2.2. Data extraction

Table 12 Prospective randomized trials - long-term use of low-molecular-weight heparins

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE recurrence	Toxicity	Death
[LOPEZ-BERET2001] Jan 1996 - Mar 1998	157 patients 35 cancer patients	12 months	Patients >18 years Documented DVT	Arm A: nadroparin adjusted to body weight (0.1 mL/10 kg) Arm B: nadroparin adjusted to body weight (0.1 mL/10 kg) + acenocoumarol (INR 2 to 3) 3 months or 6 months (iliac or femoral DVT or persistent risk factors for DVT or idiopathic DVT)	Doppler US at Months 1, 3, 6, 12 or if symptoms present Arm A: 1/17 Arm B: 3/18	Major bleeding Arm A: 0/17 Arm B: 2/18 Minor bleeding Arm A: 2/17 Arm B: 0/18	Arm A: 7/17 Arm B: 6/18 p=NS
[MEYER2002] CANTHANOX Multicenter study Apr 1995 - Mar 1999	138/146 patients Arm A : 71/75 patients Arm B : 67/71 patients	3 months	Adult cancer patients with DVT or PE Mean age: 65.5 years Metastatic: 52.7% Hemopathy: 10.9%	Arm A (control arm): enoxaparin SC (1.5 mg/kg x1/day) + warfarin *per os* (6-10mg) for 3 months (INR 2 to 3) Arm B: enoxaparin SC (1.5mg/kg x1/day) for 3 months	Arm A: 5/75 (6%) Arm B: 2/71 (3%) p=NS	Major bleeding at 3 months Arm A: 6/75 (16%); 95%CI: [8.6-26.3] Arm B: 5/71 (7%); 95%CI: [2.3-15.7] p=NS Bleeding-related death Arm A: 8%; 95%CI: [3.0-16.6] Arm B: 0%; 95%CI: [0-5.1] p=0.03	At 6 months Arm A: 17/75 (22.7%); 95%CI: [13.8-33.8] Arm B: 8/71 (11.3 %); 95%CI: [5.0-21.0] p=NS
[LEE2003] CLOT Multicenter study May 1999 - Oct 2001	671/676 patients Arm A : 335/338 patients Arm B : 336/338 patients	6 months	Adult cancer patients with DVT or PE Mean age: 62.5 years Metastatic: 67.3% Hemopathy:10.3 %	Arm A (control arm): dalteparin 200 IU/kg SC x1/day for 5-7 days + warfarin or acenocoumarol *per os* Arm B: dalteparin (200 IU/kg SC x1/day for 1 month then 150 IU/kg SC x1/day for 5 months)	Arm A: 53/336 (16.9%) Arm B: 27/336 (8%) HR = 0.48; 95%CI: [0.30-0.77]; p=0.002	All bleeding Arm A: 64/335 (19%) Arm B : 48/338 (14%); p=NS Major bleeding Arm A: 12/335 (4%) Arm B: 17/338 (6%); p=NS	Arm A: 136/336 (41%) Arm B: 130/336 (39%) p=NS
[MONREAL2004] Jan 1996 - Mar 2003	203/203 patients	3 months	Metastatic cancer and either symptomatic DVT in the lower limbs or PE	7-day course of SC dalteparin then fixed dose, 10 000 IU dalteparin once daily for at least 3 months	Total: 21/203 (10.3%) LMWH full dose: 18/203 (8.8%) LMWH reduced dose: 3/203 (1.5%)	Major bleeding 11/203 (5.4%) Bleeding-related death 6/203 (2.9%) Minor bleeding 16/203 (7.9%) Creatinine >upper limit 3/203 (1.4%)	

Table 12 Prospective randomized trials - long-term use of low-molecular-weight heparins (continued)

