5.2. Data extraction

Table 23 Thromboprophylaxis with UFH *vs*. LMWH: randomized trials in general medical patients including cancer patients

Reference	Included patients	Intervention	Efficacy whole population	Major bleeding whole population	Death
[BERGMANN1996]	Bedridden patients Age >65 year n=423 Cancer patients: 7%	Arm A: UFH 5000 IU x2/day Arm B: enoxaparin 20 mg/day	VTE at Day 10 (FUT) Arm A: 10/216 (4.6%) Arm B: 9/207 (4.3%) p=NS PE Arm A: 0/223 Arm B: 1/216 (0.5%) p=NS	Arm A: 2/223 (0.9%) Arm B: 1/216 (0.5%) p=NS	Arm A: 8/223 (3.6%) Arm B: 7/216 (3.2%) p=NS
[HARENBERG1996]	Bedridden + 1 risk factor Age 50-80 year n=1590 Cancer patients: 8%	Arm A: UFH 5000 IU x3/day Arm B: nadroparin 3400 IU/day	Proximal VTE at Days 7-11 (Doppler US) Arm A: 4/710 (0.6%) Arm B: 6/726 (0.8%) p=NS PE Arm A: 6/780 (0.7%) Arm B: 5/810 (0.6%) p=NS	Arm A: 4/780 (0.5%) Arm B: 5/810 (0.6%) p=NS	Arm A: 9/780 (1.1%) Arm B: 23/810 (2.8%) p=NS
[LECHLER1996]	Reduced mobility >7 days + 1 risk factor Mean age: 74 years n=959 Cancer patients: 14%	Arm A: UFH 5000 IU x3/day Arm B: enoxaparin 40 mg/day	VTE at Day 7 (Doppler US) Arm A: 4/482 (0.8%) Arm B: 1/477 (0.2%) p=NS PE Arm A: 4/482 (0.8%) Arm B: 0/477 p=NS	Arm A: 9/482 (1.8%) Arm B: 2/477 (0.4%) p=NS	
[KLEBER2003]	Severe respiratory disease or congestive heart failure Mean age: 70 year n=451 Cancer patients: 6%	Arm A: UFH 5000 IU x3/day Arm B: enoxaparin 40 mg/day	Venography if D-dimer or fibrin monomer positive Days 8-12 Arm A: 22/212 (10.4%) Arm B: 19/239 (7.9%) PE Arm A: 1/212 (0.5%) Arm B: 1/239 (0.4%)	Arm A: 1/333 (0.3%) Arm B: 1/332 (0.3%) p=NS	Arm A: 30/333 (9%) Arm B: 28/332 (8.7%) p=NS

Table 24 Thromboprophylaxis with LMWH or fondaparinux: randomized double-blind trials in general medical patients including cancer patients

Reference	Included patients	Intervention	Efficacy whole population	Major bleeding whole population	Death
[DAHAN1986]*	Age >65 years Mean age: 80 years n=263 Cancer patients: 13%	Arm A: placebo Arm B: enoxaparin 60 mg/day	VTE at Day 10 (FUT) Arm A: 12/131 (9.1%) Arm B: 4/132 (3.0%) p <0.05 PE Arm A: 3/135 (2.2%) Arm B: 0/135	Arm A: 3/135 (2.2%) Arm B: 1/135 (0.7%) p=NS	Arm A: 6/135 (4.4%) Arm B: 1/135 (0.7%) p=NS
[SAMAMA1999]	Age >40 years + 1 risk factor Mean age: 73 years n=1102 Cancer patients: 14%	Arm A: placebo Arm B: enoxaparin 20 mg/day Arm C: enoxaparin 40 mg/day	VTE at Day 14 (Venography or Doppler US) Arm A: 43/288 (14.9%) Arm B: 43/287 (15.0%) Arm C: 16/291 (5.5%) A *vs*. B: p=NS A *vs*. C and B *vs*. C: p <0.05	Arm A: 7/362 (1.9%) Arm B: 4/351 (1.1%) Arm C: 12/360 (3.3%) p=NS	Arm A: 50/362 (13.8%) Arm B: 51/351 (14.5%) Arm C: 41/360 (11.4%) p=NS
[LEIZOROVICZ2004]	Age >40 years + acutely ill medical patients Mean age: 69 years n=3706 Cancer patients: 5%	Arm A: placebo Arm B: dalteparin 5000 IU/day	VTE at Day 21 (Doppler US) Arm A: 73/1473 (5.0%) Arm B: 42/1518 (2.8%) p <0.05 PE: Arm A: 4/1740 (0.2%) Arm B: 5/1759 (0.2%)	Arm A: 0/1850 (0%) Arm B: 8/1856 (0.4%) p=NS	Arm A: 7/1831 (0.4%) Arm B: 8/1846 ((0.4%) p=NS
[COHEN2006]	Age >60 years + acutely ill medical patients Mean age: 75 years n=849 Cancer patients: 15%	Arm A: placebo Arm B: fondaparinux 2.5 mg/day	VTE at Day 15 (Venography) Arm A: 34/323 (10.5%) Arm B: 18/321 (5.6%) p <0.05 PE: Arm A: 5/414 (1.2%) Arm B : 0/425	Arm A: 1/414 (0.2%) Arm B: 1/425 (0.2%) p=NS	Arm A: 25/414 (6.0%) Arm B: 14/425 (3.3%) p=NS

