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

Treatment in Cancer Patients

Chapter 18

General Considerations

- **Cancer patients who develop an episode of thrombosis are at higher risk for subsequent recurrent thrombosis[1]**
  - A reported frequency of 27.1 per 100 patient years for those with cancer
  - A reported frequency of 9.0 per 100 patient years for those without cancer
- **Bleeding risk for cancer patients receiving oral anticoagulant therapy was 13.3 per 100 patient years and 2.1 per 100 patient years for non-cancer patients[1]**

1. Hutten BA, et al. J Clin Oncol 2000; 18:3078-83.

General Considerations

- **A RCT of 842 patients, 181 of whom had cancer-associated thrombosis, demonstrated:[1]**
  - 12-month cumulative incidence of recurrent thromboembolic disease of 20.7% for cancer patients compared with 6.8% for those without cancer
  - Bleeding was also more frequent in cancer patients than in non-cancer patients (12.4% versus 4.9%; HR 2.2)

1. Prandoni P, et al. Blood 2002; 100:3484-8.

VTE in Cancer
Initial Treatment

- **Studies have not addressed the initial treatment of VTE in cancer patients**
- **Meta-analyses of studies that compared UFH with LMWH for initial treatment of DVT included patients with malignant disease[1-4]**
  - IV UFH and SQ LMWH are equally effective and safe for the initial treatment of DVT
  - Recommendations generated for non-cancer patients are therefore extrapolated for use in cancer patients with thrombosis

1. Gould MK, et al. Ann Intern Med 1999; 130:800-9.
2. Dolovich LR, et al. Arch Intern Med 2000; 160:181-8.
3. van Den Belt AG, et al. Cochrane Database Syst Rev 2000:CD001100.
4. Hettiarachchi RJ, et al. Curr Opin Pulm Med 1998; 4:220-5.

VTE in Cancer
Initial Treatment

- **Post-hoc analyses from 2 randomized trials comparing the safety, efficacy and overall survival with fondaparinux versus LMWH (followed by VKA in both groups) in 237 cancer patients with VTE showed:[1]**
  - Recurrence rate in DVT patients of 5.4% in the enoxaparin group versus 12.7% in the fondaparinux group (absolute difference 7.3%, 95% CI 0.1, 14.5)
  - Among PE patients, a recurrence was observed in 8.9% in the fondaparinux group versus 17.2% in the UFH group (absolute difference –8.3% (95% CI 16.7 to 0.1)
  - Analysis did not show any difference in terms of bleeding or overall survival between groups

1. van Doormaal FF, et al. Thromb Haemost 2009; 101:762-9.

VTE in Cancer
Initial Treatment

- **LMWH therapy for the initial treatment of DVT offers an opportunity for outpatient management of patients with cancer-associated VTE[1-5]**
- **Although initial management of PE in cancer patients has not been specifically addressed, trials have evaluated IV UFH and SQ LMWH for PE treatment[4,6]**
- **A study of 108 patients with PE, 22% of whom had cancer, evaluated dalteparin for outpatient use[7]**
  - Recurrent thrombosis occurred in 5.6% of the 108 patients, with a major bleeding rate of 1.9%

1. Levine M, et al. N Engl J Med 1996; 334:677-81.
2. Koopman MM, et al. N Engl J Med 1996; 334:682-7.
3. Ageno W, et al. Haematologica 2005; 90:220-4.
4. The Columbus Investigators. N Engl J Med 1997; 337:657-62.
5. Imberti D, et al. J Thromb Haemost 2005; 3:1370-5.
6. Simonneau G, et al. N Engl J Med 1997; 337:663-9.
7. Kovacs MJ, et al. Thromb Haemost 2000; 83:209-11.

VTE in Cancer
Initial Treatment

- **Systematic review identified 13 studies that compared LMWH to UFH and 2 that compared fondaparinux to UFH[1]**
  - Meta-analysis of 11 studies showed a statistically significant reduction in mortality at 3 months of follow-up with LMWH compared with UFH (RR 0.71; 95% CI 0.52 to 0.98)
  - Meta-analysis of three studies comparing LMWH with UFH showed no reduction in VTE recurrence (RR 0.78; 95% CI 0.29 to 2.08)
  - There were no difference between heparin and fondaparinux in mortality (RR 1.27; 95% CI 0.88 to 1.84), recurrent VTE (RR 0.95; 95% CI 0.57 to 1.60), major bleeding (RR 0.79; 95% CI 0.39 to1.63) or minor bleeding (RR 1.50; 95% CI 0.87 to 2.59)

1. Akl EA, et al. Cochrane Database Syst Rev 2011; 4:CD006649.

VTE in Cancer
Initial Treatment

- **Outpatient therapy with LMWH is preferred in cancer patients with a potentially shortened duration of life where quality of life is an essential issue**
- **The safety and efficacy of inferior vena cava filters for management of cancer-associated thrombosis have not been evaluated**
- **Early benefits of vena cava filters are outweighed by longer-term risks for recurrent thrombosis in patients with malignant disease[1]**
- **Patients with a malignancy have a fourfold greater risk of recurrent thrombosis and a threefold greater risk anticoagulant-associated bleeding[2]**

1. Jarrett BP, et al. J Vasc Surg 2002; 36:704-7.
2. Louzada ML, et al. Thromb Res 2009; 123:837-44.

Secondary Prevention of VTE
Long-Term Anticoagulation

- **Study of 676 patients with cancer-associated VTE was sufficiently powered for long-term treatment outcomes[1]**
  - Patients received 5-7 days' treatment with 200 IU/kg of dalteparin
  - Continued either LMWH in the full treatment dose for the remainder of the month followed by 75-80% of the full treatment dose for the remaining 5 months, or VKA treatment (INR of 2-3) for 6 months
  - Demonstrated a 52% reduction in the frequency of recurrent thromboembolic events over 6 months in favor of dalteparin (8.0% with dalteparin vs 15.8% with VKA)
  - No significant increase in the risk of bleeding complications
- **Findings supported by data from 2 randomized open-label trials[2,3]**

1. Lee AY, et al. N Engl J Med 2003; 349:146-53.
2. Hull RD, et al. Am J Med 2006; 119:1062-72.
3. Romera A, et al. Eur J Vasc Endovasc Surg 2009; 37:349-56.

