

# Cancer-associated venous thromboembolism NCCN clinical practice guidelines—Update 2010

HOT SPOT

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## Background

Venous thromboembolism (VTE) is a common and life-threatening complication in cancer patients. VTE includes deep venous thrombosis (DVT) and/or pulmonary embolism (PE).

- Occurs in 4% to 20% of cancer patients during the course of their disease.
- Cancer patients have 4x to 7x higher risk of VTE compared to other patients.
- VTE in cancer patients → 2x to 8x higher risk of death.
- Second leading cause of death overall in cancer patients.
- Leading cause of death in initial 30 days post cancer surgery.

## NCCN Guidelines

The National Comprehensive Cancer Center Network (NCCN) is a consortium of 21 leading academic cancer institutions in the United States.

- In 2005 NCCN developed evidence-based guidelines for recommended VTE management (diagnosis, prophylaxis, treatment).
- Based on graded levels of evidence and consensus among interdisciplinary panel of oncology experts from NCCN member cancer centres (Table 1).
- Guidelines are updated each year responding to new research findings and suggestions from panel members and their institutions.

## Summary of the major guideline changes in 2010

The following are the substantive changes that have an important impact on clinical management issues. Please see the full guidelines (NCCN, 2010) for other changes and details (all recommendations are category 2A unless otherwise stated).

### 1. Prevention of VTE in cancer patients

- **VTE Risk Factors revised into five categories:** General patient risk factors, High risk outpatients on chemotherapy, Treatment-related risk factors, Modifiable risk factors, Multiple Myeloma Risk Factors (see Tables 2 to 6).
- **Prophylaxis—Ambulatory cancer patients at risk**

#### Select patients:

- receiving highly thrombotic anti-angiogenesis therapy (i.e., myeloma patients—Thalidomide/Lenalidomide and high-dose Dexamethasone (> 480 mg/month) or Doxorubicin or multi-agent chemotherapy
- myeloma patients with two or more individual or myeloma risk factors (Tables 2 to 6)

#### Recommended VTE prophylaxis:

- LMWH (prophylaxis dose)
- Warfarin (INR 2-3)

### Myeloma patients:

- one or fewer individual or myeloma risk factors (see Tables 2 to 6)

#### Recommended VTE Prophylaxis:

- ASA 81 to 325 mg od

### 2. Diagnosis of VTE in cancer patients

- D-dimer has limited utility in the diagnostic workup of VTE in cancer patients.
- New risk stratification based on Pulmonary Embolism Severity Index

**Table 1: NCCN categories of evidence and consensus (NCCN, 2010)**

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is no uniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

**Table 2: General patient risk factors (NCCN, 2010)**

- Active cancer
- Advanced stage of cancer
- Cancer types at higher risk: bladder, brain, gynecologic, lung, lymphoma, myeloproliferative, pancreas, stomach, testicular
- Regional bulky lymphadenopathy with extrinsic vascular compression
- Familial/acquired hypercoagulability (including pregnancy)
- Medical comorbidities: Infection, renal, pulmonary, heart failure, arterial thromboembolism
- Poor performance status
- Older age

**Table 3: High-risk outpatients on chemotherapy based on combinations of risk factors (Khorana, Kuderer, et al., 2008)**

- Active cancers associated with high incidence of VTE: stomach, pancreas, lung, lymphoma, gynecologic, bladder, testicular
- Pre-chemotherapy platelet count > 350 × 10<sup>9</sup>/L
- Pre-chemotherapy WBC > 11 × 10<sup>9</sup>/L
- Hemoglobin < 100 g/L
- Use of erythropoietic stimulating agents
- BMI ≥ 35 kg/m<sup>2</sup>
- Prior VTE.

**Table 4: Treatment-related risk factors (NCCN, 2010)**

- Major surgery
- Central venous catheter/IV catheter
- Chemotherapy especially:
  - Bevacizumab
  - Thalidomide/Lenalidomide plus high dose Dexamethasone
- Exogenous estrogen compounds
  - Hormone replacement (HRT)
  - Contraceptives
  - Tamoxifen/Raloxifene
  - Diethylstilbestrol

**Table 5: Modifiable risk factors (NCCN, 2010)**

- Smoking
- Obesity
- Activity level/exercise

**Table 6: Multiple myeloma risk factors (NCCN, 2010)**

- M Spike > 1.6 g/dl
- Progressive disease
- Hyperviscosity

(PESI) (Table 7) score to identify PE patients at lower or higher risk of morbidity and mortality to guide diagnostic strategies and treatment options (including out-patient treatment, thrombolysis, embolectomy and IVC filters)—see full guidelines for management algorithms.