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE recurrence	Toxicity	Death
[DEITCHER2006] ONCENOX Multicenter study Jan 2001 - Mar 2002	101/102 patients Arm A: 34/34 patients Arm B: 67/68 patients	6 months	Adult cancer patients with DVT or PE Mean age: 63.7 years Metastatic: 58.4%	Arm A (control arm): enoxaparin SC 1 mg/kg/12 h for ≥5 days + warfarin *per os* from Day 2 to Day 180 Arm B: enoxaparin SC for 175 days Arm B1 = 1 mg/kg/day Arm B2 = 1.5 mg/kg/day	Arm A: 2/30 (6.7%) Arm B1: 1/29 (3.4%) Arm B2: 1/30 (3.1%) p=NS	Major bleeding Arm A: 1/34 (2.9%) Arm B1: 2/31 (6.5%) Arm B2: 4/36 (11.1%) p=NS Serious adverse events Arm A: 50.0% Arm B1: 51.6% Arm B2: 63.9% p=NS	Arm A: 11/34 (32.4%) Arm B1: 2/31 (22.6%) Arm B2: 15/36 (41.7%)
[HULL2006] LITE Multicenter study 1994 - Jul 2003	200/200 patients Arm A: 100/100 patients Arm B: 100/100 patients	12 months	Adult cancer patients with DVT or PE Patients ≥60 years: Arm A: 62%, Arm B: 76% Metastatic: 41.5% Hemopathy: 11.5%	Arm A (control arm): UFH IV bolus 80 IU/kg or 5000 IU then continuous IV perfusion + warfarin 5-10 mg Arm B: tinzaparin SC x1/day (175 IU/kg) For 3 months	Arm A: 16/100 (16%) Arm B: 7/100 (7%) RR=0.44; p=0.044 Absolute difference: -9 %; 95%CI: [-21.7;-0.7]	Bleeding at 3 months Arm A: 24/100 (24%) Arm B: 27/100 (27%) Absolute difference: 3% 95%CI: [-9.1-15.1]; p=NS Major bleeding High risk: Arm A: 6/52 (11.5%) Arm B: 7/49 (14.3%) p=NS Low risk Arm A: 1/48 (2.1%) Arm B: 0/51 (0%) p=0.001	A 3 months Arm A: 19/100 (19%) Arm B: 20/100 (20%) Absolute difference: 1.0 %; 95%CI: [-10.2;11.9] A 12 months Arm A: 47/100 (47.0%) Arm B: 47/100 (47.0%) Absolute difference: 0.0%; 95%CI: [-14.6;13.2]
[ROMERA2009] Monocenter study Jan 2002 - Jan 2005	Arm A: 119/119 patients Cancer: 36/36 patients Arm B: 122/122 patients Cancer: 34/34 patients	12 months	General population with proven DVT treated long-term with either tinzaparin or acenocoumarol + tinzaparin	Arm A: tinzaparin SC 175 IU/kg/day Arm B: acenocoumarol *per os* 3 mg (INR 2 to 3) For 6 months	Recurrence at 6 months Arm A: 2/36 (5.5%) Arm B: 3/34 (9.1%) 95%CI: [-15.9-8.8]; p=0.58 Recurrence at 12 months Arm A: 2/36 (5.5%) Arm B: 7/34 (20.6%) 95% CI: [-31.5-0.17]; p=0.06	No data for major bleeding in cancer patients	2 patients with cancer died during the study but no data on the allocated treatment

Table 13 Other studies: idraparinux and duration of anticoagulation

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE recurrence	Toxicity	Death
[VANDOORMAAL2010] Randomized controlled trial May 2003 - Nov 2004	Idraparinux 3 months: 146/220 patients 6 months: 140/220 patients VKA 3 months: 138/201 patients 6 months: 130/201 patients	VKA: 92 days Idraparinux: 93 days	Cancer patients from the prospective randomized controlled trial VANGOGH-DVT Patients with active cancer and confirmed DVT and no sign of PE Mean age: 67 years Men: 52%	Idraparinux 2.5 mg/week first dose and then 2.5 mg/week or 1.5 mg/ week if creatinine clearance <30/mL/min or LMWH or UFH then VKA 3 months or 6 months of treatment according to the physician's judgment 92% of patients were treated for 6 months	Recurrent VTE at 3 months Idraparinux: 5/146 (3.4%) VKA: 10/138 (7.2%) OR=0.45; 95%CI: [0.15-1.36] Recurrent VTE at 6 months Idraparinux: 5/140 (3.6%) VKA: 10/130 (7.7%) HR=0.46; 95%CI: [0.16-1.36]	Any clinically relevant bleeding at 3 months Idraparinux: 9/146 (6.2%) VKA: 18/138 (13.0%) OR=0.44; 95% CI: [0.19-1.01] Any clinically relevant bleeding at 6 months Idraparinux: 15/140 (10.7%) VKA: 18/130 (16.2%) OR=0.62; 95%CI: [0.31-1.27] Major bleeding at 3 months Idraparinux: 3/146 (2.1%) VKA: 2/138 (1.4%) OR=1.43; 95%CI: [0.23-8.67] Major bleeding at 6 months Idraparinux 6/140 (4.3%) VKA 5/130 (3.8%) OR=1.12; 95%CI: [0.33-3.76]	Idraparinux: 50/220 (22.7%) VKA: 45/201 (22.3%) p=NS
[SIRAGUSA2010] Randomized controlled trial 36 months	347/409 patients	Arm A1: 1.2 years Arm A2: 1.1 years Arm B: 1.1 years	Patients with active cancer 1st episode of DVT	6 months of LMWH then Doppler US Residual vein thrombosis (RVT) Arm A1: RVT + anticoagulation + Arm A2: RVT + anticoagulation - Arm B: RVT - anticoagulation -	Arm A1: 17/119 (14.2%) Arm A2: 27/123 (21.9%) Arm B: 3/105 (2.8%) A1 *vs*. B: p=0.03 A2 *vs*. B: p=0.01 A1 *vs*. A2: p=0.73	Major bleeding: Arm A1: 5/119 (4.2%) Arm A2: 2/123 (1.6%) Arm B: 2/105 (1.9%) p=0.054	Not specified

