Evidence Table 1: Description of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism

Author, Year	Study aim	# trials	Most recent study	# pts	LMWH used in trials [a]	Systematic review quality scores					
						Overall [b]	Search [c]	Eligibility [d]	Study Quality [e]	Combining Results [f]	Aims & Conclusions [g]
Green, 1994	To compare IV or SQ LMWH to IV or SQ UFH for tx of DVT	9	1993	1308	1, 2, 3, 4, 5	22	0	33	0	0	75
Hirsh, 1995	To compare IV or SQ LMWH to IV or SQ UFH for first episode of VTE	13	1993	1723	1, 2, 3, 4, 5	77	50	83	75	75	100
Lensing, 1995	To compare IV or SQ LMWH to IV or SQ UFH for tx of DVT	10	1994	1512	1, 2, 3, 4, 6	67	67	67	0	100	100
Leizorovicz, 1996	To compare IV or SQ LMWH to IV or SQ UFH for tx of DVT	20	1996	3333	2, 5, 7, 8, 9, 10, 11	37	17	17	0	75	75
Howard, 1997	To compare IV or SQ dalteparin to IV or SQ UFH for tx of VTE	8	1995	863	7	42	50	33	0	25	100
Brewer, 1998 [h]	To compare LMWH to UFH for tx of adults with DVT	6	1997	2986	5, 7, 10, 11, 12	53	50	67	0	50	100
Hettiarachchi, 1998	To compare SQ LMWH to UFH for tx of VTE	13	1998	4509 [i]	2, 5, 7, 10, 11, 12	65	67	83	0	75	100
Hunt, 1998	To compare LMWH to UFH for tx of VTE	10	1997		5, 7, 10, 11, 12	22	33	0	0	0	75
Martineau, 1998	To compare IV or SQ LMWH to IV or SQ UFH for tx of DVT	13	1996	2825	5, 7, 10, 11	43	33	83	0	0	100
Gould, 1999	To compare SQ fixed-dose LMWH to adjusted dose UFH for tx of acute DVT	11	1997	3674	5, 7, 10, 11, 12	92	83	100	75	100	100
Dolovich, 2000	To compare SQ LMWH to IV UFH for initial tx of VTE	13	1997	4447	5, 7, 10, 11, 12	77	67	67	50	100	100
Rocha, 2000	To compare IV or different dosages of SQ LMWH to IV or SQ UFH for tx of VTE	21	1997	4472	2, 4, 5, 7, 9, 10, 12, 13	62	50	83	0	100	75

Evidence Table 1: Description of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism (continued)

Author, Year	Study aim	# trials	Most recent study	# pts	LMWH used in trials [a]	Systematic review quality scores: Overall [b]	Search [c]	Eligibility [d]	Study Quality [e]	Combining Results [f]	Aims & Conclusions [g]
van den Belt, 2000	To compare SQ LMWH to SQ or IV UFH for tx of VTE	14	1997	4754	2, 5, 7, 10, 11, 12	92	83	100	75	100	100
van der Heijden, 2000	To compare SQ LMWH to IV or SQ UFH for VTE	16	2000	6055	2, 5, 7, 9, 10, 11, 12	60	33	67	0	100	100

[a] LMWH: 1=fragmin, 2=CY222, 3=fraxiparin, 4=logiparin, 5=enoxaparin, 6=clexane, 7=dalteparin, 8=parnaparin, 9=certoparin, 10=nadroparin, 11=tinzaparin, 12=reviparin, 13=OP2123

[b] **Overall Quality Score:** The mean of the percentage scores from the categories: Search Methods, Inclusion & Description, Quality Assessment, Methods of Combination, and Aims/Conclusions (see below).

[c] **Search Methods:** Percentage score based on a total maximum score of 6 points. This included description of search methods (2 points), comprehensiveness of search methods (2 points), and reproducibility of review methods (2 points).

[d] **Eligibility and Description:** Percentage score based on a total maximum score of 6 points. This included description of study inclusion criteria (2 points), appropriateness of study inclusion criteria (2 points), and discussion of variation in the original literature based on differences in study design (2 points).

[e] **Study Quality Assessment:** Percentage score based on a total maximum score of 4 points. This included description of quality assessment (2 points), and appropriateness of quality assessment (2 points).

[f] **Combining Results:** Percentage score based on a total maximum score of 4 points. This included description of methods used to combine study results (2 points), and appropriateness of methods used to combine study results (2 points).

[g] **Aims & Conclusions:** Percentage score based on a total maximum score of 4 points. This included whether the question to be addressed by the review was clearly stated (2 points), and whether the conclusions reached by the review were supported by data and/or analyses (2 points).

[h] Review examined 3 meta-analyses and 6 RCTs. Only the data from RCTs is presented here.

[i] Not reported. Review also included 1 study (Simmoneau, 1997) that examined LMWH vs. UFH for PE.

Evidence Table 2: Results of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism

Author, Year	Pt populations in RCTs	Recurrence of symptomatic VTE (LMWH vs UFH)	Thrombus extension (LMWH vs UFH)	Major bleeding during tx (LMWH vs UFH)	All deaths (LMWH vs UFH)	Other outcomes/comments (LMWH vs UFH)
Green, 1994	Pts w/DVT	During mos 3 to 6: incidence 2.7 vs 7.4%; RRR 63% [CI 30-80%], 8 trials	64 vs 50% had thrombus size reduction, 6 vs 12% had increase in size, p<0.001; 8 trials	0.9 vs 3.2%; RRR 71% [CI 33-88%]; 8 trials		
Hirsh, 1995	Pts w/first episode of VTE	Day 1-15: incidence 0.8 vs 2.4%; RRR 68%; p=0.02; 6 trials Day 16-90: incidence 1.6 vs 2% RRR 26%; p=0.8; 6 trials Day 1-90: incidence 2.4 vs 4.5%; RRR 50%, p=0.02; 6 trials		2.2 vs 4.7%; RRR 66%, p=0.04; 10 trials	0.6 vs 1%; days 1-15: RRR 39%, p=0.3; 12 trials. 2.5 vs 4.5%; days 16-90: RRR 52%, p=0.03; 12 trials. 3.3 vs 5.9%; days 1-90: RRR 49%, p=0.01; 12 trials.	No difference in minor bleeding; 10 trials. Fatal PE, 0.4 vs 0.7%, p=0.4. Pts w/ca: mortality 13.5 vs. 28.4%; RRR 67%, p=0.01; pts w/o ca: 1.9 vs 2.6%, p=0.40; 4 trials. Level 1 studies[a] (3 trials): VTE recurrence, Day 1-15: RR 0.24 [CI 0.06-0.8]; Day 16-90: RR 0.60 [CI 0.2-1.5]; RR 0.39 [CI 0.3-0.8]; Major bleeding: RR 0.42 [CI 0.2-0.9].
Lensing, 1995	Pts w/DVT	Incidence 3.1 vs 6.6%; RRR 53% [CI 18-73%]; 5 trials	63 vs 52% had reduction in thrombus size; 6 vs 12% had increase in thrombus size; p<0.001; 9 trials.	0.9 vs 3.2%; RRR 68% [CI 31-85%]; 10 trials.	3.9 vs 7.1%; RRR 47% [CI 10-69%]; 5 trials.	Subgroup of pts w/ca: all deaths 12 vs 28%; RRR 56% [CI 17-77%].

Evidence Table 2: Results of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism (continued)

Author, Year	Pt populations in RCTs	Recurrence of symptomatic VTE (LMWH vs UFH)	Thrombus extension (LMWH vs UFH)	Major bleeding during tx (LMWH vs UFH)	All deaths (LMWH vs UFH)	Other outcomes/comments (LMWH vs UFH)
Leizorovicz, 1996	Pts w/DVT	Incidence 3.8 vs 5.2%; OR 0.77 [CI 0.55-1.08]; 20 trials	6.0 vs 9.5%; OR 0.65 [CI 0.44-0.96]; 12 trials	1.5 vs 3.1%; OR 0.59 [CI 0.35-0.98]; 20 trials	3.7 vs 5.4%; OR 0.70 [CI 0.50-0.98]; 20 trials.	Results similar for safety and efficacy for LMWH daily or bid. LMWH reduced VTE recurrence and mortality when provided at home (UFH in-hospital; 2 trials) or in-hospital (UFH in-hospital, 18 trials).
Howard, 1997	Pts w/VTE					Descriptive study.[b] Authors concluded that dalteparin may be as effective as UFH in tx for DVT and PE; more data needed.
Brewer, 1998	Adults w/VTE					Descriptive study.[b] Authors concluded that LMWH as effective and safe as UFH. Thrombocytopenia less frequent w/ LMWH. Osteoporosis may be less common w/LMWH.
Hettiarachchi, 1998	Pts w/VTE	Incidence 3.8 vs 4.8%; OR 0.77[CI 0.56-1.04]; 10 trials		1.3 vs 2.2%; OR 0.60 [CI 0.38-0.95]; 13 trials.	4.8 vs 6.5%; OR 0.72 [CI 0.55-0.96]; 9 trials.	Results similar w/ or w/o ca. Pts w/PE: VTE recurrence OR 0.91 [CI 0.42-1.97]; 2 trials.
Hunt, 1998	Pts w/VTE					Descriptive study.[b] Authors concluded that LMWH cheaper, better tolerated, potentially more effective than UFH for DVT. Insufficient data regarding PE.
Martineau, 1998	Pts w/first episode of DVT					Descriptive study.[b] Authors concluded LMWH as safe and effective as UFH.

Evidence Table 2: Results of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism (continued)

Author, Year	Pt populations in RCTs	Recurrence of symptomatic VTE (LMWH vs UFH)	Thrombus extension (LMWH vs UFH)	Major bleeding during tx (LMWH vs UFH)	All deaths (LMWH vs UFH)	Other outcomes/comments (LMWH vs UFH)
Gould, 1999	Pts w/acute DVT	Incidence 4.6 vs 5.4%; OR 0.85 [CI 0.63 to 1.14]; ARR 0.88% [CI -0.48-2.24%], NNT 114; 11 trials		Random-effects model: OR 0.71 [CI 0.40 to 1.27]; 11 trials 1.1 vs 1.9%; fixed-effects model OR 0.57[CI 0.33 to 0.99]; ARR 0.61% [CI -0.04% to 1.26%], NNT 164; 11 trials	5.0 vs 6.8%; OR 0.71 [CI 0.53-0.94]; ARR 1.65% [CI 0.36-2.94], NNT 61; 11 trials	Minor bleeding: OR 0.98 [CI 0.63 to 1.51]. Thrombocytopenia: OR 0.74 [CI 0.37-1.48]. PE during tx: OR 0.84 [CI 0.51-0.36]. DVT during tx: OR 0.85 [CI 0.59-1.23]. Pts w/ca: Mortality 16.7 vs 25.9%; OR 0.57 [CI 0.31 to 1.03]; ARR 9.75% [CI 0.34% to 19.2%], NNT 10. Reduced mortality benefit in more recent studies. Dalteparin, tizaparin, and nadroparin favored LMWH whereas studies using enoxaparin or reviparin favored UFH. Benefit of LMWH noted if all pts received inpt LMWH, but not if LMWH was permitted as outpt.
Dolovich, 2000	Pts w/VTE	Incidence 4.3 vs 5.1%; RR 0.85 [CI 0.65-1.12]; 13 trials		1.5 vs 2.6%; RR 0.63 [CI 0.37-1.05]; 13 trials	4.9 vs 6.5%; RR 0.76 [CI 0.59-0.98]; 10 trials.	PE: 1.9 vs 1.8%; RR 1.02 [CI 0.64-1.62]; 12 trials. Minor bleeding: 5.6 vs 4.7%; RR 1.18 [CI 0.87-1.61]; 12 trials. Thrombocytopenia: 1.0 vs 1.3%; RR 0.85 [CI 0.45-1.62]; 11 trials. Results similar whether LMWH daily or bid.

