4.2. Data extraction

Table 16 Randomized controlled trials - LMWH or UFH *vs*. placebo or no treatment and LMWH *vs*. UFH

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[ENOXACAN1997] Double-blind study Apr 1993 - Feb 1995	Bleeding 1115/1116 patients VTE: 631/631 patients	Three months	Patients >40 years. Elective open surgery for abdominal or pelvic cancer (gastrointestinal, urological, gynecological) Surgery >45 min	Arm A: UFH 5000 IU x 3/day Arm B: Enoxaparin 40 mg x1/day + placebo x2/day For 10±2 days Beginning of treatment: H-2	Asymptomatic DVT detected by phlebography at Day 10±2 + symptomatic proven DVT or PE Arm A: 58/319 (18.2%) Arm B: 46/312 (14.7%) p=NS	Major bleeding Arm A: 16/560 (2.9%) Arm B: 23/550 (4.1%); p=NS Minor bleeding Arm A: 80/560 (14.3%) Arm B: 81/550 (14.6%); p=NS Transfusion requirement Arm A: 242/560 (43.2%) Arm B: 284/550 (51.2%); p=NS	Day 10±2 Arm A: 7/560 (12.5%) Arm B: 4/550 (7.3%) At 3 months Arm A: 27/560 (4.9%) Arm B: 22/550 (4%)
[BAYKAL2001] Double-blind study 1998 - 1999	102/102 patients	Arm A: 9.7 days Arm B: 9.4 days	Patients undergoing pelvic and para-aortic node dissection for gynecologic cancer	Arm A: Enoxaparin 2500 IU/day Arm B: UFH 5000 IU 3/day Beginning of treatment: H-2	Clinically significant events Arm A: 0/47 Arm B: 0/55 p not specified	Wound hematoma + hemorrhage Arm A: 0/47; Arm B: 0/55; p=NS Intraoperative blood loss Arm A: 915 mL; Arm B: 798 mL; p=NS Blood transfusion Arm A: 1.43 units; Arm B: 1.2 units; p=NS Decrease in hematocrit Arm A: 10.3 g/L; Arm B: 7.6 g/L; p=NS	Not specified
[MCLEOD2001] Double-blind study Not specified	Efficacy 936/1349 patients Safety 1296/1349 patients	10 days	Adult patients undergoing colorectal resection or rectal dissection Surgery under general anesthesia and lasting >1 h Cancer patients: n=475/1349	Arm A: UFH 5000 IU 3/day Arm B: Enoxaparin 40 mg + 2 SC injections of placebo Treatment for up to 10 days Beginning of treatment: H-2	All VTE (DVT + PE): Day-9 bilateral venography or earlier if symptoms + if suspected PE perfusion/ventilation lung scintigraphy and if non-conclusive Doppler US, venography or angiography VTE all patients Arm A: 44/468 (9.4%); Arm B: 44/468 (9.4%) 95%CI of the difference: [0±3.7%] VTE cancer patients Arm A: 39/234 (16.9%); Arm B: 33/241 (13.9%); p=NS	No data for cancer patients All bleeding events Arm A: 42/643 (6.5%); Arm B: 68/653 (10.4%); p=0.02 Major bleeding events Arm A: 10/643 (1.5%) Arm B: 18/653 (2.7%); p=NS Minor bleeding events Arm A: 32/643 (5.0%) Arm B: 52/653 (8.0%); p=0.03	Not specified
[SHUKLA2008) Controlled trial Mar 2002 - Jan 2004	99/99 patients	6 days	Colorectal surgery for cancer under general anesthesia Lithotomy position Age >30 years No DVT on preoperative Doppler US	Arm A: Dalteparin 2500 IU SC for 6±1 days Arm B: No prophylaxis Beginning of treatment: H-2	Symptomatic DVT or PE and asymptomatic DVT on duplex ultrasonography at Day 6 Arm A: 0/51 Arm B: 0/48	Blood loss: Arm A: 506 mL Arm B: 445 mL; p=NS No reintervention for bleeding	No death

