One study combined both criteria, without the possibility of distinguishing patients diagnosed with one criterion.[19]The six studies utilizing the criteria of Prandoni included a total of 1917 patients with 299 recorded recurrent VTE events (16%). Pooling these

Study or Subgroup	RVT present Events	RVT present Total	RVT absent Events	RVT absent Total	Odds Ratio Weight	Odds Ratio M-H, Fixed, 95% CI
Malignancy						
Cosmi (2005b)	16	51	5	37	3.3%	2.93 [0.96, 8.90]
Siragusa (2009)	11	47	1	42	0.7%	12.53 [1.54, 101.84]
Subtotal (95% CI)		**98**		**79**	**4.0%**	**4.55 [1.76, 11.79]**
Total events	27		6			
Heterogeneity: Chi2 = 1.50, df = 1 (P = 0.22); I2 = 33%						
Test of overall effect: Z = 3.12 (P = 0.002)						
Unprovoked						
Cosmi (2005a)	41	225	26	174	19.9%	1.27 [0.74, 2.17]
Cosmi (2010)	17	151	32	246	17.9%	0.85 [0.45, 1.59]
Rodger (2008)	45	231	32	221	21.8%	1.43 [0.87, 2.35]
Siragusa (2008a)	25	92	1	78	0.7%	28.73 [3.79, 217.76]
Subtotal (95% CI)		**699**		**719**	**60.3%**	**1.50 [1.12, 2.01]**
Total events	128		91			
Heterogeneity: Chi2 = 11.75, df = 3 (P = 0.008); I2 = 74%						
Test of overall effect: Z = 2.69 (P = 0.007)						
Mixed						
Piovella (2002)	16	129	4	122	3.0%	4.18 [1.36, 12.87]
Poli (2008)	14	105	18	153	10.5%	1.15 [0.55, 2.44]
Prandoni (2002)	30	252	9	61	10.6%	0.78 [0.35, 1.74]
Prandoni (2009)	19	79	27	189	10.0%	1.90 [0.98, 3.67]
Siragusa (2008b)	63	312	2	206	1.6%	25.81 [6.24, 106.75]
Subtotal (95% CI)		**877**		**731**	**35.7%**	**2.61 [1.84, 3.69]**
Total events	142		60			
Heterogeneity: Chi2 = 24.78, df = 4 (P < 0.0001); I2 = 84%						
Test for overall effect: Z = 5.39 (P < 0.00001)						
Total (95% CI)		**1674**		**1529**	**100.0%**	**2.02 [1.62, 2.50]**
Total events	297		157			
Heterogeneity: Chi2 = 43.51, df = 10 (P < 0.00001); I2 = 77%						
Test of overall effect: Z = 6.35 (P < 0.00001)						
Test for subgroup differences: Chi2 = 5.48, df = 2 (P = 0.06); I2 = 64%						

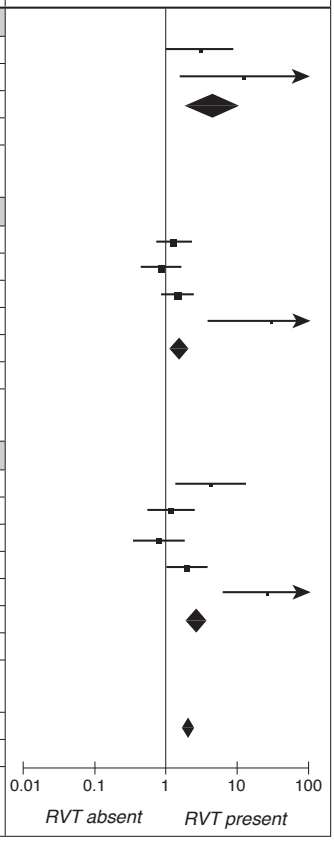

Figure 4. Forest plot of studies with different study populations. Mantel–Haenszel (M–H) methods for combining trials were used for weighting the studies. The squares represent the weighted odds ratio of the single study; the diamonds represent the mean weighted odds ratio of the (sub) totals. RVT, residual venous thrombosis: 95% CI, 95% confidence interval; df, degrees of freedom.

studies showed an I^2 of 26% with a chi-square of P = 0.24, indicating minimal heterogeneity between studies. The pooled OR was 1.3 (95% CI, 1.00–1.68) (figure 2).