Table 14 Meta-analyses

References	[FERRETI2006]	[IORO2003]	[LOUZADA2008]
Bibliographic search	Medline® ; CCTR ; ASCO abstract database, ASH abstract database, from 1966 to 2006	Medline®, Embase® up to 2003	Medline® (1950 to January 2008), Embase® (1980 to 2008 week 6), the Cochrane Register of Controlled Trials (1st quarter 2008) and Medline® in-process and other non-indexed citations (Feb 12, 2008)
Included studies	11 studies [PINI1994], [DAS1996], [GONZALEZ-FAJARDO1999] [LOPACIUK1999], [VEIGA2000], [LOPEZ-BERET2001], [MEYER2002, [HULL2002, [KAKKAR2003], [LEE2003], [DEITCHER2003] Studies with cancer patients: [MEYER2002], [HULL2002], [LEE2003], [DEITCHER2003]	7 studies [PINI1994], [DAS1996], [GONZALEZ-FAJARDO1999], [LOPACIUK1999], [VEIGA2000], [LOPEZ-BERET2001], [HULL2002] No specific study in patients with cancer	5 studies in cancer patients (LÓPEZ-BERET2001], (MEYER2002], [LEE2003], [DEITCHER2003], [HULL 2006]
Primary endpoint	VTE recurrence	VTE recurrence rate at 3 months	VTE recurrence
Secondary endpoint	None	Bleeding and death at 3 months	Bleeding and death
Statistical tests	Inverse variance and Mantel-Haenszel method	Mantel-Haenszel method	Intention-to-treat analysis Relative Risk (RR): primary measurement Heterogeneity: Cochrane Q/Chi-Square tests.
Results	Recurrence in the subgroup of cancer patients (n=1115) RR=0.525; 95%IC: [0.359-0.769]; p=0.001	No results for cancer patients Results for the general population for primary endpoint VTE recurrence VKA: 44/672 (6.5%); LMWH: 31/688 (4.5%); p=NS Bleeding VKA: 14/685 (2%); LMWH: 6/694 (0.9%); p=NS Cancer-related death VKA: 24/451 (5.3%); LMWH: 27/457 (5.9%); p=NS	VTE recurrence VKA: 73/565 (12.9%); LMWH: 40/593 (6.7%) RR=0.53; 95%CI: [0.36-0.76]; p=0.0007 Bleeding VKA: 42/685 (7.7%); LMWH: 37/593 (6.4%) RR=0.98; 95%CI: [0.49-1.93]; p=0.45 All-cause mortality VKA: 184/513 (35.8%); LMWH: 172/509 (33.8%) RR=0.94; 95%CI: [0.80-1.11]; p=0.47
Authors' conclusions	There is a significant reduction of the risk of recurrent symptomatic VTE in favor of LMWH over VKA during treatment. Patients treated with long-term LMWH do not seem to experience recurrent VTE events more frequently compared to those treated with VKA after cessation of therapy. The significant difference favoring LMWH over VKA among all patients receiving treatment is mostly derived from studies enrolling cancer patients	A 3-month course of LMWH is as effective and safe as a corresponding period of oral anticoagulant (OA) treatment, and may therefore be considered as a valuable alternative option for patients in whom OA treatment appears to be contraindicated or problematic.	Long-term use of LMWH after the first week or initial treatment is superior to VKAs for secondary prevention of VTE in adult patients with cancer.