Table 17 Meta-analyses: LMWH or UFH *vs.* placebo or no treatment and LMWH *vs.* UFH

References	[EINSTEIN2007]	[MISMETTI2001]
Bibliographic search	PubMed, DARE, ACP Journal Club, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Registry, CINAHL, Curren Contents, and Ovid Medline® from 1966–2005	Manual and computer-assisted search (Medline® and Current Contents from 1984 to 1999. Open-label, single- or double-blind randomized studies evaluating a LMWH for surgical prophylaxis in cancer and non-cancer patients
Included studies	UFH *vs.* CONTROL: [CLARKE-PEARSON1983], [CLARKE-PEARSON1984], [CLARKE-PEARSON1990] SCD *vs.* CONTROL: [CLARKE-PEARSON1984] UFH *vs.* SCD: [CLARKE-PEARSON1993] LMWH *vs.* SCD: MAXWELL2001 UFH *vs.* LMWH: [BAYKAL2001], [BORSTAD1988], [FRICKER1988], [KAAJA1992], [VONTEMPELHOFF2000]	LMWH *vs.* PLACEBO OR OBSERVATION: [LE GAGNEUX1987], [VALLE1988], [OCKELFORD1989], [PEZZUOLI1989], [BALAS1992], [MARASSI1993], [BERGQVIST1996], [HO1999] LMWH *vs.* UFH: [SCHMITZ-HUEBNER1984], [TOÈRNGREN1984], [KAKKAR1985], [BERGQVIST1986], [ONARHEIM1986], [SASAHARA1986], [VOIGT1986], [KOLLER1986 (2)], [EFS1988], (FRICKER1988], [BERGQVIST1988], [CAEN1988], (BORSTAD1988], (SAMAMA1988 (3)], [WELZEL1988], [BRIEL1988], [CATANIA1988], [SALANITRI1988], [SALCUNI1988], [KAKKAR1989], [ADOLF1989], [HEILMANN1989], [BAUMGARTNER1989], [DAHAN1989], [VERARDI1989], [CREPERIO1990], [HARTL1990], [HOFFMANN1990], [KOPPENHAGEN1990], [BARBUI1990], [LEIZOROVICZ1991], [SCHIELKE1991], [KAAJA1992], [KOPPENHAGEN1992, [BORSTAD1992], [HOFFMANN1992, [GARCEA1992, [KAKKAR1993 (2)], [GODWIN1993, [GAZZANIGA1993], [LIMMER1994], [EURIN1994], [NURMOHAMED1995], [MCLEOD1995], [GONZALEZ1996], [ENOXACAN1997], (HEILMANN1997], [HAAS1999]
Primary endpoint	Efficacy: rate of postoperative thrombosis Safety: bleeding	All VTE detected systematically (all methods) at the end of treatment or earlier if symptoms present. Positive results of impedance plethysmography or thermography had to be confirmed by venography.
Secondary endpoint		Symptomatic PE, death and major bleeding
Statistical tests	Extraction of raw data and analysis of subgroups utilizing the Mantel–Haenszel method; where possible a meta-analysis was performed. Data are presented as relative risk of outcome with 95%CI. Statistical significance was found if 95%CI did not include unity.	Logarithm of the relative risk (RR), logarithm of the odds ratio, Mantel Haenszel test. Association and heterogeneity tests were performed for each meta-analysis using the software EasyMA®