Evidence Table 2: Results of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism (continued)

Author, Year	Pt populations in RCTs	Recurrence of symptomatic VTE (LMWH vs UFH)	Thrombus extension (LMWH vs UFH)	Major bleeding during tx (LMWH vs UFH)	All deaths (LMWH vs UFH)	Other outcomes/comments (LMWH vs UFH)
Rocha, 2000	Pts w/VTE	OR 0.78 [CI 0.59-1.04]; 13 trials	OR for extension 0.73 [CI 0.59-0.90]; 12 trials	OR 0.65 [CI 0.43-0.98]; 8 trials	OR 0.68 [CI 0.50-0.91]; 9 trials.	Bid LMWH formulations more effective than UFH to prevent thrombus extension (p=0.004). Daily less likely than UFH to cause major bleeding (p=0.025). NSD between once daily and bid for VTE recurrence or mortality.
van den Belt, 2000	Pts w/VTE	Initial tx: incidence 1.8 vs 2.6%; OR 0.70 [CI 0.46-1.06]; 11 trials. 3 months f/u: incidence 3.8 vs 5.1%; OR 0.75 [CI 0.46-1.01], 9 trials 6 months f/u: OR 0.76 [CI 0.44-1.30]; 3 trials End of f/u: incidence 4.3 vs 5.6%; OR 0.76 [CI 0.57-1.01]; 11 trials	60 vs 54% had reduction in thrombus size; OR 0.77 [CI 0.61-0.97] for better venographic outcome; 8 trials	1.3 vs 2.1%; OR 0.60 [CI 0.39 to 0.93]; 14 trials	6.4 vs 8.0%; OR 0.78 [CI 0.62-0.99]; 11 trials.	Pts w/PE: VTE recurrence OR 0.91 [CI 0.42-1.97]. Pts w/ca: Mortality OR 0.53 [CI 0.33-0.85]; pts w/o ca: OR 0.97 [CI 0.61-1.56]; 6 trials. Pts w/proximal DVT: VTE recurrence, major hemorrhage and mortality all significantly lower w/LMWH. Studies that reported concealed allocation (7 studies): similar results as all studies but ORs were not significant.
van der Heijden, 2000	Pts w/VTE	OR 0.66 [CI 0.51-0.86]; 13 trials		OR 0.56 [CI 0.38-0.83]; 16 trials	OR 0.68 [CI 0.53-0.88]; 12 trials.	Greater benefit from LMWH in studies w/ higher rates of VTE recurrence in UFH group. LMWH benefit unrelated to incidence of outcomes for major hemorrhage or mortality.

[a] Blind assessment
[b] No quantitative pooling of data.

Evidence Table 3: Description of studies comparing outpatient to inpatient treatment of venous thromboembolism

Author, Year	Location	Study aims	Design	Recruit dates	Mean f/u (mos)	Surveillance	VTE character	Exclusions	
								General criteria	Risk factors
LMWH at home compared to UFH in the hospital									
Koopman, 1996	Europe & Australia	To demonstrate equivalence in efficacy and safety and evaluate use of resources.	RCT		6	N	No PE	Preg/childbirth; unlikely to comply; LE < 6 mos; tx w/ heparin for 24 hrs; age < 18yrs	Previous VTE; known thrombophilia; known malignancy
Levine, 1996	Canada	To compare use of UFH in the hospital with LMWH at home for acute DVT tx.	RCT	1992-95	3	Y	No: calf vein only, PE	Unlikely to comply; hereditary bleeding; contraindication to AC	VTE in preceding 6 months
Belcaro, 1999	Europe	To compare IV heparin or SQ heparin w/LMWH either at home or in hospital, with oral anticoagulant for tx of proximal DVT.	RCT	1992-95	3	Y	No: PE, thromb-cytopenia	Preg/childbirth; unlikely to comply; hereditary bleeding	
Pearson, 1999	United States	To present short-term outcomes of pts treated as outpt and to compare associated costs before and after implementation.	CohR	1996-97	0.5	N	No PE		
Grau, 2001	Europe	To compare incidence of recurrent VTE in UFH inpts and LMWH outpts.	CohR	1986-99		N	No PE	Inclusion: Preg/childbirth; OCPs/HRT; recent fracture/cast	Known thrombophilia
Vinson, 2001	United States	To evaluate effectiveness & safety of outpt care pathway for tx of DVT with LMWH.	CohP	1994-99	0.5	N	No: UE, calf vein only, PE, CVA, anemia	Preg/childbirth; allergy; unlikely to comply; hereditary bleeding; contraindication to AC, age <18	

Evidence Table 3: Description of studies of comparing outpatient to inpatient treatment of venous thromboembolism (continued)

Author, Year	Location	Study aims	Design	Recruit dates	Mean f/u (mos)	Surveillance	VTE character	Exclusions	
								General criteria	Risk factors
Huse, 2002	United States	To quantify the economic benefits of early discharge of pts treated for DVT with LMWH using data from managed health care plans.	CohR			N		Unlikely to comply	Known thrombophilia; recent surgery; previous VTE; positive family history
Smith, 2002	Australia	To perform a cost minimization analysis in pts receiving LMWH managed w/o hospitalization. To evaluate costs and satisfaction with at-home tx of DVT using enoxaparin vs. inpt care w/UFH.		1999-99		N	No PE	Preg/childbirth; LE < 2 yrs; allergy; unlikely to comply; hereditary bleeding; contraindication to AC	Known thrombophilia; known malignancy; recent fracture/cast; previous VTE
LWMH at home compared to LMWH in the hospital									
Boccalon, 2000	Europe	To compare LMWH inpts versus outpts for efficacy and cost.	RCT	1993-97	6	Y	No: calf vein only, PE	Preg/childbirth; unlikely to comply; contraindication to AC, age <18 or age >85	Previous VTE
Kovacs, 2000	Canada	To evaluate the use of dalteparin in outpts w/PE.	CohP	1996-98	3	N	PE	Unlikely to comply, age <18	Unstable (O_2 requirements; hemodynamic instability; pain)

Evidence Table 4: Quality of studies comparing outpatient to inpatient treatment of venous thromboembolism

Author, Year	Overall [a]	Representativeness of study population [b]	Bias & confounding [c]	Description of treatment [d]	Outcomes & f/u [e]	Statistical quality & interpretation [f]
LMWH at home compared to UFH in the hospital						
Koopman, 1996	79	88	88	50	85	83
Levine, 1996	78	100	81	50	75	83
Belcaro, 1999	67	100	75	50	60	50
Pearson, 1999	38	88	31	25	10	38
Grau, 2001	47	88	31	25	30	63
Vinson, 2001	57	100	38	50	30	67
Huse, 2002	41	50	13	0	65	75
Smith, 2002	41	75	31	25	10	63
LMWH at home compared to LMWH in the hospital						
Boccalon, 2000	64	63	63	75	80	38
Kovacs, 2000	54	75	44	50	70	33

[a] **Overall:** The mean of the percentage scores from categories: Representativeness of Study Population, Bias and Confounding, Description of Treatment, Outcomes and Followup, and Statistical Quality and Interpretation (see below).

[b] **Representativeness of Study Population:** Percentage score based on a total maximum score of 8 points. This included description of study setting and population (2 points), description of inclusion/exclusion criteria (2 points), information on excluded or non-participating patients (2 points), and description of key patient characteristics (2 points).

[c] **Bias and Confounding:** Percentage score based on a total maximum score of 6 points. This included random assignment of patients to study groups (2 points), differences between study groups in key patient characteristics (2 points), and blinding of clinicians, patients, and outcome assessors (2 points).

[d] **Description of Treatment:** Percentage score based on a total maximum score of 4 points. This included description of the details of the treatment regimen (2 points), and description of other treatments given to each study group (2 points).

[e] **Outcomes and Followup:** Percentage score based on a total maximum score of 10 points. This included description of the criteria used for determining outcomes (2 points), description of adverse events experienced by patients (2 points), reporting on numbers and reasons for withdrawals or patients lost to followup (2 points), proportion of patients who withdrew or were lost to followup (2 points), and adequacy of the planned length of followup (2 points).

[f] **Statistical Quality and Interpretation:** Percentage score based on a total maximum score of 8 points. This included reporting on the magnitude of differences between groups with an index of variability (2 points), clear identification of all statistical analyses (2 points), use of multivariate or stratified analyses to adjust for potential confounders (2 points), and appropriate handling of withdrawals, crossovers, and loss to followup (2 points).

Evidence Table 5: Characteristics of patients in studies comparing outpatient to inpatient treatment of venous thromboembolism

Author, Year	Intervention	LMWH	Therapy duration (days)	Adjuvant therapy during f/u	Clinical characteristics(%)			
					Mean age (yrs)	Male (%)	Prior VTE (%) / Family hx (%) / Thrombophilia (%)	Recent surgery/ TRF (%)
LMWH at home compared to UFH in the hospital								
Koopman, 1996	LMWH in/outpt[a], 250 IU/kg bid	Nadroparin	6	Warfarin or other AC	59	53	20 / NR / NR	49 / 69
	UFH, 5000 u then 1250 u/hr		6	"	62	48	19 / NR / NR	52 / 68
Levine, 1996	LMWH in/outpt, 1 mg/kg bid	Enoxaparin	5	Warfarin	57	62	21 / NR / 0	29 / 100
	UFH, 5000 u then 1280 u/hr		5	"	59	58	14 / NR / 0	28 / 100
Belcaro, 1999	LMWH in/outpt, 100 IU/kg bid	Nadroparin	14	Warfarin	54	55	7 / NR / 0	20 / 100
	UFH, 5000 u then 1300 u/hr			"	53	59	7 / NR / 0	22 / 100
	UFH, 12500 IU bid		90	None	54	53	9 / NR / 0	22 / 100
Pearson, 1999	LMWH in/outpt, 1 mg/kg bid	Enoxaparin	5	Warfarin	57	42	NR / NR / NR	NR / NR
	UFH			"	56	43	NR / NR / NR	NR / NR
Grau, 2001	LMWH outpt, 175 u/kg bid	Nadroparin	5	Acencoumarol	68	58	2.3 / NR / NR	30 / 81
	UFH		5	"	59	58	3.4 / NR / NR	37 / 79
Vinson, 2001	LMWH outpt, 1 mg/kg bid	Enoxaparin	7	Warfarin, Comp stockings	63	56	14 / NR / 0	25 / 100
	UFH			Warfarin	63	46	20 / NR / 0	32 / 100
Huse, 2002	LMWH in/outpt	Enoxaparin		Warfarin	48	46	NR / NR / NR	NR / NR
	UFH			"	54	44	NR / NR / NR	NR / NR
Smith, 2002	LMWH outpt, 1 mg/kg bid	Enoxaparin	5	Warfarin	57	61	0 / NR / NR	NR / NR
	UFH		5	"	57	61	0 / NR / NR	NR / NR

