CHEST Online Data Supplement

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Table S1—*[Section 2.1] Evidence Profile: Parenteral Anticoagulation vs No Parenteral Anticoagulation in Acute VTE*[a]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Parenteral Anticoagulation	With Parenteral Anticoagulation	Relative Effect (95% CI)	Risk With No Parenteral Anticoagulation	Risk Difference With Parenteral Anticoagulation (95% CI)
Mortality (important outcome)											
120 (1 study), 6 mo	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Moderate[b,c] due to imprecision	2/60 (3.3)	1/60 (1.7)	RR 0.5 (0.05-5.37)	33 per 1,000	16 fewer per 1,000 (from 31 fewer to 144 more)
Recurrent VTE (critical outcome; assessed with symptomatic extension or recurrence)											
120 (1 study), 6 mo	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[b,d] due to imprecision	12/60 (20)	4/60 (6.7)	RR 0.33 (0.11-0.98)	200 per 1,000	134 fewer per 1,000 (from 4 fewer to 178 fewer)
Major bleeding (critical outcome)											
120 (1 study), 6 mo	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Moderate[b,c] due to imprecision	3/60 (5)	2/60 (3.3)	RR 0.67 (0.12-3.85)	50 per 1,000	16 fewer per 1,000 (from 44 fewer to 142 more)

Bibliography: Brandjes et al.[1] RR = risk ratio.

[a] Both groups treated with acenocoumarol.

[b] Study described as double blinded; outcome adjudicators blinded. None of the study participants were lost to follow-up. Intention-to-treat analysis. Study was stopped early for benefit.

[c] CI includes values suggesting no effect as well as values suggesting either appreciable benefit or appreciable harm.

[d] Low number of events caused by the early stoppage of the trial.

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Table S2—*[Section 2.4] Evidence Profile: Early Warfarin (and Shorter Duration Heparin) vs Delayed Warfarin (and Longer Duration Heparin) for Acute VTE*[a-d]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Delayed Warfarin Initiation (and Longer Duration Heparin)	With Early Warfarin Initiation (and Shorter Duration Heparin)	Relative Effect (95% CI)	Risk With Delayed Warfarin Initiation (and Longer Duration Heparin)	Risk Difference With Early Warfarin Initiation (and Shorter Duration Heparin) (95% CI)
Mortality (important outcome[e])											
688 (3 studies), 3 mo[f]	No serious risk of bias[g]	No serious inconsistency	No serious indirectness	Serious[h]	Undetected	Moderate[g,h] due to imprecision	13/338 (3.8)	12/350 (3.4)	RR 0.9 (0.41-1.95)	24 per 1,000[i]	2 fewer per 1,000 (from 14 fewer to 23 more)
Recurrent VTE (critical outcome)											
688 (3 studies), 3 mo[f]	No serious risk of bias[g]	No serious inconsistency	No serious indirectness	Serious[h]	Undetected	Moderate[g,h] due to imprecision	14/338 (4.1)	12/350 (3.4)	RR 0.83 (0.4-1.74)	47 per 1,000[i]	8 fewer per 1,000 (from 28 fewer to 35 more)
Major bleeding (critical outcome)											
688 (3 studies), 3 mo[j]	No serious risk of bias[g,k]	No serious inconsistency	No serious indirectness	No serious imprecision[l]	Undetected	High[g,k,l]	10/338 (3.0)	15/350 (4.3)	RR 1.48 (0.68-3.23)	16 per 1,000[i]	14 more per 1,000 (from 9 fewer to 66 more)

Bibliography: Gallus et al,[2] Hull et al,[3] Leroyer et al.[4] Excluded Mohiuddin et al[5] because 34% of subjects had mural thrombus rather than VTE, in addition to major methodologic limitations).
LMWH = low-molecular-weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist. See Table S1 legend for expansion of other abbreviation.

[a] VKA therapy started within 1 day of starting heparin therapy (UFH in two studies and LMWH in one study).

[b] VKA therapy delayed for 4 to 10 d.

[c] Most patients had proximal DVT, some had isolated distal DVT; most DVT were symptomatic (asymptomatic DVT included in Hull et al), and few had PE (only included in Gallus et al).

[d] The early initiation of VKA was associated with a lower number of days of heparin therapy (4.1 vs 9.5 in Gallus et al; 5 vs 10 in Hull et al) and a lower number of days of hospital stay (9.1 vs 13.0 in Gallus; 11.7 vs 14.7 in Hull; 11.9 vs 16.0 in Leroyer et al).

[e] Differences in death, independently of differences in recurrent VTE and major bleeding, is unlikely.

[f] Outcome assessment was at hospital discharge in the study by Gallus et al (although there was also extended follow-up) and 3 mo in the studies by Hull et al and Leroyer et al.

[g] Patients and investigators were not blinded in two studies (Gallus et al and Leroyer et al) and were blinded in one study (Hull et al). Concealment was not clearly described but was probable in the three studies. Primary outcome appears to have been assessed after a shorter duration of follow-up in the shorter treatment arm of one study because of earlier discharge from the hospital, and 20% of subjects in this study were excluded from the final analysis postrandomization (Gallus).

[h] The 95% CI on relative effect includes both clinically important benefit and clinically important harm.

[i] Event rate corresponds to the median event rate in the included studies.

[j] Bleeding was assessed early (in hospital or in the first 10 d) in two studies (Gallus et al, Hull et al) and at 3 mo in one study (Leroyer et al).

[k] It is unclear whether bleeding was assessed at 10 d in all subjects or just while heparin was being administered, which could yield a biased estimate in favor of short-duration therapy in one study (Hull et al).

[l] Because the shorter duration of heparin therapy is very unlikely to increase bleeding, the wide 95% CIs around the relative effect of shorter therapy on risk of bleeding is not a major concern.

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Table S3—*[Section 2.5.1] Evidence Profile: LMWH vs SC UFH for Initial Anticoagulation of Acute VTE*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With SC UFH	With LMWH	Relative Effect (95% CI)	Risk With SC UFH	Risk Difference With LMWH (95% CI)
Mortality (important outcome)											
1,566 (3 studies), 3 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	Moderate[a,b] due to imprecision	31/780 (4)	34/786 (4.3)	RR 1.1 (0.68-1.76)	33 per 1,000[c]	3 more per 1,000 (from 11 fewer to 25 more)
Recurrent VTE (critical outcome)											
1,563 (3 studies), 3 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	Moderate[a,b] due to imprecision	31/777 (4)	26/786 (3.3)	RR 0.87 (0.52-1.45)	42 per 1,000[c]	5 fewer per 1,000 (from 20 fewer to 19 more)
Major bleeding (critical outcome)											
1,634 (4 studies), 3 mo	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	Moderate[b,c] due to imprecision	15/815 (1.8)	19/819 (2.3)	RR 1.27 (0.56-2.9)	16 per 1,000[c]	4 more per 1,000 (from 7 fewer to 30 more)

Bibliography: Lopaciuk et al,[21] Faivre et al,[2] Prandoni et al,[23] Kearon et al.[24] SC = subcutaneous. See Table S1 and S2 legends for expansion of other abbreviations.

[a] In the two largest trials (Prandoni et al and Kearon et al, 87% of patients), allocation was concealed, outcome adjudicators and data analysts were concealed, analysis was intention to treat, and there were no losses to follow-up.

[b] Precision judged from the perspective of whether SC heparin is noninferior to LMWH. The total number of events and the total number of participants are relatively low.

[c] Event rate corresponds to the median event rate in the included studies.

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Table S4—*[Section 2.5.1] LMWH vs SC UFH for Initial Anticoagulation of Acute VTE: Clinical Description and Results*

Author/Year (Acronym)	Interventions	Patients Analyzed[a]	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
Lopaciuk et al[21]/1992	UFH 5,000 units IV followed by 250 units/kg SC bid initially and adjusted to aPTT for 10 d	72/75	1/72 (1.4%)	1/72 (1.4%)	3/72 (4.2%)	Population: Femoral DVT in 81% and popliteal or more distal DVT in 19%. Primary outcome was repeat venography.
	Fraxiparine 97 International Units/kg SC bid for 10 d	74/74	0/74 RR 3.1 (0.1-7.5)	0/74RR 3.1 (0.1-7.5)	0/74RR 7.2 (0.4-137)	
Faivreet al[22]/1988	UFH 5,000 units IV followed by 250 units/kg SC bid and adjusted to aPTT for 10 d	29/35	1/35	3/35	1/35	Population: DVT (proportion of proximal and distal not reported). Primary outcome was repeat venography.
	CY222 2,000 International Units IV followed by 150 International Units/kg SC bid for 10 d	30/33	1/33 RR 0.9 (0.1-14.5)	0/33 RR 6.6 (0.3-123)	0/33 RR 2.8 (0.1-67)	
Prandoni et al[23]/2004 (Galilei)	UFH IV (< 50 kg: 4,000 units; 50-70 kg: 5,000 units; > 70 kg: 6,000 units) followed by SC bid doses (initially < 50 kg: 12,500 units; 50-70 kg: 15,000 units; > 70 kg: 17,500 units) adjusted to aPTT for ~6.5 d	360/360	15/360 (4.2%)	5/360 (1.4%)	12/360 (3.3%)	Population: Proximal DVT in 65%, distal DVT in 18%, and PE in 17%.
	Nadroparin 85 International Units/kg SC bid for ~6.5 d	360/360	14/360 (3.9%) RR 1.1 (0.5-2.2)	7/360 (1.9%) RR 0.7 (0.2-2.2)	12/360 (3.3%) RR 1.0 (0.5-2.2)	
Kearon et al[24]/2006 (FIDO)	UFH 333 units/kg SC followed by 250 units/kg SC bid (no adjustment) for 6.3 d	345/355	13/345 (3.8%)	6/348 (1.7%)	18/348 (5.2%)	Population: Proximal DVT in 77%, asymptomatic or distal DVT in 4%, and PE in 19%. Seventy percent of patients were treated entirely as an outpatient (76% of DVT and 39% of PE) Postrandomization exclusions in 10 patients receiving UFH and one patient receiving LMWH.
	Dalteparin (n = 261) or enoxaparin (n = 91) 100 International Units/kg SC bid for 7.1 d	352/353	12/352 (3.4%) RR 1.1 (0.5-2.3)	12/352 (3.4%) RR 0.5 (0.2-1.3)	22/352 (6.3%) RR 0.8 (0.4-1.5)	

aPTT = activated prothrombin time; FIDO = Fixed Dose Heparin. See Table S1 and S2 legends for expansion of other abbreviations.

[a]Follow-up was for 3 mo except for the study by Faivre et al[22] in which it was 10 d.

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Table S5—*[Section 2.5.1] LMWH vs SC UFH for Initial Anticoagulation of Acute VTE: Methodologic Quality*

Author/Year (Acronym)	Interventions	Study Design	Randomization Concealed	Blinding	Loss to Follow-up	Analysis	Comments
Lopaciuk et al[21]/1992	UFH 5,000 units IV followed by 250 units/kg SC bid initially and adjusted to aPTT for 10 d Fraxiparine 97 International units/kg SC bid for 10 d	RCT	PY	Patients: CN Caregivers: CN Adjudicators: CN Data Analysts: PN	Not described	ITT	
Faivre et al[22]/1988	UFH 5,000 units IV followed by 250 units/kg SC bid and adjusted to aPTT for 10 d CY222 2,000 International Units IV followed by 150 International Units/kg SC bid for 10 d	RCT	PN	Patients: PN Caregivers: PN Adjudicators: PN Data Analysts: PN	Three of CY222 group and six of UFH group who did not have repeat venography are assumed to have completed clinical follow-up	ITT	
Prandoni et al[23]/2004 (Galilei)	UFH IV (< 50 kg: 4,000 units; 50-70 kg: 5,000 units; > 70 kg: 6,000 units) followed by SC bid doses (initially < 50 kg: 12,500 units; 50-70 kg: 15,000 units; > 70 kg: 17,500 units) adjusted to aPTT for ~6.5 d Nadroparin 85 International Units/kg SC bid for ~6.5 d	RCT	CY	Patients: CN Caregivers: CN Adjudicators: CY Data Analysts: PY	Nil	ITT	
Kearon et al[24]/2006 (FIDO)	UFH 333 units/kg SC followed by 250 units/kg SC bid (no adjustment) for 6.3 d Dalteparin (n = 261) or enoxaparin (n = 91) 100 International Units/kg SC bid for 7.1 d	RCT	CY	Patients: CN Caregivers: CN Adjudicators: CY Data Analysts: PY	Nil	ITT	Postrandomization exclusions from the efficacy analysis were 10 (2.8%) for the UFH and one (0.2%) for the LMWH group.

CN = certainly no; CY = certainly yes; ITT = intention to treat; PN = probably no; PY = probably yes; RCT = randomized controlled trial. See Table S1, S2, and S4 legends for expansion of other abbreviations.

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Table S6—*[Section 2.5.1] Evidence Profile: LMWH vs IV UFH for Initial Anticoagulation of Acute VTE*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With IV UFH	With LMWH	Relative Effect (95% CI)	Risk With IV UFH	Risk Difference With LMWH (95% CI)
Mortality (important outcome)											
7,908 (17 studies), 3 mo	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias strongly suspected[b]	Low[a,b] due to risk of bias, publication bias	232/3,789 (6.1)	187/4,119 (4.5)	RR 0.79 (0.66-0.95)	46 per 1,000[c]	10 fewer per 1,000 (from 2 fewer to 16 fewer)
Recurrent VTE (critical outcome)											
7,976 (17 studies), 3 mo	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias strongly suspected[b]	Low[a,b] due to risk of bias, publication bias	208/3,869 (5.4)	151/4,107 (3.7)	RR 0.72 (0.58-0.89)	55 per 1,000[c]	15 fewer per 1,000 (from 6 fewer to 23 fewer)
Major bleeding (critical outcome)											
6,910 (20 studies), 3 mo	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[d]	Reporting bias strongly suspected[b]	Low[a,b,d] due to risk of bias, publication bias	69/3,517 (2)	41/3,393 (1.2)	RR 0.67 (0.45-1)	15 per 1,000[c]	5 fewer per 1,000 (from 8 fewer to 0 more)

Bibliography: van Dongen et al.[6] Included studies.[7,20] See Table S1 and S2 legends for expansion of abbreviations.

[a] Of the 20 trials, allocation was concealed in nine and was unclear whether concealed in the remaining 11. Eighteen trials had blinded outcome assessors. Seven trials did not have any postrandomization exclusions or losses to follow-up. Ten trials reported the number of participants lost to follow-up, which ranged from 1.0% to 12.7%. One trial did not report the drop-outs.

[b] Inverted funnel plot very suggestive of publication bias. Many of the included studies are of small size, and all are funded by industry.

[c] Event rate corresponds to the median event rate in the included studies.

[d] CI interval includes values suggesting significant benefit and no effect.

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Table S7—*[Section 2.5.1] Evidence Profile: Fondaparinux vs LMWH for Initial Anticoagulation of Acute DVT*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With LMWH	With Fondaparinux	Relative Effect (95% CI)	Risk With LMWH	Risk Difference With Fondaparinux (95% CI)
Mortality (important outcome)											
2,205 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	33/1,107 (3.0)	41/1,098 (3.7)	RR 1.25 (0.8-1.97)	30 per 1,000	7 more per 1,000 (from 6 fewer to 29 more)
Recurrent VTE (critical outcome)											
2,205 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	45/1,107 (4.1)[f]	43/1,098 (3.9)[f]	RR 0.96 (0.64-1.45)	41 per 1,000[f]	2 fewer per 1,000 (from 15 fewer to 18 more)
Major bleeding (critical outcome)											
2,205 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	13/1,107 (1.2)[g]	12/1,098 (1.1)[g]	RR 0.93 (0.43-2.03)	12 per 1,000[g]	1 fewer per 1,000 (from 7 fewer to 12 more)

Bibliography: Büller et al.[25] INR = international normalized ratio. See Table S1 and S2 legends for expansion of other abbreviations.

[a] Fondaparinux 7.5 mg (5.0 mg in patients weighing < 50 kg and 10.0 mg in patients weighing > 100 kg) SC once daily for at least 5 d and until VKAs induced an INR > 2.0.
Enoxaparin 1 mg/kg of body weight SC bid for at least 5 d and until VKAs induced an INR > 2.0.

[c] All patients had acute symptomatic DVT.

[d] Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Analysis excluded 0.6% of randomized patients. Not stopped early for benefit.

[e] CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

[f] Five fatal VTE in fondaparinux group and five fatal VTE in LMWH group.

[g] Twelve patients in the fondaparinux group and 13 in the LMWH group had a major bleeding during the initial period (7 d). Of these, two in the fondaparinux group and none in the LMWH group were fatal.

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Table S8—*[Section 2.5.2] Evidence Profile: LMWH Once vs Twice Daily for Initial Anticoagulation of Acute VTE*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Bid	With LMWH Once	Relative Effect (95% CI)	Risk With Bid	Risk Difference With LMWH Once (95% CI)
Mortality (important outcome)											
1,261 (3 studies), 3 mo	No serious risk of bias[c]	Serious[d]	No serious indirectness	Serious[e]	Undetected	Low[c-e] due to inconsistency, imprecision	20/647 (3.1)	20/614 (3.3)	RR 1.05 (0.57-1.94)	31 per 1,000	2 more per 1,000 (from 13 fewer to 29 more)
Recurrent VTE (critical outcome)											
1,261 (3 studies), 3 mo	No serious risk of bias[c]	Serious[f]	No serious indirectness	Serious[e]	Undetected	Low[c,e,f] due to inconsistency, imprecision	32/647 (4.9)	26/614 (4.2)	RR 0.86 (0.52-1.42)	49 per 1,000	7 fewer per 1,000 (from 24 fewer to 21 more)
Major bleeding (critical outcome)											
1,522 (5 studies), 10 d	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[c,e] due to imprecision	9/772 (1.2)	10/750 (1.3)	RR 1.13 (0.48-2.66)	12 per 1,000	2 more per 1,000 (from 6 fewer to 20 more)

Bibliography: van Dongen et al.[26] See Table S1, S2, and S5 legends for expansion of other abbreviations.

[a] The five included studies used four brands of LMWH (enoxaparin, tinzaparin, dalteparin, and nadroparin). In Merli et al, enoxaparin 1 mg/kg bid was compared with 1.5 mg/kg once daily. Holmström[27] et al adjusted the dose to anti-Xa levels, which resulted in different daily doses after a number of days. In the remaining studies, the dose of the once-daily administration was double the dose of the twice-daily administration (equal total daily dose).

[b] Of the five included studies, one included patients with PE and DVT, and four included only patients with DVT. All studies addressed the initial management of VTE.

[c] All included studies concealed allocation. Two studies had a double-blind design, and two others were single blind. One study did not mention blinding. ITT likely used in all studies. Participants were lost to follow-up in only two studies (0.3% and 2.2%).

[d] $I^2 = 37\%$; point effect estimate in favor of bid dose in Merli et al[16] and in favor of once-daily dose in Charbonnier et al.[28]

[e] Imprecision judged relative to no difference.

[f] $I^2 = 65\%$; point effect estimate in favor of bid dose in Merli et al[16] and in favor of once-daily dose in Charbonnier et al.[28]

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Table S9—*[Section 2.7] Evidence Profile: Home Treatment vs Hospital Treatment of Acute DVT*[a-d]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Hospital Treatment	With Home Treatment	Relative Effect (95% CI)	Risk With Hospital Treatment	Risk Difference With Home Treatment (95% CI)
Mortality (important outcome)											
1,708 (6 studies), 3 mo	No serious risk of bias[e]	No serious inconsistency	Serious[a,b]	Serious[f]	Undetected	Low[a,b,e,f] due to indirectness, imprecision	39/851 (4.6)	28/857 (3.3)	RR 0.72 (0.45-1.15)	46 per 1,000	13 fewer per 1,000 (from 25 fewer to 7 more)
Recurrent VTE (critical outcome)											
1,708 (6 studies), 3 mo	No serious risk of bias[e]	No serious inconsistency	Serious[a,b]	No serious imprecision	Undetected	Moderate[a,b,e] due to indirectness	63/851 (7.4)	39/857 (4.6)	RR 0.61 (0.42-0.9)	74 per 1,000	29 fewer per 1,000 (from 7 fewer to 43 fewer)
Major bleeding (critical outcome)											
1,708 (6 studies), 3 mo	No serious risk of bias[e]	No serious inconsistency	Serious[a,b]	Seriousf	Undetected	Moderate[a,b,e,g] due to indirectness	18/851 (2.1)	12/857 (1.4)	RR 0.67 (0.33-1.36)	21 per 1,000	7 fewer per 1,000 (from 14 fewer to 8 more)
Quality of life (important outcome)											
0 (3 studies[h]), 3 mo	No serious risk of bias	No serious inconsistency[i]	Serious[j]	Seriousk	Undetected	Low[i-k] due to indirectness, imprecision	…	…	Not pooled	See comment[h-k]	See comment[h-k]

Bibliography: Othieno et al[29]; included studies.[13,14,30-33] Quality of life.[13,34,35] See Table S1 and S2 for expansion of abbreviations.

[a] Four studies had partial hospital treatment of many in the home arm: Koopman et al (mean hospital stay 2.7 in home arm vs 8.1 d in hospital arm), Levine et al (2.1 vs 6.5 d), Boccalon et al (1 vs 9.6 d), and Ramacciotti et al (3 vs 7 d). In Daskalopoulos et al, there was no hospital stay at all in the home group. Chong et al did not report duration of hospital stay.

[b] Only one study (Boccalon et al) used LMWH in both treatment arms. Remaining studies used UFH in the inpatient arm and LMWH in the outpatient arm.

[c] Studies included in the systematic review should have recruited patients whose home circumstances were adequate.

[d] All studies included patients with lower-extremity DVT and excluded patients with suspected or confirmed PE. Studies also excluded patients who were pregnant.

[e] Out of six studies, allocation was clearly concealed in three (unclear in remaining three). Outcome adjudicators were blinded in the two largest studies (unclear in remaining). Four reported loss to follow-up (was significant in only a small study). ITT analysis was conducted in four (unclear in remaining two). No study was stopped early for benefit. Overall, the judgment was that these limitations would not warrant downgrading of quality because it has already been downgraded by at least one level based on other factors.

[f] The CI includes both values suggesting benefit and harm.

[g] Judged as precise based on the narrow CI around absolute effect.

[h] Bäckman et al[34] reported evaluation of health-related quality of life using the EQ-5D. They found no differences in mean quality-of-life scores or in the proportion of patients showing improvement in self-rated health state. Koopman et al evaluated health-related quality of life using the Medical Outcome Study Short Form-20 and an adapted version of the Rotterdam Symptom Checklist. The changes over time were similar in both groups except that the patients receiving LMWH had better scores for physical activity ($P = .002$) and social functioning ($P = .001$) at the end of the initial treatment. The authors did not report enough data to assess precision and clinical significance of results. O'Brien et al[35] assessed changes in quality of life using the Medical Outcome Study Short Form-36 in 300 patients participating in Levine et al.[14] They found that, the change in scores from baseline to day 7 was not significantly different between the treatment groups for seven of the eight domains. The one exception was the domain of social functioning, where a greater improvement was observed for the outpatient group.

[i] Potential inconsistency as Bäckman et al[34] showed no effect, whereas Koopman et al[13] and O'Brien et al[35] showed potential benefit.

[j] Two of the three studies had partial hospital treatment of many in the home arm: Koopman et al[13] (mean hospital stay 2.7 in home arm vs 8.1 d in hospital arm) and Levine et al (2.1 vs 6.5 d).

[k] Not able to evaluate but imprecision is possible. Taken together with the potential inconsistency, we downgraded the quality of evidence by one level.