Results	Heparin *vs.* controls DVT, Day 30 Heparin: 25/289 (8.6%); control: 30/200 (15%) RR=0.58; 95%CI: [0.35-0.95] PE RR=4.84; 95%CI: [0.79-30.15] LMWH *vs.* controls DVT LMWH: 9/152 (5.9%); control: 9/158 (5.4%) RR=0.91; 95%CI: [0.38–2.17] PE LMWH: 0/88; control: 2/90 No sufficient data in selected studies to perform a meta-analysis for bleeding	LMWH *vs.* no treatment or placebo Systematically detected DVT n=513 RR=0.28; 95%CI: [0.14–0·54]; p <0.001 Clinical PE n=5456 RR=0.25; 95%CI: [0.08-0.79]; p=0.018 Clinical VTE n=4890 RR=0.29; 95%CI: [0.11-0.73]; p=0.009 Death n=5142 RR=0.54; 95%CI: [0.27–1.10]; p=0.09 Major bleeding n=5456 RR=2.03; 95%CI: [1.37–3·01]; p <0.001 Total bleeding n=5431 RR=2.06; 95%CI: [1.77–2.39]; p <0.001 Wound hematoma n=5242 RR=1.88; 95%CI: [1.54–2.28]; p <0.001 Transfusion n=5054 RR=1.53; 95%CI: [1.28–1.82]; p <0.001 LMWH *vs.* UFH Systematically detected DVT n=17 995 RR=0.90; 95%CI: [0.79–1.02]; p=0.10 Clinical PE n=46 646 RR=0.88; 95%CI: [0.64–1·20]; p=0.41 Clinical VTE n=13 776 RR=0.71; 95%CI: [0.51–0·99]; p=0.049 Death n=41 387 RR=1.04; 95%CI: [0.89–1·20]; p=0.63 Major bleeding n=18 555 RR=0.89; 95%CI: [0.75–1·05]; p=0.16 Total bleeding n=19 315 RR=0.92; 95%CI: [0.79–1·07]; p=0.27 Wound hematoma n=16 087 RR=0.89; 95%CI: [0.74–1·07]; p=0.21 Transfusion n=12 777 RR=1.03; 95%CI: [0.94–1·12]; p=0.54 Meta-analysis performed for cancer and non-cancer patients showed that the efficacy and safety of LMWH relative to UFH were similar in patients with cancer to those in patients without malignant disease (data not provided)
Authors' conclusions	All gynecologic cancer patients should receive VTE prophylaxis. Although heparin, LMWH, and SCD have been shown to be safe and effective, due to the paucity of data in the gynecologic oncology literature, none of these 3 prevention modalities can be considered superior at this time. Adequately powered RCTs are urgently needed to determine the optimal regimen in these high-risk patients.	Asymptomatic DVT may be regarded as a reliable surrogate endpoint for clinical outcome in studies investigating thromboprophylaxis in general surgery. LMWH seems to be as effective and safe as UFH. Determination of the optimal dose regimen of LMWH for this indication requires further investigation.