Evidence Table 5: Characteristics of patients in studies comparing outpatient to inpatient treatment of venous thromboembolism (continued)

					Clinical characteristics(%)			
Author, Year	Intervention	LMWH	Therapy duration (days)	Adjuvant therapy during f/u	Mean age (yrs)	Male (%)	Prior VTE (%) / Family hx (%) / Thrombophilia (%)	Recent surgery/ TRF (%)
LMWH at home compared to LMWH in the hospital								
Boccalon, 2000	LMWH outpt	Dalateparin or enoxaparin or nadroparin		Comp stockings, vitamin K antagonist, or fluindione	65	54	NR / NR / NR	NR / NR
	LMWH inpt			"	63	59	NR / NR / NR	NR / NR
Kovacs, 2000	LMWH outpt, 200 u/kg qd	Dalteparin	5	Warfarin		56	NR / NR / 12	NR / NR
	LMWH in/outpt, 200 u/kg qd		5	"		59	NR / NR / 7	NR / NR

[a] Outpatient treatment after a brief inpatient stay

Evidence Table 6: Results of studies comparing outpatient to inpatient treatment of venous thromboembolism

Author, Year	Group	# pts	F/u (mos)	Outcomes n (%) DVT	PE	Major bleeding	Minor bleeding	Deaths	Inpt days	Costs /pt	Costs included in tabulation
LMWH at home compared to UFH in the hospital											
Koopman, 1996	Outpt	202		10 (5)	4 (2)	1 (0.5)	27 (13)	14 (7)	2.7		
	Inpt	190		12 (6)	5 (3)	4 (2)	15 (8)	16 (8)	8.1		
Levine, 1996	Outpt	247	3	11 (4)	2 (1)	5 (2)	6 (2)	11 (4)	1.1		
	Inpt	253	3	15 (6)	2 (1)	3 (1)	6 (2)	17 (7)	6.5		
Belcaro, 1999	Outpt	98		6 (6)	0 (0)	0 (0)	3 (3)		5.1	773 USD	Hospital, tx and monitoring costs.
	Inpt	97		6 (6)	0 (0)	0 (0)	4 (4)		5.4	2,760 USD	
	Outpt	99		7 (7)	0 (0)	0 (0)	1 (1)		0	220 USD	
Pearson, 1999	Outpt	40	0.5	1 (2.5)	0 (0)	0 (0)		0 (0)		3,719 USD [a]	Hospital, drug, home care, and outpt visit costs.
	Inpt	67								5,465 USD [a]	
Grau, 2001	Outpt	130	21.6	5 (4)	1 (1)	3 (2)	1 (1)	11 (8)			
	Inpt	149	35	13 (9)	9 (6)	1 (1)	4 (3)	17 (11)			
Vinson, 2001	Outpt	178	0.5	0 (0)	1 (1)	0 (0)	2 (1)	0 (0)	0.03		
	Inpt	96	0.5	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)	4		
Huse, 2002	Outpt	164	12	11 (7) [a]		1 (1)			4.2	1,886 USD	Outpt costs only.
	Inpt	1696	12	153 (9)[a]		14 (1)			6.8	986 USD	
Smith, 2002	Outpt	28								756 USD	U/S, doctors, nurse visits, drug, monitoring, office staff, discharge planning costs.
	Inpt	28								2,208 USD	

Evidence Table 6: Results of studies comparing outpatient to inpatient treatment of venous thromboembolism (continued)

				Outcomes n (%)							
Author, Year	Group	# pts	F/u (mos)	DVT	PE	Major bleeding	Minor bleeding	Deaths	Inpt days	Costs /pt	Costs included in tabulation
LMWH at home compared to LMWH in the hospital											
Boccalon, 2000	Outpt	99		1 (1)		2 (2)	17 (17)	0 (0)	1	9,230 FRF [a]	U/S, doctors, nurse visits, monitoring, hospital costs, drug costs.
	Inpt	102		2 (2)		2 (2)	11 (11)	2 (2)	9.6	20,932 FRF [a]	
Kovacs, 2000	Outpt	81		0 (0)	5 (6)	1 (1)	3 (4)	4 (5)			
	Inpt	27		1 (4)	0 (0)	1 (4)	2 (7)	0 (0)			

[a] $p < 0.05$ for difference

Evidence Table 7: Description of modeled analysis of the costs of using low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism

Author, year	Aims	Total quality score (%) [a]
Hull, 1997	To perform an economic evaluation comparing tinzaparin to UFH for inpt tx of prox DVT.	100
Rodger, 1998	To assess the cost-effectiveness of LMWH and UFH using data from a meta-analysis and patient-specific case-costing data.	83
Gould, 1999	To evaluate the costs and health effects of a LMWH compared to UFH for inpt tx of acute DVT.	100
Estrada, 2000	To perform an economic evaluation comparing LMWH to UFH for treating a DVT in inpts and outpts.	89
Lloyd, 1997	To evaluate the inpt cost of treating a DVT with nadroparin compared to UFH.	83
van den Belt, 1998	To assess the cost consequences of outpt management in the treatment of DVT.	89
O'Brien, 1999	To evaluate the overall cost of treating a prox DVT with enoxoparin as outpt vs UFH as inpt.	78
deLissovoy, 2000	To evaluate the overall inpt cost of treating an acute VTE with enoxoparin vs UFH.	94
Tillman, 2000	To evaluate the clinical and economic outcomes associated with implementation of outpt DVT tx w/ LMWH.	67

[a] Total quality score: Percentage score based on a total maximum score of 18 points (See Appendix H, items 1-9).

Evidence Table 8: Designs of the modeled analyses of the costs of using low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism

Author, Year	Design	Perspective	Time-horizon	Comparisons	Sources of cost estimates[a]	Sources of estimates of event rates	Units of benefits	Sensitivity analyses
Hull, 1997	CE	Payor	3 mos.	a) Inpt tinzaparin (175 IU/kg qd). b) Inpt UFH.	Direct medical costs in pts enrolled (1992 CAD and USD).	Observed in trial.	Deaths averted, recurrences averted.	Varied across range of observed data in centers.
Rodger, 1998	CE	Payor	3 mos.	a) Outpt LMWH if eligible or inpt LMWH. b) Outpt LMWH if eligible or inpt UFH. c) Inpt LMWH. d) Inpt UFH.	Case-costing using an online resource-utilization-based patient-specific cost accounting system (1995 CAD).	Systematic literature review.	Deaths averted.	Ran model using "worst case scenario", biased against LMWH.
Gould, 1999	CE	Society	Death or age 99 yrs.	a) Inpt enoxaparin (1mg/kg bid). b) Inpt UFH (includes 2° analysis of outpt enoxaparin).	ME reimbursement rates, rx costs, wholesale prices (1997 USD), (analysis included 3%/yr discounting).	From the literature, also used US life table to construct survival curves.	Quality-adjusted and unadjusted LY.	Varied across 95% CI of base case estimates.
Estrada, 2000	CE	Payor	3 mos.	a) LMWH: outpt if eligible or inpt LMWH. b) LMWH: outpt if eligible or inpt UFH. c) Inpt UFH.	Direct medical costs taken from literature review, institutional accounting, and costs to ME (1996 USD).	Literature.	Deaths averted, recurrences averted.	Based on literature.

Evidence Table 8: Designs of the modeled analyses of the costs of using low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism (continued)

Author, Year	Design	Perspective	Time-horizon	Comparisons	Sources of cost estimates[a]	Sources of estimates of event rates	Units of benefits	Sensitivity analyses
Lloyd, 1997	Cost-minimization	Payor	5 days.	a) Inpt nadroparin (weight-based bid). b) Inpt UFH (two routes: SQ or IV).	Direct costs measured as hospital charges to payor (Swiss sickness fund), public list prices of drugs. (1994 USD)	Assumed equivalent in all arms.	USD.	Did not vary the costs.
van den Belt, 1998	Cost-minimization	Payor	6 mos.	a) Outpt fraxaparine (weight adjusted). b) Inpt UFH.	Direct medical costs measured in 1 of 9 settings participating in clinical trial (1993 NLG).	Rates observed in all trial sites, considered equivalent in both groups.	NLG.	Monte Carlo simulations and one-way analyses; ranges.
O'Brien, 1999	Cost-minimization	Society	3 mos.	a) Outpt enoxaparin (1mg/kg bid). b) Inpt UFH.	Canadian national data-systems, local labor and rx costs (1997 CAD).	Observed in trial, measured health related quality of life.	Health related quality of life.	
deLissovoy, 2000	Cost-minimization	Payor	3 mos.	a) Inpt enoxaparin (1.5 mg/kg qd or 1.0 mg/kg bid). b) Inpt UFH.	Direct medical costs from 33 US sites participating in a multicenter trial (1997 USD).	Observed in the 33 US trial sites.	USD.	Varied cost data from 50 to 150% of base case.
Tillman, 2000	Decision-model	Payor	3 mos.	a) Outpt enoxaparin (1 mg/kg bid). b) Inpt UFH.	Direct medical costs measured in 391 pts treated as outpts in group-model HMO; source of inpt costs is unclear (1998 USD).	Measured in outpts.	USD.	Varied cost data from 50 to 300% of base case estimates.

[a] See Acronyms and Abbreviations list for international currencies

Evidence Table 9: Results of the modeled analyses of the costs of using low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism

Author, Year	Least costly strategy	Strategy with greatest benefits	Incremental cost-effectiveness	Cost-savings	Sensitivity analysis	Comments
Hull, 1997	Inpt tinzaparin	Inpt tinzaparin.	Tinzaparin dominates.	401 USD per person w/ tinzaparin, (11% savings).	Robust to all one-way analyses, when cost of tinzaparin is 5.8 times base cost per case it is not cost-saving.	If 37% treated as outpt, cost saving 913 USD per person.
Rodger, 1998	LMWH outpt if eligible/ LMWH inpt	Either LMWH all inpt or LMWH outpts if eligible/LMWH inpts.	LMWH outpts dominate if eligible.	767 USD per person w/ LMWH outpts/ inpts relative to UFH, (23% savings).	Even using "worst case" estimates, cost effectiveness of inpt LMWH relative to inpt UFH is 25,667 USD per life saved at 3 mos.	If equivalent efficacy and safety in all arms is assumed, LMWH is cheaper to deliver in any tx setting and dominates model.
Gould, 1999	Inpt UFH	Inpt enoxaparin.	6,910 USD per LY or 7,820 USD per QALY w/ enoxaparin.		Cost-saving when 8% of enoxaparin pts receive tx as outpts, or when 13% have an early discharge. Model sensitive to frequency of late complications, robust to other analyses.	Robustly cost-effective; becomes cost-saving if treated as outpts w/LMWH.
Estrada, 2000	LMWH in outpts/UFH in inpts	LMWH in outpts and inpts.	9,667 USD per recurrence averted or 80,685 USD per death averted w/ LWMH in outpt/inpt relative to LWMH outpt/UFH inpts.	310 USD per person for LWMH outpts/ inpts relative to UFH (10% savings).	Results sensitive to the % of pts eligible for outpt tx: if fewer than 14% eligible then UFH is less costly than LMWH outpt/inpt. Model sensitive to costs of UFH.	Lower costs primarily due to inpt savings.
Lloyd, 1997	Inpt nadroparin	NA: assumed to be equivalent for model.		153 USD per person with nadroparin 57%.	Robust even to all one-way analyses; savings if nadroparin pts have daily PTT measurement.	