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Table S10—*[Section 2.9] Evidence Profile: Catheter-Directed Thrombolysis vs No Catheter-Directed Thrombolysis for Extensive Acute DVT of the Leg*[ab]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Catheter-Directed Thrombolysis	With Catheter-Directed Thrombolysis	Relative Effect (95% CI)	Risk With No Catheter-Directed Thrombolysis	Risk Difference With Catheter-Directed Thrombolysis (95% CI)
Mortality (important outcome)											
153 (2 studies), 3 mo	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	Low[c,d] due to imprecision	3/76 (3.9)[e]	0/77 (0)	RR 0.14 (0.01-2.71)	39 per 1,000[e]	34 fewer per 1,000 (from 39 fewer to 67 more)
Nonfatal recurrent VTE (critical outcome)											
153 (1 study), 3 mo	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	Low[c,d] due to imprecision	1/76 (1.3)	0/77 (0)	RR 0.35 (0-8.09)	48 per 1,000[f]	31 fewer per 1,000 (from 48 fewer to 340 more)
Nonfatal major bleeding (critical outcome)											
153 (2 studies), 7 d	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	Low[c,d] due to imprecision	0/76 (0)	1/77 (1.3)[g]	RR 2.00 (0.19-19.46)	29 per 1,000[f,h]	29 more per 1,000 (from 23 fewer to 535 more)
Postthrombotic syndrome (critical outcome; assessed with: complete lysis on venography (Elsharawy et al); patency on ultrasound and air plethysmography (Enden et al))											
138 (2 studies), 2 y	No serious risk of bias[c]	No serious inconsistency	Serious[i]	No serious imprecision	Undetected	Moderate[c,i] due to indirectness	49/70 (70)	23/68 (33.8)	RR 0.46 (0-0.79)	588 per 1,000[j]	318 fewer per 1,000 (from 123 fewer to 588 fewer)[k]

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Table S10—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Catheter-Directed Thrombolysis	With Catheter-Directed Thrombolysis	Relative Effect (95% CI)	Risk With No Catheter-Directed Thrombolysis	Risk Difference With Catheter-Directed Thrombolysis (95% CI)
Quality of life (important outcome; measured with the Medical Outcome Survey Short Form-12, Health Utilities Index MARK version 2/3 questionnaires; better indicated by lower values)											
98 (1 study[j]), 16 mo	No serious risk of bias[m,n]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Low[m,n]	30	68	...		See footnote[o]

Bibliography: Elsharawy et al,[36] Enden et al,[37] Comerota et al.[38] CDT = catheter-directed thrombolysis; PTS = postthrombotic syndrome. See Table S1 legend for expansion of other abbreviations.

[a] All patients were anticoagulated per protocol, but the intervention group received CDT in addition to anticoagulation.

[b] In selected patients with extensive acute proximal DVT (eg, iliofemoral DVT, symptoms for < 14 d, good functional status, life expectancy ≥ 1 y) who have a low risk of bleeding.

[c] Allocation was concealed in Enden et al and unclear in Elsharawy et al. Outcome assessor blinded in both studies. Follow-up rates were 87% in Enden et al and 100% in Elsharawy et al. None of the studies was stopped early for benefit.

[d] CI includes values suggesting both benefit and harm.

[e] Three control patients died of cancer.

[f] Baseline risks for nonfatal recurrent VTE and for major bleeding derived from Douketis et al.[39]

[g] In the Enden et al study, one patient had "durable and partial impairment of sensibility of the foot" immediately after receiving CDT, and nine patients had minor bleeding complications.

[h] Most of bleeding events occur during the first 7 d.

[i] Surrogate outcome: absence of patency at 6 mo in Enden et al study; absence of complete lysis at 6 mo in Elsharawy et al study.

[j] This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes) study.[40] This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[k] Severe PTS: assuming the same RR of 0.46 and a baseline risk of 13.8%, the absolute reduction is 75 fewer severe PTS per 1,000 (from 29 fewer to 138 fewer) over 2 y.

[l] Camerota et al.[38]

[m] Participation rate was 65%.

[n] Recall was used to measure quality of life prior to the thrombotic event; we did not consider these measurements.

[o] At the initial follow-up (mean, 16 mo), patients treated with CDT reported a trend toward a higher mental summary scale ($P = .087$) and improved Health Utilities Index ($P = .078$). They reported better overall role physical functioning ($P = .046$), less stigma ($P = .033$), less health distress ($P = .022$), and fewer overall symptoms ($P = .006$) compared with patients who were treated with anticoagulation alone.

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Table S11—*[Section 2.9] CDT vs No CDT for Extensive Acute DVT of the Leg: Clinical Description and Results (All Randomized Trials and Prospective Observational Studies of at Least 20 Patients)*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Semba et al[41]/1994	Prospective registry	21 patients (27 limbs) with iliofemoral DVT ≤ 14 d (20) or > 14 d (7) duration	4.9 million units urokinase (mean) infused over 30 h (mean), followed by heparin and then warfarin for 8-12 wk Adjunctive therapy: limbs with residual stenoses > 50% received angioplasty (2) or stenting (14)	Clot lysis, complications	3 mo	Significant lysis: 18/25[a] (72%) Partial lysis: 5/25 (20%) No lysis: 2/25 (8%) Complications: 1 small hematoma at puncture site, no intervention/ transfusion
Verhaeghe et al[42]/1997	Prospective study	24 patients with iliofemoral DVT ≤ 14 d (16) or > 14 d (8) duration	3 mg/h rt-PA (mean 86 mg) infused with 1,000 U/h IV heparin, followed by heparin, adjusted to APTT Adjunctive therapy: hydrodynamic thrombectomy (3) and stents (9)	Clot lysis, bleeding	13 mo (mean)	Significant lysis: 19/24 (79%) Partial lysis: 5/24 (21%) Bleeding: 6/24 (25%) Patency: 3 mo: 84% 1 y: 78%
Bjarnason et al[43]/1997	Prospective registry	77 patients (87 limbs) with iliofemoral DVT ≤ 14 d (69) or > 14 d (18) duration	2,000-2,500 units/kg per h urokinase infused for 75 h (mean) with 5,000 International Units bolus heparin plus infusion adjusted to aPTT Adjunctive therapy: angioplasty (52 limbs), stent (38), AVF (15), surgical thrombectomy (13), mechanical thrombectomy (4), surgical bypass (3)	Clot lysis, PE, bleeding	1 y	Early results: Significant lysis: 69/87 (79%) Iliac (63%) Femoral (40%) No lysis: 18/87 (21%) PE: 1 (1%) Bleeding: major, 5/77 (6%); minor, 11/77 (14%) Patency at 1 y: Iliac: 63% Femoral, 40%

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Table S11—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Mewissen et al[44]/1999 (National Multicenter Registry)	Prospective multicenter registry	287 patients (312 infusions) with lower limb DVT ≤ 10 d (188) or > 10 d (99) duration	7.8 million units urokinase (mean) infused for 53.4 h (mean) in 297 limbs In 6 limbs, only systemic infusion (no CDT) Adjunctive therapy: stents (104), systemic infusion (54)	Clot lysis, PE, bleeding, death	1 y	Early results: 50%-100% lysis: 258/312 (83%) <50% lysis: 54/312 (17%) PE: 6/473[b] (1%) Bleeding: 54/473[b] (11%) Death: 2/473[b] (< 1%) Patency at 1 y: Iliac: 64% Femoral: 47%
AbuRahma et al[45]/2001	Prospective study	51 patients (51 limbs) with iliofemoral DVT given choice between conventional therapy (heparin + warfarin) orlysis + angio/stent (if needed). Lysis offered only to patients with DVT ≤ 14 d duration and no contraindications	Anticoagulation: 33 patients given 1,000-2000 units/h heparin infusion for 5-7 d.	Clot lysis, PE, bleeding	Anticoag: 6 mo	Anticoagulation: 30-d significant lysis: 1/33 (3%) 6-mo patency: 8/33 (24%) Bleeding: 2/33 (6%) PE: 2/33 (6%)
			CDT: 18 patients given loading dose 4,500 units urokinase followed by 4,500 units/kg per h for 24-48 h or 4-8-mg bolus of rt-PA followed by 2-4-mg/h infusion Adjunctive therapy: patients with residual stenosis > 50% received stents (10)		CDT: 6 mo?	CDT: 30-d significant lysis: 15/18 (83%) 6-mo patency: 15/18 (83%) Bleeding: 2/18 (11%)
Elsharawy et al[36]/2002)	RCT, single center	35 patients with DVT < 10 d duration randomized to CDT or anticoagulation alone	CDT: 18 patients received ~1 million units SK pulse-spray for 1 h, followed by 100,000 units/h SK infusion until complete lysis, no change in 12 h, or complication Adjunctive therapy: angioplasty/stent (1)	Clot lysis, PE, bleeding	1 wk and 6 mo	CDT, 1 wk Complete lysis: 11/18 (61%) No lysis: 0 (0%) PE: 0 Bleeding: 0 Anticoagulation, 1 wk: Complete lysis: 0/17 (0%) No lysis: 17/17 (100%) PE: 1/17 (6%) Bleeding: 0

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Table S11—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
			Anticoagulation: 17 patients received 5,000 units heparin bolus, followed by heparin adjusted to aPTT			CDT, 6 mo Complete lysis: 13/18 (72%) No lysis: 0 (0%) Anticoagulation, 6 mo Significant lysis:2/17 (12%) No lysis: 7/17 (41%)
Enden et al[37]/2009 (CaVenT)	RCT, multicenter	Iliofemoral DVT < 21 d duration	CDT: tPA 0.01 mg/kg per h, maximum of 20 mg/24 h for 4 d. Treated in four referral centers Anticoagulation alone: usual practice, administered locally	Clot lysis, PE, bleeding (PTS at 24 mo pending)	1 wk and 6 mo	CDT, 1 wk ≥50%lysis: 44/50 (68%) PE: 0 Major bleeding: 1/50 Anticoagulation, 1 wk: Lysis not assessed PE: 0 Major bleeding: 0 (puncture site nerve damage: 0) CDT, 6 mo Iliofemoral patency: 32/50 (64%) Anticoagulation, 6 mo Iliofemoral patency: 19/53 (36%)

Early prospective observational studies with < 20 patients and retrospective studies are described in Table 3 of the eighth edition of these guidelines.[46] AVF = arteriovenous fistula; CaVenT = Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis; rt-PA = recombinant tissue plasminogen activator; SK = streptokinase. See Table S2, S4, S5, and S10 legends for expansion of other abbreviations.

[a] Twenty-five of 27 limbs treated with CDT; two could not be crossed with the guidewire.

[b] Calculated from total number of patients in Venous Registry.

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Table S12—*[Section 2.9] CDT vs No CDT for Extensive Acute DVT of the Leg: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to follow-up
Semba et al[41]/1994	N/A	N/A	N/A	N/A
Verhaeghe et al[42]/1997	N/A	N/A	N/A	N/A
Bjarnason et al[43]/1997	N/A	N/A	N/A	N/A
Mewissen et al[44]/1999	N/A	N/A	N/A	N/A
AbuRahma et al[45]/2001	N/A	N/A	N/A	N/A
Elsharawy et al[36]/2002	Computer-designated cards	PN	N for patients, caregivers, and probably data analysts. Y for vascular imaging	0
Enden et al[37]/2009	Computer-designated cards	Y	No for patients and caregivers. Yes for vascular imaging.	One loss to follow-up (CDT), five withdrawals, five postrandomization exclusions

N = no; N/A = not applicable; Y = yes. See Table S10 legend for expansion of other abbreviation.

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Table S13—*[Section 2.10] Systemic Lysis vs No Systemic Lysis for Extensive Acute DVT of the Leg: Clinical Description and Results (Randomized Trials That Compared Systemic Thrombolytic Therapy With No Thrombolytic Therapy)*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Browse et al[52]/1968	RCT, single center	10 patients with lower-extremity DVT confirmed by phlebography	Lysis: 600,000 units SK plus 100 mg hydrocortisone for first hour, then continued every 6 h for 3 d (5 patients) Anticoagulation: 4-6 hourly doses of heparin 5,000 units for 48 h followed by warfarin (5 patients)	Clot lysis, PE, bleeding	7-10 d	Thrombolysis: Complete clot lysis: 3/5 (60%) Partial lysis: 1/5 (20%) No lysis: 1 (20%) PE: 0 Bleeding: 0 Anticoagulation: Complete clot lysis: 0/5 Partial lysis: 0/5 No lysis: 5/5 (100%)) PE: 0 Bleeding: 0
Robertson et al[53]/1968	RCT, single center	16 patients with DVT	Thrombolysis: SK 200,000 units over 90 min, then 100,000 units as maintenance dose for 22.5 h; heparin 500 mg given during 24 h, plus prednisone (8 patients) Anticoagulation: Heparin plus prednisone (8 patients)	Clot lysis, bleeding	7 d	Thrombolysis: Significant lysis: 5/8 (63%) Partial lysis: 2/8 (25%) No lysis: 1/8 (12%) Bleeding: Major: 2/8 (25%) Minor: 2/8 (25%) Anticoagulation: Significant lysis: 1/8 (12%) Partial lysis: 2/8 (25%) No lysis: 5/8 (63%) Bleeding: Major: 1/8 (12%) Minor: 1/8 (12%)
Kakkar et al[54]/1969	RCT, single center	30 patients with DVT of <4 d	Thrombolysis: SK 500,000 units IV over 30 min; 900,000 units every 6 h $\times 5$ d (10 patients)	Clot lysis, PE, bleeding, death	6-12 mo	Thrombolysis: Complete clot lysis: 6/9 (67%) Partial lysis: 1/9 (11%) No lysis: 2/9 (22%) PE: 0 Bleeding: 4/10 (40%) Death: 2/9 (22%) Note: (1 patient excluded from treatment)

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Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
			Arvin: Arvin loading dose 80 units IV over 6 h; 80 units over 15 min; 40-80 units every 6 h × 5 d (10 patients) Anticoagulation: Heparin 10,000 units IV over 5 min, then 10,000-15,000 units every 6 h × 5 d (10 patients)			Arvin: Complete lysis: 1/10 (10%) Partial lysis: 3/10 (30%) No lysis: 6/10 (60%) PE: 0 Bleeding: 0 Death: 0 Anticoagulation: Complete clot lysis: 2/9 (22%) Partial lysis: 2/9 (22%) No lysis: 5/9 (55%) PE: 1/10 Death: 2/9 (22%) Bleeding: 2/9 (22%) Note: (1 patient excluded from treatment)
Tsapogas et al[55]/1973	RCT, single center	34 patients with DVT of < 5 d	Thrombolysis: titrated initial dose of SK IV, then SK 100,000 units/h maintained and adjusted up to 72 h IV heparin for 1 wk 6-12 h post SK (19 patients) Anticoagulation: Heparin IV into affected limb, 7,000 units bolus then 1,500 units/h adjusted; continued for 7 d (15)	Clot lysis, PE, bleeding	7 d	Thrombolysis: Complete/partial lysis: 10/19 (53%) No lysis: 9/19 (47%) PE: 0 Minor bleeding: 3 (16%) Anticoagulation: Complete/partial lysis: 1/15 (7%) No lysis: 14/15 (93%) PE: 1/15 (7%) Bleeding: 0
Duckert et al[56]/1975	Prospective study	134 patients with acute or subacute DVT	Thrombolysis: initial dose SK calculated according to tolerance injected over 15-30 min; maintenance dose at 30 mL/h was two-thirds of first dose (92 patients) Anticoagulation: 5,000 units heparin for initial dose followed by 25,000 units/24 h infusion (42 patients).	Clot lysis, PE, bleeding	~7 d	Thrombolysis: Significant lysis: 39/92 (42%) Partial lysis: 23/92 (25%) No lysis: 30/92 (33%) PE: 7 (8%) Major bleeding: 58 (62%) Minor bleeding: 24 (26%)s Anticoagulation: Significant lysis: 0/42 (0%) Partial lysis: 4/42 (10%) No lysis: 38/42 (90%) PE: 5/42 (12%) Major bleeding: 2/42 (5%) Minor bleeding: 4/42 (10%)

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Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Porter et al[57]/1975	RCT, single center	50 patients with DVT < 14 d duration	Thrombolysis: SK 250,000 units IV over 30 min, then 100,000 units/h titrated for 72 h followed by IV heparin titrated over 7 d (23 patients) Anticoagulation: IV heparin 150 units/kg loading dose then titrated for 10 d (26 patients)	Clot lysis, PE, bleeding, death due to treatment	10 d	Thrombolysis Complete lysis: 6/23 (26%) Partial lysis: 15/23 (65%) No lysis: 2/23 (9%) PE: 0 Bleeding: 4/23 (17%) Death: 1 (4%) Anticoagulation: Complete lysis: 1/26 (4%) Partial lysis: 20/26 (77%) No lysis: 5/26 (19%) PE: 0 Bleeding: 1/26 (4%) Death: 0
Marder et al[58]/1977	RCT, single center	24 patients with DVT	Thrombolysis: initial dose of 250,000 units SK for 20 min, followed by 100,000 units/h for 72 h (12 patients) Anticoagulation: initial dose heparin 150 units/kg IV, followed by titrated infusion for 72 h Cotreatment: 100 mg bolus hydrocortisone prior to treatment	Clot lysis, death due to treatment	5 d	Thrombolysis: Significant lysis: 5/12 (42%) Partial lysis: 2/12 (16%) No lysis: 5/12 (42%) Death: 1/12 (8%) Anticoagulation: Significant lysis: 0/12 (0%) Partial lysis: 3/12 (25%) No lysis: 9/12 (75%) Death: 0
Arnesen et al[59]/1978	RCT, single center	42 patients with proximal DVT of < 5 d.	Thrombolysis: loading dose of SK 250,000 units IV, then 100,000 International Units/h IV for 72-96 h (21 patients) Anticoagulation: heparin 15,000 International Units IV bolus, then total of 30,000 International Units IV infusion for 72-90 h (21 patients)	Clot lysis, PE, bleeding	21 d-6 y	Thrombolysis: Significant lysis: 15/21 (71%) No lysis: 6/21 (29%) PE: 1/21 (5%) Bleeding: 2/21 (9%) Anticoagulation: Significant lysis: 5/21 (24%) No lysis: 16/21 (76%) PE: 0 Bleeding: 2/21 (9%)

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Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Elliot et al[60]/1979	RCT, single center	51 patients with clinical history of DVT of < 8 d	Thrombolysis: loading dose of SK 600,000 units infused over 30 min, followed by 100,000/h for 3 d; heparin for 4 d following SK (26 patients) Anticoagulation: heparin 10,000 units IV initially, followed by 10,000 units IV daily for a 6-h infusion to maintain clotting time of 2.5-3 times normal for 7 d (25 patients)	Immediate: clot lysis, PE, bleeding Long term: symptom free	Immediate: 5 d Long term: 19 mo (mean)	Immediate: Thrombolysis: Significant lysis:17/26 (65%) Partial lysis: 1/26 (4%) No lysis: 8/26 (31%) PE: 0 Bleeding: 2 (8%) Anticoagulation: Significant lysis: 0/25 (0%) Partial lysis: 0/25 (0%) No lysis: 25/25 (100%) PE: 0 Bleeding: 2/21 (9%) Long term: Thrombolysis: Symptom-free: 12/20[a] (60%) Treatment 2 Symptom-free: 2/21[b] (9%)
Watz et al[61]/1979	Prospective study	35 patients with DVT	Thrombolysis: initial dose of SK 250,000 units in 30 min, followed by maintenance 100,000 units/h (18 patients) Anticoagulation: heparin 45,000 units daily with warfarin (17)	Clot lysis, PE, bleeding	1-2 mo	Thrombolysis: Significant lysis: 8/18 (44%) Partial lysis: 4/18 (22%) No lysis: 6/18 (34%) PE: 1/18 (5%) Minor bleeding: 3/18 (12%) Anticoagulation: Significant lysis: 1/17 (6%) Partial lysis: 5/17 (29%) No lysis: 11/17 (65%) PE: 1/17 (6%) Minor bleeding: 2/17 (12%)

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Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Kiil et al[62]/1981	RCT, single center	20 patients with DVT of < 72 h	Thrombolysis: urokinase 200,000 units IV for 24 h; after 18 h, heparin loading dose of 15,000 units, then 40,000 units/d for 5 d (11 patients) Anticoagulation: heparin 40,000 units/day 4 for 6 d (9 patients)	Clot lysis, PE, bleeding	2 wk	Thrombolysis: Partial lysis: 1/11 (9%) No lysis: 10/11 (91%) PE: 0 Bleeding: 3/11 (27%) Anticoagulation: Partial lysis: 1/8 (12%) No lysis: 7/8 (88%) PE: 0 Bleeding: 3/9 (33%) Note: 1 patient excluded from group
Arnesen et al[63]/1982	Follow-up to RCT of Arnesen (1978)	35/42 patients from RCT	Phlebography and clinical examination by blinded evaluators	Normal legs, PTS symptoms	6.5 y	Thrombolysis: Normal legs: 13/17 (77%) PTS symptoms (moderate): 4/17 (24%) Anticoagulation: Normal legs: 6/18 (33%) PTS symptoms (moderate): 9/18 (50%)
Schulman et al[49]/1986	RCT, single center	36 patients with calf DVT of < 7 d	Thrombolysis: SK 50,000 International Units IV over 15 min, then 100,000 International Units over 12 h for up to 7 d, titrated; given with heparin 5,000 International Units IV over 12 h (17 patients) Anticoagulation: heparin 5,000 International Units IV for 15 min then 30,000 International Units/d, titrated over 7 d (19 patients)	Clot lysis, bleeding, PE	5 y	Thrombolysis: Complete lysis: 7/17 (41%) Bleeding:3/17 (18%) PE: 0 Anticoagulation: Complete lysis: 2/19 (10%) Bleeding: 1/19 (5%) PE: 0
Verhaeghe et al[51]/1989	Prospective cohort study (A) and multicenter RTC (B)	32 patients with DVT of < 10 d	Study A: open-label study with rt-PA 100 mg over IV 8 h (day 1), 50 mg rt-PA over 8 h (day 2); 10% dose as bolus (11 patients)	Clot lysis, bleeding	72 h	Note: Authors assigned veins a relative value reflecting degree of thrombosis (maximum, 40 units: complete thrombosis). The unit scores reflect the reduction in thrombosis postlysis.