The four studies using the criteria of Piovella included 1028 patients, totaling 123 recurrent VTE events (12%). Pooling these studies showed an I2 of 46% with a chi-square of P = 0.14, also showing less heterogeneity than pooling all studies together. The pooled OR was 13.68 (95% CI, 6.58–28.44) for the Piovella criteria (figure 2). Measurement of the heterogeneity between the subgroups using Prandoni, Piovella and mixed methods revealed large heterogeneity with a chi-square of 31.15 on 2 degrees of freedom, resulting in an I^2 of 94%.

Difference in timing of measurement of residual thrombosis

Four studies measured residual thrombosis after discontinuation of anticoagulant therapy [1-4,8,9,15,17] which was after at least 3 months in one study,[17] after 6 months in two studies [2,3,8,15] and after 9 (median) months in the fourth study.[9] Seven studies measured residual thrombosis at fixed time points[6,7,10,13,14,16,18], three studies after 3 months[14,16,18] two after 6 months[10,13] and two multiple times after at least 3 months of treatment [6,7] (Table 3). The test of heterogeneity between the 3 subgroups (measuring residual thrombosis at 3 months, 6 months and the group with various times of measurement) showed a chi-square of 10.93, with a I^2 82% indicating heterogeneity between these subgroups.

Residual thrombosis at fixed time after 3 months (three studies) included 956 patients, in whom 137 (14%) suffered a recurrent VTE event. Pooling these studies showed an I^2 of 89% with a chi-square of P = 0.001, this indicates significant heterogeneity between the studies and therefore a pooled OR could not be determined. One study used the criteria of Prandoni [OR: 1.90 (95% CI, 0.98–3.67)] and two studies used the criteria of Piovella [OR: 25.81 (95% CI, 6.24–106.75) and 28.73 (95% CI, 3.79–217.76)]. In the two studies measuring residual thrombosis at fixed time after 6 months, 541 patients were included of whom 89 (16%) suffered a recurrent VTE event. The criteria of Prandoni [OR: 1.43 (95% CI,0.87–2.35)] and of Piovella [OR: 12.53 (95% CI,1.54–101.84)] were used. Of note, this latter study included solely patients with active malignancy (figure 3).

Difference in study population

Four studies included solely patients with an unprovoked DVT,[8,10,17,18] five studies with a mixed group of provoked and unprovoked[6,7,9,16,18] and two studies included only patients with a malignancy.[13,15]

In the four studies that included solely unprovoked DVT patients, 1766 patients were included and 258 patients had a recurrent VTE event (15%); threeof these studies used the criteria of Prandoni and ORs ranged from 0.85 to 1.43; the fourth study used the criteria of Piovella with an OR of 25.81 (95% CI,6.24–106.75). Pooling these studies showed an I^2 of 74% with a chi-square of P = 0.008, indicating significant heterogeneity between the studies. Three studies evaluated patients with a malignancy. In one study,[6] the data of the patients with malignancy could not be distinguished from the other patients.

In the other two studies 177 patients were included, 33 patients had a recurrent VTE event (19%). One study used the criteria of Prandoni [OR of 2.93 (95% CI,0.96–8.90)] and the other study used the criteria of Piovella [OR of 12.53 (95% CI,1.54–101.84)]. Pooling these studies showed an I^2 of 33% with a chi-square of P = 0.22, showing minimal heterogeneity between studies. The pooled OR was 4.55 (95% CI, 1.76–11.79) (figure 4). Heterogeneity between subgroups [provoked (all due to malignancy), unprovoked and

the mixed group] was present (χ^2 = 5.48 on 2 degrees of freedom, resulting in an I^2 of 64%).

DISCUSSION

This systematic review showed a positive correlation between residual thrombosis and the risk of recurrent VTE. The effect size depended heavily on the included study population, the timing of the ultrasonography assessment and the method of residual thrombosis assessment. Because of significant heterogeneity between the included studies, pooling all data was not meaningful. Nonetheless, the majority of studies indicated a 1.5- to 4-fold increased risk associated with residual thrombosis.

The heterogeneity of studies was minimal in studies using only Prandoni criteria or Piovella criteria and in studies which included solely patients with a malignancy. Studies using the Prandoni criteria showed a pooled OR of 1.3 (95% CI, 1.00–1.68), while studies with the Piovella criteria showed a ten times higher pooled OR [13.68 (95% CI, 6.58–28.44)]. Patients with a malignancy showed a pooled OR of 4.55 (95% CI, 1.76–11.79).