Evidence Table 9: Results of the modeled analyses of the costs of using low molecular weight heparin compared to unfractionated heparin for treatment of venous thrombolembolism (continued)

Author, Year	Least costly strategy	Strategy with greatest benefits	Incremental cost-effectiveness	Cost-savings	Sensitivity analysis	Comments
van den Belt, 1998	Outpt fraxaparine	NA: assumed to be equivalent for model.		5,528 NLG per person with fraxaparine (64% savings).	Fraxaparine cost saving w/50% home care visits, cost saving w/ 50% requiring inpt care.	
O'Brien, 1999	Outpt enoxaparin	Higher social functioning on SF 36 in the enoxaparin group, otherwise NSD in health-related QOL or events.		3,045 USD per person w/ enoxaparin (57% savings).	Robust to all one-way analyses.	
deLissovoy, 2000	NSD	Inpt enoxaparin bid. Fewest readmissions for recurrent DVT and for all causes.		None.	Robust to all one-way analyses.	Protocol blood testing and costs of medication offset by fewer readmissions with enoxaprin.
Tillman, 2000	Outpt enoxaparin	Unknown.		2,828 USD per person w/enoxaparin (60% savings).	Enoxaparin not cost saving if drug cost increase 750% or if hospitalization costs decrease 77%.	Rates of events in the UFH arm not explicitly stated.

Evidence Table 10: Description of the studies evaluating optimal duration of therapy with warfarin after venous thromboembolism

Author, Year	Location	Design	Aims	Recruitment yrs	Planned f/u (mos)	Recurrence surveillance	Inclusion/exclusion criteria	
							Inclusion criteria (Participants-%)	Exclusion criteria
O'Sullivan, 1972	Australia	Single site RCT	To determine: 1) the number of recurrent VTE & bleeding episodes after 6 wks vs 6 mos of warfarin, 2) whether a gradual decrease or abrupt discontinuation of warfarin results in more thrombotic complications.		> 12	None	DVT ± PE (DVT alone-63%, DVT+PE-20%, PE-16%)	Depends on attending MD preference.
Holmgren, 1985	Europe	Multicenter RCT	To study VTE recurrence rate among patients with a 1st DVT treated for 1 vs 6 mos w/warfarin.	1979 - 81	12	IPG or thermography in 48%	1st DVT, calf or proximal (Proximal-83%, Calf-17%)	Contraindication to AC.
Lagerstedt, 1985	Europe	Single site RCT	To assess the need for oral AC after calf DVT.	1981 - 84	12	99m Tc-plasmin isotope scans	Calf vein DVT	Unlikely to comply; requires LT AC; sx of PE; predisposition to recurrence or malignancy.
Schulman, 1985	Europe	Single site RCT	To evaluate whether a shorter course of warfarin can be given w/o risks to pts with a 1st DVT & a TRF, 1st DVT and a PRF or 2nd DVT.		> 15	IPG	Proximal DVT	Preg; low compliance.
Petitti, 1986	United States	Retro-spective Multicenter CohR	To determine the risk of thrombosis & bleeding with warfarin in retrospective review of patients treated in Kaiser-Permanente clinics in Northern CA.	1970 - 80		None	DVT ± PE	Preg/childbirth; systemic disease associated with thrombophilia; malignancy; recent surgery or trauma (w/i 6 wks); death w/i 1 wk of admission; missing chart.

Evidence Table 10: Description of the studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

Author, Year	Location	Design	Aims	Recruitment yrs	Planned f/u (mos)	Recurrence surveillance	Inclusion/exclusion criteria	
							Inclusion criteria (Participants-%)	Exclusion criteria
Fennerty, 1987	Europe	Single site RCT	To compare outcomes w/ 3 wks vs 6 wks of AC after DVT/PE.		12	None	DVT ± PE	Preg; malignancy; prolonged immobility; previous VTE w/in 5 yrs.
British Thoracic Society (BTS), 1992	Europe	Multicenter RCT	To compare efficacy of 4 wks vs 3 mos of AC for VTE.	1988 - 90	12	None	DVT± PE. (DVT-51%, DVT+PE-19%, PE-31%)	Preg/childbirth; requires LT AC; thrombolytic therapy; pulmonary embolectomy; malignancy; prolonged immobility; previous VTE in last 3 yrs.
Levine, 1995	Canada & Europe	Multicenter RCT	To test whether 1) normal IPG after 4 wks of warfarin for a proximal DVT identifies a group whose warfarin can be d/c 2) normal IPG at 4 wks predicts a lower risk of recurrence than an abnormal IPG 3) continuing risk factors are associated w/ recurrence.	1987 - 92	11	IPG	Proximal DVT	Preg; major psychiatric disorder; life expectancy < 3 mos; unlikely to f/u; requires LT AC; familial bleeding disorder; active bleeding; peptic ulcer; thrombophilia; ≥2 previous VTE.
Schulman, 1995	Europe	Multicenter RCT	To compare 6 wks with 6 mos of AC for a 1st VTE.	1988 - 91	24	None	1st VTE, DVT ±PE (DVT-88%, PE-12%)	Preg; allergy; requires LT AC; unable to f/u; arterial insufficiency; venous ulcerations precluding compression stockings; age < 14 yrs; thrombophilia; malignancy; previous VTE; total limb paresis.

Evidence Table 10: Description of the studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

Author, Year	Location	Design	Aims	Recruitment yrs	Planned f/u (mos)	Recurrence surveillance	Inclusion/exclusion criteria	
							Inclusion criteria (Participants-%)	Exclusion criteria
Schulman, 1997	Europe	Multicenter RCT	To compare 6 mos vs indefinite oral AC for a 2nd VTE.	1988 - 91	48	None	2nd VTE, DVT ± PE (DVT-85%, PE - 15%)	Preg; allergy to warfarin/ dicoumarol; requires LT AC; unable to f/u; arterial insufficiency; venous ulcerations precluding comp stockings; age <14 yrs; thrombophilia; malignancy; or total limb paresis.
Kearon, 1999	United States & Canada	Multicenter RCT	To determine whether 24 additional mos of warfarin is more effective than 3 mos for 1st idiopathic VTE.	1994 - 97	24	None	1st idiopathic VTE, DVT±PE (DVT-75%, PE - 25%)	Preg; major psychiatric disorder; life expectancy <2 yrs; requires LT therapy w/ASA/NSAIDs or AC; allergy; unlikely to comply; familial bleeding disorder; contraindication to AC; or tx w/unlicenced LMWH preparation; thrombophilia; malignancy within last 5 yrs; immobilization for > 3 days; recent fracture or cast of lower limb; recent general anesthesia.

Evidence Table 10: Description of the studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

Author, Year	Location	Design	Aims	Recruitment yrs	Planned f/u (mos)	Recurrence surveillance	Inclusion/exclusion criteria	
							Inclusion criteria (Participants-%)	Exclusion criteria
Agnelli, 2001	Europe	Multicenter RCT	To evaluate LT benefit of extending AC from 3 mos to 1 yrs after a 1st idiopathic DVT in terms of symptomatic recurrence, bleeding, & death.	1995 - 98	24	None	1st idiopathic proximal DVT	Preg/childbirth; major psychiatric disorder; life expectancy < 2 yrs; unlikely to f/u; requires LT AC; age <15 or >85 yrs; thrombophilia or malignancy; recent surgery or trauma (w/in 3 mos); immobilization >7 days; OCPs.
Pinede, 2001	Europe	Multicenter RCT	To determine optimal duration of oral AC for a 1st proximal or calf DVT or PE.	1993 - 98	15	None	1st DVT, calf or proximal, or PE (Proximal DVT-43%, Proximal DVT+PE-18%, Calf DVT-27%, Calf DVT+PE - 7%)	Preg; BF; requires LT AC; thrombolytic therapy; surgical thrombectomy; free-floating IVC clot; liver disease; severe PE; age < 18 yrs; thrombophilia; malignancy; previous DVT; vena caval filter.

Evidence Table 11: Quality of the studies evaluating optimal duration of therapy with warfarin after venous thromboembolism

Author, Year	Overall [a]	Representativeness of study population [b]	Bias & confounding [c]	Description of tx [d]	Outcomes & f/u [e]	Statistical quality & interpretation [f]
O'Sullivan, 1972	15	0	25	25	25	0
Holmgren, 1985	46	75	50	50	55	0
Lagerstedt, 1985	73	50	63	100	70	83
Schulman, 1985	63	50	69	50	80	67
Petitti, 1986	46	75	0	0	80	75
Fennerty, 1987	31	25	25	25	45	33
BTS, 1992	53	50	63	25	60	67
Levine, 1995	83	100	88	50	75	100
Schulman, 1995	90	88	81	100	80	100
Schulman, 1997	86	88	88	75	80	100
Kearon, 1999	82	75	100	50	85	100
Agnelli, 2001	87	100	88	50	95	100
Pinede, 2001	82	75	88	75	70	100

[a] **Overall** The mean of the percentage scores from categories: Representativeness of Study Population, Bias and Confounding, Description of Treatment, Outcomes and Followup, and Statistical Quality and Interpretation (see below).

[b] **Representativeness of Study Population:** Percentage score based on a total maximum score of 8 points. This included description of study setting and population (2 points), description of inclusion/exclusion criteria (2 points), information on excluded or non-participating patients (2 points), and description of key patient characteristics (2 points).

[c] **Bias and Confounding:** Percentage score based on a total maximum score of 6 points. This included random assignment of patients to study groups (2 points), differences between study groups in key patient characteristics (2 points), and blinding of clinicians, patients, and outcome assessors (2 points).

[d] **Description of Treatment:** Percentage score based on a total maximum score of 4 points. This included description of the details of the treatment regimen (2 points), and description of other treatments given to each study group (2 points).

[e] **Outcomes and Followup:** Percentage score based on a total maximum score of 10 points. This included description of the criteria used for determining outcomes (2 points), description of adverse events experienced by patients (2 points), reporting on numbers and reasons for withdrawals or patients lost to followup (2 points), proportion of patients who withdrew or were lost to followup (2 points), and adequacy of the planned length of followup (2 points).