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Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
			Study B: rt-PA 100 mg: IV of 100 mL containing rt-PA 100 mg infused over 8 h (day 1), IV of 100 mL containing 50 mg rt-PA infused over 8 h (day 2); 10% dose as bolus (8 patients) rt-PA 50 mg: IV of 100 mL containing rt-PA 50 mg infused over 8 h on both days 1 and 2; 10% dose as bolus (6 patients) Placebo: IV of 100 mL containing placebo infused over 8 h on both days 1 and 2 (7 patients) Co-treatment: heparin 5,000 units IV bolus then continuous infusion 1,000 units/h for up to 72 h			Study A Change in unit score: −3.2 Study B rt-PA 100 mg: Change in unit score: −24.3 Bleeding: 6 rt-PA 50 mg: Change in unit score: −34.3 Bleeding: 3 Placebo: Change in unit score: −2.8 Bleeding: 0
Goldhaber et al[64]/1990	RCT, multicenter	64 patients (65 randomizations) with DVT of < 14 d	rt-PA: rt-PA 0.05 mg/kg per h IV for 24 h, then heparin 100 units/kg bolus, then 1,000 units/h, adjusted (36 patients) rt-PA + heparin: rt-PA as in group 1 plus heparin concomitantly (17 patients) Anticoagulation: heparin 100 units/kg bolus, then 1,000 units/h (12 patients)	Clot lysis, bleeding	36 h	rt-PA: Complete lysis: 2/32 (6%) Partial lysis: 18/32 (57%) No lysis: 12/32 (38%) Bleeding: 1/32 (3%) rt-PA + heparin: Complete lysis: 1/17 (6%) Partial lysis: 8/17 (48%) No lysis:8/17 (48%) Bleeding: 0 Anticoagulation: Partial lysis: 2/11 (18%) No lysis: 9/11 (89%) Bleeding: 0 Note: 5/65 venograms not analyzed

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Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Turpie et al[50]/1990	RCT, multicenter	83 patients with DVT of <7 d	Phase 1: Lysis + heparin: two-chain rt-PA 0.5 mg/kg IV for 4 h (12 patients)	Clot lysis, bleeding	24-48 h	Phase 1: Lysis + heparin: ≥50% lysis: 7/12 (58%) <50% lysis: 2/12 (17%) No lysis: 3/12 (25%) Bleeding: 4/12 (33%)
			Placebo + heparin (12 patients)			Placebo + heparin: <50% lysis: 2/12 (17%) No lysis: 10/12 (83%) Bleeding: 1/12 (8%)
			Phase 2: Lysis + heparin: one-chain rt-PA 0.5 mg/kg IV for 8 h and repeated in 24 h (29 patients)			Phase 2: Lysis + heparin: ≥50% lysis: 6/29 (21%) <50% lysis: 7/29 (24%) No lysis: 15/29 (52%) Bleeding: 1/29 (3%)
			Placebo + heparin (30 pts)			Placebo + heparin ≥50% lysis: 2/30 (7%) <50 lysis:5/30 (17%) No lysis: 23/30 (77%) Bleeding: 1/30 (3%)
			Cotreatment: heparin 5,000-unit IV bolus then 30,000 units/24 h, adjusted for 7-10 d			
Schweizer et al[65]/1998	RCT, single center	69 patients with DVT of <7 d	rt-PA 20 mg IV into pedal vein 4 h/d for 7 d; heparin IV given concomitantly; warfarin day 7-12 mo	7 d: clot lysis, bleeding 1 y: PTS symptoms	7 d and 1 y	rt-PA: Complete lysis: 6/22 (27%) Bleeding: 1/22 (5%) PTS symptoms: 14/22 (64%)
			Urokinase 100,000 International Units/hr IV into pedal vein continuously 7 d; heparin IV 7 d; plasminogen monitored; warfarin day 7-12 mo			Urokinase: Complete lysis: 11/22 (50%) Bleeding: 1/22 (5%) PTS symptoms: 9/22 (41%)

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Table S13—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
			Anticoagulation: heparin IV adjusted for 7 d; warfarin day 1-12 mo			Anticoagulation: Complete lysis: 0 Bleeding: 0 PTS Symptoms: 15/22 (68%)
Schweizer et al[66]/2000	RCT, multicenter	250 patients with DVT of < 9 d	rt-PA: locoregional rt-PA 20 mg/day for 4 h through pedal vein for 4-7 d; IV heparin given simultaneously at 1,000 International Units/h, adjusted Urokinase: locoregional urokinase 100,000 International Units infused continuously; fibrinogen and plasminogen monitored; IV heparin given concomitantly Systemic SK: 3 million units/d for 6 h with heparin for up to 7 d. Premedications: hydrocortisone 100 mg, ranitidine 50 mg, clemastine 2 mg Systemic urokinase: 5 million International Units/d for 4 h up to 7 d; IV heparin given concomitantly Anticoagulation: heparin IV, adjusted. Cotreatment: bed rest, compression bandages, compression therapy, warfarin for 12 mo	Clot lysis, bleeding, mortality	1 y	rt-PA: Complete lysis: 10/50 (20%) ≥ 50% lysis: 7/50 (14%) < 50% lysis: 16/50 (32%) No lysis: 13/50 (26%) Bleeding: 2/50 (4%) Urokinase: Complete lysis: 10/50 (20%) ≥ 50% lysis: 9/50 (18%) < 50% lysis: 17/50 (34%) No lysis: 11/50 (22%) Bleeding: 1/50 (2%) Systemic SK: Complete lysis: 20/50 (40%) ≥ 50% lysis: 7/50 (14%) < 50% lysis: 13/50 (26%) No lysis: 8/50 (16%) Bleeding: 5/50 (10%) PE: 5/50 (10%) Systemic urokinase: Complete lysis: 17/50 (34%) ≥ 50% lysis:10/50 (20%) < 50% lysis: 13/50 (26%) No lysis: 8/50 (16%) Bleeding: 4/50 (8%) PE: 4/50 (8%)

See Table S1, S2, and S11 legends for expansion of abbreviations.

[a] Four deaths, other causes, two lost to follow-up.

[b] Four deaths, two PEs, two other causes.

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Table S14—*[Section 2.10] Systemic Lysis vs No Systemic Lysis for Extensive Acute DVT of the Leg: Methods*

Author/Year	Randomization	Allocation concealment	Blinding	Loss to follow-up
Browse et al[52]/1968	N/A	N/A	N/A	0
Robertson et al[53]/1968	Patients given consecutive code numbers and divided into equal groups of 2—not truly randomized	Labels on SK and heparin coded	Y, data assessors; unclear for patients, caregivers, analysts	0
Kakkar et al[54]/1969	Sequential sealed envelope	Adequate	Y, patients No, caregivers, assessors, analysts	0
Tsapogas et al[55]/1973	Sealed envelope	Adequate	Not blinded	0
Duckert et al[56]/1975	N/A	N/A	N/A	N/A
Porter et al[57]/1975	Assigned at random to one of two groups	N/A	N/A	N/A
Marder et al[58]/1977	Assigned at random to one of two groups. Five-day follow-up venograms were not performed in 3 of the SK patients, so an additional 3 patients were added to SK group in nonrandomized fashion.	Unclear	Not blinded	23
Arnesen et al[59]/1978	Assigned at random to either group by sealed envelope	Adequate	Y, radiologic assessors No, patients, caregivers, analysts	0
Elliot et al[60]/1979	Assigned at random to one of two groups	Unclear	Y, assessors N, patients, caregivers, analysts	N/A
Watz et al[61]/1979	N/A	N/A	N/A	N/A
Kiil et al[62]/1981	Assigned at random to either group	Unclear	Y, assessors, analysts N, patients, caregivers	0
Arnesen et al[63]/1982	N/A	N/A	Evaluator blinded	7
Schulman et al[49]/1986	Assigned at random to either group by sealed envelope	Adequate	Single blind	0
Verhaeghe et al[51]/1989	Assigned at random to one of three groups	Unclear	Y, patients, assessors N, caregivers, analysts	0
Goldhaber et al[64]/1990	Assigned at random to one of three groups through sealed envelope	2:2:1 allocation scheme	Not blinded	0
Turpie et al[50]/1990	Assigned at random to one of two groups in each phase of study	Unclear	Y, patients, assessors N, caregivers, analysts	37
Schweizer et al[65]/1998	Assigned at random to one of three groups	Adequate	Y, assessors N, patients, caregivers, analysts	1
Schweizer et al[66]/2000	Assigned at random to one of five groups	Unclear	Single blind—not sure who	12

Y = yes. See Table S5 and S12 legends for expansion of other abbreviations.

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Table S15—*[Section 2.10] Evidence Profile: Systemic Lysis vs No Systemic Lysis for Extensive Acute DVT of the Leg*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Systemic Lysis	With Systemic Lysis	Relative Effect (95% CI)	Risk With No Systemic Lysis	Risk Difference With Systemic Lysis (95% CI)
Mortality (important outcome)											
688 (5 studies), 3 mo[a]	No serious risk of bias[b]	No serious inconsistency	No serious indirectness[c,d]	Very serious[e]	Undetected	Low[b-e] due to imprecision	5/233 (2.1)	4/455 (0.9)	RR 0.86 (0.27-2.68)	21 per 1,000	3 fewer per 1,000 (from 16 fewer to 36 more)
Nonfatal recurrent VTE (critical outcome)											
687 (3 studies), 3 mo[f]	No serious risk of bias[g]	No serious inconsistency	No serious indirectness[d]	Very serious[e]	Undetected	Low[d,e,g] due to imprecision	2/233 (0.9)	10/454 (2.2)	RR 1.28 (0.25-6.68)	48 per 1,000[h]	13 more per 1,000 (from 36 fewer to 273 more)
Nonfatal major bleeding (critical outcome)											
688 (10 studies), 3 mo[f]	No serious risk of bias[i]	No serious inconsistency	No serious indirectness[c,d]	Serious	Undetected	Moderate[c,d,i] due to imprecision	10/234 (4.3)	38/454 (8.4)	RR 1.84 (0.94-3.59)	29 per 1,000[h,j]	24 more per 1,000 (from 2 fewer to 75 more)

(Continued)

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Table S15—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Systemic Lysis	With Systemic Lysis	Relative Effect (95% CI)	Risk With No Systemic Lysis	Risk Difference With Systemic Lysis (95% CI)
Postthrombotic syndrome (critical outcome)											
678 (2 studies), 2 y[k]	Serious[l,m]	No serious inconsistency	No serious indirectness[d3]	Serious[e4]	Undetected	Low[d,e,l,m] due to risk of bias, imprecision	24/230 (10.4)	27/448 (6)	RR 0.71 (0.49-1.04)	588 per 1,000[n]	171 fewer per 1,000 (from 300 fewer to 24 more)[o]
Quality of life not measured											
…	…	…	…	…	…	…	…	…	-	…	…

Bibliography: Watson et al.[47] We excluded Elsharawy et al[36] from the analysis because it used catheter directed thrombolysis.[36] We identified no studies published since the search date of the systematic review. See Table S1, S10, and S11 legends for expansion of abbreviations.

[a] Range of follow-up in included studies, 1 to 72 mo.

[b] Allocation concealed in three of five studies. Follow-up inadequate in one of five (Common et al[48]). Excluding this study from the analysis does not change the effect estimate. All studies had blinded outcome assessors. None of the studies used a placebo control.

[c] The population of one study (Schulman et al[49]) consisted of patients with calf vein thrombosis.

[d] Interventions varied across studies with regard to agent (eg, tPA, SK, urokinase), dose, use of the pedal vein administration, duration of treatment, and concomitant drugs (eg, steroids). However, we did not downgrade for indirectness given that there is no standard regimen, and all analyses showed no heterogeneity in results.

[e] CI included both no effect and a potentially significant effect.

[f] Range of follow-up in included studies, 1 to 30 d.

[g] Allocation concealed in two of three studies. Follow-up adequate in all studies. All studies had blinded outcome assessors. None of the studies used a placebo control.

[h] Baseline risks for nonfatal recurrent VTE and for major bleeding derived from Douketis et al.[39i]Allocation concealed in seven of 10 studies. Follow-up inadequate in one 10 studies (Common et al[48]). Excluding this study from the analysis does not affect the effect estimate. All studies had blinded outcome assessors. Two studies used placebo (Turpie et al; [50]Verhaeghe et al[51]).

[j] Only 4% of all major bleeding events were intracranial bleeds.

[k] Range of follow-up in included studies: 1 to 6 y.

[l] Allocation concealed in two of two studies. Follow-up adequate in all studies. All studies had blinded outcome assessors. None of the studies used placebo control.

[m] No use of a standardized validated tool reported.

[n] This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes) study.[40] This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[o] Severe PTS: assuming the same RR of 0.71 and a baseline risk of 13.8%,[40] the absolute reduction is 40 fewer severe PTS per 1,000 (from 70 fewer to 6 more) over 2 y.

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Table S16—*[2.11] Evidence Profile: Surgical Thrombectomy Vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg*[a]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Surgical Thrombectomy	With Surgical Thrombectomy	Relative Effect (95% CI)	Risk With No Surgical Thrombectomy	Risk Difference With Surgical Thrombectomy (95% CI)
Mortality not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Nonfatal recurrent VTE (critical outcome)											
51 (1 study), 3 mo	Serious[b]	No serious inconsistency	No serious indirectness[c]	Very serious[c]	Undetected	Low[b,c] due to risk of bias, imprecision	1/27 (3.7)[d]	0/24 (0)	RR 0.37 (0.02-8.75)	48 per 1,000[d,e]	30 fewer per 1,000 (from 47 fewer to 372 more)
Nonfatal major bleeding (critical outcome)											
51 (1 study), 3 mo	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	Undetected	See comment	0/27 (0)	0/24 (0)[f]	Not estimable	See comment	…
PTS (critical outcome)											
51 (1 study), 2 y	Serious[g]	No serious inconsistency	No serious indirectness	Serious[h]	Undetected	Low[g,h] due to risk of bias, imprecision	25/27 (92.6)	14/24 (58.3)	RR 0.63 (0.44-0.9)[i]	588 per 1,000[j]	218 fewer per 1,000 (from 59 fewer to 329 fewer)[k]
Quality of life not measured											
…	…	…	…	…	…	…	…	…	-	…	…

Bibliography: Plate et al.[67] See Table S1, S5, and S10 legends for expansion of abbreviations.

[a] The study included patients with DVT with symptoms of leg swelling not exceeding 7 d and a proximal extension of the thrombus above the inguinal ligament, but not into the vena cava.

[b] Not clear whether allocation was concealed. No blinding reported. Not clear whether analysis was ITT. Follow-up rate 88% at 6 mo. Study not stopped early for benefit.

[c] CI includes values suggesting either harm or benefit.

[d] One event, which was a symptomatic PE.

[e] Baseline risks for nonfatal recurrent VTE derived from Douketis et al.[39]

[f] No severe bleeding complications were recorded in either group. Three patients in thrombectomy group developed local wound hematoma.

[g] In addition to other study limitations, this outcome was assessed by those who did the surgery and anticoagulation. No standardized tool was used. One surgical patient had an amputation secondary to venous gangrene and was not counted in the PTS assessment.

[h] Few number of events. This warrants rating down the quality of evidence by a second level when considered along with study limitations.

[i] The RR is based on the 6-mo data.

[j] This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes study.[40] This probably underestimates PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[k] Severe PTS: assuming the same RR of 0.63 and a baseline risk of 13.8% over 2 y,[40] the absolute reduction is 51 fewer severe PTS per 1,000 (from 14 fewer to 77 fewer) over 2 y.

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Table S17—*[Section 2.11] Surgical Thrombectomy vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg: Clinical Description and Results (All Randomized Trials and Prospective Observational Studies of at Least 20 Patients)*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Plate et al[67]/1984	RCT, multicenter	58 patients with acute iliofemoral venous thrombosis	Medical: 5,000-unit bolus heparin followed by 500 units/kg per 24 h adjusted to aPTT, and oral anticoagulation (31 patients) Surgical: operative venous thrombectomy with temporary AVF plus anticoagulation as above (27 patients)	PTS sequelae: iliofemoral patency, valve competence	6 mo	Medical: PTS sequelae: 25/27 (93%) Iliofemoral patency: 9/26 (35%) Valve competence: 7/27 (26%) (PE in 1 patient) Surgical: PTS sequelae: 14/24 (58%, $P < .005$) Iliofemoral patency: 16/21 (76%, $P < .025$) Valve competence: 13/23, (52% $P < .05$) (venous gangrene in 1 patient)
Einarsson et al[68]/1986	Prospective registry	70 patients (71 legs) with iliofemoral DVT (age of clot mean, 3 d)	Iliofemoral venous thrombectomy with temporary AVF closed at 6-8 wk, heparin preoperatively and postoperatively plus warfarin postoperatively	Venous patency, hematoma, AVF patency, PE, wound infection	56 d (mean)	Patent iliac vein: 88% Hematoma: 11% AVF patency: 86% PE: 4% Wound infection: 26%:
Einarsson et al[69]/1986		57 patients (58 limbs) with prior operative venous thrombectomy and AVF closed at 6-8 wk for iliofemoral DVT	Clinical PTS, venography, venous pressure, venous plethysmography, foot volumetry	Venous insufficiency: Good, fair, poor Venography (vein segment): Normal, postthrombotic, occluded Venous pressure: Normal, abnormal Plethysmography: Normal, abnormal Foot volumetry: Normal, abnormal	9-10 mo	Venous insufficiency: Good: 75% Fair: 20% Poor: 5% Venography (iliofemoral): Normal: 61% Postthrombotic: 23% Occluded: 39% IV pressure: Normal: 82% Abnormal: 18% Plethysmography: Normal: 29% Abnormal: 71% Foot volumetry: Normal: 29% Abnormal: 71%
Plate et al[70]/1990	Five-year follow-up to RCT (Plate, 1984[67])	41/58 patients (22 medical, 19 surgical) available for evaluation at 5 y	Prior treatment: Medical: anticoagulation alone vs Surgical: operative venous thrombectomy plus anticoagulation	PTS sequelae, iliac patency, venous pressure	5 y	Medical: PTS sequelae: 6/22 (27%) Iliac patency: 11/22 (50%) Venous pressure: 60 mm Hg (mean)

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Table S17—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
						Surgical: PTS sequelae: 2/19 (11%) Iliac patency: 15/19 (78%) Venous pressure: 43 mm Hg (mean, $P < .05$)
Neglén et al[71]/1991	Prospective registry	48 patients with iliofemoral DVT of 1-14 d	Operative venous thrombectomy with temporary AVF (closed 6-12 wk postoperative) Adjunctive therapy: transvenous percutaneous dilatation of severe iliac stenosis (3 patients)	Patency, PE, clinical symptoms, normal photoplethysmography, successful AVF closure	24 mo (mean)	Patency: Iliofemoral: 88% Popliteal: 94% PE: 16% symptomatic, 31% asymptomatic Symptom-free: 81% Normal photoplethysmography (no reflux): 56% AVF closure success rate: 87%
Plate et al[72]/1997	Ten-year follow-up to RCT (Plate, 1984 [10] and 1990 [20])	30/58 patients (17 from medical arm, 13 from surgical arm) available for evaluation	Prior treatment Medical: anticoagulation alone vs Surgical: operative venous thrombectomy plus anticoagulation	PTS sequelae, iliac patency, venous pressure	10 y	Medical: PTS sequelae: 15/17 (88%) Iliac patency: 7/17 (41%) Venous pressure: 63 mm Hg (mean) Surgical: PTS sequelae: 7/13 (54%) Iliac patency: 10/12 (83%) Venous pressure: 55 mm Hg (mean)

Early prospective observational studies with <20 patients and retrospective studies are described in Table 5 of the eighth edition of these guidelines.[46] See Table S1, S2, S4, S10, and S11 legends for expansion of abbreviations.

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Table S18—*[Section 2.11] Surgical Thrombectomy vs No Surgical Thrombectomy for Extensive Acute DVT of the Leg: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up
Plate et al[67]/1984	ND	PN	N, patients, caregivers, assessors, and data analysts	7
Einarsson et al[68]/1986	N/A	N/A	N/A	N/A
Einarsson et al[69]/1986	N/A	N/A	N/A	N/A
Plate et al[70]/1990	N/A	N/A	N/A	17
Neglén et al[71]/1991	N/A	N/A	N/A	N/A
Plate et al[72]/1997	N/A	N/A	N/A	28

See Table S5 and S12 legends for expansion of abbreviations.

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Table S19—*[Section 2.13] Evidence Profile: Vena Cava Filter vs No Vena Cava Filter for Acute Proximal DVT of the Leg Treated With Anticoagulation*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Vena Cava Filters	With Vena Cava Filters	Relative Effect (95% CI)	Risk With No Vena Cava Filters	Risk Difference With Vena Cava Filters (95% CI)
Mortality (important outcome)											
400 (1 study), 8 y	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[c,d] due to imprecision	103/200 (51.5)	98/200 (49.0)	RR 0.95 (0.78-1.16)[e]	515 per 1,000	26 fewer per 1,000 (from 113 fewer to 82 more)
Symptomatic PE (critical outcome)											
304 (1 study), 8 y	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[c,f] due to imprecision	24/159 (15.1)	9/145 (6.2)	RR 0.41 (0.2-0.86)[g]	151 per 1,000	89 fewer per 1,000 (from 21 fewer to 121 fewer)
Recurrent DVT (important outcome)											
310 (1 study), 8 y	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[c,f] due to imprecision	41/150 (27.3)	57/160 (35.6)	RR 1.3 (0.93-1.82)[h]	273 per 1,000	82 more per 1,000 (from 19 fewer to 224 more)
Major bleeding (important outcome)											
337 (1 study), 8 y	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[c,d] due to imprecision	31/168 (18.5)	26/169 (15.4)	RR 0.83 (0.52-1.34)[i]	185 per 1,000	31 fewer per 1,000 (from 89 fewer to 63 more)

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Table 19—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Vena Cava Filters	With Vena Cava Filters	Relative Effect (95% CI)	Risk With No Vena Cava Filters	Risk Difference With Vena Cava Filters (95% CI)
PTS (important outcome)											
308 (1 study), 8 y	Serious[j]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Low[d,j] due to risk of bias, imprecision	107/153 (69.9)	109/155 (70.3)	RR 0.87 (0.66-1.13)	699 per 1,000	91 fewer per 1,000 (from 238 fewer to 91 more)
Complications (important outcome)											
379 (1 study), 2 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[f] due to imprecision	0/186 (0)	0/193 (0)	…	…	…[k]
Quality of life not reported											
…	…	…	…	…	…	…	…	…	-	…	…

Bibliography: Decousus et al,[8] The PREPIC Investigators.[73] See Table S1, S2, S5, and S10 legends for expansion of abbreviations.

[a] Four types of permanent vena cava filters were used: Vena Tech LGM (B. Braun Melsugen AG), titanium Greenfield (Boston Scientific Corporation), Cardial (C.R. Bard, Inc), and Bird's Nest (Cook Group Incorporated).

[b] Anticoagulation consisted of LMWH or UFH initially (according to a 2 × 2 factorial design) followed by oral anticoagulation for at least 3 mo.

[c] Allocation concealed. Data collectors and outcome adjudicators blinded. ITT analysis. Data missing for 4% at 2 y and 1% at 8 y. Enrollment was stopped at 400 instead of targeted 800 due to slow recruitment.

[d] CI includes both negligible effect and appreciable benefit or appreciable harm.

[e] RR, 1.0 (95% CI, 0.29-3.4) at 12 d; RR, 1.08 (95% CI, 0.73-1.58) at 2 y.

[f] Small number of events.

[g] RR, 0.23 (95% CI, 0.05-1.05) at 12 d (both symptomatic and asymptomatic PE). RR, 0.54 (95% CI, 0.21-1.41) at 2 y (symptomatic PE)

[h] RR, 1.78 (95% CI, 1.09-2.94) at 2 y.

[i] RR, 1.5 (95% CI, 0.54-4.14) at 12 d. RR, 0.74 (95% CI, 0.41-1.36) at 2 y.

[j] No standardized validated tool used to measure PTS.

[k] No complications directly related to the filter or its insertion reported in the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) trial.[8] Mismetti et al[74] (prospective study) reported an incidence of 3.2% (excluding filter tilting and puncture site hematoma) among 220 patients receiving retrievable vena cava filter for secondary prevention of VTE, whereas while Athanasoulis et al[75] (retrospective study) reported an incidence of 0.3% for major complications among 1,731 patients receiving vena cava filters predominantly for secondary prevention of VTE.

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Table S20—*[Section 2.14] Evidence Profile: Early Ambulation vs Delayed Ambulation for Acute DVT of the Leg*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Delayed Ambulation	With Early Ambulation	Relative Effect (95% CI)	Risk With Delayed Ambulation	Risk Difference With Early Ambulation (95% CI)
Mortality (important outcome)											
385 (4 studies), 3 mo[c]	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[e]	Undetected	Low[d,e] due to risk of bias, imprecision	2/186 (1.1)	3/199 (1.5)	RR 1.3 (0.23-7.55)	11 per 1,000	3 more per 1,000 (from 8 fewer to 70 more)
PE (critical outcome; assessed with symptomatic or asymptomatic PE)											
385 (4 studies), 4-12 d	Serious[d]	No serious inconsistency	No serious indirectness[f]	Serious[e]	Undetected[g]	Low[d-g] due to risk of bias, imprecision	22/186 (11.8)	27/199 (13.6)	RR 1.16 (0.66-2.05)	118 per 1,000	19 more per 1,000 (from 40 fewer to 124 more)
Quality of life (important outcome; measured with quality of life questionnaire in chronic limb venous insufficiency [CIVIQ]; better indicated by lower values)											
53 (1 study), 2 y	Serious[h]	No serious inconsistency	Serious[i]	No serious imprecision	Undetected	Low[h,i] due to risk of bias, indirectness	17	36	-	See footnote[j]	
PTS (important outcome; assessed with Villata-Prandoni score [value >5])											
37 (1 study) 2 y	Serious[h]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Low[e,h] due to risk of bias, imprecision	9/11 (81.8)	14/26 (53.8)	RR 0.66 (0.42-1.03)	Moderate	
										400 per 1,000	136 fewer per 1,000 (from 232 fewer to 12 more)

Bibliography: Kahn et al,[76] Aissaoui et al.[77] Included studies.[78-82] See Table S1, S2, S5, and S10 legends expansion of other abbreviations.

[a] In two of four eligible trials, all patients received early compression therapy (bandages or stockings). In the two other trials, only patients randomized to early ambulation received early compression therapy.

