

PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

International Consensus Statement 2013 Guidelines According to Scientific Evidence

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European Venous Forum

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Treatment in Cancer Patients

Chapter 18

General Considerations

- **Cancer patients who develop an episode of thrombosis are at higher risk for subsequent recurrent thrombosis¹**
 - ▶ 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 patients¹**

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)

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 disease¹⁻⁴**
 - ▶ 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

VTE in Cancer

Initial Treatment

- **LMWH therapy for the initial treatment of DVT offers an opportunity for outpatient management of patients with cancer-associated VTE¹⁻⁵**
- **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 use⁷**
 - ▶ 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 UFH¹**
 - ▶ 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 to 1.63) or minor bleeding (RR 1.50; 95% CI 0.87 to 2.59)

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 disease¹**
- **Patients with a malignancy have a fourfold greater risk of recurrent thrombosis and a threefold greater risk anticoagulant-associated bleeding²**

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 outcomes¹**
 - ▶ 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 tinzaparin¹
- At 12 months, the rate of recurrent VTE was 15% in the usual-care group versus 7% in the tinzaparin group (P=0.044)

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-analyses¹⁻³**
- **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 survival¹⁻⁸**
- **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*

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)

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