[f] **Statistical Quality and Interpretation:** Percentage score based on a total maximum score of 8 points. This included reporting on the magnitude of differences between groups with an index of variability (2 points), clear identification of all statistical analyses (2 points), use of multivariate or stratified analyses to adjust for potential confounders (2 points), and appropriate handling of withdrawals, crossovers, and loss to followup (2 points).

Evidence Table 12: Characteristics of patients in studies evaluating optimal duration of therapy with warfarin after venous thromboembolism

Author, year	Group[a]	Intervention		Type of VTE	Mean age (yrs)	Male (%)	% Prior VTE/ % Family hx/ % Thrombophilia	TRF/ Proximal DVT (%)
		Drug	Duration (days)					
O'Sullivan, 1972	I	Warfarin	42				NR / NR / NR	NR / NR
	III	"	180				NR / NR / NR	NR / NR
Holmgren, 1985	I	Warfarin	30	Comp stockings	62	59	NR / NR / NR	NR / 87
	III	"	180	"	62	64	NR / NR / NR	NR / 79
Lagerstedt, 1985	NA	No warfarin		Comp stockings	61	54	21 / NR / NR	NR / NR
	II	Warfarin	90	"	65	61	13 / NR / NR	NR / NR
Schulman, 1985	I	Warfarin	45		56	50	NR / NR / NR	100 / NR
	II	"	90		60	50	NR / NR / NR	100 / NR
	II[b]	"	90		58	60	NR / NR / NR	NR / NR
	III[b]	"	180		66	75	NR / NR / NR	NR / NR
	III	"	180		64	40	100 / NR / NR	NR / NR
	IV	"	360		66	40	100/ NR / NR	NR / NR
Petitti, 1986	I	Warfarin	7-42				NR / NR / NR	NR / NR
	I/II/III	"	49-182				NR / NR / NR	NR / NR
	IV	"	>182				NR / NR / NR	NR / NR
Fennerty, 1987	I	Warfarin	21		56	51	NR / NR / NR	NR / NR
	I	"	42		57	61	NR / NR / NR	NR / NR
BTS, 1992	I	Warfarin	28		58	56	NR / NR / NR	NR / NR
	II	"	90		58	51	NR / NR / NR	NR / NR

Evidence Table 12: Characteristics of patients in studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

Author, year	Group[a]	Intervention		Type of VTE	Mean age (yrs)	Male (%)	% Prior VTE/ % Family hx/ % Thrombophilia	TRF/ Proximal DVT (%)
		Drug	Duration (days)					
Levine, 1995	I/I	Warfarin/ warfarin	28/56		63	48	10 / NR / NR	40 / NR
	I/I	Warfarin/ placebo	28/56		63	54	8 / NR / NR	36 / NR
	II	Warfarin	90		62	59	9 / NR / NR	24 / NR
Schulman, 1995	I	Warfarin or dicumarol	42	Comp stockings	61	56	NR / 16 / NR	NR / 55
	III	"	180	"	61	57	NR / 14 / NR	NR / 58
Schulman, 1997	III	Warfarin or dicumarol	180	"	65	63	NR / 22 / NR	20 / 72
	IV	"	1460	"	64	59	NR / 19 / NR	18 / 66
Kearon, 1999	II/IV	Warfarin/ placebo	90/720		58	53	4 / NR / NR	NR / NR
	II/IV	Warfarin/ warfarin	90/720		59	68	6 / NR / NR	NR / NR
Agnelli, 2001	II	Warfarin/ acenocoumarol	90		68	61	NR / NR / NR	NR / 100
	IV	"	360		67	55	NR / NR / NR	NR / 100
Pinede, 2001[c]	I	Fluindione	42				NR / 19.2 / NR	68.3 / NR
	I	"	84				NR / 25.8 / NR	69.7 / NR
	I	"	84				NR / 15.5 / NR	45.8 / NR
	III	"	168				NR / 15.2 / NR	46 / NR

[a] I: Less than 3 months (1 - 89 days); II: 3 to 4 months (90 - 149 days); III: 5 to 6 months (150 - 180 days); IV: Greater than 6 months (181+ days); NA: not applicable

[b] All had first DVT with a permanent risk factor

Evidence Table 12: Characteristics of patients in studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

[c] The first two subject groups consist of patients with calf vein DVT (comparing 42 and 84 days of therapy) while the third and fourth groups consist of patients with proximal DVT/PE (84 and 168 days of therapy)

Evidence Table 13: Results of studies evaluating optimal duration of therapy with warfarin after venous thromboembolism

Author, Year	Group[a]	# of pts	Mean f/u (mos)	Intensity of therapy	VTE Recurrence			Adverse Events		Deaths n (%)
					All VTE n (%)	DVT n (%)	PE n (%)	Major bleeding n (%)	Minor bleeding n (%)	
O'Sullivan, 1972	I	94				6 (6)	2 (2)			
	III	92				9 (9)	3 (3)			
Holmgren, 1985	I	69				7 (10)	5 (7)			6 (9)
	III	66				5 (8)	5 (8)			4 (6)
Lagerstedt, 1985	NA	28			9 (32) [b]					
	II	23			1 (4) [b]					
Schulman, 1985	I	10	24	[c]		1 (10)	0 (0)			0 (0)
	II	10	20			2 (20)	0 (0)			0 (0)
	II	20	22			3 (15)	1 (5)			3 (15)
	III	20	21			2 (10)	0 (0)			2 (10)
	III	10	33			0 (0)	1 (10)			1 (10)
	IV	10	28			3 (30)	0 (0)			1 (10)
Petitti, 1986	I				[d]					
	I/II/III				[d]					
	IV				[d]					
Fennerty, 1987	I	49			2 (4) [e]					1(2)
	I	51			2 (4) [e]					5 (10)
BTS, 1992	I	358		86% [f]	14 (4) [e]			5 (1)	10 (3)	26 (7)
	II	354		80% [f]	7 (2) [e]			4 (1)	18 (5)	28 (8)
Levine, 1995	I/I	109		2.3 ($\pm$0.4)[g]	7 (7)	7 (7)	0 (0)	1 (1)		9 (9)
	I/I	105			12 (12)[h]	9 (9)	3(3)	0 (0)		9 (9)
	II				19 (13)					

Evidence Table 13: Results of studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

Author, Year	Group[a]	# of pts	Mean f/u (mos)	Intensity of therapy	VTE Recurrence			Adverse Events		Deaths n (%)
					All VTE n (%)	DVT n (%)	PE n (%)	Major bleeding n (%)	Minor bleeding n (%)	
Schulman, 1995	I	443		65% [i]	80 (18) [b]			1(0.2)		22 (5)
	III	454		59% [i]	43 (10) [b]			5 (1)		17 (4)
Schulman, 1997	III	111			23 (21) [b]			3 (3)		16 (14)
	IV	116		62% [j]	3 (3) [b]			10 (9)		10 (9)
Kearon, 1999	II/IV	83	9			11 (13)	6 (7)	0 (0)	1 (1)	3 (4)
	II/IV	79	12	2.5 (±1.0)[h]		0 (0)	1 (1)	3 (4)	6 (8)	1 (1)
Agnelli, 2001	II	133	37.2			18 (14)	3 (2)	2 (2)		7 (5)
	IV	134	37.8	81% [j, k] [l]		16 (12)	5 (4)	4 (3)		7 (5)
Pinede, 2001	I	105				2 (2)	0 (0)	1 (1)	12 (12)	
	I	92				2 (2)	1 (1)	3 (3)	16 (18)	
	I	270				18 (7)	6 (2)	5 (2)	38 (14)	
	III	269				15 (6)	6 (2)	7 (3)	38 (14)	

[a] I: Less than 3 months (1 - 89 days); II: 3 to 4 months (90 - 149 days); III: 5 to 6 months (150 - 180 days); IV: Greater than 6 months (181+ days) NA: Not applicable
[b] $p<0.05$ for the difference between groups
[c] Effective anticoagulation [Thrombotest ® (Nyegaard, Norway) < 13%] achieved in 68% and 67% respectively of the reduced duration and regular duration subjects.
[d] Relative risk of recurrence: Group A (1-6 weeks of therapy) vs Group C (>26 weeks)= 1.1; Group B (7-26 weeks) vs Group C (>26 weeks)= 0.7.
[e] Only objectively confirmed events included.
[f] In therapeutic range 67% of time in 86% of participants in Group A and 80% of participants in Group B. Test and therapeutic range not specified.
[g] Mean INR (± standard deviation (SD))
[h] VTE at 2 mos. f/u: Group A= 1 (1%), Group B= 9 (9%), $p<0.009$
[i] % w/ effective AC (INR 2.0 for 75% or more of PTT).
[j] % of pts in target range (INR 2.0-2.85).
[k] INR was 2.0-3.0 in 81% of tests during additional 9 mos. of therapy.
[l] Median INR 2.0 in 96% of subjects, distribution similar between arms.

Evidence Table 14: Description of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism

Author, Year	Location	Study aims	Recruitment dates	Study test	Reference standard	Inclusions	Exclusions
Deep Venous Thrombosis							
Nypaver, 1993	United States	To define clinical criteria that might predict the diagnostic value of VDS.		Clinical model		Suspected DVT in inpts	PE.
Wells, 1995	Canada	To assess the ability of a clinical model to stratify symptomatic outpatients with suspected DVT into groups with high, moderate, and low probability of DVT and to evaluate this model in combination with U/S.	1992 - 93	Wells model	Venogram	Referral for suspected DVT in outpts	Preg/childbirth; contrast dye allergy; renal failure; suspected PE; below the knee amputation.
Wells, 1997	Canada		1994 - 96	Wells model	Venogram U/S	Referral for suspected DVT in outpts	Age < 18 yrs; previous VTE; requires LT AC; PE; imminent death.
Anderson, 1999	Canada	To determine the accuracy of a clinical model, and determine if the model is safe and feasible.	1997	Wells model	U/S	Suspected DVT in ED	Age < 18 yrs; Preg/childbirth; previous VTE; short life expectancy; unlikely to be compliant; hereditary bleeding; contraindication to AC; thrombolytic therapy; PE.
Aschwanden, 1999	Europe		1997	Wells model Wells model + D-dimer	U/S	Referral for suspected idiopathic DVT	