[b] Two of four eligible studies excluded patients with symptomatic PE; in the third study, 24% of participants had symptomatic PE at baseline. It was not clear whether the fourth study excluded patients with symptomatic PE.

[c] Three studies reporting acute phase mortality reported no deaths.

[d] Concealment of allocation reported in one of four studies; blinding of outcome assessors reported in two of four studies; ITT analysis reported in two of four studies. Follow-up 97%-100%. In two of four trials, only patients randomized to early ambulation received early compression therapy (bandages or stockings). In the two other trials, all patients received early compression therapy.

[e] CI includes both values of clinically significant benefit and values of clinically significant harms.

[f] PE assessed as both symptomatic and asymptomatic PE.

[g] Funnel plot reported as not asymmetrical by Aissaoui et al.[77]

[h] Concealment of allocation not reported, outcome assessors not blinded for this outcome; 70% follow-up rate; compression stockings used on patients with early mobilization but in patients with delayed mobilization.

[i] No explanation was provided.

[j] Psychologic and overall somatic quality of life did not differ significantly between the treatment groups, whereas DVT-related items, especially those reflecting the ease of locomotion, showed significantly greater improvement with compression than with bed rest ($P < .001$ for bandages, $P < .05$ for stockings).

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Table S21—*[Section 2.14] Early Ambulation vs Delayed Ambulation for Acute DVT of the Leg: Clinical Description and Results*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Schellong et al[82]/1999	RCT, single center	126 patients with acute proximal DVT	Ambulation: leg elevation until day 2, then ambulation and compression (64 patients) Bed rest for 8 d with leg elevation and compression (62 patients)	PE by V̇/Q̇ scan	10 d	Ambulation: PE: 10/59 (17%) Bed Rest: PE: 14/63 (22%)
Partsch et al[81]/2000	RCT, multicenter	45 patients with proximal DVT $<$14 d duration	Ambulation + bandages: inelastic Unna boot bandages plus walking exercises (15 patients) Ambulation + stockings: elastic compression stockings plus walking exercises (15 patients) Bed rest, no compression, LMWH (15 patients)	Walking distance, pain levels, leg circumference, clinical scores, PE, side effects	9 d	Summary results between groups: Walking distance, pain, leg circumference and clinical scores significantly improved in groups A and B compared with group C PE, group A: 2/15 (13%) PE, group B: 1/15 (7%) PE, group C: 1/15 (7%)
Aschwanden et al[78]/2001	RCT, single center	129 patients with acute DVT	Ambulation $\geq$4 h/d for 4 d under supervision, LMWH (69 patients) Bed rest for 4 d (60 patients)	New PE between baseline and day 4 by V̇/Q̇ scan	3 mo	Ambulation: PE: 10/69 (14%) Bed rest: PE: 6/60 (10%) Note: new PEs were asymptomatic; 12/16 patients had baseline PEs
Partsch et al[83]/2001	Prospective study	1,289 patients with acute DVT	All treated with LMWH, compression, and immediate ambulation	PE on V̇/Q̇ scan at admission and after 10 d of treatment,	10 d	PE at admission: 629/1,270 (50%) PE at 10 d: 77/1,256 (61%) Note: initial lung scans were performed in 1,270/1,289 patients; follow-up scans were performed in 1,256/1,289 patients
Blättler et al[79]/2003	RCT	53 patients with proximal DVT	Ambulation + bandages: firm inelastic bandages, ambulation (18 patients) Ambulation + stockings: elastic compression stockings, ambulation (18 patients)	Walking distance, well-being, and DVT-related quality of life, leg pain by visual analog scale, edema, clinical scores, thrombus progression	9 d	Well-being/quality of life: Improved with stockings ($P < .05$), bandages ($P < .01$) Leg pain: Decreased faster during first 4 d w/ bandages and stockings vs bed rest ($P < .01$); near absence of pain at 9 d achieved with bandages only

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Table S21—*Continued*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
			Bed rest only (17 patients)			Edema: Marked reduction in leg size with bandages and stockings vs bed rest ($P < .001$) Clinical scores: Improved with bandages and stockings vs bed rest ($P < .001$) Thrombus progression: Improved with bandages and stockings vs bed rest ($P < .01$) PE: No difference between groups
Partsch et al[84]/2004	2-y follow-up to RCT (77)	37 patients followed up 2 y post-RCT	Anticoagulation and bed rest vs anticoagulation and ambulation with compression bandages or stockings	PTS assessment (Villalta-Prandoni scale)	2 y	PTS scores: Ambulatory group (mean score, 5.1) had improved outcome vs bed rest group (mean score, 8.2; $P < .01$)
				Pain assessment by visual analog scale and modified Lowenberg test		Pain: Lower pain levels in mobile group vs bed rest (ns)
				Thrombus regression		Thrombus extension: No difference in thrombus regression of thrombus remnants between groups
Trujillo-Santos et al[85]/2005	Prospective study	2,650 patients with acute DVT (2,038 [77%]) or PE (612 [23%])	DVT group, bed rest or ambulation: 1,050 (52%) patients received bed rest, and 988 (48%) ambulated. All received LMWH. PE group, bed rest or ambulation: 385 (63%) patients received bed rest, and 227 (37%) ambulated. All received LMWH.	Symptomatic, confirmed PE during first 15 d of therapy	3 mo	DVT group, bed rest: PE: 7/1050 (0.7%) DVT group, ambulate: PE: 4/988 (0.4%) PE group, bed rest: PE: 2/385 (0.5%) PE group, ambulate: PE: 2/227 (0.9%)
Jünger et al[80]/2006	RCT, multicenter open design stratified by age	103 patients with proximal DVT	Bed rest: 50 patients received 5 d of strict bed rest, LMWH, compression bandages. Ambulation: 52 patients ambulated for 5 d, LMWH, compression bandages	PE, progression of or new thrombosis, infection or serious adverse event	5 d	New PE bed rest: 8/50 (16%) ambulation: 2/52 (4%) Primary target variable: Bed rest: 14/50 (28%) Ambulation: 7/52 (13%)

ns = not significant; $\dot{V}/\dot{Q}$ = ventilation/perfusion. See Table S2, S5, and S10 legends for expansion of other abbreviations.

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Table S22—*[Section 2.14] Early Ambulation vs Delayed Ambulation for Acute DVT of the Leg: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up
Schellong et al[82]/1999	Patients randomized to 1 of 2 study groups	Unclear	Y, assessors N, patients, caregivers, analysts	4
Partsch et al[81]/2000	Patients randomized to 1 of 3 study groups by sealed envelope	Unclear	Y, assessors N, patients, caregivers, analysts	0
Aschwanden et al[78]/2001	Patients randomized to 1 of 2 study groups	Sealed envelope	Not blinded	5
Partsch et al[83]/200	N/A	N/A	N/A	N/A
Blättler et al[79]/2003	Patients randomized to 1 of 3 study groups by sealed envelope	Not specified	Y, assessors N, patients, caregivers, analysts	0
Partsch et al[84]/2004	N/A	N/A	N/A	21
Trujillo-Santos et al[85]/2005	N/A	N/A	N/A	N/A
Jünger et al[80]/2006	Patients randomized to 1 of 2 study groups by sealed envelope	Unclear	Y, analysts N, patients, caregivers, assessors	

See Table S5 and S12 legends for expansion of abbreviations.

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Table S23—*[Sections 3.1.1-3.1.4] Evidence Profile: Four or Six Weeks vs Three or Six Months as Minimum Duration of Anticoagulation for VTE*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall quality of Evidence	With Control	With 4 or 6 wk vs 3 or 6 mo of Anticoagulation	Relative Effect (95% CI)	Risk With Control	Risk Difference With 4 or 6 wk vs 3 or 6 mo of Anticoagulation (95% CI)
Recurrent VTE (critical outcome)											
2,185 (5 studies[c]), 1-2 y[d]	No serious risk of bias[e]	No serious inconsistency[f]	No serious indirectness	No serious imprecision[g]	Undetected	High[e-g]	70/1,090 (6.4)	127/1,095 (11.6)	RR 1.83 (1.39-2.42)	64 per 1,000	53 more per 1,000 (from 25 more to 91 more)
Major bleeding (critical outcome)											
2,185 (5 studies), 1-2 y[d]	No serious risk of bias	No serious inconsistency[f]	No serious indirectness	No serious imprecision	Undetected	High[f]	13/1,090 (1.2)	7/1,095 (0.6)	RR 0.54 (0.22-1.32)	12 per 1,000	5 fewer per 1,000 (from 9 fewer to 4 more)
Mortality (important outcome)											
2,098 (5 studies), 1-2 y[d]	No serious risk of bias[e]	No serious inconsistency[f]	No serious indirectness	No serious imprecision[h]	Undetected	High[e,f,h]	55/998 (5.5)	57/1,100 (5.2)	RR 0.97 (0.68-1.38)	55 per 1,000	2 fewer per 1,000 (from 18 fewer to 21 more)

Bibliography: Kearon et al,[86] Pinede et al,[87] Schulman et al,[88] Levine et al,[89] British Thoracic Society.[90] See Table S1, S5, and S2 legends for expansion of abbreviations.

[a] Short vs longer duration of anticoagulation was 6 wk vs 6 mo for Schulman et al, 6 wk vs 3 mo for Pinede et al, and 4 wk vs 3 mo for the other three studies.

[b] Populations varied among studies: first provoked isolated distal DVT, proximal DVT or PE provoked in Kearon et al; first isolated distal DVT in Pinede et al; first isolated distal DVT, proximal DVT, or PE in Schulman et al; proximal DVT (21% had cancer) in Levine et al; and DVT or PE (29% not objectively confirmed) in British Thoracic Society.

[c] Timing of randomization relative to the start of treatment varied across studies: Pinede et al, Schulman et al, and British Thoracic Society randomized at diagnosis; Kearon et al and Levine et al randomized to stop or to continue treatment of 2 more months after the initial 4 wk of treatment.

[e] Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Kearon et al, Pinede et al). In one study (British Thoracic Society), 44 randomized patients were excluded centrally as they did not satisfy eligibility criteria. Patients and caregivers were blinded in two studies (Kearon et al, Levine et al). Adjudicators of outcomes were blinded in all but one study (British Thoracic Society). All studies appeared to have used effective randomization concealment, ITT analysis, and appears to have a low unexplained drop-out frequency.

[f] No heterogeneity with $I^2 = 0\%$.

[g] No imprecision for overall estimates. However, for the subgroup of patients with isolated distal DVT, who are known to have a very low risk of recurrence, there is imprecision and the possibility that the shorter duration of anticoagulation is adequate and not associated with a clinically important higher risk of recurrence.

[d] Follow-up was for $\sim$1 y in all studied except for Schulman et al in which it was 2 y.

[h] Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.

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Table S24—*[Sections 3.1.1-3.1.4] Comparison of Durations of Anticoagulant Therapy for DVT and PE: Clinical Description and Results*

Author/Year (Acronym)	Intervention	No. Patients Analyzed	Length Follow-up	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
Short (4 or 6 wk) vs intermediate (3 or 6 mo) durations of anticoagulation							
Kearon et al[86]/2004 (SOFAST)	VKA stopped (placebo)	84/84	11 mo	5/84 (6%)	0/84	0/84	Population: first DVT or PE. Treated for 1 mo. VTE was asymptomatic in 9% and isolated calf DVT in 18%. One VTE occurred while on warfarin.
	VKA (INR 2.0-3.0) For 2 more mo.	81/81	11 mo	3/81 (4%) RR 0.6 (0.1-2.5)	0/81 RR 1.0 (0.0-51.6)	1/81 (1%) RR 3.1 (0.1-74.4)	
Pinede et al[87]/2001 (DOTAVK)	VKA (INR 2.0-3.0) for 1.5 mo	105/105	15 mo	2/105 (2%)	1/105 (1%)	Not specified	Population: first isolated calf DVT.
	VKA (INR 2.0-3.0) for 3 mo	92/92		3/92 RR 1.7 (0.3-10.0)	3/92 RR 3.4 (0.4-33.4)		
Schulman et al[88]/1995 (DURAC 1)	VKA (INR 2.0-2.85) for 1.5 mo	443/443	2 y	80/443 (18%)	1/443	22/443 (5%)	First VTE: DVT (distal or proximal) or PE. Only asked about bleeding while on VKAs.
	VKA (INR 2.0-2.85) for 6 mo	454/454		43/454 (9%) RR 0.5 (0.4, 0.7)	5/454 (1%) RR 4.9 (0.6-41.6)	17/454 (4%) RR (0.7-1.4)	
Levine et al[89]/1995	VKA stopped (placebo)	105/107	9 mo	12/105 (11%)	0/105	9/105 (9%)	Proximal DVT (first episode in 91%). Cancer in 21%.
	VKA (INR 2.0-3.0) for 2 more mo.	109/113		7/109 (6%) RR 0.6 (0.2-1.4)	1/109 (1%) RR 2.9 (0.1-70.2) (within 2 mo of randomization)	9/109 (8%) RR 1.0 (0.4-2.5)	
British Thoracic Society et al[90]/1992	VKA (INR 2.0-3.0) For 1 mo	358/358	1 y	28/358 (11%)	5/358 (1%)	26/358 (7%)	Population: DVT or PE; only 71% objectively diagnosed; proportion with a previous VTE not known.
	VKA (INR 2.0-3.0) for 3 mo	354/354	1 y	14/354 (4%) RR 0.5 (0.3-0.9)	4/354 (1%) RR 0.8 (0.2-3.0)	28/354 (8) RR 1.1 (0.6-1.8)	All bleeds were on VKA. Only 1 recurrent VTE among 116 patients with postoperative VTE.

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Table S24—*Continued*

Author/Year (Acronym)	Intervention	No. Patients Analyzed	Length Follow-up	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
Different intermediate durations (6 or 12 mo vs 3 mo) of anticoagulation							
Campbell et al[91]/2007	VKA (INR 2.0.0-3.5) for 3 mo	369/396	1 y	31/369 (8%)	0/369 (during 3 mo. treatment)	15/369 (4%)	Population: DVT or PE; proportion with calf DVT not known. Only bleeding during treatment is reported; 20% of VTE outcomes were not objectively verified.
	VKA (INR 2.0-3.5) for 6 mo	380/414	1 y	29/380 (8%) RR0.9 (0.6-1.5)	8/380 (2%) (during 6 mo. treatment) RR 16.5 (1.0-285)	19/369 (5%) RR 1.3 (0.6-2.5)	
Agnelli et al[92]/2003 (WODIT PE)	VKA stopped	91/91	2.6 y (mean)	11/91 (12%)	1/91 (1%)	7/91 (8%)	Population: first unprovoked PE. Treated for ≥3 mo. Among the 4 groups, only 1 recurrent VTE while on VKA.
	VKA (INR 2.0-3.0) for 9 more mo	90/90	2.9 y (mean)	11/90 (12%) RR 1.0 (0.5-2.2)	2/90 (2%) RR 2.0 (0.5-21.9)	8/90 (9%) RR 1.16 (0.4-3.0)	
	VKA stopped	70/70	2.8 y (mean)	7/70 (10%)	0/70 (0%)	0/70 (0%)	Population: first provoked PE. Treated for ≥3 mo (see above)
	VKA (INR 2.0-3.0) for 3 more mo	75/75	2.9 y (mean)	4/75 (5%) RR 0.5 (0.2-1.7)	1/75 (1%) RR 1.9 (0.1-56)	4/75 (5%) RR 8.4 (0.5-153)	
Agnelli et al[93]/2001 (WODIT DVT)	VKA stopped	133/133	3.2 y (mean)	21/133 (16%)	2/133 (2%)	7/133 (5%)	Population: first unprovoked proximal DVT treated for 3 mo. One patient had recurrent VTE on VKA. Bleeding in the intervention group was while on VKA.
	VKA (INR 2.0-3.0) for 9 mo	134/134	3.1 y (mean)	21/134 (16%) RR 1.0 (0.6-1.7)	4/134 (3%) RR 2.0 (0.4-10.7)	7/134 (5%) RR 1.0 (0.4-2.8)	
Pinede et al[87]/2001 (DOTAVK)	VKA (INR 2.0-3.0) for 3 mo	270/270	15 mo	21/270 (8%)	5/270 (2%)	Not specified	Population: first proximal DVT or PE. Recurrent VTE occurred after VKA in 26/28 of the short duration groups and 21/27 of the long duration groups.
	VKA (INR 1.0-3.0) for 6 mo	269/269		23/269 (9%) RR 1.1 (0.6-1.9)	7/269 (3%)) RR 1.4 (0.4-4.4)		
Siragusa et al[94]/2008 (DACUS)	VKA stopped	92/92	1.8 y	27/92 (29%)	1/92 (1%)	Not specified (total of 3 non-VTE/bleed deaths)	Population: first proximal DVT (provoked, 24%; unprovoked, 76%) treated for 3 mo and residual DVT on baseline ultrasound

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Table S24—*Continued*

Author/Year (Acronym)	Intervention	No. Patients Analyzed	Length Follow-up	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
Indefinite vs intermediate durations of anticoagulation (INR ~2.0-3.0)							
Palareti et al[95]/2006 (PROLONG)	Remain off (stop) VKA	103/105	1.4 y (mean)	18/120 (15%)	0/103	1/103 (1%)	Population: first unprovoked proximal DVT or PE. Treated for ≥ 3 mo. VKA stopped and D-dimer positive 1 mo later. Eight control patient. Restarted VKA, some after superficial phlebitis. One recurrent VTE in VKA group after VKA stopped.
	Restart indefinite VKA (INR 2.0-3.0) (not blinded)	120/122	(maximum, 1.5 y)	2/103 (2%) RR 0.1 (0.0-0.4)	1/120 (1%) RR 2.6 (0.1-62.6)	1/120 (1%) RR 0.9 (0.1-13.6)	
Kearon et al[96]/1999 (LAFIT)	VKA stopped (placebo)	83/83	10 mo (mean)	17/83 (20%)	0/83	3/83 (4%)	Population: first unprovoked proximal DVT or PE (5% had previous provoked VTE). The recurrent VTE in the VKA patient was after stopping VKA.
	VKA (INR 2.0-3.0) for 2 more years	79/79	(maximum, 2 y)	1/79 (1%) RR 0.1 (0.0-0.5)	3/79 (4%) RR 7.4 (0.4-140)	1/79 (1%) RR 0.3 (0.0-3.3)	
Schulman et al[97]/1997 (DURAC 2)	VKA (INR 2.0-2.85) for 6 mo	111/111	4 y	23/111 (2%)	3/111 (3%)	16/111 (14%)	Second VTE: DVT (distal or proximal) or PE. All recurrent VTE in the indefinite VKA group were after stopping VKAs. Bleeding during the first 6 mo of VKA in 1 of 6 mo group and 6 of indefinite group (only asked about bleeding while on VKAs).
	VKA (INR 2.0-2.85) indefinitely	116/116		3/116 (3%) RR 0.1 (0.0-0.4)	10/116 (9%) RR 3.2 (0.9-11.3)	10/116 (9%) RR 0.6 (0.3-1.3)	
Farraj et al[98]/2004	VKA (INR 2.0-3.0) for 6 mo	32/36	3 y	7/32 (22%)	2/32 (6%)	0/32	In total: 2 VTE after 24 mo (24 mo group); 1 VTE on therapy (24 mo group)
	VKA (INR 2.0-2.85) for 24 mo	32/36		3/32 (3%) RR 0.4 (0.1-1.5)	2/32 (6%) RR 1.0 (0.2-6.7)	0/32	

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Table S24—*Continued*

Author/Year (Acronym)	Intervention	No. Patients Analyzed	Length Follow-up	Recurrent DVT or PE	Major Bleeding	Total Mortality	Comments
Fixed vs flexible duration, depending on presence of residual thrombosis on follow-up ultrasound (INR 2.0-3.0)							
Prandoni et al[99]/2009 (AESOPUS)	VKA stopped if provoked and 3 more months if unprovoked	268/268	33 mo	46/268 (17%)	2/268 (1%)	11/268 (4%)	Population: first provoked (43%) or unprovoked (57%) proximal DVT treated for 3 mo. One VTE in each group while on VKAs. The flexible group was treated for a mean of 4 mo (provoked) and 5 mo (unprovoked) longer.
	Stopped if no residual vein thrombosis and until resolved or 9 more mo if provoked or 21 more mo if unprovoked	270/270		32/270 (12%) RR 0.7 (0.4-1.1)	4/270/255 (1%) RR 2.0 (0.4-10.8)	4/255 (6%) RR 1.5 (0.7-3.2)	
Indefinite vs intermediate durations of anticoagulation (INR ~1.5-2.0, after initial INR 2.0-3.0 in both groups)							
Ridker et al[100]/2003 (PREVENT)	VKA stopped or not restarted (placebo)	253/253	2.1 y (mean)	37/253 (15%)	2/253 (1%)	8/253 (3%)	Population: unprovoked DVT (distal or proximal) or PE (first episode in 38%). Eight recurrent VTE in the VKA group after stopping VKAs.
	VKA INR 1.5-2.0	255/255	(maximum, 4.3 y)	14/255 (5%) RR 0.4 (0.2-0.7)	5/255 (2%) RR 2.5 (0.5-12.7)	4/255 (2%) RR 0.5 (0.1-1.6)	
Low intensity (INR 1.5-1.9) vs conventional intensity (INR 2.0-3.0)							
Kearon et al[101]/2003 (ELATE)	VKA INR 1.5-1.9	369/369	2.4 y (mean)	16/369 (4%)	9/369 (2%)	16/369 (4%)	Population: unprovoked proximal DVT or PE (first episode in 31%). Treated for ≥3 mo. VKA (INR 2.0-3.0) (mean 12 mo). Five recurrent VTE in INR 1.5-1.9 and three in the INR 2.0-3.0 group after stopping VKAs.
	VKA INR 2.0-3.0 (blinded)	369/369		6/369 (2%)RR 0.4 (0.1-0.9)	8/369 (2%) RR 0.9 (0.3-2.3)	8/369 (2%) RR 0.5 (0.2-1.2)	

AESOPUS = Ultrasound Findings to Adjust the Duration of Anticoagulation; DACUS = Duration of Anticoagulation based on Compression UltraSonography; DOTAVK = Durée Optimale du Traitement AntiVitamines K; DURAC = Duration of Anticoagulation; ELATE = Anticoagulation for Thrombo-Embolism; LAFIT = Long-term Anticoagulation for a First episode of Idiopathic venous Thromboembolism; PREVENT = Prevention of Recurrent Venous Thromboembolism; SOFAST = First Acute Secondary Thrombosis; WODIT DVT = Warfarin Optimal Duration Italian Trial in patients with DVT; WODIT PE = Warfarin Optimal Duration Italian Trial in patients with Pulmonary Embolism. See Table S1, S2, and S7 legends for expansion of other abbreviations.

