PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

International Consensus Statement 2013
Guidelines According to Scientific Evidence

Developed under the auspices of the:

Cardiovascular Disease Educational and Research Trust (UK)
European Venous Forum
North American Thrombosis Forum
International Union of Angiology and
Union Internationale du Phlebologie

Cancer Patients

Chapter 11

Risk of VTE in Cancer Patients

- **Cancer produces a 7-fold increased risk compared with patients without malignancy[1]**
- **Risk for developing VTE in cancer patients undergoing surgery is approximately twice that for patients without cancer[2-4]**
- **PE is the most common cause of death in patients undergoing general, urologic or gynecologic surgery for cancer[5]**
- **For patients with solid tumors the risk of VTE is greater in the presence of metastatic disease compared with patients with only local disease[6-8]**

1. Blom JW, et al. JAMA 2005; 293:715-22.
2. Koopman MM, et al. N Engl J Med 1996; 334:682-7.
3. The Columbus Investigators. N Engl J Med 1997; 337:657-62.
4. Sifontes MT, et al. Br J Haematol 1997; 96:484-9.
5. Agnelli G, et al. Ann Surg 2006; 243:89-95.
6. Blom JW, et al. JAMA 2005; 293:715-22.
7. Blom JW, et al. J Thromb Haemost 2006; 4:529-35.
8. Chew HK, et al. Arch Intern Med 2006; 166:458-64.

Risk of VTE by Tumor Types

- **Highest rates of VTE[1]**
  - Tumors of the bone (37.7 per 1000)
  - Ovary (32.6 per 1000)
  - Brain (32.1 per 1000)
  - Pancreas (22.7 per 1000)
- **Studies demonstrate higher risk of VTE during the first 6 months of cancer diagnosis, decreasing rapidly thereafter[2-4]**
  - This early risk is likely to be related to the use of cancer treatments, especially chemotherapy and hormonal therapy[2,5-6]

1. Blom JW, et al. J Thromb Haemost 2006; 4:529-35
2. Blom JW, et al. JAMA 2005; 293:715-22.
3. Chew HK, et al. Arch Intern Med 2006; 166:458-64.
4. Alcalay A, et al. Clin Oncol 2006; 24:1112-8.
5. Blom JW, et al. J Thromb Haemost 2006; 4:529-35.
6. Ikhlaque N, et al. Am J Hematol 2006; 81:420-2.

VTE and Breast Cancer

- **VTE in patients with breast cancer is often associated with the risk of chemotherapy-associated thrombosis**
  - VTE rates range from 1% to 17%[1-6]
- **Incidence of VTE varies according to breast cancer stage (summarized in tables that follow)**

1. Weiss RB, et al. Cancer Treat Rep 1981; 65:677-9.
2. Levine MN, et al. N Engl J Med 1988; 318:404-7.
3. Fisher B, et al. J Clin Oncol 1990; 8:1005-18.
4. Saphner T, et al. J Clin Oncol 1991; 9:286-94.
5. Clahsen PC, et al. J Clin Oncol 1994; 12:1266-71.
6. Pritchard KI, et al. J Clin Oncol 1996; 14:2731-7.

Incidence of Thrombosis
Early-Stage Breast Cancer

Study	Treatment	Patients (n)	Patients with Thrombosis (%)
Node-Negative			
Fisher et al, 1990[1]	T Placebo CMFT T	1318 1326 768 771	0.9 0.15 4.2 0.8

A, adriamycin; C, cyclophosphamide; F, fluorouracil; M, methotrexate; P, prednisone; T, tamoxifen; V, vincristine

1. Fisher B, et al. J Clin Oncol 1990; 8:1005-18.

Incidence of Thrombosis
Early-Stage Breast Cancer

Study	Treatment	Patients (n)	Patients with Thrombosis (%)
Node-Positive			
Levine et al, 1988[1]	CMFVP CMFVP + AT	102 103	8.8 4.9
Pritchard et al, 1996[2]	CMF + T T	353 352	9.6 1.4
Clahsen et al, 1994[3]	Perioperative FAC	1292	2.1
Rivkin et al, 1994[4]	No Rx CMFVP + T CMFVP	1332 303 300	0.8 3.6 1.3
Fisher et al, 1990[5]	T ACT	295 383	0 3.1
Weiss et al, 1981[6]	T CMFVP CMF	367 143 144	1.6 6.3 3.5

A, adriamycin; C, cyclophosphamide; F, fluorouracil; M, methotrexate; P, prednisone; T, tamoxifen; V, vincristine

1. Levine MN, et al. N Engl J Med 1988; 318:404-7.
2. Pritchard KI, et al. J Clin Oncol 1996; 14:2731-7.
3. Clahsen PC, et al. J Clin Oncol 1994; 12:1266-71.
4. Rivkin SE, et al. J Clin Oncol 1994; 12:2078-85.
5. Fisher B, et al. J Clin Oncol 1990; 8:1005-18.
6. Weiss RB, et al. Cancer Treat Rep 1981; 65:677-9.