Evidence Table 14: Description of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Location	Study aims	Recruitment dates	Study test	Reference standard	Inclusions	Exclusions
Lennox, 1999	Europe	To determine the actual value of the D-dimer test and its combination with clinically derived risk stratification in the diagnostic work up of patients with suspected DVT.		Risk assessment score for DVT (RAS) RAS + D-dimer	U/S	Suspected DVT in inpts/outpts	Previous VTE; chronic DVT on US; symptoms > 1 mos; AC > 48 hours; PE.
Wells, 1999	Canada	To evaluate the accuracy of D-dimer in hospitalized patients.	1994 - 96	Wells Model Wells Model + D-dimer	U/S, thigh/ popliteal	Referral for suspected DVT in inpts	Age < 18 yrs; previous VTE; short life expectancy; unlikely to be compliant; requires LT AC; PE; screening.
Anderson, 2000	Canada	To determine the accuracy of D-dimer and to determine the potential of combining the D-dimer with the Wells model.		Wells Model Wells Model + D-Dimer	U/S	Suspected DVT in ED	Age < 18 yrs; hereditary bleeding; contraindication to AC; thrombolytic therapy; PE.
Constans, 2001	Europe	To determine whether one or two of these scores maintained the same level of performance in various hands.	1999 - 99	Kahn model Wells model Sant-Andre hospital model	U/S, thigh/ popliteal		Previous VTE
Dryjski, 2001	United States	To evaluate the efficacy and cost effectiveness of a DVT screening protocol consisting of global PTP, selective D-dimer, and selective venous Doppler imaging.	2000 - 01	Wells model Wells + D-dimer + PTP	U/S, thigh/ popliteal	Suspected DVT in ED	

Evidence Table 14: Description of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Location	Study aims	Recruitment dates	Study test	Reference standard	Inclusions	Exclusions
Funfsinn, 2001	Europe	To determine the reliability of several rapid D-dimer tests in combination with a simple clinical model to predict the pretest probability.		Wells model	Venogram, central, thigh/popliteal, calf; U/S, thigh/ popliteal	Referral for suspected DVT	Preg/childbirth; hospitalization; AC for 24 hours.
Kearon, 2001	Canada	Test if U/S can be withheld from pts w/ low probability scores.	1995 - 97	Wells model Wells model + D-dimer	U/S	Referral for suspected DVT	
Cornuz, 2002	Europe	To compare clinical assessment and the Wells score, in isolation and in combination with rapid quantitative D-dimer.		Wells model Wells model + D-dimer	Venogram, thigh/popliteal; U/S	Referral for suspicion of DVT	Preg/childbirth; PE.
Kraaijenhagen, 2002	Europe	To study if combination of normal results of compression ultrasonography and rapid whole blood bedside D-dimer assay at referral can safely exclude the presence of thrombosis.	1995 - 99	Wells model	U/S		<18 yrs, previous VTE PE, AC >48 hrs, geographic inaccessibility.
Pulmonary Embolism							
Wells, 1998	Canada	To find a clinical model for safe management of patients with suspected PE.	1993 - 96	Wells PE model	V/Q	PE, suspected PE in inpts/ outpts	UE VTE; Preg/childbirth; short life expectancy; contrast dye allergy; recent AC use.

Evidence Table 14: Description of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Location	Study aims	Recruitment dates	Study test	Reference standard	Inclusions	Exclusions
Sanson, 2000	Europe	To compare the accuracy and variability of the clinical probability estimate between the PIOPED and the two clinical models by Wells.	1997 - 98	PIOPED study model Wells simplified model Wells extended model for PE	V/Q, SPECT (tomographic) Helical CT, PA	Unsuspected DVT in inpts/outpts	Age < 18 yrs; Preg/childbirth; undergone testing for PE; inability to complete protocol.
Stollberger, 2000	Europe	To derive and validate a prediction rule based on clinical and easily obtained instrumental findings by which PE can be diagnosed.		Clinical model	V/Q	High suspicion for PE (enough to start heparin)	Contraindication for PE evaluation.
Wells, 2000	Canada	Simplify the clinical model and examine the potential safety and clinical utility of combining the new model with D-dimer results to enable exclusion of PE.		Wells PE model Wells PE model + D-dimer	V/Q	Suspected PE	
Wells, 2001	Canada	Demonstrate the safety of excluding the diagnosis of pulmonary embolus in an emergency department using diagnostic algorithms that were based on pretest probability and D-dimer assay results.	1998 - 99	Wells PE model	V/Q	Acute dyspnea or chest pain less than 30 days.	Suspected DVT of the upper extremity, AC >24 hrs, and short LE contraindication to contrast media, Preg, geographic inaccessibility, age <18 yrs.

Evidence Table 15: Quality of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism

Author, year	Overall [a]	Representativeness of study population [b]	Bias & confounding [c]	Description of prediction rule [d]	Test interpretation [e]	Statistical quality & interpretation [f]
Deep Venous Thrombosis						
Nypaver, 1993	64	38	30	83	67	100
Wells, 1995	84	75	60	83	100	100
Wells, 1997	82	100	25	100	83	100
Anderson, 1999	78	100	25	83	83	100
Aschwanden, 1999	70	38	60	100	100	50
Lennox, 1999	63	63	35	100	67	50
Wells, 1999	78	100	25	83	83	100
Anderson, 2000	85	100	40	83	100	100
Constans, 2001	66	75	40	100	67	50
Dryjski, 2001	74	88	30	100	100	50
Funfsinn, 2001	71	75	30	67	83	100
Kearon, 2001	75	88	20	83	83	100
Cornuz, 2002	88	88	50	100	100	100
Kraaijenhagen, 2002	93	100	80	100	100	100
Pulmonary Embolism						
Wells, 1998	61	75	45	83	100	0
Sanson, 2000	90	100	50	100	100	100
Stollberger, 2000	51	50	20	67	67	50
Wells, 2000	49	38	25	83	100	0
Wells, 2001	84	88	60	100	100	100

[a] **Overall:** The mean of the percentage scores from the categories: Representativeness of Study Population, Bias and Confounding, Description of Test Protocols, Test Interpretation, and Statistical Quality and Interpretation (see below).

Evidence Table 15: Quality of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

[b] **Representativeness of Study Population:** Percentage score based on a total maximum score of 8 points. This included description of study setting and population (2 points), description of inclusion/exclusion criteria (2 points), information on excluded or non-participating patients (2 points), and description of key patient characteristics (2 points).

[c] **Bias and Confounding:** Percentage score based on a total maximum score of 10 points. This included use of the reference test on all subjects receiving the study test (2 points), use of the study test in the decision to obtain the reference test (2 points), blinding of test interpretation and clinical data (2 points), interpretation of the study test by two or more independent observers (2 points), and interpretation of the reference test by two or more independent observers (2 points).

[d] **Description of Prediction Rule:** Percentage score based on a total maximum score of 6 points. This included description of the clinical model being tested (2 points), description of the reference test protocol (2 points), and reporting on the methods used in the development of the clinical model being tested (2 points).

[e] **Test Interpretation:** Percentage score based on a total maximum score of 6 points. This included description of the criteria for a positive interpretation of the study test (2 points), description of the criteria for a positive interpretation of the reference test (2 points), and reporting on numbers and reasons for withdrawals or patients lost to followup (2 points).

[f] **Statistical Quality and Interpretation:** Percentage score based on a total maximum score of 4 points. This included reporting of a summary index of test performance and of an index of variability (2 points), and use of multivariate or stratified analyses to adjust for potential confounders (2 points).

Evidence Table 16: Characteristics of patients in studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism

Author, Year	N	Age (yrs) Mean	Age (yrs) Range/SD	Male (%)	Prior VTE (%)	Family history (%)	TRF (%)	Malignancy (%)
Deep Venous Thrombosis								
Nypaver, 1993	68							
Wells, 1995	605							
Wells, 1997	593	57.1		41			22	13
Anderson, 1999	344	53.8		45			19	5
Aschwanden, 1999	343	61 [a]	17 - 94 [b]					
Lennox, 1999	200	58	18 - 91 [b]	37				
Wells, 1999	150	63.8		49			49	
Anderson, 2000	214	54.8		45			19	6
Constans, 2001	273	68	17 [c]	38	20	7		17
Dryjski, 2001	66	63	19 - 92 [b]	25				
Funfsinn, 2001	106	56.3	16 - 88 [b]	49				
Kearon, 2001	445							
Cornuz, 2002	278	60	19 [c]	62	18		10	10
Kraaijenhagen, 2002	1726	60	18 - 96 [b]	37			15	13
Pulmonary Embolism								
Wells, 1998	1401							
Sanson, 2000	517	51		42	14	20		10
Stollberger, 2000	168	64	21 - 86 [b]	47				
Wells, 2000	295							
Wells, 2001	903	50.5	16 - 93 [b]	37			16	7.2

[a] Median [b] Range [c] Standard deviation

Evidence Table 17: Results of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism

Author, Year	Study test	Clinical prediction probability [a]	# pts w/VTE (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC curve area
Deep Venous Thrombosis								
Nypaver, 1993	Clinical model			91	51	26	97	
Wells, 1995	Wells model	High	69 (81%)	61	97	81	91	0.90
		Moderate	34 (24%)	91	70	45	97	
		Low	10 (3%)	–	–	–	--	
Wells, 1997	Wells model	High	53 (75%)	53	96	75	91	0.87
		Moderate	35 (18%)	88	64	33	96	
		Low	12 (4%)	--	--	--	--	
Anderson, 1999	Wells model	High	24 (49%)	53	92	49	93	0.79
		Moderate	15 (14%)	87	62	25	97	
		Low	6 (3%)	--	--	--	--	
Aschwanden, 1999	Wells model	High		84	56	26	95	
	Wells model + D-dimer	High		96	46	32	98	
Lennox, 1999	Risk assessment score for DVT (RAS)	High	30 (67%)	65	90	67	90	0.87
		Moderate	12 (18%)	91	54	38	95	
		Low	4 (5%)	--	--	--	--	
	RAS + D-dimer							0.91
Wells, 1999	Wells model	High	22 (76%)	54	94	76	84	0.81
		Moderate	14 (20%)	88	41	36	90	
		Low	5 (10%)	--	--	--	--	
	Wells model + D-dimer	High				79	33	
		Moderate				28	89	
		Low				20	96	

Evidence Table 17: Results of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Study test	Clinical prediction probability [a]	# pts w/VTE (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC curve area
Anderson, 2000	Wells model	High	15 (50%)	54	92	50	93	0.83
		Moderate	9 (14%)	86	61	25	97	
		Low	4 (3%)	--	--	--	--	
	Wells model + D-Dimer							0.87
Constans, 2001	Wells model	High	33 (51%)	50	85	52	84	0.74
		Moderate	26 (19%)	89	32	31	90	
		Low	7 (10%)	--	--	--	--	
	Kahn model	High	2 (100%)	3	100	100	75	0.59
		Moderate	47 (28%)	74	43	29	81	
		Low	17 (19%)	--	--	--	--	
	Sant-Andre hospital model	High	13 (76%)	20	98	76	79	0.77
		Moderate	38 (33%)	77	61	39	89	
		Low	15 (11%)	--	--	--	--	
Dryjski, 2001	Wells model	High	6 (17%)	100	50	17	100	0.75
		Moderate	0 (0%)	100	12	10	100	
		Low	0 (0%)	--	--	--	--	
	Wells model + D-dimer + PTP			100	25	12	100	
Funfsinn, 2001	Clinical Model (Well's DVT)[b]	High	30 (71%)	75	77	71	80	0.77
		Moderate	10 (28%)	100	27	51	100	
		Low	0 (0%)	--	--	--	--	
Kearon, 2001	Wells model	High	35 (69%)	55	96	69	93	0.87
		Moderate	24 (13%)	92	53	25	98	
		Low	5 (2%)	--	--	--	--	
	Wells model + D-dimer	Low					99	