*Included in the ACCP guidelines

Table 25 Prospective studies of primary prophylaxis of VTE in children with Acute Lymphocytic Leukemia (ALL) treated with L-asparaginase

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[MEISTER2008] Two prospective non-randomized studies Arm A: 1st period 1995 - 2000 Arm B: 2nd period 2001 - 2006	112 patients/ not specified	240 days	Children, with ALL treated with L-asparaginase	Arm A: n=71 Antithrombin supplementation Arm B: n=41 Antithrombin supplementation + enoxaparin 0.75 - 1.2 mg/kg/day	Arm A: 9/71 (12.7%) (3 intracranial dural sinus thromboses) Arm B: 0/41 (0%) p=0.02	Bleeding Arm A: 0/71 (0%) Arm B: 0/41 (0%) p=NS	Not specified
[MITCHELL2003] Open, randomized, controlled, extended phase II PARKAA study Jul 1997 - May 1999	61/85 patients	Not specified	Children, with ALL treated with L-asparaginase	For all cancer patients with a CVC: either continuous (1-3 IU/mL) or ≤4 /day flushes with heparinized saline (50-100 IU/mL) Arm A: antithrombin III (ATIII) infusion on Days 1, 8, 15, 22 for an ATIII level between 3 and 4 IU/mL Arm B: observation	No separate data for asymptomatic VTE and symptomatic VTE from Day 28 to Month 3 (screening with venography, MRI, Doppler US) Arm A: all VTE 7/25 (28%) Arm B: all VTE 22/60 (36.7%) Absolute difference -8.7 %; 95%CI: [-30.0-12.7); p=0.43 Upper limb VTE : Arm A: 7/7 (100%) Arm B: 19/22 (86%)	Major bleeding Arm A: 0/25 (0%) Arm B: 1/60 (1.7%) p=NS	Not specified

Table 26 Ambulatory patients treated with chemotherapy

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[HAAS 2012] Prospective randomized double-blind study Not specified	Not specified/351 patients	6 months	Patients with metastatic breast cancer: TOPIC 1 Patients with metastatic lung cancer: TOPIC 2	Arm A: certoparin 3000 IU/day for 6 months Arm B: placebo for 6 months	TOPIC 1 Arm A: 7/174 (4%) Arm B: 7/177 (4%) TOPIC 2 Arm A: 12/268 (4.5 %) Arm B: 22/264 (8.3 %) TOPIC-1: OR= 1.02; 95%CI: [0.30-3.48] TOPIC-2: OR=0.52; 95%CI: [0.23-1.12]	TOPIC 1: any bleeding Arm A: 9/174 (5.2 %) Arm B: 3/177 (1.7 %) OR=3.18; 95%CI: [0.88-18.53] p=0.084 TOPIC 2: any bleeding Arm A: 37/268 (13.5 %) Arm B: 20/264 (7.3 %) OR=1.98; 95%CI: [1.08-3.71] p=0.024	
[MARAVEYAS2011] Randomized controlled study Apr 2003 - Jan 2009	123/123 patients	3 months	Patients aged 18 years or older Histologically/cytologically confirmed advanced or metastatic pancreatic cancer Karnofsky performance status (KPS): 60-100	Arm A: gemcitabine 1000 mg/m² Arm B: gemcitabine 1000 mg/m² + dalteparin 200 IU anti-Xa/kg in metastatic cancer patients + dalteparin 150 IU anti-Xa/kg in locally advanced cancer patients For 3 months	At 3 months Arm A: 16/64 (25%) Arm B: 2/59 (3.5%) Entire study Arm A: 20/64 (31%) Arm B: 7/59 (12%)	Major bleeding Arm A: 2/62 (3%) Arm B: 2/59 (3%)	Sudden death and lethal VTE Arm A: 6/64 (9%) Arm B: 0/59 (0%) p=NS
[AGNELLI2009] Prospective randomized double-blind study Oct 2003 - May 2007	Arm A: 769/779 patients Arm B: 381/387 patients	120 days	Ambulatory patients >18 years Chemotherapy Metastatic or locally advanced lung, gastrointestinal, breast, ovarian, or head and neck cancer	Arm A: nadroparin 3800 IU/day Arm B: placebo For duration of chemotherapy (up to 4 months maximum)	Arm A: Total: 11/769 (1.4%) Lung cancer: 7/199 (3.5%) Arm B : Total: 11/381 (2.9%) Lung cancer: 7/80 (8.8%) p=0.02 (calculated with stroke and arterial thrombosis at a rate of 0.4% in Arm A and 0.8% in Arm B)	Major bleeding Arm A: 5/769 (0.7%) Arm B: 0/381 p=0.18 Minor bleeding Arm A: 57/769 (7.4%) Arm B: 30/381 (7.9%) p=NS	Arm A: 33/769 (4·3%) Arm B: 16/381 (4.2%) p=NS
[PERRY2010] Prospective randomized double-blind study Oct 2002 - May 2006	Arm A: 99/99 patients Arm B: 87/87 patients	Arm A: 183 days Arm B: 15 days	Age >18 years Pathologically confirmed glioma grade III or IV Surgery + further treatment of glioma Chemotherapy	Arm A: dalteparin 5000 IU/day Arm B: placebo For 6 months	Symptomatic DVT or PE at 6 months Arm A: 9/99 (9%) Arm B: 13/87 (15%) HR=0.51; 95%CI: [0.19-1.4]; p=0.17 Symptomatic DVT or PE at 12 months Arm A: 11/99 (11%) Arm B: 14/87 (16%) p=NS	Major bleeding at 6 months Arm A: 3/99 (3%) Arm B: 0/87 Major bleeding at 12 months Arm A: 5/99 (5%) Arm B: 1/87 (2.3%) HR=4.2; 95%CI: [0.48-36] All major bleeding were intracranial	At 6 months Arm A: 18/99 (18%) Arm B: 11/87 (12.6%) HR=1.4; 95%CI: [0.6-3.2] At 12 months Arm A: 45/99 (45%) Arm B: 32/87 (38.7%) HR=1.2; 95%CI: [0.73-2]