Incidence of Venous Thrombosis
Different Tumors

Study	Tumor Type	Patients (n)	Cumulative Incidence of VTE (%)	Follow-Up
Alcalay et al, 2006[1]	Colorectal	68,142	3.1	2 y
Agnelli et al, 2009[2]	Advanced colorectal + chemotherapy	266	10.2	3.3 y
Caruso et al, 2010[3]	Lymphoma Non-Hodgkin Hodgkin	18,018 997 2505	5.3 6.5 4.7	1-3 y 1-3 y 1-3 y
Tateo et al, 2005[4]	Ovarian	253	16.6	12 y
Brandes et al, 1997[5]	Malignant glioma	77	26	---
Weijl et al, 2000[6]	Germ cell	179	8.4	---

1. Alcalay A, et al. Clin Oncol 2006; 24:1112-8.
2. Agnelli G, et al. Lancet Oncol 2009; 10:943-9.
3. Caruso V, et al. Blood 2010; 115:5322-8.
4. Tateo S, et al. Gynecol Oncol 2005; 99:119-25.
5. Brandes AA, et al. Eur J Cancer 1997; 33:1592-6.
6. Weijl NI, et al. J Clin Oncol 2000; 18:2169-78.

Incidence of Venous Thrombosis

Patients with Different Tumors

Study	Tumor Type	Patients (n)	Cumulative Incidence of VTE (%)	Follow-Up
Chew et al, 2006[1]	Prostate (localized)	33,383	1.0	2 y
	Prostate (regional)	7041	1.3	2 y
	Prostate (remote)	3515	1.2	2 y
	Breast (localized)	27,014	0.8	2 y
	Breast (regional)	13,629	1.3	2 y
	Breast (remote)	2029	2.6	2 y
	Uterus (localized)	6437	1.2	2 y
	Uterus (regional)	1302	2.2	2 y
	Uterus (remote)	598	4.8	2 y
	Lung (localized)	6558	1.3	2 y
	Lung (regional)	8775	2.2	2 y
	Lung (remote)	22,486	2.4	2 y
Jacobson et al, 2009[2]	Cervical cancer	436	11.7	7 y
Jacobson et al, 2009[3]	Invasive cervical + chemoradiation	48	16.7	≥8 mos.

1. Chew HK, et al. Arch Intern Med 2006; 166:458-64.
2. Jacobson G, et al. Gynecol Oncol 2009; 113:240-4.
3. Jacobson GM, et al. Gynecol Oncol 2005; 96:470-4.

VTE Risk Assessment

- **Validated VTE risk assessment model for ambulatory cancer patients on chemotherapy is available[1]**
- **Five predictive variables have been identified**
  - Cancer site (2 points for very high-risk site, 1 point for high-risk site)
  - Platelet count of ≥ $350x10^9$/L
  - Hemoglobin < 100 g/L (10 g/dL) and/or use of erythropoiesis-stimulating agents
  - Leukocyte count > $11x10^9$/L
  - Body mass index ≥ 35 kg/m^2 (1 point each)
- **Rates of VTE over a median of 2.5 months**
  - 0.8% and 0.3% in low-risk (score = 0)
  - 1.8% and 2% in intermediate-risk (score = 1-2)
  - 7.1% and 6.7% in high-risk category (score ≥ 3)

1. Khorana AA, et al. Blood 2008; 111:4902-7.

Review of Evidence
Surgical Cancer Patients

- **In surgical patients with malignancy, LDUH reduces the risk of DVT and fatal PE; LMWH is at least as effective as LDUH[1-10]**
- **In gynecologic oncology patients, LDUH twice a day demonstrated no benefit when compared with no prophylaxis, whereas administration 3 times a day was effective (RR 0.47; 95% CI 0.22 to 0.98)[5,11]**

1. Saphner T, et al. J Clin Oncol 1991; 9:286-94.
2. Ballard RM, et al. J Obstet Gynaecol Br Commonw 1973; 80:469-72.
3. An international multicentre trial. Lancet 1975; 2:45-51.
4. Clagett GP, Reisch JS. Ann Surg 1988; 208:227-40.
5. Clark-Pearson DL, et al. Am J Hematol 2006; 81:420-2.
6. ENOXACAN. Br J Surg 1997; 84:1099-103.
7. McLeod RS, et al. Ann Surg 2001; 233:438-44.
8. Mismetti P, et al. Br J Surg 2001; 88:913-30.
9. Leonardi MJ, et al. Ann Surg Oncol 2007; 14:929-36.
10. Akl EA, et al. Arch Intern Med 2008; 168:1261-9.
11. Clarke-Pearson DL, et al. Am J Obstet Gynecol 1983; 145:606-13.