Evidence Table 17: Results of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Study test	Clinical prediction probability [a]	# pts w/VTE (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC curve area
Cornuz, 2002	Wells model	High	32 (67%)	39	92	67	78	0.75
		Moderate	36 (30%)	83	48	40	87	
		Low	14 (13%)	--	--	--	--	
	Wells model + D-dimer	High				73	100	
		Moderate				38	90	
		Low				16	100	
Kraaijenhagen, 2002	Wells model	High	228 (66%)	53	91	66	91	0.87
		Moderate	135 (27%)	85	63	43	63	
		Low	62 (8%)	--	--	--	--	
Pulmonary Embolism								
Wells, 1998	Wells PE model	High	80 (78%)	37	98	78	88	0.88
		Moderate	112 (28%)	88	69	38	97	
		Low	25 (3%)	--	--	--	--	
Sanson, 2000	PIOPED study model	High	35 (45%)	28	85	45	73	0.61
		Moderate	80 (29%)	91	16	33	81	
		Low	11 (19%)	--	--	--	--	
	Wells simplified model	High	3 (38%)	2	98	38	71	0.52
		Moderate	78 (30%)	66	36	30	72	
		Low	41 (28%)	--	--	--	--	
	Wells extended model for PE pulmonary angiogram	High	18 (46%)	20	86	46	64	0.58
		Moderate	54 (39%)	81	29	41	72	
		Low	17 (28%)	--	--	--	--	

Evidence Table 17: Results of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Study test	Clinical prediction probability [a]	# pts w/VTE (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC curve area
Stollberger, 2000	Clinical model	> 0.65		55	100			
		> 0.35		98	82			
		> 0.02		100	5	35	100	
Wells, 2000	Wells PE model	High	10 (50%)	28	95	50	89	0.82
		Moderate	24 (19%)	94	46	23	98	
		Low	2 (2%)	--	--	--	--	
	Wells PE model +							0.85
Wells, 2001	Wells PE model	High	24 (41%)	27	95	36	95	0.85
		Moderate	55 (16%)	92	62	20	98	
		Low	7 (1.3%)	--	--	--	--	

[a] High probability≥3, moderate probability=1 or 2, low probability<1.

b Models with D-dimer testing also presented in paper.

Table 18: Summary of systematic reviews on ultrasound in the diagnosis of deep venous thrombosis

Author, Year	Study aim	Most recent study	Systematic review quality scores					
			Overall [a]	Search [b]	Eligibility [c]	Study quality [d]	Combining results [e]	Aims & Conclusions [f]
White, 1989	To assess accuracy of duplex U/S for the dx of prox DVT in symptomatic pts.	1988	65	33	67	75	75	75
Becker, 1989	To review the evidence for the use of real-time U/S in dx of suspected DVT.	1988	73	33	83	100	100	100
Cogo, 1995	To assess accuracy of non-invasive dx of 1st episode of suspected DVT.	1992	38	17	50	0	75	75
Wells, 1995	To evaluate accuracy of screening U/S for dx of DVT in post-operative orthopedic pts.	1993	82	50	83	75	100	100
Kearon, 1998	To review non-invasive methods of dx for a 1st DVT.	1997	83	83	100	50	100	100
Gottlieb, 1999	To determine the accuracy of U/S for detection of isolated calf DVT.	1996	58	50	67	0	100	100
Mustafa, 2002	To determine sensitivity and specificity of U/S for dx of upper extremity DVT.	1997	63	50	67	75	100	100

[a] **Overall Quality Score:** The mean of the percentage scores from the categories, Search Methods, Inclusion & Description, Quality Assessment, Methods of Combination, and Aims/Conclusions (see below).

[b] **Search Methods:** Percentage score based on a total maximum score of 6 points. This included description of search methods (2 points), comprehensiveness of search methods (2 points), and reproducibility of review methods (2 points).

[c] **Eligibility and Description:** Percentage score based on a total maximum score of 6 points. This included description of study inclusion criteria (2 points), appropriateness of study inclusion criteria (2 points), and discussion of variation in the original literature based on differences in study design (2 points).

[d] **Study Quality Assessment:** Percentage score based on a total maximum score of 4 points. This included description of quality assessment (2 points), and appropriateness of quality assessment (2 points).

[e] **Combining Results:** Percentage score based on a total maximum score of 4 points. This included description of methods used to combine study results (2 points), and appropriateness of methods used to combine study results (2 points).

[f] **Aims & Conclusions:** Percentage score based on a total maximum score of 4 points. This included whether the question to be addressed by the review was clearly stated (2 points), and whether the conclusions reached by the review were supported by data and/or analyses (2 points).

Table 19: Results of systematic reviews on ultrasound in the diagnosis of deep venous thrombosis

Author, Year	Design of trials [a]	# of trials	Total pts	% DVT	Patient population [b]	Ultrasonography	Mean sensitivity (95% CI), %	Mean specificity (95% CI), %	Comments
White, 1989	Prosp/ consec	4	266	46	Symp/prox DVT/level 1	Compression	93 (88-97)	98 (96-100)	Level 1 studies had both tests w/i 24 hrs of each other; blinded.
		9	424	61	Symp/prox DVT/level 2	Compression	98 (96-100)	96 (93-99)	
Becker, 1989		15	1578	50	Symp/lower extremity DVT	Compression +/- Doppler	96 (92-100) [c]	99 (96-100) [c]	Only 3 studies looked for calf DVT.
Cogo, 1995	Prosp/ consec	9	989	43	Symp/1st prox DVT	Compression	96	98	Consistency in results despite different qualities of studies. Duplex + color Doppler offered no advantage over compression; low sens for calf DVT.
		4	247	42	Symp/1st prox DVT	Compression +/- Doppler	95	93	
		4	340	37	Symp/1st prox DVT	Compression +/- color Doppler	97	97	
		4			Symp/1st calf DVT	All types	75 (56-88)	N/A	
Wells, 1995	Prosp/ consec	11	1616	9	Asymp/post-op prox DVT/level 1	Compression +/- Doppler	62	97	Only moderate sens for detecting DVT in asymp patients; sens lower among studies that minimize potential for bias.
		5	385	17	Symp/post-op prox DVT/level 2	Compression +/- Doppler	95	97	
		2			Symp/post-op calf DVT/level 1	Compression +/- Doppler	48 (29-67)	100	
Kearon, 1998	Prosp/ consec	18	2763	40	Symp/1st prox DVT	Compression +/- Doppler	89 (85-92)	94 (90-98)	Sens dependent on presence of symptoms; low sens for calf DVT.
		11 [d]	1316 [d]		Calf DVT [d]		73 (54-93)	N/A	
		16	2035	16	Symp/1st prox DVT	Compression +/- Doppler	47 (37-57)	94 (91-98)	
		12 [d]	1681 [d]	N/A	Calf DVT [d]		53 (32-74)	N/A	
Gottlieb, 1998		5	212 [e]	25	Symp/calf vein DVT	Compression	93 (82-98)	99 (96-99)	High frequency of indeterminate studies.

Table 19: Results of reviews on ultrasound in the diagnosis of deep venous thrombosis (continued)

Author, Year	Design of trials [a]	# of trials	Total pts	% DVT	Patient population [b]	Ultrasonography	Mean sensitivity (95% CI), %	Mean specificity (95% CI), %	Comments
Mustafa, 2002	Prosp	6	170	73	Symp/upper extremity DVT	Doppler +/- compression	(56-100) [c]	(77-100) [c]	Highest quality study used compression and color Doppler; sens 100 and spec 93.

[a] Prosp=prospective design, consec=consecutively enrolled patients
[b] Level 1=higher quality trial, level 2= lower quality trials, post-op=evaluated post-operatively
[c] Mean and range, or just range
[d] Subset of studies
[e] Number of legs screened

Evidence Table 20: Description of the systematic reviews on the use of computed tomography for the diagnosis of pulmonary embolism

Author, Year	Main Inclusion Criteria	Date of most recent study	# studies	Total pts	Systematic review quality scores					
					Overall [a]	Search [b]	Eligibility [c]	Study quality [d]	Combining results [e]	Aims & Conclusions [f]
Harvey, 2000	Prospective and retrospective studies with pulmonary arteriography as reference standard.	1998	11	931	77	50	83	75	75	100
Mullins, 2000	Diagnosis established by pulmonary arteriography or a clinical reference standard.	1998	11	714	75	33	67	75	100	100
Rathburn, 2000	Prospective studies evaluating the use of CT for diagnosis of PE using any reference standard.	1999	15	1330	78	50	67	75	100	100
Cueto, 2001	Prospective studies with positive and negative CT results; pulmonary arteriography reference standard.	1998	7	268	72	50	83	75	50	100
van Beek, 2001	Prospective studies reporting sensitivity and specificity of CT relative to arteriography or V/Q scan.	1999	12	1171	55	33	67	50	50	75
Safriel, 2002	Diagnosis established by pulmonary arteriography or high-probability V/Q scan; not limited to acute PE.	1999	12	1250	55	50	83	0	50	75

[a] **Overall Quality Score:** The mean of the percentage scores from the categories, Search Methods, Inclusion & Description, Quality Assessment, Methods of Combination, and Aims/Conclusions (see below).

[b] **Search Methods:** Percentage score based on a total maximum score of 6 points. This included description of search methods (2 points), comprehensiveness of search methods (2 points), and reproducibility of review methods (2 points).

[c] **Eligibility and Description:** Percentage score based on a total maximum score of 6 points. This included description of study inclusion criteria (2 points), appropriateness of study inclusion criteria (2 points), and discussion of variation in the original literature based on differences in study design (2 points).

[d] **Study Quality Assessment:** Percentage score based on a total maximum score of 4 points. This included description of quality assessment (2 points), and appropriateness of quality assessment (2 points).

[e] **Combining Results:** Percentage score based on a total maximum score of 4 points. This included description of methods used to combine study results (2 points), and appropriateness of methods used to combine study results (2 points).

[f] **Aims & Conclusions:** Percentage score based on a total maximum score of 4 points. This included whether the question to be addressed by the review was clearly stated (2 points), and whether the conclusions reached by the review were supported by data and/or analyses (2 points).