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Table S25—*[Sections 3.1.1-3.1.4] Comparison of Durations of Anticoagulant Therapy for DVT and PE: Methodologic Quality*

Author/Year (Acronym)	Intervention	Study Design	Randomization Concealed	Blinding	Loss to Follow-up	Analysis	Comments
Kearon et al[86]/2004 (SOFAST)	VKA stopped (placebo) VKA (INR 2.0-3.0) for 2 more mo	RCT	CY	Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY	Placebo: 0/84 VKA: 0/81	ITT	Stopped early because of slow recruitment.
Pinede et al[87]/2001 (DOT AVK)	VKA (INR 2.0-3.0) for 1.5 and 3 mo VKA (INR 1.0-3.0) for 3 and 6 mo	RCT	CY	Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN	Not specified Probably low or nil	ITT	Stopped early because of slow recruitment. Patient withdrawals: 4 in short- and 16 in long-duration groups. Total of 22 patients dropped out.
Schulman et al[88]/1995 (DURAC 1)	VKA (INR2.0-2.85) for 1.5 mo VKA (INR 2.0-2.85) for 6 mo	RCT	CY	Patients: CN Caregivers: CN Adjudications: VTE, CY Other: PN Data Analysts: PN	Total of 44 patients dropped out during follow-up but partial follow-up achieved	ITT	Five patient were excluded because protein C found after randomization.
Levine et al[89]/1995	VKA stopped (placebo) VKA (INR 2.0-3.0) for 2 more mo.	RCT	CY	Patients: CY Caregivers: CY Adjudications: VTE, CY Data Analysts: PN	Placebo: 1/105 VKA: 6/109 (did not complete 11-mo follow-up)	ITT	Two placebo and 4 warfarin patients withdrew consent shortly after randomization.
British Thoracic Society et al[90]/1992	VKA (INR 2.0-3.0) For 1 mo VKA (INR 2.0-3.0) for 3 mo	RCT	CY	Patients: CN Caregivers: CN Adjudications: CN Data Analysts: PN	No VKA: 27/354 VKA: 30/358	ITT	Forty-four randomized patients excluded centrally as did not satisfy entry criteria.
Campbell et all[91]/2007	VKA (INR 2.0.0-3.5) for 3 mo VKA (INR 2.0-3.5) for 6 mo	RCT	CY	Patients: CN Caregivers: CN Adjudications: CN Data Analysts: PN	3- mo VKA: 6/369 6- mo VKA: 4/380	ITT	Sixty-one randomized patients excluded centrally as did not satisfy entry criteria. Stopped early because of low recruitment.
Agnelli et al[92]/2003 (WODIT PE)	VKA stopped VKA (INR 2.0-3.0) for 9 more mo.	RCT	CY	Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN	Not specified Probably low or nil	ITT	Two patients in the control groups and 2 patients in the intervention groups crossed over. Five patients in the intended group did not stop VKA. Four patients in the control groups restarted VKAs.
Agnelli et al[93]/2001 (WODIT DVT)	VKA stopped VKA (INR 2.0-3.0) for 9 mo	RCT	CY	Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN	Not specified Probably low or nil	ITT	Trial stopped early for lack of adequate benefit. Four patients in the intervention and 2 patients in the control group crossed over.

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Table S25—*Continued*

Author/Year (Acronym)	Intervention	Study Design	Randomization Concealed	Blinding	Loss to Follow-up	Analysis	Comments
Siragusa et al[94]/2008 (DACUS)	VKA stopped VKA (INR 1.0-3.0) for 9 mo.	RCT	PY	Patients: CN Caregivers: CN Adjudications: PY Data Analysts: PN	None	ITT	Not known whether the many postenrollment exclusions were postrandomization. Trial stopped early because recurrent VTE was higher than expected.
Palareti et al[95]/2006 (PROLONG)	Remain off (stop) VKA Restart indefinitely VKA (INR 2.0-3.0) (not blinded)	RCT	CY	Patients: CN Caregivers: CN Adjudications: CY Data Analysts: PN	No VKA: < 3/105 VKA: 0/122	ITT	Four patients excluded because lupus anticoagulant found after randomization.
Kearon et al[96]/1999 (LAFIT)	VKA stopped (placebo) VKA (INR 2.0-3.0) for 2 more y	RCT	CY	Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY	None	ITT	Trial stopped early because of overall benefit. After recurrent VTE, patients were not followed. resulting in shorter follow-up and potential for underestimation of bleeding in the no-VKA group.
Schulman et al[97]/1997 (DURAC 2)	VKA (INR 2.0-2.85) for 6 mo VKA (INR 2.0-2.85) indefinitely	RCT	CY	Patients: CN Caregivers: CN Adjudications: VTE, CY Other, PN Data Analysts: PN	Total of 14 patients dropped out during follow-up, but partial follow-up achieved	ITT	Actual mean duration of VKA was 7.7 mo in 6-mo group and 42.7 mo in indefinite (48 mo) group.
Prandoni et al[99]/2009 (AESOPUS)	VKA stopped if provoked and 3 more mo if unprovoked Stopped if no residual vein thrombosis and until resolved or 9 more mo if provoked or 21 more mo if unprovoked	RCT	CY	Patients: CN Caregivers: CN Adjudications: VTE, CY Data Analysts: PY	4 subjects in each group	ITT	
Ridker et al[100]/2003 (PREVENT)	VKA stopped or not restarted (placebo) VKA INR 1.5-2.0	RCT	CY	Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY	Not specified Probably low or nil	ITT	Trial stopped early because of overall benefit. Number of crossovers not described.
Farraj et al[98]/2004	VKA (INR 2.0-3.0) for 6 mo VKA (INR 2.0-2.85) for 24 mo	RCT	PY	Patients: CN Caregivers: CN Data Collectors: PN. Adjudicators: PN Data Analysts: PN	0/32 0/32 (see comments)	ITT	Four postrandomization exclusions for each group because of poor compliance.
Kearon et al[101]/2003 (ELATE)	VKA INR 1.5-1.9 VKA INR 2.0-3.0 (blinded)	RCT	CY	Patients: CY Caregivers: CY Adjudications: CY Data Analysts: CY	INR 1.5-1.9: ≤ 1/369 INR 1.5-1.9: ≤ 1/369	ITT	Crossover to INR 2.0-3.0 in 21 patients

See Table S1, S2, S7, and S24 legends for expansion of abbreviations.

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Table S26—*[Sections 3.1.1-3.1.4] Evidence Profile: Six or Twelve Months vs Three Months as Minimum Duration of Anticoagulation for VTE*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With 3 mo	With 6 or 12 mo	Relative Effect (95% CI)	Risk With 3 mo	Risk Difference With 6 or 12 mo (95% CI)
Recurrent VTE (critical outcome)											
2,061 (6 studies), 1-3 y	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious[d,e]	Undetected	Moderate[d-e] due to imprecision	118/1,025 (11.5)	105/1,036 (10.1)	RR 0.89 (0.69-1.14)	115 per 1,000	13 fewer per 1,000 (from 36 fewer to 16 more)
Major bleeding (critical outcome)											
2,061 (6 studies), 1-3 y	No serious risk of bias[f]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High[f]	9/1,025 (0.9)	24/1,036 (2.3)	RR 2.49 (1.2-5.16)	9 per 1,000	13 more per 1,000 (from 2 more to 37 more)
Mortality (important outcome[g])											
1,331 (5 studies), 1-3 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[d] due to imprecision	29/663 (4.4)	38/668 (5.7)	RR 1.3 (0.81-2.08)	44 per 1,000	13 more per 1,000 (from 8 fewer to 47 more)

Bibliography: Pinede et al,[87] Campbell et al,[91] Agnelli et al,[93] Agnelli et al,[92] Siragusa.[94] See Table S1, S2, and S5 legends for expansion of abbreviations.

[a] Timing of randomization relative to the start of treatment and length of treatment in the non-3-mo group varied across studies: Pinede et al and Campbell et al randomized at diagnosis, and Agnelli et al randomized after the initial 3 mo of treatment to stop, or continue, treatment. The longer duration of treatment was 6 mo in Pinede, Campbell, and Agnelli et al (2003) (provoked PE), and 12 mo in Agnelli (2001) and Agnelli (2003) (unprovoked PE).

[b] Study populations varied across studies: Pinede et al enrolled provoked and unprovoked proximal DVT and PE; Campbell et al enrolled provoked and unprovoked isolated distal DVT, proximal DVT and PE; Agnelli et al (2003) had separate randomizations for provoked PE (3 vs 6 mo) and unprovoked (3 vs 12 mo); and Agnelli et al (2001) enrolled unprovoked proximal DVT.

[c] Generally, study design was strong. No study stopped early for benefit; two stopped early because of slow recruitment (Campbell et al, Pinede et al), and one stopped because of lack of benefit (Agnelli et al [2001]). In one study (Campbell), 20% of VTE outcomes were not objectively confirmed. Patients and caregivers were not blinded in any study. Adjudicators of outcomes were blinded in all but one study (Campbell). All studies used effective randomization concealment and ITT analysis and appear to have a low unexplained drop-out frequency.

[d] CIs include both values suggesting no effect and values suggesting either benefit or harm.

[e] Low number of events and a total number of participants $<2,000$.

[f] One study may have confined the assessment of bleeding to when subjects were receiving anticoagulant therapy, which could have inflated the increase in bleeding associated with the longer duration of therapy (Campbell et al).

[g] Differences in mortality are expected to be mediated by differences in recurrent VTE and bleeding.

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Table S27—*[Sections 3.1.1-3.1.4] Extended Anticoagulation vs No Extended Anticoagulation for Different Groups of Patients With VTE and Without Cancer*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Extended Anticoagulation	With Extended Anticoagulation	Relative Effect (95% CI)	Risk With No Extended Anticoagulation	Risk Difference With Extended Anticoagulation (95% CI)
Mortality (important outcome)											
1,184 (4 studies), 10-36 mo	No serious risk of bias	No serious inconsistency[c]	No serious indirectness	Serious[d,e]	Undetected	Moderate[c-e] due to imprecision	38/599 (6.3)	16/585 (2.7)	RR 0.57 (0.31-1.03)	63 per 1,000	27 fewer per 1,000 (from 44 fewer to 2 more)
Recurrent VTE at 1 y (critical outcome)											
1,184 (4 studies), 10-36 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	102/599 (17)	21/585 (3.6)	RR 0.12 (0.09-0.38)	First VTE provoked by surgery[f-j]	
										10 per 1,000	10 per 1,000
										First VTE provoked nonsurgical/first unprovoked distal DVT[f-j]	
										50 per 1,000	44 fewer per 1,000 (from 31 fewer to 45 fewer)
										First unprovoked VTE[f-j]	
										100 per 1,000	88 fewer per 1,000 (from 62 fewer to 91 fewer)
										Second unprovoked VTE[f-j]	
										150 per 1,000	132 fewer per 1,000 (from 93 fewer to 137 fewer)
Major bleeding at 1 y (critical outcome)											
1,184 (4 studies), 10-36 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious	Undetected	Moderate due to imprecision	7/599 (1.2%)	21/585 (3.6%)	RR 2.63 (1.02-6.76)	Low risk of bleeding[k,l]	
										3 per 1,000	5 more per 1,000 (from 0 more to 17 more)
										Moderate risk of bleeding[k,l]	
										6 per 1,000	10 more per 1,000 (from 0 more to 35 more)
										High risk of bleeding[k,l]	
										12 per 1,000	20 more per 1,000 (from 0 more to 69 more)

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Table S27—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Extended Anticoagulation	With Extended Anticoagulation	Relative Effect (95% CI)	Risk With No Extended Anticoagulation	Risk Difference With Extended Anticoagulation (95% CI)
Recurrent VTE at 5 y (critical outcome)											
1,184 (4 studies), 10-36 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	102/599 (17%)	21/585 (3.6%)	RR 0.12 (0.09-0.38)	First VTE provoked by surgery[f-j]	
										30 per 1,000	26 fewer per 1,000 (from 19 fewer to 27 fewer)
										First VTE provoked nonsurgical/first unprovoked distal DVT[f-j]	
										150 per 1,000	132 fewer per 1,000 (from 93 fewer to 137 fewer)
										First unprovoked VTE[f-j]	
										300 per 1,000	264 fewer per 1,000 (from 186 fewer to 273 fewer)
										Second unprovoked VTE[f-j]	
										450 per 1,000	396 fewer per 1,000 (from 279 fewer to 409 fewer)
Major bleeding at 5 y (critical outcome)											
1,184 (4 studies), 10-36 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious	Undetected	Moderate due to imprecision	7/599 (1.2%)	21/585 (3.6%)	RR 2.63 (1.02-6.77)	Low risk of bleeding[k,l]	
										15 per 1,000	24 more per 1,000 (from 0 more to 87 more)
										Moderate risk of bleeding[k,l]	
										30 per 1,000	49 more per 1,000 (from 1 more to 173 more)
										High risk of bleeding[k,l]	
										60 per 1,000	98 more per 1,000 (from 1 more to 346 more)
Burden of anticoagulation not reported											

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Table S27—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Extended Anticoagulation	With Extended Anticoagulation	Relative Effect (95% CI)	Risk With No Extended Anticoagulation	Risk Difference With Extended Anticoagulation (95% CI)
…	…	…	…	…	…	…	…	…	…	See comment[m]	See comment[m]
PTS not reported											
…	…	…	…	…	…	…	…	…	…	See comment[n]	See comment[n]

Bibliography: Schulman et al (DURAC 2),[97] Kearon et al (LAFIT),[96] Farraj,[98] Palareti (PROLONG).[95] See Table S1, S2, S7, and S10 legends for expansion of abbreviations.

[a]Studies vary in follow-up duration (10 mo to 3 y) and in duration of time-limited VKA (3 to 6 mo).

[b]We excluded Ridker et al (PREVENT)[100] because target INR was 1.75 (low intensity), which has been shown in an RCT to be less effective than a target of 2.5.

[c]$I^2 = 0\%$.

[d]CI includes both values suggesting no effect and values suggesting either appreciable harms or appreciable benefit.

[e]Small number of events. Decision to rate down also takes into account that two studies were stopped early for benefit.

[f]Annual risk of VTE recurrence after discontinuing oral anticoagulation therapy in patients with first VTE provoked by surgery: 1% (Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. *Arch Intern Med*. 2010;170(19):1710-1716); we assumed a 0.5% yearly risk thereafter (3% over 5 y).

[g]Annual risk in patients with first VTE provoked by non surgical factor: about 5% the first year (Iorio et al); we assumed 2.5% yearly thereafter (15% over 5 y).

[h]Annual risk in patients with first episode of unprovoked VTE: 9.3% over 1 y in Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ*. 2008;179(5):417-426; 11.0% over 1 y, 19.6% over 3 y, and 29.1% over 5 y in Prandoni et al (2007). We assumed a risk of 10% the first year after discontinuation and 5% yearly thereafter (30% over 5 y).

[i]Annual risk in patients with second episode of unprovoked VTE: we assumed an RR of 1.5 compared with a first episode of unprovoked VTE: 15% the first year after discontinuation, 7.5% yearly thereafter (45% over 5 y).

[j]Case fatality rate of recurrent VTE after discontinuing oral anticoagulation therapy: 3.6% (Carrier 2010).

[k]Annual risk of major bleeding is based on three risk levels: low, intermediate, and high. The corresponding 0.3%, 0.6%, and 1.2% risks are estimates based on control arms of included studies (see Table 3).

[l]Case fatality rate of major bleeding during initial oral anticoagulation therapy: 11.3% (Carrier et al) (no data available for after discontinuing oral anticoagulation therapy).

[m]Burden of anticoagulation: endured by all patients who continue extended-duration anticoagulation (100%) and applies to patients who stop anticoagulation (no extended-duration anticoagulation) who subsequently experience a recurrent VTE (5%, 10%, 15% at 1 y; 15%, 30%, 45% at 5 y).

[n]Baseline risk over 2 y of 58.8% for PTS and 13.8% for severe PTS (VETO [Venous Thrombosis Outcomes study]; *Ann Intern Med*. 2008) and threefold (Prandoni. *Ann Intern Med*. 2004) to 10-fold (Van Dongen. *J Thromb Haemost*. 2005) increase in PTS.

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Table S28—*[Section 3.3] Evidence Profile: LMWH vs VKA for Long-term Treatment of VTE*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With VKA	With LMWH	Relative Effect (95% CI)	Risk With VKA	Risk Difference With LMWH (95% CI)
Mortality (important outcome)											
2,496 (7 studies), 6 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	202/1,231 (16.4)	204/1,265 (16.1)	RR 0.96 (0.81-1.13)	164 per 1,000	7 fewer per 1,000 (from 31 fewer to 21 more)
Recurrent VTE (critical outcome)											
2,727 (8 studies), 6 mo	Serious[f]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate[f] due to risk of bias	105/1,349 (7.8)	67/1,378 (4.9)	RR 0.62 (0.46-0.84)	No cancer[g]	
										30 per 1,000	11 fewer per 1,000 (from 5 fewer to 16 fewer)
										Nonmetastatic cancer[g]	
										80 per 1,000	30 fewer per 1,000 (from 13 fewer to 43 fewer)
										Metastatic cancer[g]	
										200 per 1,000	76 fewer per 1,000 (from 32 fewer to 108 fewer)
Major bleeding (critical outcome)											
2,737 (8 studies), 6 mo	No serious risk of bias[h]	No serious inconsistency	No serious indirectness	Serious[i]	Undetected	Moderate[h,i] due to imprecision	53/1,351 (3.9%)	45/1,386 (3.2%)	RR 0.81 (0.55-1.2)	No cancer or nonmetastatic cancer[j]	
										20 per 1,000	4 fewer per 1,000 (from 9 fewer to 4 more)
										Metastatic cancer[j]	
										80 per 1,000	15 fewer per 1,000 (from 36 fewer to 16 more)

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Table S28—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With VKA	With LMWH	Relative Effect (95% CI)	Risk With VKA	Risk Difference With LMWH (95% CI)
Burden of anticoagulation (important outcome)[k]											
…	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Not applicable	High	Warfarin: daily medication, dietary interactions, frequent blood testing/monitoring, increased hospital/clinic visits	LMWH: daily injection, no dietary interactions, no frequent blood testing/monitoring	…	…	
PTS (important outcome; assessed with self-reported leg symptoms and signs)											
100 (1 study), 2 y	Serious[l]	No serious inconsistency	Serious[m]	No serious imprecision	Undetected	Low[l,m] due to risk of bias, indirectness	31/44 (70.5%)	34/56 (60.7%)	RR 0.85 (0.77-0.94)	Moderate[n] 200 per 1,000	30 fewer per 1,000 (from 12 fewer to 46 fewer)

Bibliography: Included studies: Deitcher et al,[102] Hull et al,[103] Hull et al,[104] Lee et al,[105] Lopaciuk et al,[106] Lopez-Beret et al,[107] Meyer G et al,[108] Romera et al[109] Two of these studies enrolled only patients without cancer,[104,107] 3 enrolled only patients with cancer[108,102,105], and 3 enrolled both patients with and without cancer[103,106,109] (separate data provided for cancer and non-cancer patients in one study[103,110]). Excluded studies (less than 50% of therapeutic dose LMWH during extended phase): Pini et al,[111] Das et al,[112] Gonzalez-Fajardo et al,[113] Veiga et al,[114] Kakkar et al,[115] (Cesarone 2003 Circ abstract). PTS data from: Hull et al.[104] See Table S1, S2, S5, and S10 legends for expansion of abbreviations.

[a]Limited to LMWH regimens that used ≥50% of the acute treatment dose during the extended phase of treatment.

[b]The initial parenteral anticoagulation was similar in both arms for all except one study (Hull et al [2007]) in which patients randomized to LMWH received initially the same LWMH, whereas patients randomized to VKA received initially UFH.

[c]Two of these studies enrolled only patients without cancer, three enrolled only patients with cancer, and three enrolled both patients with and without cancer (separate data provided for cancer and non-cancer patients in one study).

[d]One study did not report deaths, which is unusual and could reflect selective reporting of outcomes.

[e]CI includes both no effect and harm with LMWH.

[f]None of the studies were blinded, although the diagnosis of recurrent VTE has a subjective component and there could be a lower threshold for diagnosis of recurrent VTE in VKA-treated patients because switching the treatment of such patients to LMWH is widely practiced. At the same time, there is reluctance to diagnose recurrent VTE in patients who are already on LMWH because there is no attractive alternative treatment option.

[g]Risk of recurrent VTE: low corresponds to patients without cancer (3% estimate taken from recent large RCTs of acute treatment), intermediate corresponds to patients with local or recently resected cancer (based on average rate across the six studies in this analysis and appears to be consistent with Prandoni et al [particularly if low risk is increased to 4%]), and high to patients with locally advanced or distant metastatic cancer (Prandoni et al[116]).

[h]No study was blinded; diagnosis of major bleeding has a subjective component.

[i]The 95% CIs for the RR for major bleeding includes a potentially clinically important increase or decrease with LMWH and may vary with the dose of LMWH used during the extended phase of therapy.

[j]Risk of bleeding: low corresponds to patients without risk factor for bleeding (ie, >75 y, cancer, metastatic disease; chronic renal or hepatic failure; platelet count <800,000; requires antiplatelet therapy; history of bleeding without a reversible cause) (Table 2) (based on Prandoni et al[116] and Beyth et al,[117] adjusted to a 6-mo time frame).

[k]Hull et al reported no significant difference in quality of life but suggested greater satisfaction with LMWH over VKA (questionnaire did not directly assess the burden of injections).

[l]Patients and investigators not blinded. Self-reported leg symptoms and signs after 3 mo of treatment.

[m]The association between leg symptoms and signs at 3 mo and long-term PTS is uncertain.

[n]Baseline risk assumes that patients all wear pressure stockings. Control event rate comes from observational studies in review by Kahn et al,[118] adjusted to 2-y time frame.

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Table S29—*[Section 3.3] Evidence Profile: Rivaroxaban vs LMWH and VKA Therapy for Short- and Long-term Treatment of VTE*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies) Follow up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With LMWH and VKA Therapy	With Rivaroxaban	Relative Effect (95% CI)	Risk With LMWH and VKA Therapy	Risk Difference With Rivaroxaban (95% CI)
Death (important outcome)											
3,449 (1 study), 6-12 mo[d]	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[e,f] due to imprecision	49/1,718 (2.9)	38/1,731 (2.2)	HR 0.67 (0.44-1.02)	29 per 1,000	9 fewer per 1,000 (from 16 fewer to 1 more)
Recurrent VTE (critical outcome)											
3,449 (1 study), 6-12 mo[d]	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious[g]	Undetected	Moderate[e,g] due to imprecision	51/1,718 (3)[h]	36/1,731 (2.1)[h]	HR 0.68 (0.44-1.04)	30 per 1,000[h]	9 fewer per 1,000 (from 17 fewer to 1 more)
Major bleeding (critical outcome)											
3,429 (1 study), 6-12 mo[d]	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious[g]	Undetected	Moderate[e,g] due to imprecision	19/1,711 (1.1)[i]	13/1,718 (0.8)[i]	HR 0.68 (0.34-1.38)[j]	11 per 1,000[i]	4 fewer per 1,000 (from 7 fewer to 4 more)
Burden of anticoagulation (important outcome) not reported											
…	…	…	…	…	…	…	Warfarin: daily medication, dietary interactions, frequent blood testing/monitoring, increased hospital/clinic visits	Rivaorxaban: daily medication, no dietary interactions, no frequent blood testing/monitoring	…	…	…

Bibliography: Einstein DVT.[119] HR = hazard ratio. See Table S1, S2, S5, and S7 legends for expansion of other abbreviations.

[a]Rivaroxaban 15 mg bid for 3 wk and then 20 mg/d for a total of 3 (12%), 6 (63%), or 12 (25%) months.

[b]Enoxaparin 1 mg/kg bid for ~8 d and then VKA therapy targeted to INR 2.5 for 3, 6, or 12 mo.

[c]Included patients had acute, symptomatic, objectively verified proximal DVT of the legs (unprovoked, 62%; cancer, 6%; previous VTE, 19%).

[d]Follow-up was prespecified to be 3 mo (12%), 6 mo (63%), or 12 mo (25%).

[e]Allocation was concealed. Patients, providers, and data collectors were not blinded, but outcome adjudicators were blinded. ITT analysis; 1.0% loss to follow-up. Not stopped early for benefit.

[f]CI includes values suggesting benefit or no effect; relatively low number of events.

[g]CI includes values suggesting benefit and harm.

[h]One definite or possible fatal VTE in rivaroxaban group and one in LMWH/VKA group.

[i]Bleeds contributing to death: one in the rivaroxaban group and five in the warfarin group.

[j]Calculated from reported data.

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Table S30—*[Section 3.3] Evidence Profile: Rivaroxaban vs Placebo for Extended Anticoagulation of VTE*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Placebo	With Rivaroxaban	Relative Effect (95% CI)	Risk With Placebo	Risk Difference With Rivaroxaban (95% CI)
Mortality (important outcome)											
1,196 (1 study), 6 or 12 mo[c]	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	2/594 (0.34)	1/602 (0.17)	RR 0.49 (0.04-5.4)[f]	3 per 1,000	2 fewer per 1,000 (from 3 fewer to 15 more)
Recurrent VTE (critical outcome)											
1,196 (1 study), 6 or 12 mo[c]	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High[d]	42/594 (7.1)[g]	8/602 (1.3)[g]	HR 0.18 (0.09-0.39)	71 per 1,000[g]	58 fewer per 1,000 (from 43 fewer to 64 fewer)
Major bleeding (critical outcome)											
1,188 (1 study), 6 or 12 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[h]	Undetected	Moderate[d,h] due to imprecision	0/590 (0)[i]	4/598 (0.7)[i]	RR 4.9 (0.58-42)[f]	[i]	7 more per 1,000 (from 3 more to 16 more)
Burden of anticoagulation (important outcome) not reported											
…	…	…	…	…	…	…	…		Rivaroxaban: daily medication, no dietary interactions, no frequent blood testing/ monitoring	…	…
PTS (important outcome) not reported											
…	…	…	…	…	…	…	…	…	…	…	[j]

Bibliography: Einstein DVT.[119] See Table S1, S2, S5, S10, and S29 legends for expansion of abbreviations.