Review of Evidence
Surgical Cancer Patients

- **In a study of 2070 patients, 65% of whom underwent laparotomy for malignant disease, 2 different doses of the LMWH (dalteparin sodium) were assessed[1]**
  - The frequency of VTE was reduced from 14.9% in patients receiving 2500 anti-Xa U to 8.5% in patients receiving 5000 units once daily (RR 0.52; 95% CI 0.37 to 0.74) without any significant increase in peri-operative bleeding complications

1. Bergqvist D, et al. Br J Surg 1995; 82:496-501.

Review of Evidence
Surgical Cancer Patients

- **Continuation of LMWH for 4 weeks after discharge home reduces the risk of asymptomatic DVT as demonstrated by venography from 13.8% to 5.5% (RR 0.36; 95% CI 0.16 to 0.79)[1]**
- **Extended thrombophylaxis was associated with increased bleeding at 4 weeks (RR 2.94; 95% CI 0.12 to 71.85) and failed to demonstrate a reduction in death at 3 months (RR 0.49; 95% CI 0.12 to 1.94)[2]**

1. Bergqvist D, et al. N Engl J Med 2002; 346:975-80.
2. Akl EA, et al. Thromb Haemost 2008; 100:1176-80.

Review of Evidence
Surgical Cancer Patients

- **CANBESURE, a randomized, double-blind study of 625 patients admitted for abdominal or pelvic surgery for cancer received bemiparin once daily for 8 days followed by either bemiparin or placebo for 20 days[1]**
  - Extended thromboprophylaxis with bemiparin had no effect on the primary efficacy endpoint of venographically detected DVT, non-fatal PE and all-cause mortality (10.1% in bemiparin group vs 13.3% in the placebo group)
  - However, the incidence of major VTE (proximal DVT, non-fatal PE and VTE-related deaths) was decreased from 4.6% to 0.8% (RRR 82.4%; 95% CI 21.5 to 96.1%; P = 0.010) without any increase in major bleeding complications

1. Kakkar VV, et al. J Thromb Haemost 2010; 8:1223-9.

Review of Evidence
Medical Cancer Patients

- **In a prospective study of 311 ambulant cancer patients with metastatic breast cancer receiving chemotherapy, patients were randomized to low dose warfarin (INR between 1.3 and 1.9) or placebo[1]**
  - Frequency of symptomatic VTE was reduced from 4.5% in the placebo group to 0.8% in the warfarin group (Fisher's exact test 0.038) (RR 0.14; 95% CI 0.02 to 1.18)

1. Levine M, et al. Lancet 1994; 343:886-9.

Review of Evidence
Medical Cancer Patients

- **In a randomized, double-blind study in ambulatory patients with metastatic or locally advanced cancer, 1150 patients were randomized to either nadroparin (3,800 IU anti-Xa od, SC) or placebo[1]**
  - The rate of symptomatic venous or arterial events was halved in the LMWH group (2.0% for nadroparin vs 3.9% for placebo; single-sided P=0.02); similar reductions in events were reported for VTE (1.4% vs 2.9%, respectively)
  - The rate of major bleeding events did not differ between treatment groups (0.7% vs 0%, respectively; two-sided P=0.18)

1. Agnelli G, et al. Lancet Oncol 2009; 10:943-9.

Review of Evidence
Medical Cancer Patients

- **Semuloparin 20 mg o.d. was compared with placebo for ambulatory patients receiving chemotherapy for cancer with a median treatment duration of 3.5 months[1]**
  - VTE occurred in 20 (1.2%) of 1608 patients receiving semuloparin, as compared with 55 (3.4%) of 1604 receiving placebo (RR 0.36; 95% CI 0.21 to 0.60)
  - The incidence of clinically relevant bleeding was 2.8% and 2.0% in the semuloparin and placebo groups respectively (RR 1.40; 95% CI, 0.89 to 2.21)
  - Major bleeding occurred in 19 (1.2%) of 1589 patients receiving semuloparin and 18 (1.1%) of 1583 receiving placebo (RR 1.05; 95% CI, 0.55 to 1.99)