Table 17 Meta-analyses: LMWH or UFH *vs*. placebo or no treatment and LMWH *vs*. UFH (continued)

References	[OATESWHITEHEAD2005]	[AKL2008D]
Bibliographic search	Randomized controlled trials comparing treatments for the prevention of postoperative VTE after major gynecological surgery Medline® - 1966 to April 2003, Embase® - 1980 to April 2003, CINAHL - 1982 to April 200	Medline® from 1966, Embase® from 1980, ISI Web of Science, and CENTRAL (The Cochrane Central Register of Controlled Trials), abstracts from ASCO and ASH congress in January 2007
Included studies	[BAYKAL2001], [CLARKE-PEARSON1983], [CLARKE-PEARSON1990], [HEILMANN1989], [HEILMANN1998], [STEINER1989], [TABERNER1978], [VONTEMPELHOFF1997] No study evaluating VKA or aspirin prophylaxis	[ONARHEIM1986], (FRICKER1998], (EFS1988], [BERGQVIST1990], [DAHAN1990], [GALLUS1993], [GODWIN1993], [ENOXACAN1997], [VON TEMPELHOFF1997], [HEILMANN1998], [VONTEMPELHOFF2000], [BAYKAL2001], [BONCINELLI2001], [MCLEOD2001],
Primary endpoint	Incidence of identified DVT by either venography, ^{125}I-fibrinogen-uptake test, or Doppler US. Incidence of PE identified by either ventilation perfusion lung scan, pulmonary angiogram, or post-mortem examination	Efficacy: VTE Safety: death, thrombocytopenia and bleeding
Secondary endpoint	Death resulting from confirmed thromboembolism identified by either ventilation perfusion lung scan, pulmonary angiogram, or post-mortem examination	
Statistical tests	For dichotomous data, calculation of odds ratio with 95%CI, combination of OR for meta-analysis with the Peto-modified Mantel-Haenszel method. Calculation of summary statistics with a fixed-effect and random-effects model. Analysis of the heterogeneity of studies by inspecting the scatter data points and the overlap in the confidence intervals and by checking the results of the Chi-Square test.	For categorical variables, calculation of the pooled relative risk (RR). For continuous variables calculation of the standardized mean difference (SMD). Measure of the homogeneity across trial results using the I^2 test. Results pooled using random effects
Results	PE, all patients Heparin: 5/289 (1.7%); placebo: 1/200 (0.5%); OR=2.13; 95%CI: [0.42-10.91] LMWH: 8/204 (3.8%); UFH: 5/225 (2.2%); OR=1.82; 95%CI: [0.57-5.80] PE, cancer patients LMWH: 7/139 (5.0%); UFH: 4/157 (2.5%); OR=2.03; 95%CI: [0.56-7.28] DVT, cancer patients Heparin: 17/292 (5.8%); placebo: 32/204 (15.6%); OR=0.30; 95%CI: [0.10-0.90] LMWH: 15/289 (5.2%); UFH: 15/307 (4.8%); OR=1.10; 95%CI: [0.25-4.83] Too many endpoints for bleeding complications (wound hematoma, postoperative blood loss, blood transfusion, injection site hematoma, total transfusion, major bleeding) with too few data for each one to provide results. Meta-analyses of UFH and LMWH showed no statistical difference in any comparison. No study compared aspirin alone to placebo, heparin or warfarin. There was a statistically significant increase in injection-site hematomas associated with heparin compared to placebo (OR=0.30; 95%CI: [0.10-0.89].	DVT (symptomatic + asymptomatic any search strategy) LMWH *vs*. UFH x2/day - LMWH: 41/1222 (3.3%); UFH: 65/961 (6.7%); RR=0.66; 95%CI: [0.44-0.99] LMWH *vs*. UFH x3/day - LMWH: 44/971 (4.5%); UFH: 53/980 (5.4%); RR=0.78; 95%CI: [0.53-1.15] LMWH *vs*. UFH global - LMWH: 85/2193 (3.9%); UFH: 118/1941 (6.0%); RR=0.72; 95%CI: [0.55-0.94] Death LMWH: 67/1480 (4.6%); UFH: 79/1528 (5.1%); RR=0.88; 95%CI: [0.65-1.19] Minor bleeding 3 studies; RR=0.88; 95%CI: [0.47-1.66] Major bleeding 6 studies; RR=0.95; 95%CI: [0.51-1.77] Thrombocytopenia 3 studies; RR=1.18; 95%CI: [0.49-2.81] (no case of HIT)
Authors' conclusions	The meta-analysis of heparin *vs*. placebo found a statistically significant decrease in the number of DVT in both the all women group (including those with and without malignancy) (OR=0.30; 95%CI: [0.12-0.76]) and the subgroup of only women with malignancy (OR=0.30; 95%CI: [0.10-0.89]). There was no significant difference in the incidence of PE. Oral warfarin reduced DVT compared to placebo in all women (OR=0.22; 95%CI: [0.06-0.86]) and in women with malignancy (OR=0.18; 95%CI: [0.04-.87]).	There was no difference in mortality rate between patients with cancer receiving perioperative thromboprophylaxis with LMWH *vs*. UFH. Further trials are needed to evaluate the benefits and the harms of different heparin thromboprophylaxis strategies in this cancer population.