Table 14 Meta-analyses (continued)

References	[AKL2008B]	[NOBLE2008]	[AKL2008C]
Bibliographic search	The Cochrane Central Register of Controlled Trials, Medline® from 1966, Embase® and ISI Web of Science. Date of search: January 2007	Medline®, The Cochrane Library, Embase® CINAHL, the British Nursing Index, AMED, Web of Science, and SCOPUS between January 1966 and December 2006	The Cochrane Central Register of Controlled Trials, Medline®, Embase® and ISI the Web of Science up to 2007
Included studies	6 studies of cancer patients + subgroups of cancer patients of 2 studies: [LÓPEZ-BERET2001], [CESARONE2003], [MEYER2002], [LEE2003, [DEITCHER2003], (SCHULMAN2003], [WELLS2005], [HULL2006]	4 prospective randomized studies (VKA *vs*. LMWH): [MEYER2002], (LEE2003], [DEITCHER2003], [HULL2006] 7 retrospective studies (VKA after UFH): [ELTING2004], (DEBOURDEAU1996], [CLARKE-PEARSON1983], [KRAUTH1987], [HARRINTON1997], [CHAN1992], [MOORE1981]	6 studies in cancer patients: [LÓPEZ-BERET2001], (CESARONE2003], [MEYER2002], (LEE2003], [DEITCHER2003], [HULL2006]
Primary endpoint	Survival	Incidence of recurrent venous thromboembolism	No definition of primary or secondary endpoints for comparison between LMWH and VKA. Outcomes of interest included: survival, symptomatic recurrent DVT, symptomatic recurrent PE, major bleeding, minor bleeding, thrombocytopenia, and postphlebitic syndrome.
Secondary endpoint	Symptomatic recurrent DVT	Incidence of major and minor bleeding	
Statistical tests	Agreement between the two review authors for the assessment of trial eligibility using Kappa statistics. For binary data: intention-to-treat principle to calculate the relative risk.	Risk ratios pooled by use of the fixed-effect model of Mantel and Haenszel. Statistical significance for heterogeneity assessed by use of the Chi-Square-based Q statistic and the I^2 statistic for the extent of heterogeneity.	For time-to-event data: random-effects model and the generic inverse variance facility. For binary data: intention-to-treat principle to calculate the relative risk
Results	Survival (follow-up: 3-12 months) VKA: 204/659 (31%); LMWH: 203/687 (30%) RR=0.95; 95% CI: [0.81-1.11] Recurrent VTE (follow-up: 3-12 months): VKA: 75/541 (13.8%); LMWH: 40/568 (6.9%) RR=0.51; 95%CI: (0.35-0.74] Minor bleeding (follow-up: 3–6 months) VKA: 94/544 (17.2%); LMWH: 92/576 (15.9%) RR=0.85; 95%CI: (0.53-1.35] Major bleeding (follow-up: 3–6 months) VKA: 32/544 (5.8%); LMWH: 37/576 (6.4%) RR=1.05; 95%CI: [0.53-2.1]	Recurrence LMWH *vs*. VKA RR=0.51; 95%CI: [0.35-0.74]; p <0.0001 VKA after UFH RR=0.21; 95%CI: [0.15-0.30]; p <0.0001 Bleeding LMWH *vs*. VKA RR=1.10; 95%CI: [0.77-1.58]; p=0.595	Survival VKA: 204/659 (31%); LMWH=203/687 (30%) HR=0.95; 95%CI: [0.81-1.11] Recurrent VTE: n=1109 Follow-up: 3-12 months RR=0.51; 95%CI: [0.35-0.74] Major bleeding: n=1120 Follow-up: 3-6 months RR=1.05; 95%CI: [0.53-2.1]
Authors' conclusions	For the long-term treatment of VTE in patients with cancer, LMWH compared to VKA reduces VTE but not death. The decision for a patient with cancer and VTE to start long-term LMWH *vs.* oral anticoagulation should balance the benefits and downsides and integrate the patient's values and preferences for the important outcomes and alternative management strategies.	Long-term full-dose LMWH is more effective than warfarin in the secondary prophylaxis of VTE in patients with cancer of any stage, performance status, or prognosis; warfarin should not be used in patients with advanced progressive disease. In patients at high risk of bleeding, full-dose LMWH for 7 days followed by long-term treatment at a decreased fixed dose can be considered.	For the long-term treatment of VTE in patients with cancer, LMWH compared to VKA reduces VTE but not death.