1. Agnelli G, et al. N Engl J Med 2012; 366:601-9.

Review of Evidence
Medical Cancer Patients

- **In a meta-analysis of 3 randomized trials of patients with lung cancer, concomitant treatment with warfarin was associated with an increased risk of bleeding (odds ratio 1.7; 95% CI 1.2 to 2.6) whereas no such association was apparent for LMWH[1]**
  - Prophylactic anticoagulation with warfarin reduced significantly (5.5% vs 23.7%, P=0.010) the risk of DVT in patients treated with thalidomide for a variety of indications[2]
  - The potential role of LMWH in prolonging survival among patients with cancer is currently under investigation[3]

1. Le Maitre A, et al. J Thorac Oncol 2009; 4:586-94.
2. Ikhlaque N, et al. Am J Hematol 2006; 81:420-2.
3. Lazo-Langner A, et al. J Thromb Haemost 2007; 5:729-37.

Review of Evidence
Cancer Patients with Central Venous Catheters

- **Historical data suggest that cancer patients with central venous catheters have a high frequency of VTE**
- **Recent research suggests a low incidence of symptomatic catheter-related thrombosis of 5% or less[1-4]**
- **Reported rates of venographically detected upper limb DVT in the absence of thromboprophylaxis, while highly variable, remain high (18%)[2,5]**

1. Couban S, et al. J Clin Oncol 2005; 23:4063-9.
2. Verso M, et al. J Clin Oncol 2005; 23:4057-62.
3. Karthaus M, et al. Ann Oncol 2006; 17:289-96.
4. Lee AY, et al. J Clin Oncol 2006; 24:1404-8.
5. Cunningham MS, et al. Br J Cancer 2006; 94:189-94.

Review of Evidence
Cancer Patients with Central Venous Catheters

- **Dalteparin 2500 U od has been shown to reduce DVT from 62% to 6% (RR 0.04; 95% CI 0.01 to 0.42)[1]**
- **Warfarin (1 mg/day) has been shown to reduce the risk of DVT from 37% to 9.5% (RR 0.17; 95% CI 0.05 to 0.59)[2]**
- **Recent clinical trials evaluating low dose warfarin, fixed dose warfarin or LMWH, and several meta-analyses have shown no benefit of routine thromboprophylaxis[1-12]**
  - This may be due to changes in the way that newer generations of catheters are inserted or maintained and improvements in catheter biocompatibility

1. Monreal M, et al. Thromb Haemost 1996; 75:251-3.
2. Bern MM, et al. Ann Intern Med 1990; 112:423-8.
3. Couban S, et al. J Clin Oncol 2005; 23:4063-9.
4. Verso M, et al. J Clin Oncol 2005; 23:4057-62.
5. Karthaus M, et al. Ann Oncol 2006; 17:289-96.
6. Young AM, et al. Lancet 2009; 373:567-74.
7. Heaton DC, et al. Intern Med J 2002; 32:84-8.
8. Walshe LJ, et al. J Clin Oncol 2002; 20:3276-81.
9. Verso M, Agnelli G. J Clin Oncol 2003; 21:3665-75.
10. Niers TM, et al. J Thromb Haemost 2007; 5:1878-82.
11. Cunningham MS, et al. Br J Cancer 2006; 94:189-94.
12. Akl EA, et al. Cancer 2008; 112:2483-92.
13. Chaukiyal P, et al. Thromb Haemost 2008; 99:38-43.
14. Carrier M, et al. J Thromb Haemost 2007; 5:2552-4.

VTE Prophylaxis Recommendations
Cancer Patients

- **In surgical patients with cancer, LDUH (5000 IU 8 hourly commenced prior to operation) or LMWH (initiated and dosed according to manufacturer's recommendations) should be used**
  - Level of evidence: High
- **In the post-discharge period prolonged prophylaxis with LMWH (enoxaparin, dalteparin or bemivarin) for up to 4 weeks after operation should be considered**
  - Level of evidence: Moderate

VTE Prophylaxis Recommendations
Cancer Patients

- **In ambulant non-surgical patients with advanced breast cancer receiving chemotherapy, the use of VKA to maintain an INR of between 1.3 and 1.9 may be considered**
  - Level of evidence: Moderate
- **Semuloparin is an alternative**
  - Level of evidence: High

VTE Prophylaxis Recommendations
Cancer Patients

- **For cancer patients hospitalized with acute medical illness, thromboprophylaxis should be based on the risk for VTE determined by the acute medical co-morbidity. LMWH (initiated and dosed according to manufacturer's recommendations) or LDUH should be used (5000 IU 8 hourly)**
  - Level of evidence: High
- **For cancer patients with central venous catheters, routine use of thromboprophylaxis to prevent central venous catheter associated thrombosis is not recommended**
  - Level of evidence: Moderate