Evidence Table 21: Results of the systematic reviews on the use of computed tomography in the diagnosis of pulmonary embolism

Author, Year	Subgroup	Total pts	Overall prevalence of PE (%)	Combined sensitivity % (range) or [95% CI]	Combined specificity % (range) or [95% CI]	Conclusions
Harvey, 2000	Studies in which all participants had arteriography as reference standard; segmental PE data.	190	46	82 (53-100)	91 (78-100)	CT may be less accurate in diagnosis of PE than previously reported
	Studies in which some or all participants had arteriography reference standard; segmental PE data.	813	34	79 (47-100)	89 (75-100)	
	Studies that included data on diagnosis of segmental and subsegmental PE.	358	44	66 (45-91)	91 (78-100)	
Mullins, 2000	Studies that compared CT with arteriography for segmental PE diagnosis.	367	35	93 (50-100)	97 (92-100)	CT may have role as "rule-in" test for large central emboli, but additional research is required to establish its place in clinical practice
Rathburn, 2000	All studies.	1330		(53-100)	(81-100)	Use of CT in diagnosis of PE has not been adequately evaluated; all studies satisfied few criteria for methodological quality
Cueto, 2001	All studies.	268		80 [73-86]	94 [91-98]	CT may be an appropriate study in clinical evaluation of suspected PE
	Studies reporting segmental PE data.	166		77 [67-88]	91 [86-97]	
	Studies reporting combined segmental and subsegmental PE data.	169		81 [72-90]	98 [95-100]	
van Beek, 2001	All studies.	1171	39	88 [83-91]	92 [89-94]	Exact role of CT in management of suspected PE needs to be determined in prospective studies
Safriel, 2002	All studies.	1250		74 [57-100]	90 [68-100]	CT has acceptable sensitivity and specificity.

Evidence Table 22: Study design and characteristics of patients in studies evaluating computed tomography or magnetic resonance imaging for diagnosis of pulmonary embolism

Author, Year	Location	Aims	Test evaluated	Reference standard	Source of participants	N	Mean age in yrs (range)	Male (%)
Computed tomography								
Remy-Jardin, 1992	Europe	To compare quality and effectiveness of helical CT with results of pulmonary arteriography in dx of central PE.	HCT	PA	Referral with clinically suspected PE or unexplained chest radiograph abnormality.	42	34 (21-65)	71
Blum, 1994	Europe	To compare helical CT versus pulmonary arteriography in diagnosis of acute massive PE.	HCT	PA	Clinical suspicion of massive PE.	10	43 (18-76)	40
Goodman, 1995	United States	To prospectively compare helical CT with pulmonary arteriography for detecting PE in patients with unresolved clinical and V/Q scan dx.	HCT	PA	Non-diagnostic V/Q scan.	20	53 (25-84)	60
Remy-Jardin, 1996	Europe	To evaluate accuracy of helical CT in dx of PE.	HCT	PA	Referral for pulmonary arteriography.	75	59 (22-83)	43
Christiansen, 1997		To test diagnostic validity of CT compared to pulmonary arteriography in acute PE.	HCT	PA	High clinical suspicion of PE.	70	67 (22-87)	48
Drucker, 1998	United States	To determine sensitivity and specificity of helical CT for the dx of acute PE.	HCT	PA	Referral for pulmonary arteriography.	47	57 (22-89)	47
Qanadli, 2000	Europe	To evaluate the accuracy of dual-section helical CT in acute PE dx.	HCT (dual section)	PA	Referral to radiology department.	157	58 (14)[a]	46
Velmahos, 2001	United States	To evaluate sensitivity and specificity of helical CT for dx of PE in critically ill surgical patients.	HCT	PA	Surgical ICU patients with explicitly defined clinical findings associated with PE.	22	38 (20-75)	73
Magnetic Resonance Imaging								
Grist, 1993	United States	To study the accuracy of MRA in pts w/PE	MR (fast GRE)	PA	Pts referred for PA.	14	(35-82)	50
Erdman, 1994	United States	To assess accuracy of MRI in the evaluation of patients with suspected PE.	MRI of clot (SE, GRE)	PA or V/Q	Suspected PE referred for PA or V/Q.	64	(18-73)	47

Evidence Table 22: Study design and characteristics of patients in studies evaluating computed tomography or magnetic resonance imaging for diagnosis of pulmonary embolism (continued)

Author, Year	Location	Aims	Test evaluated	Reference standard	Source of participants	N	Mean age in yrs (range)	Male (%)
Loubeyre, 1994	Europe	To evaluate contrast-enhanced MRA in the diagnosis of thrombi in both the proximal and peripheral portions of the pulmonary arteries	MRA (fast GRE + Gd)	PA	Suspected PE.	23	50 (20-66)	52
Meaney, 1997	United States	To compare MRA with PA in for diagnosing PE in patients referred for PA.	MRA (fast GRE + Gd)	PA	Suspected PE referred for PA.	30	52 (22-83)	50
Berthezene, 1999	Europe	To assess accuracy of MR perfusion imaging compared with perfusion scintigraphy in patients with suspected lung perfusion defects (due to PE or emphysema).	Perfusion MRI (fast GRE + Gd)	V/Q	Suspected PE referred for V/Q.	48	(34-83)	63
Gupta, 1999	Australia	To prospectively evaluate MRA to dx pts w/ suspected PE in whom V/Q scans are of intermediate probability or clinical suspicion is high, and who are referred for PA.	MRA (fast GRE + Gd)	PA	Suspected PE referred for PA .	36	59 (28-84)	47
Oudkerk, 2001	Europe	To assess accuracy of MRA for diagnosis of PE in non-selected patients with suspected PE and an abnormal V/Q scan.	MRA (fast GRE + Gd)	PA	Suspected PE with abnormal V/Q referred for PA.	115	53 (16-87)	43

[a] Standard deviation

Evidence Table 23: Quality of studies evaluating computed tomography or magnetic resonance imaging for diagnosis of pulmonary embolism

Author, year	Overall [a]	Representativeness of study population [b]	Bias & confounding [c]	Description of test protocols [d]	Test interpretation [e]	Statistical quality & interpretation [f]
Computed tomography						
Remy-Jardin, 1992	82	88	70	100	100	50
Blum, 1994	44	25	70	50	25	50
Goodman, 1995	74	88	80	100	100	0
Remy-Jardin, 1996	77	75	60	100	100	50
Christiansen, 1997	61	0	30	75	100	100
Drucker, 1998	81	75	80	100	100	50
Qanadli, 2000	84	88	80	100	100	50
Velmahos, 2001	83	100	90	75	100	50
Magnetic Resonance Imaging						
Grist, 1993	75	38	70	75	100	50
Erdman 1994	67	63	20	100	100	50
Loubeyre	68	25	60	100	100	50
Meaney 1997	77	75	10	100	100	100
Berthezene 1999	60	13	10	100	75	100
Gupta 1999	77	75	10	100	100	100
Oudkerk 2001	76	75	5	100	100	100

[a] **Overall:** The mean of the percentage scores from the categories: Representativeness of Study Population, Bias and Confounding, Description of Test Protocols, Test Interpretation, and Statistical Quality and Interpretation (see below).

[b] **Representativeness of Study Population:** Percentage score based on a total maximum score of 8 points. This included description of study setting and population (2 points), description of inclusion/exclusion criteria (2 points), information on excluded or non-participating patients (2 points), and description of key patient characteristics (2 points).

[c] **Bias and Confounding:** Percentage score based on a total maximum score of 10 points. This included use of the reference test on all subjects receiving the study test (2 points), use of the study test in the decision to obtain the reference test (2 points), blinding of test interpretation and clinical data (2 points), interpretation of the study test by two or more independent observers (2 points), and interpretation of the reference test by two or more independent observers (2 points).

[d] **Description of Test Protocols:** Percentage score based on a total maximum score of 4 points. This included description of the study test protocol (2 points), and description of the reference test protocol (2 points).

[e] **Test Interpretation:** Percentage score based on a total maximum score of 6 points. This included description of the criteria for a positive interpretation of the study test (2 points), description of the criteria for a positive interpretation of the reference test (2 points), and reporting on numbers and reasons for withdrawals or patients lost to followup (2 points).

[f] **Statistical Quality and Interpretation:** Percentage score based on a total maximum score of 4 points. This included reporting of a summary index of test performance and of an index of variability (2 points), and use of multivariate or stratified analyses to adjust for potential confounders (2 points).

Evidence Table 24: Results of studies evaluating computed tomography or magnetic resonance imaging for diagnosis of pulmonary embolism

Author, Year	Most distal arterial level interpreted	Subgroup	N	TP[a]	FP[b]	TN[c]	FN[d]	Sensitivity % [95% CI]	Specificity % [95% CI]	Accuracy % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Prevalence %
Computed tomography													
Remy-Jardin, 1992	Segmental		42	18	1	23	0	100 [81-100]	96 [79-100]	98 [87-100]	95 [74-100]	100 [85-100]	43
Blum, 1994	Segmental		10	7	0	3	0	100 [59-100]	100 [29-100]	100 [69-100]	100 [59-100]	100 [29-100]	70
Goodman, 1995	Segmental		20	6	1	12	1	86 [42-100]	92 [64-100]	90 [68-99]	86 [42-100]	92 [64-100]	35
	Subsegmental		20	7	1	8	4	64 [31-89]	89 [52-100]	75 [51-91]	88 [47-100]	67 [35-90]	55
Remy-Jardin, 1996	Segmental	All cases	75	39	7	25	4	91 [78-97]	78 [60-91]	85 [75-92]	85 [71-94]	86 [68-96]	57
		Excluding inconclusive cases	65	39	0	25	1	98 [87-100]	100 [86-100]	98 [92-100]	100 [91-100]	96 [80-100]	62
Christiansen, 1997	Segmental		70	17	2	49	2	89 [67-99]	96 [87-100]	94 [86-98]	89 [67-99]	96 [87-100]	27
Drucker, 1998	Segmental	Inexperienced readers	47	9	6	26	6	60 [32-84]	81 [64-93]	74 [60-86]	60 [32-84]	81 [64-93]	32
		Experienced readers	47	8	1	31	7	53 [27-79]	97 [84-100]	83 [69-92]	89 [52-100]	82 [66-92]	32
Qanadli, 2000	Subsegmental	All cases	157	56	6	89	6	90 [80-96]	94 [87-98]	92 [87-96]	90 [80-96]	94 [87-98]	39
		Excluding inconclusive cases	151	56	3	89	3	95 [86-99]	97 [91-99]	96 [92-99]	95 [86-99]	97 [91-99]	39

Evidence Table 24: Results of studies evaluating computed tomography or magnetic resonance imaging for diagnosis of pulmonary embolism (continued)

Author, Year	Most distal arterial level interpreted	Subgroup	N	TP[a]	FP[b]	TN[c]	FN[d]	Sensitivity % [95% CI]	Specificity % [95% CI]	Accuracy % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Prevalence %
Velmahos, 2001	Subsegmental		22	5	2	9	6	45 [17-77]	82 [48-98]	64 [41-83]	71 [29-96]	60 [32-84]	50
Magnetic Resonance Imaging													
Grist, 1993	All cases	Referred for PA	14	6	3	5	0	100	62	79	67	100	43
Erdman, 1994	Segmental	All cases	63	31	3	26	4	88	90	90	91	87	55
Loubeyre, 1994	Segmental	All cases	23	10	0	11	2	83	100	91	100	85	52
Meaney, 1997	Segmental	All cases	30	8	1	21	0	100	95	97	89	100	27
Bertheze ne, 1999	Segmental	All cases	24					69	91				
Gupta, 1999	Segmental	All cases	36	11	2	22	1	85	96	92	85	96	36
Oudkerk, 2001	Segmental	All cases	118	27	2	81	8	77	98	92	93	91	30

[a] TP=true positive [b] FP=false positive [c] TN=true negative [d] FN=false negative