[a]Rivaroxaban 20 mg/d for 6 or 12 mo after initial long-term therapy.

[b]Included patients had acute, symptomatic, objectively verified proximal DVT of the legs or PE (unprovoked, 73%; cancer, 5%; previous VTE, 19%).

[c]Follow-up was prespecified to be 6 mo (60%) or 12 mo (40%).

[d]Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. ITT analysis; 0.2% loss to follow-up. Not stopped early for benefit.

[e]CI includes values suggesting benefit or no effect; relatively low number of events.

[f]Calculated from reported data with addition of one event to each event rate as event rate 0 in control group.

[g]One definite or possible fatal VTE in rivaroxaban group and one in LMWH/VKA group.

[h]CI includes values suggesting benefit and harm.

[i]Bleeds contributing to death: none in the rivaroxaban group and none in the warfarin group.

[j]PTS: baseline risk over 2 y of 58.8% for PTS and 13.8% for severe PTS (Kahn et al[40]). There is threefold (Prandoni et al[120]) to 10-fold (van Dongen et al[121]) increase in PTS with recurrent VTE in the ipsilateral leg.

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Table S31—*[Section 3.3] Dabigatran vs VKA Therapy for Long-term Treatment of VTE*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Warfarin	With Dabigatran	Relative Effect (95% CI)	Risk With Warfarin	Risk Difference With Dabigatran (95% CI)
Death (important outcome)											
2,539 (1 study), 6 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	21/1,265 (1.7)	21/1,274 (1.6)	HR 0.98 (0.53-1.79)	17 per 1,000	0 fewer per 1,000 (from 8 fewer to 13 more)
Recurrent VTE (critical outcome)											
2,539 (1 study), 6 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	24/1,265 (1.9)[f]	30/1,274 (2.4)[f]	HR 1.01 (0.65-1.84)	19 per 1,000[f]	0 more per 1,000 (from 7 fewer to 16 more)
Major bleeding (critical outcome)											
2,539 (1 study), 6 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	24/1,265 (1.9)[g]	20/1,274 (1.6)[g]	HR 0.82 (0.45-1.48)	19 per 1,000[g]	3 fewer per 1,000 (from 10 fewer to 9 more)
Burden of anticoagulation (important outcome) not reported											
…	…	…	…	…	…	…	Warfarin: daily medication, dietary restrictions, frequent blood testing/monitoring, increased hospital/ clinic visits	Dabigatran: daily medication, No dietary restrictions, no frequent blood testing/ monitoring	…	…	…

Bibliography: Schulman et al.[122] See Table S2, S5, and S29 legends for expansion of abbreviations.

[a]Dabigatran 150 mg bid taken orally for 6 mo after an initial treatment with LMWH or IV UFH.

[b]Warfarin adjusted to achieve an INR of 2.0 to 3.0 for 6 mo after an initial treatment with LMWH or IV UFH.

[c]Included patients had acute, symptomatic, objectively verified proximal DVT of the legs or PE.

[d]Allocation was concealed. Patients, providers, data collectors, and outcome adjudicators were blinded. Modified ITT analysis; 1.1% loss to follow-up. Not stopped early for benefit.

[e]CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

[f]One fatal VTE in dabigatran group and three fatal VTEs in warfarin group.

[g]One fatal major bleeding event in dabigatran group and one fatal major bleeding event in warfarin group.

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Table S32—*[Section 4.1] Elastic Stocking for Prevention of PTS: Clinical Description and Results*

Author/Year	Type of Publication	Participants	Interventions	Outcomes	Follow-up	Results
Brandjes et al[127]/1997	RCT	194 patients with first symptomatic proximal DVT	Compression stockings: below-knee customized elastic compression stockings with ankle pressure 30-40 mm Hg (96 patients) Control group: no intervention (98 patients)	Cumulative incidence of mild to moderate and severe PTS	3 and 6 mo, then every 6 mo to a median of 76 mo	Compression stockings: Mild-moderate PTS: 20% (RR, 0.42; 95% CI 0.27-0.66; $P < .001$) Severe PTS: 11% (RR, 0.49; 95% CI, 0.25-0.95; $P < .001$) Control group: Mild-moderate PTS: 47% Severe PTS: 23%
Ginsberg et al[124]/2001	RCT	47 asymptomatic patients with valvular incompetence 1 y post-DVT	Compression stockings: below-knee elastic compression stockings 20-30 mm Hg (24 patients) Placebo: placebo stocking (23 patients)	PTS symptoms	57 mo (mean)	Compression stockings: PTS symptoms: 0% Placebo: PTS symptoms: 4%
Prandoni et al[120]/2004	RCT	180 patients with first episode of symptomatic, acute proximal DVT	Compression stockings: below-knee elastic compression stockings 30-40 mm Hg (90 patients) Control group: no intervention (90 patients)	Cumulative incidence of mild to moderate and severe PTS	3-5 y	Compression stockings: PTS symptoms: 25% (CI, 15.6%-33.4%) Control group: PTS symptoms: 49% (CI, 38.7%-59.4%)
Partsch et al[84]/2004	2-y follow-up to RCT	37 symptomatic patients with acute DVT followed long term	All anticoagulated with LMWH followed by oral anticoagulation Inelastic bandages + early ambulation (13 patients) Elastic stockings (30 mm Hg) + early ambulation (13 patients) Bed rest for 9 d, no compression (11 patients)	Overall leg pain Leg circumference PTS score (Villalta-Prandoni)	2 y	Leg pain: No difference between groups Calf circumference: No difference between groups PTS score: Significantly better outcome with ambulation and bandaging or stockings compared with bed rest ($P < .01$)
Ashwanden et al[130]/2008	RCT, single center	169 first or recurrent proximal DVT without PTS after 6 mo of compression stockings	Compression stockings: below-knee, 26-36 mm Hg (84 patients) Control group: stopped stockings (85 patients)	PTS shin changes (≥ C4 on CEAP)	0-7 y (mean, 3 y)	PTS compression stockings: 13% Control group: 20% HR: 0.8 (95 % CI, 0.3-1.3)

See Table S1, S2, S5, S10, and S29 legends for expansion of other abbreviations.

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Table S33—*[Section 4.1] Elastic Stocking for Prevention of PTS: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up
Brandjes et al[127]/1997	Y	Y (sealed envelopes)	Patients: N Caregivers: N Assessors: Y Data analysis: PY	Intervention group: 4 lost to follow-up, 19 died Control group: 2 lost to follow-up, 18 died
Ginsberg et al[124]/2001	Y	Probably, but not specified	Patients: Y Caregivers: Y Assessors: Y data analysis: PY	Intervention: lost to follow-up not reported, 3 died Control group: lost to follow-up not reported
Prandoni et al[120]/2004	Y	Y	Patients: N caregivers: N Assessors: Y Data analysis: PY	Intervention: 2 lost to follow-up, 6 died Control group: 13 lost to follow-up
Ashwanden et al[130]/2008	Y	Y	Patients: N Caregivers: N Assessors: N Data analysis: N	Intervention: 19 (described) Control group: 13 (described)

See Table S5 legend for expansion of abbreviations.

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Table S34—*[Section 4.1] Evidence Profile: Elastic Compression Stockings vs No Elastic Compression Stockings To Prevent PTS of the Leg*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Elastic Compression Stockings	With Elastic Compression Stockings	Relative Effect (95% CI)	Risk With No Elastic Compression Stockings	Risk Difference With Elastic Compression Stockings (95% CI)
PTS (critical outcome; assessed with Villalta Score)											
421 (2 studies), 2 y	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate[c] due to risk of bias	91/211 (43.1)[d]	41/210 (19.5)	RR 0.46 (0.34-0.63)[e]	479 per 1,000[d,f]	259 fewer per 1,000 (from 177 fewer to 316 fewer)[g]
Recurrent VTE (critical outcome)											
374 (2 studies), 5 y	No serious risk of bias[h]	No serious inconsistency	No serious indirectness	Serious[i]	Undetected	Moderate[h,i] due to imprecision	26/188 (13.8)	26/186 (14)	RR 1.01 (0.61-1.67)[e]	210 per 1,000[j]	2 more per 1,000 (from 82 fewer to 141 more)
Quality of life (important outcome)											
0 (0[k])							…	…	…	See comment[k]	…

Bibliography: Kolbach et al.[123] We excluded Ginsberg et al[124] and Belcaro et al[125] because they respectively randomized patients 7 and 12 mo after their DVT rather than at the time of the acute DVT. We also excluded Arpaia et al[126] because they randomized patients to receive stockings at the time of diagnosis of DVT vs 2 wk later.[126] See Table S1 and S5 legends for expansion of abbreviations.

[a]Brandjes[127] used graded elastic compression stockings (40 mm Hg of pressure at the ankle, 36 mm Hg at the lower calf, and 21 mm Hg at the upper calf); stockings were applied 2 to 3 wk after the first episode of proximal DVT. Prandoni[120] used flat-knitted stockings (30-40 mm Hg of pressure at the ankle); stockings were started at hospital discharge an average of 1 wk after admission. In both studies, stockings were used for 2 y.

[b]Prandoni[120] excluded patients with recurrent ipsilateral DVT, preexisting leg ulcers, or signs of CVI, bilateral thrombosis, a short life expectancy, or a contraindication for use of stockings (eg, advanced-stage peripheral arterial insufficiency). Brandjes et al excluded patients with short life, paralysis of the leg, bilateral thrombosis, leg ulcers, or extensive varicosis.

[c]Patients were not blinded to the treatment assignment, and outcomes were partly based on subjective report of symptoms.

[d] In Prandoni,[120] most events occurred during the first 6 mo: the cumulative incidence of PTS in the control group was 40% after 6 mo, 47% after 1 y, and 49% after 2 y.

[e] The effect estimate shown here results from a meta-analysis (Mantel-Haenszel fixed-effects model) of the two relevant trials. A fixed-effects model was chosen because of the small number of studies available.

[f]This estimate is based on the findings of the VETO (Venous Thrombosis Outcomes) study.[40] This probably underestimates the PTS baseline risk given that overall, 52% of patients reported the current use of compression stockings during study follow-up.

[g]Severe PTS: assuming the same RR of 0.46 and a baseline risk of 8.1% over 2 y, the absolute reduction is 44 fewer severe PTS per 1,000 (from 30 fewer to 53 fewer) over 2 y.

[h]We did not rate down the quality of evidence for recurrent VTE for the lack of blinding because this a more objective outcome than PTS.

[i]CI includes both negligible effect and appreciable benefit or appreciable harm.

[j]This estimate is the mean of two estimates derived from two studies: 12.4% probable/definite VTE (Heit[128]) and 29.1% confirmed VTE (Prandoni[129]).

[k]This is an important outcome that should be considered in future studies.

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Table S35—*[Section 4.2.1] Evidence Profile: Compression Stockings vs No Compression Stockings for Patients With PTS*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Compression Stockings	With Compression Stockings	Relative Effect (95% CI)	Risk With No Compression Stockings	Risk Difference With Compression Stockings (95% CI)
Symptomatic relief (critical outcome; assessed with treatment success[d])											
115 (2 studies), 12-26 mo	Serious[e]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected[g]	Low[e-g] due to risk of bias, imprecision	33/57 (57.9)	32/58 (55.2)	RR 0.96 (0.70-1.31)	579 per 1,000	23 fewer per 1,000 (from 174 fewer to 179 more)
Quality of life not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Recurrent VTE not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Ulceration not reported[h]											
…	…	…	…	…	…	…	…	…	…	…	…

Bibliography: Ginsberg 2001[124]; Frulla. 2005[131] See Table S1, S2, S5, and S10 legends for expansion of abbreviations.

[a]Ginsberg et al: graduated compression stockings, 30-40 mm Hg (calf or thigh length, depending on symptoms). Patients were encouraged to wear stockings as much as possible during waking hours. Frulla (2005): below-knee graded elastic compression stockings (ECS) (30-40 mm Hg at the ankle). Patients in both arms of the study received hydroxyethylrutosides (HR) (we considered the ECS + HR vs HR comparison).

[b]Ginsberg et al: placebo stockings (calf or thigh length, depending on symptoms).

[c]Ginsberg et al included patients with PTS 1 y after chronic, typical proximal DVT. Frulla (2005) included patients with clinical symptoms and signs suggestive of PTS.

[d]Ginsberg et al reported treatment failure (defined a priori based on any of five clinical criteria, including symptoms and ulcer development). Treatment success refers to the absence of treatment failure. Frulla used the Villalta scale.

[e]Ginsberg et al: Adequacy of sequence generation and allocation concealment were unclear; patients and outcome assessors were adequately blinded; unclear whether analysis followed the ITT principle; unclear whether follow-up was complete. Frulla (2005): outcome assessors were blinded; follow-up was complete. ITT principle was adhered to, but sequence generation and allocation concealment were unclear, and patients were not blinded.

[f]Very small number of patients.

[g]Publication bias not detected but not ruled out given that we identified only one small study partially supported by industry (provision of graduated compression stockings).

[h]Indirect evidence from the CLOTS1 (Clots in Legs Or sTockings after Stroke) trial suggests that compression stockings is associated with an RR of 4 for skin complications.

[i]Absence of ulcer included in the treatment success outcome in Ginsberg et al.

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Table S36—*[Section 4.2.2] Evidence Profile: Intermittent Compression Device vs No Intermittent Compression Device for Patients With Severe PTS*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Intermittent Compression Device	With Intermittent Compression Device	Relative Effect (95% CI)	Risk With No Intermittent Compression Device	Risk Difference With Intermittent Compression Device (95% CI)
Symptomatic relief (critical outcome; measured with symptom score (includes scoring of pain, swelling, and limitation of activity); range of scores, 10-70; better indicated by higher values)											
82 (2 studies[d]), 8 wk	No serious risk of bias[e]	No serious inconsistency[f]	No serious indirectness[g]	Serious[h]	Undetected[i]	Moderate[e-i] due to imprecision	41[d]	41[d]	…	The mean symptomatic relief in the control groups was 0	The mean symptomatic relief in the intervention groups was 0.41 SDs higher (0.02 lower to 0.85 higher)
Quality of life (critical outcome; measured with VEINES-QOL; range of scores, 0-100; better indicated by higher values)											
0 (1 study[d,j]), 8 wk	No serious risk of bias[k]	No serious inconsistency	No serious indirectness[g]	Serious[h]	Undetected[d,l]	Moderate[f-h,k,l] due to imprecision	…	0	…	The mean quality of life in the control groups was 50.2	The mean quality of life in the intervention groups was 2.3 higher (1.04 lower to 5.64 higher)

(Continued)

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Table S36—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Intermittent Compression Device	With Intermittent Compression Device	Relative Effect (95% CI)	Risk With No Intermittent Compression Device	Risk Difference With Intermittent Compression Device (95% CI)
Recurrent VTE not reported[m]											
…	…	…	…	…	…	…	…	…	…	…	…
Ulceration not reported[n]											
…	…	…	…	…	…	…	…	…	…	…	…

Bibliography: Ginsberg 1999,[132] O'Donnell, 2008.[133] See Table S1, S5, and S10 legends for expansion of other abbreviations.

[a]Ginsberg et al: Extremity pump used bid for 20 min each session; 50 mm Hg (therapeutic pressure) for 1 mo. O'Donnell et al: Venowave lower-limb venous return assist device to wear for most of the day for 8 wk.

[b]Ginsberg et al: Extremity pump used bid for 20 min each session; 15 mm Hg (placebo pressure) for 1 mo. O'Donnell et al: Venowave lower-limb venous return assist device with no connection between motor and planar sheet for 8 wk.

[c]Patients with previous DVT with symptoms of severe PTS.

[d]Crossover RCTs.

[e]In both studies, sequence generation was adequate; patients were blinded. Analysis adhered to ITT principle, and there were no missing outcome data. In Ginsberg et al (but not in O'Donnell et al), outcome assessors were not blinded, and it was not clear whether allocation was concealed.

[f]$I^2 = 0\%$.

[g]Some concerns with indirecteness given relatively short follow-up (8 wk).

[h]Very small number of patients. CI includes both values suggesting no effect and values suggesting a beneficial effect.

[i]Publication bias not detected but not ruled out given that we identified only two small studies with one (Ginsberg et al) partially supported by industry (provision of devices).

[j]O'Donnell et al.

[k]Sequence generation was adequate; patients were blinded; analysis adhered to ITT principle; and there were no missing outcome data. However, outcome assessors were not blinded, and it was not clear whether allocation was concealed.

[l]Publication bias not detected but not ruled out given that we identified only one small study.

[m]O'Donnell et al indicated no cases of recurrent VTE by the end of this study but judged the follow-up period to be short.

[n]O'Donnell et al indicated that one patient in the control group developed a venous ulceration. Three other participants developed nonserious skin-related side effects. Indirect evidence from the CLOTS1 (Clots in Legs Or sTockings after Stroke) trial suggests that compression stockings are associated with an RR of 4 for skin complications: Common side effects are attributed to Venowave were heat sensation, skin irritation, and increased sweating.

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Table S37—*[Section 4.3] Evidence Profile: Venoactive Medication vs No Venoactive Medication for Patients With PTS*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Venoactive Medication	With Venoactive Medication	Relative Effect (95% CI)	Risk With No Venoactive Medication	Risk Difference With Venoactive Medication (95% CI)
Symptomatic relief (critical outcome; assessed with PTS score (Villalta scale) < 5 or decreased by 30% at 12 mo compared with baseline in Frulla et al; improved tiredness of the leg at 8 wk in de Jongste et al[c])											
163 (2 studies)	No serious risk of bias[d]	Serious[e]	No serious indirectness	Serious[f]	Undetected[g]	Low[d-g] due to inconsistency, imprecision	39/82 (47.6)	44/81 (54.3)	RR 1.14 (0.85-1.52)	476 per 1,000	67 more per 1,000 (from 71 fewer to 247 more)
Quality of life not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Recurrent VTE not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Ulceration not reported											
…	…	…	…	…	…	…	…	…	…	…	…
Side effects (critical outcome)											
203 (2 studies)	No serious risk of bias[d]	No serious inconsistency[h]	No serious indirectness	Serious[f]	Undetected[g]	Moderate[d,f-h] due to imprecision	5/82 (6.1%)	13/121 (10.7%)	RR 2.04 (0.76-5.51)	61 per 1,000	63 more per 1,000 (from 15 fewer to 275 more)

Bibliography: Frulla 2005[131] de Jongste 1989.[134] See Table S1, S5, and S10 legends for expansion of abbreviations.

[a]Included studies assessed rutosides; we excluded Monreal et al[135] because it compared two venoactive medications.

[b]Patients with PTS and history of DVT in PTS leg.

[c]Investigators assessed other symptoms (pain, heaviness, swelling feeling, restless legs, and cramps) but did not report a composite score. The symptom we chose to report showed the most benefit; the effect estimates for the other symptoms ranged from 0.8 to 1.4, and none was statistically significant.

[d]In both studies, sequence generation and allocation concealment were unclear. Both studies blinded outcome assessors and had complete follow-up. Although de Jongste et al blinded patients, they did not adhere to the ITT principle and did not use a validated scale to measure symptomatic relief. Although Frulla (2005) adhered to the ITT principle, it did not blind patients.

[e]$I^2 = 77\%$.

[f]Small number of patients. CI including both values suggesting harms and values suggesting benefits.

[g]Publication bias not detected but not ruled out given that we identified only two small studies, and it was unclear whether they were funded by industry.

[h]$I^2 = 7\%$.

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Table S38—*[Section 5.4] Evidence Profile: Fondaparinux vs IV UFH for Initial Anticoagulation of Acute PE*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With UFH	With Fondaparinux	Relative Effect (95% CI)	Risk With UFH	Risk Difference With Fondaparinux (95% CI)
Mortality (important outcome)											
2,213 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	48/1,110 (4.3)	57/1,103 (5.2)	RR 1.20 (0.82-1.74)	43 per 1,000	9 more per 1,000 (from 8 fewer to 32 more)
Recurrent VTE (critical outcome)											
2,213 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	56/1,110 (5.0)[f]	42/1,103 (3.8)[f]	RR 0.75 (0.51-1.12)	50 per 1,000[f]	13 fewer per 1,000 (from 25 fewer to 6 more)
Major bleeding (critical outcome)											
2,213 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e]	Undetected	Moderate[d,e] due to imprecision	26/1,110 (2.3)[g]	22/1,103 (2.0)[g]	RR 0.85 (0.49-1.49)	23 per 1,000[g]	4 fewer per 1,000 (from 12 fewer to 11 more)

Bibliography: Büller et al.[136] See Table S1, S2, S4, and S7 legends for expansion of abbreviations.

[a]Fondaparinux (5.0, 7.5, or 10.0 mg in patients weighing < 50, 50 to 100, or > 100 kg, respectively) SC once daily given for at least 5 days and until the use of VKAs resulted in an INR > 2.0.

[b]UFH continuous IV infusion (ratio of the aPTT to a control value, 1.5-2.5) given for at least 5 days and until the use of VKAs resulted in an INR > 2.0.

[c]All patients had acute symptomatic hemodynamically stable PE.

[d]Allocation was concealed. Patients, providers, and data collectors not blinded. Outcome adjudicators were blinded; 0.6% of randomized patients were lost to follow-up. Not stopped early for benefit.

[e]CI includes values suggesting no effect and values suggesting either benefit or harm; relatively low number of events.

[f]Sixteen fatal VTE in fondaparinux group and 15 fatal VTE in UFH group.

[g]Fourteen patients in the fondaparinux group and 12 in the LMWH group had a major bleeding during the initial period (6-7 d). Of these, one in the fondaparinux group and one in the UFH group were fatal.

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Table S39—*[Section 5.5] Evidence Profile: Early Discharge vs Standard Discharge in the Treatment of Acute PE*[a,b]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Standard Discharge	With Early Discharge	Relative Effect (95% CI)	Risk With Standard Discharge	Risk Difference With Early Discharge (95% CI)
Mortality (critical outcome)											
471 (2 studies), 3 mo	Serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[c,d] due to imprecision	6/228 (2.6)	4/243 (1.6)	RR 0.58 (0.17-1.97)	26 per 1,000	11 fewer per 1,000 (from 22 fewer to 26 more)
Nonfatal recurrent PE (critical outcome)											
471 (2 studies), 3 mo	Serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[c,d] due to imprecision	2/228 (0.9)	3/243 (1.2)	RR 1.23 (0.25-6.03)	9 per 1,000	2 more per 1,000 (from 7 fewer to 44 more)
Major bleeding (critical outcome)											
471 (2 studies), 3 mo	Serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Moderate[c,d] due to imprecision	1/228 (0.4)	4/243 (1.6)	RR 2.74 (0.45-16.71)	4 per 1,000	8 more per 1,000 (from 2 fewer to 69 more)
Quality of life not reported											
…	…	…	…	…	…	…		…	…	…	…

Bibliography: Otero et al,[137] Aujesky et al.[138] See Table S1, S2, and S5 legends for expansion of abbreviations.

[a]Mean length of hospital stay: 3.4 (SD 1.1) vs 9.3 (SD 5.7) in Otero et al and 0.5 (SD 1.0) vs 3.9 (SD 3.1) in Aujesky et al.

[b]The two RCTs included only patients with low risk: risk classes I or II on the Pulmonary Embolism Severity Index in Aujesky et al[139]; low risk on clinical prediction rule by Uresandi et al[140] in Otero et al.

[c]Otero et al: allocation concealed, no patients lost to follow-up, ITT analysis, no blinding of outcome assessors reported, study stopped early because the rate of short-term mortality was unexpectedly high in the early discharge group (2 [2.8%] vs 0 [0%]). Aujesky et al: unclear whether allocation was concealed, three (1%) patients had missing outcome data, ITT analysis, outcome adjudicators blinded, no early stoppage.