Table 26 Ambulatory patients treated with chemotherapy (continued)

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[VERSO2010] Patients with lung cancer in 2 randomized double-blind studies, PROTECHT and TOPIC 2 Not specified	811/811 patients	Not specified	Patients with metastatic or locally advanced cancer treated with chemotherapy	Arm A: LMWH nadroparin 3800 IU/day for 4 months or certoparin 3000 IU/day for 6 months Arm B: placebo for 4 or 6 months	Symptomatic VTE LMWH: 15/467 (3.2%) Placebo: 19/344 (5.5%) RR=0.58; 95%CI: [0.28-1.06] NNT=50 Overall VTE events LMWH: 20/467 (4.3%) Placebo: 27/344 (7.8%) RR=0.54; 95%CI: [0.31-0.95] NNT=28	Major bleeding LMWH: 12/472 (2.5%) Placebo: 6/353 (1.7%) RR=1.50; 95%CI: [0.57-3.95]	Not specified
[RIESS2009] Open, prospective, randomized, multicenter study From a date not specified up to Jan 2009	312 patients /not specified	Not specified	Patients with pancreatic cancer treated with palliative chemotherapy	Arm A: enoxaparin 1mg/kg/day Arm B: observation For 3 months	Arm A: 8/160 (5%) Arm B: 22/152 (14.4%) p <0.01 Absolute RR= 8.6% RRR= 87% NNT=12	Major bleeding Arm A: 9.9% Arm B: 6.3% p=NS	Time to progression Arm A: 22 weeks Arm B: 19 weeks p=NS Overall survival Arm A: 31 weeks Arm B: 29 weeks p=NS

Table 27 Studies of prophylaxis in patients with myeloma treated with thalidomide or lenalidomide