Table 18 Randomized controlled trials - Comparison of drugs and dose of LMWH

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[BERGQVIST1995] Double-blind study Mar 1988 - Nov 1991	Intent to treat 1303/1375 patients Correct prophylaxis 1154/1375 patients	Not specified	Patients >40 years undergoing major elective abdominal surgery (>30 min) 70% of patients undergoing surgery for cancer	Arm A: Dalteparin 2500 IU/day Arm B: Dalteparin 5000 IU/day Treatment for 8 days Beginning of treatment: evening before surgery	DVT diagnosed with I-labeled fibrinogen uptake performed daily for 7 days or until discharge or VTE occurrence Intent to treat Arm A: 14,9% Arm B: 8.5% 95%CI of the difference: [2.1-8.9]; p<0.001 Correct prophylaxis Arm A: 15.1% Arm B: 8.8% 95%CI of the difference: [2.1-9.4]; p=0.001	Bleeding complications (major and minor bleeding, wound hematoma, surgical bleeding) Arm A: 3.6% Arm B: 4.6% 95%CI of the difference: [-2.8-1.4]; p >0.05	Cancer and non-cancer patients Arm A: 12% Arm B: 15%
[AGNELLI2005] Double-blind study Oct 2001 - Oct 2002	Total population Safety 2858/2927 patients Efficacy 2048/2927 patients Cancer patients Efficacy 1408/1941 patients Safety 1841/1941 patients	30 days	Abdominal surgery >45 min under general anesthesia Patients >60 years or >40 years + one additional risk factor (cancer)	Arm A: Fondaparinux 2.5 mg/day Arm B: Dalteparin 5000 IU/day Treatment for 5-9 days Beginning of treatment: Fondaparinux: H+6 Dalteparin H-2	Symptomatic and asymptomatic VTE (bilateral ascending contrast venography at Day 5 to Day 10 + DVT and PE confirmed by objective tests) Arm A: 33/696 (4.7%) Arm B: 55/712 (7.7%) Relative risk reduction: 38.6%; 95%CI: [6.7-59·6]	Major bleeding Arm A: 32/954 (3.4%) Arm B: 25/987 (2.5%)	Total population on Day 32 Arm A: 40/1433 (2.8%) Arm B: 55/1425 (3.9%)
[SIMONNEAU2006] Double-blind study Sep 1994 - Feb 1999	Efficacy 950/1296 patients Safety 1271/1296 patients	60 days	Elective resection of colorectal adenocarcinoma under general anesthesia No contraindication for anticoagulant therapy	Arm A: 2850 anti-FXa IU of nadroparin + placebo enoxaparin Arm B: 4000 anti-FXa IU of enoxaparin + placebo nadroparin Treatment for 7-11 days Beginning of treatment: H-4 to H-2	Primary efficacy outcome: DVT detected by bilateral venography or documented Symptomatic DVT or PE up to Day 12 All VTE at Day 12 (primary endpoint) Arm A: 74/464 (15.9%) Arm B: 61/486 (12.6%) RR=1.27; 95%CI: [0.93–1.74] Symptomatic VTE at D12 Arm A: 1/464 (0.2%) Arm B: 9/486 (1.4%) RR=0.12; 95%CI: [0.01-0.92] Symptomatic VTE at Day 60 Arm A: 4/464 (0.6%) Arm B: 13/486 (2.1%) p=NS	Major bleeding Arm A: 47/643 (7.3%) Arm B: 72/628 (11.5%) RR=0.64; 95%CI: [0.45-0.91]; p=0.012 Severe thrombocytopenia Arm A: 9/643 (1.4%) Arm B: 8/628 (1.3%) p=NS	Death from any cause on Day 60 Arm A: 23/653 (3.5%) Arm B: 23/635 (3.6%)