[d]CI includes both values suggesting no effect and values suggesting appreciable harm or appreciable benefit.

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Table S40—*[Section 5.6.1] Evidence Profile: Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE*[a-d]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Systemically Administered Thrombolytic Therapy	With Systemically Administered Thrombolytic Therapy	Relative Effect (95% CI)	Risk With No Systemically Administered Thrombolytic Therapy	Risk Difference With Systemically Administered Thrombolytic Therapy (95% CI)
Mortality (critical outcome)											
847 (12 studies), 30 d	Serious[e]	No serious inconsistency[f]	No serious indirectness	Serious[g]	Undetected[h]	Low[e-h] due to risk of bias and imprecision	26/423 (6.1)	15/424 (3.5)	RR 0.7 (0.37-1.31)	Low[i,j]	
										11 per 1,000	3 fewer per 1,000 (from 7 fewer to 3 more)
										High[i,j]	
										89 per 1,000	27 fewer per 1,000 (from 56 fewer to 28 more)
Recurrent PE (important outcome)											
801 (9 studies), 30 d	Serious[e]	No serious inconsistency[f]	No serious indirectness	Serious[g]	Undetected[h]	Low[e-h] due to risk of bias and imprecision	30/404 (7.4)	18/397 (4.5)	RR 0.7 (0.4-1.21)	57 per 1,000	17 fewer per 1,000 (from 34 fewer to 12 more)
Major bleeding (critical outcome)											
847 (12 studies), 10 d	Serious[e]	No serious inconsistency[f]	No serious indirectness	Serious[k]	Undetected[h]	Moderate[e,f,h,k] due to risk of bias and imprecision	24/423 (5.7)	38/424 (9)	RR 1.63 (1-2.68)[l]	Low[m]	
										1 per 1,000	1 more per 1,000 (from 0 more to 2 more)

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Table S40—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Systemically Administered Thrombolytic Therapy	With Systemically Administered Thrombolytic Therapy	Relative Effect (95% CI)	Risk With No Systemically Administered Thrombolytic Therapy	Risk Difference With Systemically Administered Thrombolytic Therapy (95% CI)
										High[m]	
										62 per 1,000	39 more per 1,000 (from 0 more to 104 more)

Bibliography: Nine earlier studies[141-149] extracted from three systematic reviews (Dong et al,[150] Wan et al,[151] Agnelli et al[152]) and two recently published studies (Becattini C et al,[153] Fassulo et al[154]). See Table S1 and S2 legends for expansion of abbreviations.

[a]Included studies used different thrombolytic agents with varying doses and durations of administration; no statistical heterogeneity was noted.

[b]Thrombolysis was in addition to anticoagulation (most of the studies used heparin followed by warfarin; three studies used warfarin only).

[c]One study included exclusively patients with hemodynamic compromise (shock); six excluded them, whereas the rest either included a number of such patients or did not specify related eligibility. criteria. Of studies not restricted to patients with hemodynamic compromise (n = 11), only three were clearly restricted to patients with right ventricular dysfunction; the rest either did not specify related eligibility criteria or included both patients with and without right ventricular dysfunction. As a result, it was not possible to perform reliable categorization of studies to conduct subgroup analyses based on the presence or absence of right ventricular dysfunction or hemodynamic compromise.

[d]Studies included patients at low risk of bleeding.

[e]Report of methodologic quality was poor in most studies. Of the 12 eligible studies, allocation was concealed in five, three were single blinded (outcome assessor), six were double blinded, and three were not blinded. Most studies did not report on missing outcome data. None of the studies was stopped early for benefit. For the increase in bleeding with thrombolytic therapy, quality of evidence is increased from low to moderate because there is high quality evidence of this association in patients with myocardial infarction and the indirectness of this evidence to patients with PE is minor.

[f]$I^2 = 0\%$.

[g]CI includes values suggesting both benefit and no effect or harm; small number of events.

[h]Inverted funnel plots suggested possible publication bias in favor of thrombolytics.

[i]Recurrent PE stratification based on the simplified Pulmonary Embolism Severity Index validated in the RIETE (Registro Informatizado de la Enfermedad Tromboembólica) cohort.[155]

[j]Some studies suggest that the baseline risk of mortality in patients with hemodynamic instability is high as 30% (Wood et al).[156] In that case, the absolute number of death associated with thrombolytics would be 90 fewer per 1,000 (from 189 fewer to 93 more).

[k]CI includes values suggesting both harm and no effect; small number of events.

[l]Indirect evidence from studies of thrombolysis for myocardial infarction and acute stroke provide more-precise estimates of increase major bleeding with thrombolytics use.

[m]Major bleeding risk stratification derived from the RIETE cohort.[157] The median risk of bleeding over the first 10 d reported in the eligible trials was 3.1%. In that case, the absolute number of major bleeds with thrombolysis would be 20 per 1,000 (from 0 more to 52 more).

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Table S41—*[Section 5.6.1] Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE: Clinical Description and Results*

Author/Year	Interventions	No. Patients Analyzed	Length of Follow-up	Recurrent DVT and PE (%) RR (95% CI)	Major Bleeding (%) RR (95% CI)	Total Mortality (%) RR (95% CI)	Comments
			SK + heparin vs heparin				
Tibbutt et al[148]/1974	SK 600,000 units intrapulmonary followed by 100,000 units for 72 h	SK: 11/13 (84.6%)	72 h	SK: 0/11	SL: 1/11 (9.1%)	SK: 0/11	All hydrocortisone 100 mg and at 60 h of treatment warfarin initial dose 25 mg for 6 mo.
	Heparin 5,000 units intrapulmonary followed by 2,500 units for 72 h	Heparin: 12/17 (70.6%)		Heparin: 0/12	Heparin: 1/12 (8.3%) RR 0.92 (0.06-12.95)	Heparin: 0/12	Seven patients who failed to complete the treatment regimen were excluded from the analysis.
							Patients reporting major bleeding required a blood transfusion.
							Some 6-mo follow-up data available
Ly et al[146]/1978	SK 250,000 units followed by 100,000 units/h for 72 h	SK: 14/14	10 d	SK: 1/14 (7.1%)	SK: 4/14 (28.6%)	SK: 1/14 (7.1%)	Primary outcome was angiographic reperfusion.
	Heparin 15,000 units followed by 1,250 units/h for 7 d	Heparin: 11/11		Heparin: 2/11 (18.2%) RR 2.55 (0.26-24.56)	Heparin: 2/11 (18.2%) RR 0.64 (0.14-2.86)	Heparin: 2/11 (18.2%) RR 2.55 (0.26-24.56)	Five of the 25 patients received nonrandomized therapy. Uncertain if deaths were in patients who were randomized or not randomized.
Dotter et al[143]/1979	SK 250,000 units followed by 100,000 units/h for 18-72 h	SK: 15/15	In hospital	SK: 0/15	SK: 3/15 (20.0%)	SK: 1/15 (6.7%)	All: warfarin/VKA. Primary outcome was angiographic reperfusion (not clearly stated).
	Heparin 1,500 units per kg for 2-7 d	Heparin: 16/16		Heparin: 1/16 (6.3%) RR 2.82 (0.12-64.39)	Heparin: 4/16 (25.0%) RR 1.25 (0.33-4.68)	Heparin: 2/16 (12.5%) RR 1.88 (0.19-18.60)	
Jerjes-Sanchez et al[145]/1995	SK 1,500,000 units over 1 h followed by a bolus of heparin 10,000 units + constant infusion of 1,000 units/h	SK: 4/4	In hospital	SK: 0/4 (0%)	SK: 0/4 (0%)	SK: 0/4 (0%)	Primary outcome not stated. Trial stopped early for benefit. All patients had cardiogenic shock at randomization. Heparin-treated patients appear to have failed heparin therapy before randomization, whereas the SK patients had not.
	Heparin 10,000 units followed by 1,000 units/h	Heparin: 4/4		Heparin: 4/4 (100%) RR 9.00 (0.64-126.85)	Heparin: 0/4 (0%)	Heparin: 4/4 (100%) RR 9.00 (0.64-126.85)	

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Table S41—*Continued*

Author/Year	Interventions	No. Patients Analyzed	Length of Follow-up	Recurrent DVT and PE (%) RR (95% CI)	Major Bleeding (%) RR (95% CI)	Total Mortality (%) RR (95% CI)	Comments
				Urokinase vs heparin			
UPET Study Group et al[141]/1970	Urokinase: infusion of 2,000 CTA units/lb followed by 2,000 CTA units/lb per h	Urokinase 82/82	2 wk	Urokinase: 12/82 (14.6%)	Urokinase: 37/82 (45.1%)	Urokinase: 6/82 (7.3%)	All: heparin for a minimum of 5 d. The major bleeding reported includes moderate + severe bleeding.
	Heparin: infusion of 75 units/lb followed by 10 units/lb per h	Heparin: 78/78		Heparin: 15/78 (19.2%) RR 1.31 (0.66-2.63)	Heparin: 21/78 (26.9%) RR 0.60 (0.39-0.92)	Heparin: 7/78 (8.9%) RR 1.23 (0.43-3.49)	Angiographic follow-up data available up to 12 mo.
Marini et al[147]/1988	High dose: urokinase 3,300,000 units over 12 h	High-dose urokinase: 10/10	7 d	High-dose urokinase: 0/10	High-dose urokinase: 0/10	High-dose urokinase: 0/10	Primary outcome was lung scan perfusion.
	Low dose: urokinase 800,000 units over 12 h daily for 3 d	Low-dose urokinase: 10/10		Low-dose urokinase: 0/10	Low-dose urokinase: 0/10	Low-dose urokinase: 0/10	Thrombolysis arms did not receive heparin.
	Heparin 30,000 units/d for 7 d followed by OAC	Heparin: 10/10		Heparin: 0/10	Heparin: 0/10	Heparin: 0/10	All patients: OACs continued for 1 y.
				rt-PA (alteplase) + heparin vs heparin			
Dalla-Volta et al[142]/1992	rt-PA 10 mg followed by 90 mg over 2 h	rt-PA alteplase: 20/20	30 d	rt-PA alteplase: 1/20 (5.0%)	rt-PA alteplase: 3/20 (15.0%)	rt-PA alteplase: 2/20 (10.0%)	Primary outcome was angiographic reperfusion.
	Heparin 10,000 units followed by 1,750 units/h for 7-10 d	Heparin: 16/16		Heparin: 0/16 RR 2.43 (0.11-55.89)	Heparin: 2/16 (12.5%) RR 1.20 (0.23-6.34)	Heparin: 0/16 RR 4.05 (0.21-78.76)	
Goldhaber et al[158]/1993	rt-PA alteplase 100 mg over 2 h followed by heparin 1,000 units/h	rt-PA: 46/46	In hospital 14-21 d	rt-PA: 0/46	rt-PA: 3/46 (6.5%)	rt-PA: 0/46	Primary outcome was echocardiographic right ventricular function.
	Heparin 5,000 units followed by 1,000 units/h	Heparin: 55/55		Heparin: 5/55 (9.1%) RR 0.11 (0.01-1.91)	Heparin: 1/55 (1.8%) RR 3.59 (0.39-33.33)	Heparin: 2/55 (3.6%) RR 0.24 (0.01-4.84)	
Konstantinides et al[159]/2002	Alteplase 100 mg followed by alteplase 90 mg over 2 h + heparin 1,000 units/h	Alteplase: 118/118	30 d	Alteplase: 4/118 (3.4%)	Alteplase: 1/118 (0.8%)	Alteplase: 4/118 (3.4%)	Primary outcome was death or need for escalation of therapy (later decision could be made after unblinding).
	Heparin 5,000 units followed by 1,000 units/h + placebo	Heparin + placebo: 138/138		Heparin + placebo: 4/138 (2.9%) RR 1.17 (0.30-4.57)	Heparin + placebo: 5/138 (3.6%) RR 0.23 (0.03-1.97)	Heparin + placebo: 3/138 (2.2%) RR 1.56 (0.36-6.83)	

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Table S41—*Continued*

Author/Year	Interventions	No. Patients Analyzed	Length of Follow-up	Recurrent DVT and PE (%) RR (95% CI)	Major Bleeding (%) RR (95% CI)	Total Mortality (%) RR (95% CI)	Comments
Levine et al[160]/1990	rt-PA 0.6mg/kg over 2 min	rt-PA: 33/33	10 d	rt-PA: 0/33	rt-PA: 0/33	rt-PA: 1/33 (3.0%)	Primary outcome was lung scan reperfusion
	Placebo plus heparin 5,000 units followed by 30,000/d	Placebo: 25/25		Placebo: 0/25	Placebo: 0/25	Placebo: 0/25 RR 2.29 (0.10-54.06)	
PIOPED Investigators[144]/1990	rt-PA 40-80 mg at 1 mg/min	rt-PA: 9/9	7 d	rt-PA: 0/9	rt-PA: 1/9 (11.1%)	rt-PA: 0/9	Primary outcome not stated (serial angiographic and lung scans were assessed).
	Placebo + heparin (doses determined by physician)	Placebo: 4/4		Placebo: 0/4	Placebo: 0/4 RR 1.50 (0.07-30.59)	Placebo: 0/4	Heparin doses determined by attending physician in both groups One death occurred 19 d after treatment
Fasullo et al[154]/2011	Alteplase 100 mg over 2 h	Alteplase: 37/37	10 d	Alteplase: 0/37	Alteplase: 2/37 (5.4%)	Alteplase: 0/37	All had right ventricular dysfunction. Primary outcome was echocardiographic changes.
	Placebo + heparin 5,000 units followed by 1,000 units/h	Placebo: 35/35		Placebo: 3/35 (8.5%)	Placebo: 1/35 (2.9%)	Placebo: 5/35 (14.2%)	Three recurrent PE were fatal. One additional fatal and nonfatal PE in heparin arm by 180 d. No fatal or intracranial bleeds.
			Tenectaplase + heparin vs heparin				
Becattini et al[153]/2010	Tenectaplase: ~2 mg/kg bolus	Tenectaplase: 28/28	30 d	Tenectaplase: 2/28	Tenectaplase: 2/28	Tenectaplase: 0/28	All had right ventricular dysfunction. Primary outcome was echocardiographic changes.
	Placebo + heparin (80 International Units/kg and 18 International Units/kg per h)	Placebo: 32/32		Placebo: 1/32	Placebo: 1/32	Placebo: 1/32	No fatal PE or major bleeding; one intracranial bleed (tenectaplase).

CTA = Committee on Thrombolytic Agents; OAC = oral anticoagulant; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; UPET = Urokinase Pulmonary Embolism Trial. See Table S1, S2, and S11 legends for expansion of other abbreviations.

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Table S42—*[Section 5.6.1] Systemic Thrombolytic Therapy vs Anticoagulation Alone in Patients With Acute PE: Methodologic Quality*

Author/Year	Intervention	Study Design	Randomize Concealed	Blinding	Lost to Follow-up	Analysis	Comments
			SK + heparin vs heparin				
Tibbutt et al[148]/1974	SK 600,000 units intrapulmonary followed by 100,000 units for 72 h	RCT	PY	Patients: PY Caregivers: PN Data Collectors: PN Adjudicators: PN Data Analysts: PN	SK: 0/11 (0%)	Per protocol	All hydrocortisone 100 mg and at 60 h of treatment, warfarin initial dose 25 mg for 6 mo.
	Heparin 5,000 units intrapulmonary followed by 2,500 units for 72 h				Heparin: 0/12 (0%)		Seven patients who failed to complete the treatment regimen were excluded from the analysis.
Lyet al[146]/1978	SK 250,000 units followed by 100,000 units/h for 72 h	RCT	CY	Patients: PY Caregivers: PN Data Collectors: PN Adjudicators: PN Data Analysts: PN	SK: 0/14 (0%)	As treated	Included 5 nonrandomized patients, and uncertain if deaths occurred in those who were randomized or not randomized.
	Heparin 15,000 U followed by 1250 U/h for 7days				Heparin: 0/11 (0%)		
Dotter et al[143]/1979	SK 250,000 units followed by 100,000 units/h for 18-72 h	RCT	PY	Patients: PY Caregivers: PN Data Collectors: PN Adjudicators: PN Data Analysts: PN	SK plus heparin: 0/15 (0%)	ITT	
	Heparin 1,500 units per kg for 2-7 d				Heparin: 0/16 (0%)		
Jerjes-Sanchez et al[145]/1995	SK 1,500,000 units over 1 h followed by a bolus of heparin 10,000 units + constant infusion of 1,000 units/h	RCT	CY	Patients: PY Caregivers: PN Data Collectors: PN Adjudicators: PN Data Analysts: PN	SK + heparin: 0/4 (0%)	ITT	
	Heparin 10,000 units followed by 1,000 units/h				Heparin: 0/4 (0%)		
			Urokinase vs heparin				
UPET Study Group[141,149]/1970	Urokinase: infusion of 2,000 CTA units/lb followed by 2,000 CTA units/lb per h Heparin: infusion of 75 units/lb followed by 10 units/lb per h	RCT	CY	Patients: CY Caregivers: CN Data Collectors: CY Adjudicators: CY Data Analysts: CY	Urokinase: 0/82 (0%) Heparin: 0/78 (0%)	As treated	

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Table S42—*Continued*

Author/Year	Intervention	Study Design	Randomize Concealed	Blinding	Lost to Follow-up	Analysis	Comments
Marini et al[147]/1988	High dose: urokinase 3,300,000 units over 12 h	RCT	PY	Patients: PN Caregivers: CN Data Collectors: PN Adjudicators: PN Data Analysts: PN	High-dose urokinase: 0/10 (0%)	ITT	
	Low dose: urokinase 800,000 units over 12 h daily for 3 d				Low-dose urokinase: 0/10 (0%)		
	Heparin 30,000 units/d for 7 d followed by OAC				Heparin: 0/10 (0%)		
			rt-PA (alteplase) + heparin vs heparin				
Dalla-Volta et al[142]/1992	rt-PA (alteplase) 10 mg followed by 90 mg over 2 h	RCT	PY	Patients: PN Caregivers: CN Data Collectors: PN Adjudicators: PN Data Analysts: PN	rt-PA: 0/20 (0%)	ITT	
	Heparin 10,000 units followed by 1,750 units/h for 7-10 d				Heparin: 0/16 (0%)		
Goldhaber et al[158]/1993	rt-PA 100 mg over 2 h followed by heparin 1,000 units/h	RCT	CY	Patients: PN Caregivers: CN Data Collectors: PN Adjudicators: PN Data Analysts: PN	rt-PA: 0/46 (0%)	ITT	
	Heparin 5,000 units followed by 1,000 units/h				Heparin: 0/55 (0%)		
Konstantinides et al[159]/2002	rt-PA (alteplase) 100 mg followed by alteplase 90 mg over 2 h + heparin 1,000 units/h	RCT	CY	Patients: PY Caregivers: CN Data Collectors: PY Adjudicators: PN Data Analysts: PY	rt-PA: 0/118 (0%)	ITT	All: UFH 5,000 units.
	Heparin 5,000 units followed by 1,000 units/h				UFH: 0/138 (0%)		
Levine et al[160]/1990	rt-PA 0.6 mg/kg over 2 min	RCT	PY	Patients: CY Caregivers: CY Data Collectors: CY Adjudicators: CY Data Analysts: CY	rt-PA: 0/33(0%)	ITT	All: UFH initial bolus of 5,000 units followed by continuous infusion at starting dose of 30,000 for the first 24 h.
	Placebo + heparin 5,000 units followed by 30,000/d				Heparin: 0/25(0%)		

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Table S42—*Continued*

Author/Year	Intervention	Study Design	Randomize Concealed	Blinding	Lost to Follow-up	Analysis	Comments
PIOPED Investigators[144]/1990	rt-PA 40-80mg at 1 mg/min	RCT	PY	Patients: CY Caregivers: CY Data Collectors: PY Adjudicators: PY Data Analysts: PY	rt-PA: 0/9(0%)	ITT	All: heparin doses determined by attending physician.
	Placebo plus heparin (doses determined by physician)				Heparin: 0/4(0%)		
Fasullo et al[154]/2011	Alteplase 100 mg over 2 h	RCT	CY	Patients: CY Caregivers: CY Data Collectors: PY Adjudicators: CY Data Analysts: PY	rt-PA: 0/37	ITT	Primary outcome was echocardiographic changes.
	Placebo + heparin 5,000 units followed by 1,000 units/h				Heparin: 0/35		
			rt-PA (alteplase) + heparin vs heparin				
Becattini et al[153]/2010	Tenectaplase: ~2 mg/kg bolus	RCT	CY	Patients: CY Caregivers: CY Data Collectors: CY Adjudicators: CY Data Analysts: PY	Tenectaplase: 0/28(0%)	ITT	Primary outcome was echocardiographic changes.
	Placebo + heparin (80 International Units/kg and 18 International Units/kg per h)				Heparin: 0/30(0%)		

See Table S1, S2, S5, S11, and S41 legends for expansion of other abbreviations.

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Table S43—*[Section 8.1] Evidence Profile: Fondaparinux vs Placebo for Acute SVT*[a-c]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With No Fondaparinux	With Fondaparinux	Relative Effect (95% CI)	Risk With No Fondaparinux	Risk Difference With Fondaparinux (95% CI)
Mortality (important outcome)											
3,002 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e,f]	Undetected	Moderate[d-g] due to imprecision	1/1,500 (0.1)	2/1,502 (0.1)	RR 1.99 (0.18-21.87)	4 per 1,000[h]	4 more per 1,000 (from 3 fewer to 83 more)
VTE (critical outcome)											
3,002 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High[d]	22/1,500 (1.5)	4/1,502 (0.3)	RR 0.18 (0.06-0.53)	33 per 1,000[h]	27 fewer per 1,000 (from 16 fewer to 31 fewer)
SVT recurrence (important outcome)											
3,002 (1 study), 3 mo	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[f,g]	Undetected	High[d] due to imprecision	26/1,500 (1.7)	8/1,502 (0.5)	RR 0.31 (0.14-0.68)	19 per 1,000[h]	13 fewer per 1,000 (from 6 fewer to 16 fewer)
Major bleeding (critical outcome)											
2,987 (1 study), 47 d	No serious risk of bias[d]	No serious inconsistency	No serious indirectness	Serious[e,i]	Undetected	Moderate[d,e,i] due to imprecision	1/1,488 (0.1)	1/1,499 (0.1)	RR 0.99 (0.06-15.86)[e]	1 per 1,000	0 fewer per 1,000 (from 1 fewer to 10 more)
Quality of life not measured											
…	…	…	…	…	…	…		…	…	…	…

Bibliography: CALISTO study by Decousus et al.[161] CALISTO = Comparison of ARIXTRA™ in lower LImb Superficial Thrombophlebitis with placebo; SVT = superficial vein thrombosis. See Table S1 and S5 legends for expansion of other abbreviations.

[a]Fondaparinux 2.5 mg for 45 d.

[b]Patients in the two treatment groups benefited from close clinical monitoring with adequate diagnostic procedures in the event of new and persistent symptoms.

[c]Patients with infusion-related SVT were excluded if from CALISTO.

[d]Allocation concealed. Outcome adjudicators, steering committee, patients, providers, and data collectors blinded. Follow-up rate was 98%. ITT analysis for efficacy outcomes. Not stopped early for benefit.

[e]CI includes values suggesting large benefit and values suggesting large harm.

[f]We rated down by only one level because the low event rate and large sample size.

[g]Small number of events.

[h]Baseline risk derived from a large prospective cohort study.[162]

[i]The upper limit of the CI for absolute effect (10 more bleeds) is not low enough to suggest a clear balance of benefits vs harms.