Secondary Prevention of VTE
Long-Term Anticoagulation

- **In the prospective, multicenter LITE trial, 200 patients with cancer and acute symptomatic proximal vein thrombosis were randomized to usual care (IV UFH followed by long-term warfarin sodium) or tinzaparin[1]**
- **At 12 months, the rate of recurrent VTE was 15% in the usual-care group versus 7% in the tinzaparin group (P=0.044)**

1. Hull RD, et al. Am J Med 2006; 119:1062-72.

Secondary Prevention of VTE
Long-Term Anticoagulation

- **The superiority of long-term treatment with LMWH over VKA for secondary prevention of VTE in patients with cancer has been confirmed in several meta-analyses[1-3]**
- **One analysis involving 6 RCTs comparing LMWH with VKA showed:[2]**
  - A reduction in risk of VTE with LMWH (HR 0.47; 95% CI 0.32 to 0.71)
  - No increased risk of bleeding (RR 0.91; 95% CI 0.64 to 1.31)
  - No thrombocytopenia (RR 1.02; 95% CI 0.60 to 1.74)
  - No survival benefit (HR 0.96; 95% CI 0.81 to 1.14)

1. Louzada ML, et al. Thromb Res 2009; 123:837-44.
2. Akl EA, et al. Thromb Haemost 2008; 100:1176-80.
3. Noble SI, et al. Lancet Oncol 2008; 9:577-84.

Potential Survival Benefit of LMWH

- **Patients receiving LMWH over a prolonged period have an improved survival[1-8]**
- **The potential role of LMWH in prolonging survival appears dependent upon the tumor stage**
- **Two randomized trials in patients with advanced malignancy did not demonstrate any survival benefit with LMWH therapy versus placebo[9,10]**

1. Lee AY, et al. N Engl J Med 2003; 349:146-53.
2. Hull RD, et al. N Engl J Med 1992; 326:975-82.
3. Green D, et al. Lancet 1992; 339:1476.
4. Prandoni P, et al. Lancet 1992; 339:441-5.
5. Siragusa S, et al. Am J Med 1996; 100:269-77.
6. Lee AY, et al. J Clin Oncol 2005; 23:2123-9.
7. von Tempelhoff GF, et al. Int J Oncol 2000; 16:815-24.
8. Akl EA, et al. Cochrane Database Syst Rev 2007:CD006652.
9. Kakkar AK, et al. J Clin Oncol 2004; 22:1944-8.
10. Sideras K, et al. Mayo Clin Proc 2006; 81:758-67.

Potential Survival Benefit of LMWH

- **In one study, Kaplan-Meier survival estimates in patients alive 17 months after randomization showed:[1]**
- **Improved survival with LMWH versus placebo (78% vs 55% at 2 years and 60% vs 36% at 3 years, respectively, P=0.03)**
- **But these patients were not defined *a priori***

1. Kakkar AK, et al. J Clin Oncol 2004; 22:1944-8.

Potential Survival Benefit of LMWH

- **Study of 302 patients with advanced solid malignancy without VTE compared a 6-week course of nadroparin versus placebo:[1]**
  - Nadroparin group demonstrated a lower risk of death at 12 months (median survival 8.0 vs 6.6 months; HR 0.75, 95% CI 0.59 to 0.96), which remained significant after adjustment for confounders
  - A-priori analysis in patients with a life expectancy of 6 months or more at enrollment demonstrated:
    - A greater benefit of LMWH treatment (15.4 vs 9.4 month survival; HR 0.64, 95% CI 0.45 to 0.90)
    - Which was reduced in patients with a shorter life expectancy (HR 0.88, 95% CI 0.62 to 1.25)

1. Klerk CP, et al. J Clin Oncol 2005; 23:2130-5.

Potential Survival Benefit of LMWH

- **Systematic review of 5 randomized clinical trials involving heparin treatment (UFH or LMWH) demonstrated:**
  - A survival benefit with heparin treatment (HR 0.77; 95% CI 0.65 to 0.91) without any increased risk of bleeding (RR 1.78; 95% CI 0.73 to 4.38)
  - The benefit was most notable in the subgroup with limited small cell lung cancer (HR 0.56; 95% CI 0.38 to 0.83), and was not significant for patients with extensive small cell lung cancer (HR 0.80; 95% CI 0.60 to 1.06) or advanced cancer (HR 0.84; 95% 0.68 to 1.03)
- **These data suggest that LMWH may offer a survival benefit, which is greater in patients with less advanced disease and better prognosis**

Recommendations
Treatment in Cancer Patients

- **The initial and long term treatment of DVT and PE in patients with cancer is LMWH administered for 3-6 months**
  - Level of evidence: High
- **If the health care economics of a system do not allow the use of long-term LMWH, it is acceptable to treat initially with UFH or LMWH followed by long-term VKA therapy**
  - Level of evidence: High