Table 19 Randomized controlled trials - Duration of prophylaxis

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[LAUSEN1998] Controlled trial Nov 1991 - May 1993	Arm A: 58/87 patients Arm B: 60/89 patients	28 days	Major elective abdominal or non-cardiac thoracic operations Duration >1 hour Patients >18 years No contraindication to LMWH No use of other anticoagulants Cancer patients: Arm A: 39/58; Arm B: 42/60	Tinzaparin 3500 IU/day for 7 days + high-length graded CS then: Arm A: tinzaparin 3500 IU/day for 3 weeks Arm B: observation Beginning of treatment: H-2	Bilateral venography on Day 28 or earlier if symptoms present. If suspected PE, perfusion/ventilation lung scintigraphy. Arm A: 3/58 (5.2%); 95%CI: [1-14] Arm B: 6/60 (10%); 95%CI: [4%-21] p=NS	Reoperation: 12/118 No differences between groups for anastomotic leaks, wound dehiscence, wound infections, abscesses, or pneumonia No data for each group	Not specified
[BERGQVIST2002] Double-blind study Oct 1998 - Jun 2000	Bleeding complications 501/501 patients Recurrent VTE 332/332 patients	3 months	Patients >40 years. Elective open surgery for cancer (gastrointestinal other than the esophagus, genitourinary tract, or female reproductive organs Surgery >45 min	Enoxaparin 40 mg/day Placebo Arm A: Enoxaparin for 6-10 days + placebo for 19-21 days Arm B: Enoxaparin for 25-31 days Beginning of treatment: H-14 to H-10	Phlebography between Days 25 and 31 Arm A: 20/167 (12%) Arm B: 8/165 (4,8%); p=0.02 At 3 months Arm A: 23/167 (13.8%) Arm B: 9/165 (5.5%); p=0.01	Double-blind phase Minor bleeding Arm A: 9/248 (3.6%) Arm B: 12/253 (4.7%); p=NS Major bleeding Arm A: 0/248 Arm B: 1/253(0.4%); p=NS At 3 months Minor bleeding Arm A: 9/248 (3.6%) Arm B: 12/253 (4.7%); p=NS Major bleeding Arm A: 1/248 (0.4%) Arm B: 3/253 (1.2%)	Double-blind phase No death At 3 months Arm A: 6/248 (3.6%) Arm B: 3/253 (1.8%)
[RASMUSSEN2006] Controlled trial Jan 1997 - Jun 2003	Arm A: 165/205 patients Arm B: 178/222 patients	28 days	Patients >18 years Open abdominal surgical intervention Surgery >1 hour Cancer patients Arm A: 123/205 (60%); Arm B: 124/222 (56%)	Dalteparin 5000 IU + GCS for 7 days After day 7 Arm A: dalteparin 5000 IU for 21 days Arm B: observation Beginning of treatment: the evening of surgery and H-2	Asymptomatic DVT detected by venography (Day 28), symptomatic DVT or PE verified by objective means or by autopsy Arm A: 12/165 (7.3%) Arm B: 29/178 (16.3%) Risk Reduction: 55%; 95%CI: [15-76]; p=0.012 DVT Arm A: 12/165 (7.3%) Arm B: 26/178 (14.9%) Risk Reduction: 51%; 95%CI: [6-74]; p=0.027	Major bleeding Arm A: 1/205 Arm B: 4/222	Arm A: 22/205 Arm B: 17/222
[KAKKAR2010] Double-blind study Jul 2005 - Feb 2008	Efficacy patients 488/625 Safety patients 625/625	22 days	Patients aged 40 years or older Open, curative or palliative surgery for a malignant disease of the gastrointestinal (excluding esophagus) tract, genitourinary tract or female reproductive organs Duration of surgery >30 min Cancer patients Arm A: 39/58; Arm B: 40/60	Bemiparin 3500 IU (0.2 mL) for 8±2 days then: Arm A: bemiparin 3500 IU (0.2 mL) for 20 days Arm B: placebo (0.9% sodium chloride, 0.2 mL) for 20 days Beginning of treatment: H+6	Bilateral venography on Day 18-22 Endpoint: phlebographic and symptomatic DVT, PE and death at the end of double-blind phase Arm A: 25/248 (10.1%) Arm B: 32/240 (13.3%) RR=24.4; 95%CI: [23.7-53.8]; p=0.26 Only DVT Arm A: 19/248 (7.7%) Arm B: 29/240 (12.1%) RR = 36.6; 95%CI: [10.0-63.4]; p=0.10	During double-blind period Major bleeding (primary safety endpoint) 2/315 (0.6%) *vs.* 1/310 (0.3%); p=NS Minor bleeding 1/315 (0.3) *vs.* 1/310 (0.3%); p=NS	All-cause death Arm A: 8/248 (3.2%) Arm B: 6/240 (2.5%) RR= -29.0%; 95%CI: [-266.4-54.6]; p=0.63