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Table S44—*[Section 8.1] Superficial Vein Thrombosis Treatment: Clinical Description and Results (Randomized Trials Comparing Treatments)*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
STENOX Study[163] Group/2003	Parallel RCT, multicenter	436 patients with ultrasound-confirmed acute symptomatic SVT (≥ 5 cm length) of the lower extremity	Enoxaparin 40 mg SC daily Enoxaparin 1.5 mg/kg SC daily Tenoxicam, 20 mg po daily Placebo once daily All given for 8-12 d All patients prescribed elastic bandages or compression stockings for at least 15 d	Day 12 (end of treatment): Screening ultrasound or symptomatic recurrence: VTE SVT recurrence/extension to saphenofemoral junction 3-mo VTE SVT recurrence/ extension Major bleeding Death	3 mo	VTE day 12: Placebo: 4/112 (3.6%) (PE 0) Enoxaparin 40 mg: 1/110 (0.9%) (PE 0); RR 0.25 (95% CI, 0.03-2.24) Enoxaparin 1.5 mg/kg: 1/106 (0.9%) (PE 0); RR 0.26 (95% CI, 0.03-2.33) Tenoxicam: 2/99 (2.0%) (PE 1); RR 0.57 (95% CI, 0.11-3.02) *P* = ns for all comparisons of active treatment vs placebo SVT recurrence/extension day 12: Placebo: 33/112 (29.5%) Enoxaparin 40 mg: 9/110 (8.3%); RR 0.28 (95% CI, 0.14-0.55) Enoxaparin 1.5 mg/kg: 6/106 (5.7%); RR 0.19 (95% CI, 0.08-0.44) Tenoxicam: 13/99 (13.1%); RR 0.45 (95% CI, 0.25-0.80) VTE 3 mo: Placebo: 5/112 (4.5%) (PE 0) Enoxaparin 40 mg: 6/110 (5.7%); (PE 2); RR 1.22 (95% CI, 0.38-3.89) Enoxaparin 1.5mg/kg: 4/106 (3.9%) (PE 0); RR 0.85 (95% CI, 0.23-3.06) Tenoxicam: 4/99 (4.3%) (PE 1); RR 0.91 (95% CI, 0.25-3.28) *P* = ns for all comparisons of active treatment vs placebo SVT recurrence/extension 3 mo: Placebo: 37/112 (33.0%) Enoxaparin 40 mg: 16/110 (14.5%); RR 0.44 (95% CI, 0.26-0.74)

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Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
						Enoxaparin 1.5 mg/kg: 16/106 (15.1%); RR 0.46 (95% CI, 0.27-0.77) Tenoxicam: 15/99 (15.2%); RR 0.46 (95% CI, 0.27-0.78) Major bleeding: 0 Death: 0
Titon et al[164] /1994	Parallel RCT, multicenter	117 patients with ultrasound-confirmed SVT of the lower extremities	Nadroparin fixed dose, 6,150 anti-Xa International Units daily	Echocardiographic extension of thrombus at day 7 and at 8 wk	8 wk	Day 7 extension of thrombus: Fixed-dose nadroparin: 1/38 (2.6%)
			Nadroparin 31.5 anti-Xa International Units/kg SC daily	Changes in symptoms and clinical signs (warmth, flushing, edema, pain on palpation)		Weight-based nadroparin: 2/40 (5%); RR 1.90 (95% CI, 0.18-20.1)
			Naproxen 500 mg po daily	DVT		Naproxen: 1/39 (2.6%); RR 0.97 (95% CI, 0.06-15.02)
			Treatments given for 6 d	PE		P = ns
			All patients wore compression stockings for 7 d	Major bleeding		8-wk extension of thrombus or new SVT: Fixed-dose nadroparin: 2/36 (5.6%) Weight-based nadroparin: 0/40 (0%); RR 0.18 (95% CI, 0.01-3.64) Naproxen: 0/39 (0%); RR (95% CI) 0.19 (0.01-3.73) No DVT, PE, or major bleeding in any group Intensity of symptoms/signs: Overall improvement in score from day 0 to day 7: Fixed-dose nadroparin: 79.1% improved Weight-based nadroparin: 63.0% improved Naproxen: 46.4% improved P≤ .01 in favor of nadroparin vs naproxen; this difference was maintained at 8 wk
Prandoni for Vesalio Investigators Group[165]/2005	Parallel RCT, multicenter	164 patients with ultrasound-confirmed acute SVT of the greater saphenous vein	High-dose weight-adjusted nadroparin (190 anti-Xa International Units/kg for 10 d followed by 95 anti-Xa International Units/kg for 20 d)	Composite outcome of asymptomatic or symptomatic SVT extension, asymptomatic or symptomatic DVT, symptomatic PE at 3 mo	3 mo	3 mo follow-up:

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Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
				Improvement in clinical symptoms and signs at 1 mo		
			Low-dose nadroparin (2,850 anti-Xa International Units for 30 d)	Major bleeding		SVT High dose: 2/83 (2.4%) (1 occurred while on treatment) Low dose: 5/81 (6.2%) (all occurred while on treatment) RR 2.56 (95% CI, 0.51-12.83)
				Death		
			No placebo group NSAIDS and aspirin use discouraged			VTE High dose: 4/83 (4.8%) (3 symptomatic events; 1 [PE] occurred while on treatment) Low dose: 2/81 (2.5%) (both symptomatic DVT) RR 0.51 (95% CI, 0.10-2.72) Rate of improvement in clinical symptoms and signs similar both groups Major bleeding: 0 Death: 0
Marchiori et al[166]/2002	Parallel RCT, single center	60 patients with ultrasound-confirmed first acute SVT of greater saphenous vein	Low-dose UFH (5,000 International Units bid SC for 4 wk)	VTE	6 mo	VTE during treatment period: Low dose: 4/30 (13.3%) (3 asymptomatic DVT, 1 PE)
				Extension/Recurrence of thrombosis		
			High-dose UFH (12,500 International Units for 1 wk then 10,000 International Units for 3 wk)	Major bleeding		High dose: 0/30 (0%); RR 0.11 (95% CI, 0.01-1.98; P = ns)
				HIT		
				Death		Extension/recurrence SVT during treatment period: Low dose: 7/30 (23.3%) High dose: 3/30 (10%); RR 0.40 (95% CI, 0.11-1.40; P = ns)
			Use of concomitant systemic or local antiinflammatory drugs permitted but use not described			Overall VTE during follow-up period: Low dose: 6/30 (20%) High dose: 1/30 (3.3%); RR 0.17 (95% CI, 0.02-1.30; P = ns) Overall extension/recurrence SVT during follow-up period: Low dose: 11/30 (36.7%) High dose: 8/30 (26.7%); RR 0.73 (95% CI, 0.34, 1.55; P = ns)

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Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
						No major bleeding, HIT, or death in any group
Belcaro et al[167]/1999	Parallel RCT, multicenter	562 patients with ultrasound-confirmed SVT and large varicose veins or venous incompetence	A. Elastic compression stockings alone B. Elastic compression stockings and simple flush ligation C. Elastic compression stockings and complete stripping and perforator ligation D. Elastic compression stockings and low-dose SC heparin E. Elastic compression stockings and LMWH F. Elastic compression stockings and VKA Doses and duration of anticoagulants not specified	Extension of SVT at 3 mo Extension of SVT at 6 mo New DVT at 3 mo	6 mo	Extension of thrombus at 3 mo: A: 32/78 (41%) B: 11/78 (14.1%); RR 0.34 (95% CI, 0.19-0.63) C: 0/70; RR 0.02 (95% CI, 0.00-0.27) D: 4/71 (5.6%); RR 0.14 (95% CI, 0.05-0.37) E: 4/76 (5.2%); RR 0.13 (95% CI, 0.05-0.35) F: 5/71 (7.0%); RR 0.17 (95% CI, 0.07-0.42) $P < .05$ for groups C, D, E, F vs A or B Extension at 6 mo: A: 13/78 (16.7%) B: 6/78 (7.7%); RR 0.46 (95% CI, 0.18-1.15) C: 1/70 (1.4%); RR 0.09 (95% CI, 0.01-0.64) D: 2/71 (2.8%); RR 0.17 (95% CI, 0.04-0.72) E: 1/76 (1.3%); RR 0.08 (95% CI, 0.01-0.59) F: 5/71 (7%); RR 0.42 (95% CI, 0.16-1.13) *P* not stated New DVT at 3 mo: A: 6/78 (7.7%) B: 2/78 (2.5%); RR 0.33 (95% CI, 0.07-1.60) C: 2/70 (2.8%); RR 0.37 (95% CI, 0.08-1.78) D: 0/71 (0%); RR 0.08 (95% CI, 0.0-1.47) E: 0/76 (0%); RR 0.08 (95% CI, 0.0-1.38) F: 0/71 (0%); RR 0.08 (95% CI, 0.0-1.47) P = ns
Lozano et al[168]/2003	Parallel RCT, single center	60 patients with ultrasound-confirmed above-knee internal saphenous SVT	Saphenofemoral disconnection under local anesthesia with short-term use of a compression bandage	Recurrence/extension of SVT VTE Complications of surgery	6 mo	Recurrent SVT Surgical group: 1/30 (3.3%) Enoxaparin group: 3/30 (10%); RR 3.0 (95% CI, 0.33-27.24)

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Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
			Outpatient enoxaparin 1 mg/kg bid for 1 wk then once daily for 3 wk	Major bleeding		VTE Surgical group: 2/30 (6.7%) (both symptomatic PE) Enoxaparin group: 0/30 (0%); RR 0.20 (95% CI, 0.01-4.0)
				Death		
			No placebo/control group	Costs		Wound infections: Surgical group: 2/30 (6.7%)
			All patients were instructed to wear elastic compression stockings and used acetaminophen for pain			Major bleeding: 0
						Death: 0
						Cost of treatment: Surgical group: $1,400/patient; mean, 1.6 d in hospital Enoxaparin group: $300/patient; 0 d in hospital
Sullivan et al[169]/2001	Systematic review of 6 studies (includes Belcaro (14 patients) and 5 small case series)	Patients with objectively confirmed above-knee SVT	Ligation of greater saphenous vein at saphenofemoral junction with or without vein stripping (n = 246)	SVT progression	Surgical group: 4-6 mo	SVT progression: Surgical group: 18/148 (12%) Medical group: 10/71 (14%); RR 1.16 (95% CI, 0.56-2.38)
				DVT	Medical group: 6 d to 14 mo	DVT: Surgical group: 7/204 (3.4%) Medical group: 2/88 (2.2%) RR 0.66 (95% CI, 0.14-3.13)
				PE		PE: Surgical group: 2/98 (2.0%) Medical group: 0/17 (0%); RR 1.10 (95% CI, 0.06-21.98)
			Anticoagulation (IV heparin followed by VKA for 6 wks-6 mo) (n = 88)	Surgical complications Bleeding complications		Surgical complications: 6/78 (7.7%) (hematoma, seroma, infection) Bleeding complications: 0/17 (0%)

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Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
Górski et al[170]/2005	Parallel RCT, multicenter	46 patients with ultrasound-confirmed SVT	Topical liposomal heparin spray gel (4 sprays of 458 International Units tid) Enoxaparin 40 mg SC once daily Treatment given for 7-14 d	Pain by visual analog scale (0-10) Area of erythema Subjective efficacy assessment by investigator and patient Duplex assessment for thrombus regression day 21 DVT Adverse events Death	21 d	Data extrapolated from graphs and figures in article by reviewer Pain by visual analog scale, day 21: Topical heparin: 0 LMWH: 0 Improvement noted at each time point; no pain at 21 d, no significant difference between groups Area of erythema: Improvement noted at each time point; no erythema at 21 d, no significant difference between groups Subjective efficacy assessment: Majority of patients (> 75%) reported good or very good treatment efficacy, no significant difference between groups Thrombus regression: Topical heparin: 10/21 (47.6%) LMWH: 9/23 (39.1%); RR 0.82 (95% CI, 0.42-1.62) DVT: Topical heparin: 3/21 (14.3%) LMWH: 1/23 (4.3%); RR 0.30 (95% CI, 0.03-2.70) Adverse events: Allergic reaction in 1 patient in enoxaparin group Death: 0
Andreozzi et al[171]/1996	Parallel RCT, multicenter	56 patients with SVT of the lower limbs	A: Dermatan sulfate 100 mg SC once daily B: Dermatan sulfate 100 mg SC bid C: Dermatan sulfate 200 mg intramuscular once daily	Pain Increase in functional ability Local edema	30 d	Data extrapolated from graphs and figures in article by reviewer Resolution of pain, day 30: Group A: 47% Group B: 83% Group C: 79% *P* not stated

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Table S44—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
			Treatment given for 30 d			Increase in ability to perform normal daily activities, day 30: Group A: 44% Group B: 67% Group C: 84% $P < .05$ groups B and C vs group A Local edema, day 30: Progressive improvement in all 3 groups; no significant differences between groups

The CALISTO study that compared fondaparinux with no fondaparinux is described in Table 28 and Table S42. HIT = heparin-induced thrombocytopenia; NSAID = nonsteroidal antiinflammatory drug; STENOX = Superficial Thrombophlebitis Treated by Enoxaparin. See Table S1, S2, S5, S21, and S43 legends for expansion of other abbreviations.

[a]Study design: RCT, cohort.

[b]Drugs: VKA, UFH, LMWH, NSAIDs, aspirin, topical treatments, surgery vs placebo, no treatment, each other or different durations or regimens of the same agent.

[c]Outcomes: extension of thrombus, symptomatic relief, DVT and PE, major bleeding, surgical complications, and death.

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Table S45—*[Section 8.1] SVT Treatment: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up/ ITT
STENOX Study Group[163]/2003	Central randomization	Visually identical drugs and packaging; triple dummy design	Investigators, patients, and assessors blinded	9 lost to follow-up/ ITT
Titon et al[164]/1994	Randomized to one of three treatment groups; method of randomization not specified	Open label	Not blinded	8 lost to follow-up/ not specified
Prandoni for Vesalio group et al[165]/2005	Computer-generated random number sequence assigned to each patient to determine treatment group	Double dummy	Patients and adjudicators of outcome events blind	0 lost to follow-up/ ITT
Marchiori et al[166]/2002	Randomized to treatment group by computer-generated list	Not specified	Assessors blinded	0 lost to follow-up/ not specified
Belcaro et al[167]/1999	Not specified	Not blinded	Not blinded	118 lost to follow-up/not specified
Lozano et al[168]/2003	Method not specified	Not blinded	Not blinded	3 lost to follow-up/not specified
Sullivan et al[169]/2001	Review of six studies; includes one RCT (Belcaro [14 patients]) and five small case series	N/A	N/A	N/A
Andreozzi et al[170]/1996	Patients randomly assigned to one of three therapeutic groups (method not specified)	Open label	Not blinded	Not specified/not specified
Górski et al[171]/2005	Performed according to a prespecified randomization list; treatment allocated according to next number on list; no stratification was performed	Open trial	Not blinded	6 lost to follow-up/ITT

See Table S5, S12, S43, and S44 legends for expansion of abbreviations.

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Table S46—*[Section 9.1] Initial Treatment of Acute UEDVT With Anticoagulant Therapy: Clinical Description and Results (Randomized Trials [None Performed] and Prospective Observational Studies of at Least 20 Patients)*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
Savage et al[172]/1999	Prospective cohort, two center	46 outpatients with UEDVT (includes 16 with CVC)	Dalteparin daily for 5-7 d (200 International Units/kg) and VKA with target INR of 2.0-3.0 Duration of VKA not provided	Symptomatic recurrence/extension of DVT PE Major bleeding Death	3 mo	Recurrence/extension DVT: 1/46 (2%) PE: 0/46 Major bleeding: 1/46 (2%) (on VKA) Death: 7/46 (15%) (none from PE or bleeding)
Karabay et al[173]/2003	Prospective cohort, single center	36 inpatients with UEDVT (includes 13 with CVC)	Nadroparin SC bid, 86 anti-Xa International Units/kg for up to 7 d, then VKA (started on day 3; target INR 2-2.5) for mean of 4.7 mo	Symptom relief Lysis of thrombus on ultrasound Recurrent DVT PE Death	1 y	Significant symptom relief, day 7: 32/36 (89%) Lysis, day 10: ≥ 35%: 16/36 (45%) < 35%: 17/36 (47%) None: 3/36 (8%) Recurrent DVT: 0/36 PE: 0/36 Death: 9/36 (25%) (none due to PE or bleeding)
Prandoni et al[120]/2004	Prospective cohort, number of centers not stated	53 patients with first UEDVT (included 6 with CVC)	Therapeutic-dose heparin (81% received UFH, 19% received LMWH) then VKA (median, 3 mo)	Recurrent VTE Death	Median of 48 mo	Results not presented according to initial treatment with UFH vs LMWH Recurrent VTE: 3/53 (5.7%) (2 arm, 1 leg) Cumulative incidence 1, 2, and 5 y: 2.0%, 4.2%, 7.7% Death: 11/53 (20.8%) (due to cancer, PE, congestive heart failure [numbers not provided])

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Table S46—*Continued*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
Kovacs et al[174]/2007	Prospective cohort, multicenter	74 cancer patients with confirmed UEDVT (all had CVC)	Dalteparin daily for 5-7 d (200 International Units/kg) and VKA to achieve target INR of 2.0-3.0	Recurrent VTE PE Major bleeding Death Catheter failure due to DVT or inability to infuse	3 mo	Recurrent VTE: 0/74 PE: 0/74 Major bleeding: 3/74 (4%) Death: 7/74 (6 cancer, 1 major bleed) Catheter failure due to DVT or inability to infuse: 0/74

CVC = central venous catheter; UEDVT = upper-extremity DVT. See Table S2, S7, and S41 legends for expansion of other abbreviations.

[a]Study design: prospective cohort studies.

[b]Drugs: IV UFH or LMWH followed by OACs.

[c]Outcomes: recurrent DVT and PE, major bleeding, total mortality, and early symptom relief.

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Table S47—*[Section 9.1] Initial Treatment of Acute UEDVT With Anticoagulant Therapy: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up/ ITT
Savage et al[172]/1999	N/A	N/A	N/A	1 lost to follow-up/N/A
Karabay et al[173]/2003	N/A	N/A	N/A	0 lost to follow-up/N/A
Prandoni et al[120]/2004	N/A	N/A	N/A	2 lost to follow-up/N/A
Kovacs et al[174]/2006	N/A	N/A	N/A	0 lost to follow-up/N/A

See Table S12 and S46 legends for expansion of abbreviations.

Table S48—*[Section 9.2] Initial Treatment of Acute UEDVT With Thrombolytic Therapy: Clinical Description and Results (Randomized Trials [None Performed] and Prospective Observational Studies of at Least 10 Patients)*

Author/Year	Type of Publication[a]	Participants	Intervention[b]	Outcomes[c]	Follow-up	Results
Horne et al[175]/2000	Prospective cohort, single center	18 patients with axillary or subclavian DVT	Catheter-directed rt-PA (2 mg/cm of thrombus to maximum of 20 mg) then VKA for 3 mo	Immediate patency	6 mo	Immediate patency: 10/18 (56%)
				Establishment of antegrade flow		Antegrade flow: 11/18 (61%)
				Bleeding events		Bleeds (all minor): 5/18 (28%)
Lee et al[176]/2006	Prospective case series, single center	35 patients with primary UEDVT who had complete resolution of acute symptoms with CDT (n = 29) or IV heparin (n = 6)	Oral VKA for mean of 5.2 mo	Recurrent DVT	54 mo	Ipsilateral recurrent DVT: 8/35 (23%)

Early prospective observational studies with < 10 patients and retrospective studies are described in Table 3 of the eighth edition of these guidelines.[46] See Table S2, S10, S11, and S46 legends for expansion of abbreviations.

[a]Study design: retrospective and prospective cohort studies.

[b]Drugs: thrombolytic therapy compared with different types of lytic therapy or with anticoagulants.

[c]Outcomes: recurrent DVT and PE, vein patency, major bleeding, total mortality, and PTS of the arm.

Table S49—*[Section 9.2] Initial Treatment of Acute UEDVT With Thrombolytic Therapy: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up
Horne et al[175]/2000	No	N/A	N/A	Not specified
Lee et al[176]/2006	No	N/A	N/A	0 lost to follow-up

See Table S12 legend for expansion of abbreviation.

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Table S50—*[Section 9.3] Long-term Treatment of Acute UEDVT: Clinical Description and Results*

Author/Year	Type of Publication	Participants	Intervention[a]	Outcomes[b]	Follow-up	Results
Savage et al[172]/1999	Prospective cohort, two center	46 outpatients with confirmed UEDVT (includes 16 with CVC)	Dalteparin 200 International Units/kg daily for 5-7 d and VKA to achieve target INR of 2.0-3.0 for 3 mo Duration of VKA not provided	Symptomatic recurrence/ extension of DVT PE Major bleeding Death	3 mo	Recurrence/extension: 1/46 (2%) PE: 0 Major bleeding: 1/46 (2%) (on VKA) Death: 7/46 (15%) (none from PE or bleeding)
Karabay et al[173]/2003	Prospective cohort, single center	36 inpatients with confirmed UEDVT (includes 13 with CVC)	Nadroparin SC bid, 86 anti-Xa International Units/kg for up to 7 d, then VKA (started on day 3; target INR 2-2.5) for mean of 4.7 mo	Symptom relief Lysis of thrombus on ultrasound Recurrent DVT PE Death PTS	1 y	Significant symptom relief, day 7: 32/36 (89%) Lysis, day 10: ≥ 35%: 16/36 (45%) < 35%: 17/36 (47%) None: 3/36 (8%) Recurrent DVT: 0 PE: 0 Death: 9/36 (25%) (none due to PE or bleeding) PTS: 0
Martinelli et al[177]/2004	Case-control study with prospective follow-up of cases, single center	98 patients with primary UEDVT (none with CVC)	VKA for mean 6 mo (77 patients), heparin SC (14 patients), or antiplatelet agents (7 patients) for ≤ 3 mo	Recurrent VTE after anticoagulants stopped	Median of 5.1 y	Recurrent VTE: 12/98 (12%) overall (all UEDVT) Annual incidence recurrent VTE: 2.4% (95% CI, 1.2%-4.0%) (results not provided by treatment group)
Prandoni et al[178]/2004	Prospective cohort, number of centers not stated	53 patients with confirmed first UEDVT (included 6 with CVC)	Therapeutic-dose heparin (81% received UFH, 19% received LMWH) then VKA (median, 3 mo)	Recurrent VTE	Median of 48 mo	Results not presented according to initial treatment with UFH vs LMWH

(Continued)

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Table S50—*Continued*

Author/Year	Type of Publication	Participants	Intervention[a]	Outcomes[b]	Follow-up	Results
				Death PTS		Recurrent VTE: 3/53 (5.7%) (2 arm, 1 leg) Cumulative incidence 1, 2, and 5 y: 2.0%, 4.2%, 7.7% Death: 11/53 (20.8%) (due to cancer, PE, congestive heart failure [breakdown not provided]) PTS: 13/53 (24.5%); 2 y Cumulative incidence: 27.3%
Kovacs et al[174]/2007	Prospective cohort, multicenter	74 cancer patients with confirmed UEDVT (all had CVC)	Dalteparin 200 International Units/kg daily for 5-7 d and VKA to achieve target INR of 2.0-3.0	Recurrent VTE PE Major bleeding Death Catheter failure due to DVT or inability to infuse	3 mo	Recurrent VTE: 0 PE: 0 Major bleeding: 3 (4%) Death: 7 (6 cancer, 1 major bleed) Catheter failure due to DVT or inability to infuse: 0

Early prospective observational studies with < 20 patients, and retrospective studies, are described in Table 3 of the Eight edition of these guidelines[46] See Table S2, S7, S10, and S46 legends for expansion of abbreviations.

[a]Drugs: VKA, UFH, LMWH vs placebo, control or each other.

[b]Outcomes: recurrent DVT and PE, major bleeding, total mortality, and PTS of the arm.

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Table S51—*[Section 9.3] Long-term Treatment of Acute UEDVT: Methodologic Quality*

Author/Year	Randomization	Allocation Concealment	Blinding	Loss to Follow-up
Savage et al[172]/1999	N/A	N/A	N/A	1 lost to follow-up
Karabay et al[173]/2003	N/A	N/A	N/A	0 lost to follow-up
Martinelli et al[177]/2004	N/A	N/A	N/A	Not specified
Prandoni et al[178]/2004	N/A	N/A	N/A	2 patients lost to follow-up
Kovacs et al[174]/2007	N/A	N/A	N/A	0 lost to follow-up

See Table S12 and S46 legends for expansion of abbreviations.

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