The elevated risk of recurrent VTE in patients with residual thrombosis is physiologically plausible. First, the residual thrombosis could be a mechanical risk factor, which, by obstructing blood flow, facilitates recurrent thrombosis due to local stasis. Keeping this hypothesis in mind, it would be expected that the rate of ipsilateral recurrent DVT would be higher than contra-lateral recurrent DVT. However previous studies showed that the risk of ipsilateral recurrent DVT is lower than contra-lateral recurrent DVT.[19,20] A second hypothesis is that the presence of residual thrombosis indicates a higher thrombogenic state of the patient, e.g. in patients with active malignancy.[20] The cause of the large difference in pooled OR between the Prandoni and Piovella criteria is unclear. Hypothetically the criteria of Piovella could be stricter, therefore identifying patients with a more substantial residual thrombosis and potentially more prone to recurrent VTE. Also, residual thrombosis is a strong prognostic factor for recurrent VTE in patients with malignancy using the Prandoni as well as the Piovella criteria. However, whether this is of clinical relevance could be debated. The presence of residual thrombosis could, on one hand, identify patients with a low or high risk for recurrent VTE. On the other hand, patients with a malignancy are currently treated indefinitely or until the cancer is resolved, which would diminish the need for residual thrombus testing.[1]

Other factors which influence the prognostic capacity of residual thrombosis on recurrent VTE are the timing of measurement of residual thrombosis and whether patients with an unprovoked or provoked DVT, irrespective of patients with malignancy, are included. The clinical applicability of residual thrombosis assessment in a provoked VTE population could be questioned, as these patients have a very low recurrence risk

rate and short-term therapy for 3 months is considered sufficient in these cases.[1] The most common timing of measuring residual thrombosis is after a fixed period of 3 or 6 months, but it is unknown whether the timing of measuring residual thrombosis would influence the prognostic capacity of residual thrombosis. Other parameters have been evaluated to predict VTE recurrence after a first DVT, including D-dimer testing. Elevated D-dimer levels give a 2.4 increase of the recurrence risk in patients with an unprovoked DVT.[5,21] An advantage of D-dimer testing is the simple and standardized technique. A drawback of D-dimer testing is that this evaluation takes place after 1 month of stopping oral anticoagulant therapy and that, in case of an elevated D-dimer level, anticoagulant therapy should be restarted. This is in contrast to measuring residual thrombosis, which could be determined during anticoagulant therapy, and if present anticoagulant therapy can be continued without stopping. Drawbacks of residual thrombosis are the lack of standardization and consensus on which criteria of residual thrombosis should be used. Furthermore, a previous study reported low interobserver agreement of residual thrombosis measurement.[22]

Whether residual thrombosis has added value in addition to D-dimer testing remains a matter of debate. Recent studies show little added value of residual thrombosis on D-dimer testing.[8,17] Both studies used the criteria of Prandoni. The additional value of residual thrombosis on D-dimer testing using the criteria of Piovella has not been reported. Management studies are currently being performed on the topic of D-dimer combined with residual thrombosis.

We consider our results to be representative because our findings are based on an extended literature search with a large cohort of over 3200 patients. Second, the analysed studies were of high quality with a prospective design and using standardized diagnostic tests. Finally all endpoints were well-defined and confirmed by objective tests by predefined criteria. This analysis has limitations. Included studies used different criteria to determine residual thrombosis. Also, duration of follow-up and definitions of endpoints varied among the studies. In addition, most studies did not mention completeness of follow-up. Finally, a limitation is the published data approach, whereby time to recurrence cannot be used as an outcome measure and by which it was not possible to identify independent prognostic factors. Further studies are needed to further define the role of residual thrombosis in the prognostic risk assessment and to overcome the heterogeneity of the published studies. Furthermore, a direct comparative study between the Piovella and Prandoni criteria is lacking. Finally, an individual patient data meta-analysis (using raw data) may be worthwhile to identify independent prognostic factors with time to recurrence as outcome.

In conclusion, patients with the presence of residual thrombosis after DVT are at higher risk of recurrent VTE than patients without residual thrombosis. This higher risk is more pronounced when utilizing the Piovella criteria for measuring residual thrombosis

compared to the Prandoni criteria. However this systematic review also shows that the determination of residual thrombosis needs further standardization. Detection of residual thrombosis might be helpful in prognostic risk assessment.

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