Table 20 Extended prophylaxis meta-analysis

References	[AKL2008E]
Bibliographic search	Medline® from 1966, Embase® from 1980, ISI the Web of Science, and The Cochrane Central Register of Controlled Trials in January 2007
Included studies	[JORGENSEN2002], [BERGQVIST2002], [RASMUSSEN2006]
Primary endpoint	Efficacy: VTE
Secondary endpoint	Safety: death and bleeding
Statistical tests	Not specified in the paper and in the appendix
Results	DVT screening venography (198 patients, 1 study) RR=0.21; 95%CI: [0.05-0.94] - low evidence Major bleeding (501 patients, 1 study) RR=2.94; 95%CI: [0.12-71.85] - low evidence Minor bleeding (501 patients, 1 study) RR=1.31; 95%CI: [0.56-3.05] - moderate evidence Mortality (501 patients, 1 study) RR=0.49; 95%CI: [0.12-1.94] - low evidence
Authors' conclusions	There is limited and low-quality evidence that extended duration LMWH for perioperative thromboprophylaxis reduces DVT in patients with cancer undergoing major abdominal or pelvic surgery. More and better quality evidence is needed to justify extended regimens.

Table 21 Randomized controlled trials: external compression device with intermittent compression device (ICD)

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[TURPIE1989] Not specified	173/239 patients	3 months	Patients >16 years undergoing surgery for a brain tumor, spinal cord tumor, head injury, spinal cord injury or subarachnoid hemorrhage Cancer patients Arm A: 38/80 Arm B: 39/78 Arm C: 40/81	Arm A: GCS for 14 days Arm B: GCS for 14 days+IPC for 7 days Arm C: control	^{125}I-labeled fibrinogen scanning x1/day until discharge + impedance plethysmography on Days 3, 5, 7, 9, 11, 14 with double-blind interpretation of results Arm A: 7/80 (8.8%) Arm B: 7/79 (9%) Arm C: 16/81 (19.8%) p=0.023 A *vs*. C p=0.027 B *vs*. C p=0.028 A + B *vs*. C	Compliance with treatment Arm A: 77/80 (96%) Arm B: 69/79 (87%)	Arm A: 10/80 (12.5%) Arm B: 4/79 (50.6%) Arm C: 4/81 (49.4%)
[DICKINSON1998] Jan 1990 - Dec 1992	66/66 patients	1 month	Patients 18 years of age or older with an intracranial neoplasm and undergoing craniotomy	Arm A: SCD alone Arm B: enoxaparin 30 mg/day Arm C: SCD+enoxaparin 30 mg/day Duration: up to discharge Beginning of treatment: during anesthesia	Venous duplex ultrasonographic examinations at Day 1-3, Day 5-7, Day 10-14, Month 1 Arm A: 3/22 (13.6%) Arm B: 1/21 (4.7%) Arm C: 2/23 (8.7%) p=NS	Major bleeding Arm A: 0/22 (0%) Arm B: 2/21 (9.5%) Arm C: 3/23 (13.1%) Difference between enoxaparin groups and SCD group p=0.024 Intracranial bleeding LMWH: 4/44 (9.1%) SCD: 0/22 (0%); p=0.29	Arm A: 1/22 (4.5%) Arm B: 1/21 (4.8%) Arm C: 0/23 (0%)
[MAXWELL2001] Not specified	211/231 patients	Hospitalization	Patients >40 years Major abdominal or pelvic surgery for a known or suspected gynecologic malignancy	Arm A: external pneumatic compression sleeves, beginning at induction of anesthesia, for 5 days, then temporarily removed when the patient is ambulatory Arm B: dalteparin 2500 IU postoperatively and then 12 h after, then 5000 IU/day for 5 days or until discharge Beginning of treatment: H-2	Doppler US at Day 3 to 5 Arm A: 1/106 (1%) Arm B: 2/106 (2%) p=NS	Blood loss Arm A: m=350 mL, >2000 mL: n=3 Arm B: m=350 mL, >2000 mL: n=4 Transfusions in operating room Arm A: 22/106 (20.7%) Arm B: 20/105 (19%) Postoperative transfusions Arm A: 12/106 (11.3%) Arm B: 13/105 (12.4%)	Not specified