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[ZANGARI2004] Retrospective study of VTE prophylaxis in myeloma patients with and without thalidomide Not specified	369/386 patients	Not specified	Patients with myeloma 4 cycles of combination chemotherapy followed by 2 cycles of high-dose therapy (HDT) with melphalan at 200 mg/m^2 supported by autologous PBSC rescue. Randomization with (thal +) or without thalidomide (thal-)	Thal -: no VTE prophylaxis Thal +: 1st cohort: coumadin 1 mg/day *vs*. no coumadin 2nd cohort: enoxaparin 40 mg/day	Chemotherapy+thal+no coumadin: 30/87 (34.4%) Chemotherapy+thal+coumadin: 10/35 (28.5%) HR=0.58; 95%CI: [0.271-1.233] p=0.156 Chemotherapy+thal+enoxaparin: 10/68 (14.7%) Chemotherapy+no thal+no prophylaxis: 28/196 (14.3%) p=0.81	No bleeding in the enoxaparin subgroup	Not specified
[PALUMBO2011] Multicenter, randomized, open-label study May 2006 - Jan 2009	Arm A: 220/224 patients Arm B: 220/222 patients Arm C: 219/221 patients	2.9 months	Patients with myeloma included in 2 studies of first-line chemotherapy: <65 years Bortezomib (Bor), thalidomide (Thal) and dexamethasone (Dex) or Thal Dex + autologous transplantation >65 years Melphalan - Bor - prednisone ± Thal	Patients receiving thalidomide: Arm A: aspirin 100 mg/day Arm B: warfarin 1.25 mg/day Arm C: enoxaparin 40 mg/day For 3 months if <65 years For 6 months if >65 years	At 6 months / Whole period Arm A: 12/220 (5.4%) / 16/220 (7.2%) Arm B: 18/220 (8.2%) / 21/220 (9.5%) Arm C: 6/219 (2.7%) / 10/219 (4.5%) At 6 months ASA *vs*. LMWH p=0.544 WAR *vs*. LMWH p=0.183 Whole period: p=NS Results including arterial events: All patients: p=NS, but the rate of arterial events was the same in the 3 groups >65 years: LMWH=ASA absolute difference: 3.2% 95%CI: [1.2-7.5]; p=0.151 >65 years: LMWH >VKA absolute difference: 11.3% 95%CI: [3.4-19.2]; p=0.06	Major bleeding Arm A: 3/220 (1.4%) Arm B: 0/220 (0%) Arm C: 0/219 (0%) p=NS Minor bleeding Arm A: 6/220 (2.7%) Arm B: 1/220 (0.4%) Arm C: 3/219 (1.4%) p=NS	Not specified
[IKHLAQUE2006] Retrospective study 2000 - 2004	131/131 patients	Arm A: 26 weeks Arm B: 24 weeks Arm C: 22 weeks	All patients prescribed thalidomide during the 4-year period Myeloma: n=93 Myelofibrosis or Myelodysplasia: n=12 Others: n=26	Arm A: no warfarin Arm B: warfarin 1-2 mg/day Arm C: warfarin (INR 2 to 3)	Arm A: 18/78 (23%) Arm B: 1/37 (2.7%) Arm C: 2/18 (11.1%) p=0.010, no warfarin compared to any dose of warfarin, p=0.011, no warfarin compared to low-dose warfarin	Arm A: 0/78 (0%) Arm B: 0/37 (0%) Arm C: 4/18 (22.2%)	Not specified

Table 28 Meta-analysis: patients with myeloma treated with thalidomide or lenalidomide

References	[HICKS2008]	[EL ACCAOUI2007]
Bibliographic search	Medline® (1966 - November 2007), Embase® (1980 - November 2007), Cochrane Library (2007, Issue 3), abstracts ASH (1999-2006), abstracts ASCO (1999-2007)	PubMed until 2006
Included studies	[MINNEMA2004], [LUDWIG2005], [PALUMBO2006], [BARLOGIE2006], [RAJKUMAR2006], [RAJKUMAR2006], [MACRO2006], [FACON2007], [HULIN2007}, [ZERVAS2007], Studies with subgroups of patients treated with LMWH: [MINNEMA2004], [PALUMBO2006], [BARLOGIE2006], [ZERVAS2007]	42 studies of patients with hematological malignancy, solid tumor or myeloma
Primary endpoint	Overall survival	Results for risk factors not specified Thalidomide Dexamethasone Chemotherapy Adequate VTE prophylaxis (LMWH or VKA with an INR between 2 and 3)
Secondary endpoint	Progression, response rate and adverse events (VTE)	
Statistical tests	Hazard ratios (HR) for OS, weighted relative risk (RR) for response and adverse events using the inverse variance method	Pearson Chi-Square test for the association between risk factors and VTE, then multivariate logistic regression to test for the significance of each variable
Results	All studies - Overall rate of VTE: Thalidomide: 260/1514 (17%) No thalidomide: 113/1595 (7%) RR=2.56; 95%CI: [1.88-3.49] Rate of VTE in subgroups of patients treated with LMWH: Thalidomide: 61/509 (11.9%) No thalidomide: 42/542 (7.7%) RR=1.54; 95%CI: [1.07-2.22]	Patients with myeloma: Patients with adequate VTE prophylaxis: 55/521 (9.5%) OR=0.6; 95%CI: [0.4–0.8] Patients with low-dose VKA: 22/154 (14.3%) OR=1.0; 95%CI: [0.6-1.7] Patients with antiplatelet therapy: 31/237 (13.1%) OR=0.7; 95%CI: [0.5-1.1] No prophylaxis: 268/2355 (11.4%) OR=1
Authors' conclusions	The relative risk of VTE with LMWH is lower than that seen without LMWH in the treatment regimen for multiple myeloma including thalidomide, but this RR is still significantly greater than one.	Administering prophylactic doses of LMWH or warfarin to maintain INR within the therapeutic range reduces the risk of VTE among multiple myloma patients.