Table 22 Meta-analysis of studies in neurosurgical cancer patients: external compression device

References	[COLLEN2008]
Bibliographic search	Published literature (from 1960 through August 2007) Medline®; PubMed; Cochrane RCT; Embase®; Biosis; PASCAL; Sci Search; IPA; and Computer Retrieval of Information on Scientific Projects
Included studies	Patients included in randomized trials or prospective cohort studies evaluating pharmacologic VTE prophylaxis (with UFH or LMWH) or in randomized trials or prospective cohort studies evaluating mechanical VTE prophylaxis (with ICD or CS) [AGNELLI1998], [BARNETT1977], [BOSTROM1986], [BUCCI1989], [BYNKE1987], [CERRATO1978], [CONSTANTINI2001], [DICKINSON1998], [EPSTEIN2005], [EPSTEIN2006], [FRIM1992], [GERLACH2003], [GOLDHABER2002], [GRUBER1984], [KURTOGLU2004], [MACDONALD1999], [MACDONALD2003], [NORWOOD2002], [NURMOHAMED1996], [PAOLETTI1989], [PRESTAR1992], [ROKITO1996], [SKILLMAN1978], [SMITH1994], [TURPIE1989], [VOTH1992], [WAUTRECHT 1996], [WEN198], [WOOD1997]
Primary endpoint	Objective assessment of DVT
Secondary endpoint	Major and minor bleeding, death
Statistical tests	RRs were pooled using the Der Simonian and Laird random-effects method. Calculation of the overall rate of events. Calculation of the variance for each outcome using the binomial method Heterogeneity was assessed visually by Galbraith plots, as well as Q statistics (Chi-Square test) and the I^2 statistic.
Results	ICD *vs*. CS: 3 studies DVT RR=0.81; 95%CI: [0.32-1.78] PE RR=0.49; 95%CI: [0.08-2.80] ICD vs. placebo: 2 studies DVT RR=0.41; 95%CI: [0.21-0.78] PE RR=0.37; 95%CI: [0.03-4.06] LMWH *vs*. CS: 2 studies DVT RR=0.60; 95%CI: [0.44-0.81] PE RR=0.29; 95%CI: [0.05-1.85] LMWH *vs*. ICD: 2 studies DVT RR=0.79; 95%CI: [0.30-2.12] PE RR=1.62; 95%CI: [0.35-7.46] LMWH *vs*. UFH: 4 studies DVT RR=1.46; 95%CI: [0.61-3.51] PE RR=0.43; 95%CI: [0.08-2.41] UFH *vs*. placebo: 3 studies DVT RR=0.50; 95%CI: [0.11-2.38] PE RR=0.96; 95%CI: [0.10-9.06] LMWH *vs*. non-pharmacologic management: 4 studies Minor bleeding RR=2.06; 95%CI: [1.07-3.96] Major bleeding RR=0.95; 95%CI: [0.18-5.09] ICH RR=1.97; 95%CI: [0.64-6.09] Death RR=0.96; 95%CI: [0.47-1.96] UFH *vs*. non-pharmacologic management: 3 studies Minor bleeding RR=1.00; 95%CI: [0.48-2.11] Major bleeding RR=0.85; 95%CI: [0.12-5.99] ICH RR=2.11 95%CI: [0.39-11.31] Death RR=0.97; 95%CI: [0.13-7.37] LMWH *vs*. UFH: 4 studies Minor bleeding RR=1.28; 95%CI: [0.64-2.59] Major bleeding RR=1.00; 95%CI: [0.18-5.74] ICH RR=1.78; 95%CI: [0.37-8.50] Death RR=0.72; 95%CI: [0.11-4.42]
Authors' conclusions	In a mixed neurosurgical population, LMWH and ECD are both effective in the prevention of VTE. Sensitivity analyses suggested that isolated high-risk groups, such as patients undergoing craniotomy for a brain neoplasm, may benefit from a combination of prophylactic methods, suggesting the need for a more individualized approach to these patients.