<b>Table 7: Pulmonary Embolism Severity Index – PESI</b> (Donze, Le Gal, et al., 2008)	
<b>Predictor</b>	<b>Score Points</b>
Age per year	Age in years
Male sex	+10
History of heart failure	+10
History of chronic lung disease	+10
Pulse $\geq$ 110/min	+20
Resp. rate $\geq$ 30/min ( $\pm$ supplemental O <sub>2</sub> )	+20
Temp. $<$ 36°C	+20
Arterial O <sub>2</sub> sat. $<$ 90% ( $\pm$ supplemental O <sub>2</sub> )	+20
Systolic BP $<$ 100 mm Hg	+30
History of cancer	+30
Altered mental state* (*confusion, disorientation, somnolence)	+60
<b>Total Score Points</b>	
<b>Low risk <math>\leq</math> 85 points</b>	<b>2% mortality at 90 days</b>
<b>Higher risk <math>\geq</math> 86 points</b>	<b>19% mortality at 90 days</b>

### 3. Treatment of venous thromboembolism<sup>1,2</sup>

#### • Acute management:

- Low-molecular weight heparin (LMWH)<sup>3</sup>
- Dalteparin (200 u/kg s.c. daily)<sup>4</sup>
- Enoxaparin (1 mg/kg s.c. q 12h)
- Tinzaparin<sup>5</sup> (175 u/kg s.c. daily)
- Fondaparinux<sup>6</sup> (5 mg [ $<$  50 kg]; 7.5 mg [50–100 kg]; 10 mg [ $>$  100 kg] subcutaneous daily)
- Unfractionated Heparin (IV) Target aPTT of 2.0–2.5  $\times$  control or as per institution’s standard operating protocol.

<sup>1</sup> Agent selection based on: Renal failure (C<sub>cr</sub>,  $<$  30 ml/min), inpatient/outpatient FDA approval, cost, ease of administration, monitoring, ability to reverse anticoagulation.

<sup>2</sup> Hemoglobin, hematocrit, platelet count every two to three days for first 14 days and every two weeks thereafter, or as clinically indicated.

<sup>3</sup> LMWHs should be used with caution in patients with renal dysfunction. Dose adjustment and Anti-Xa monitoring may be required.

<sup>4</sup> Although each LMWH has been studied in clinical trials in cancer patients, Dalteparin’s efficacy in this population has the highest quality evidence and is the only LMWH approved by the FDA for this indication.

<sup>5</sup> Tinzaparin should be avoided in patients over 70 years with renal insufficiency.

<sup>6</sup> Fondaparinux is contraindicated in patients with creatinine clearance  $<$  30 ml/min. Should be used with caution in patients with moderate renal insufficiency (creatinine clearance 30–50 ml/min), weight  $<$  50 kg, or age  $>$  75 yrs.

#### • Chronic management:

- LMWH: **preferred treatment for first six months** as monotherapy without warfarin for patients with proximal DVT or PE and for prevention of recurrent VTE in patients with advanced/metastatic cancer (**category 1 recommendation**).

#### • Chronic management

- If warfarin is selected for chronic anticoagulation:
  - Initiate warfarin concurrently with parenteral agent (IV UFH or LMWH) used for acute treatment and continue both therapies for at least five days and until INR  $>$  2.0 for 24+ hours.
  - During transition to warfarin, INR should be measured at least two times per week. Once on warfarin alone, INR measured at least once weekly initially. Once INR stable, between 2–3, can reduce frequency of INR testing, but no less than once monthly.

#### • Catheter-associated thrombosis

- **If catheter still required (no contraindication to anticoagulants)**
  - Anticoagulate as long as catheter in place. **Recommended duration of therapy at least three months**
  - Consider catheter removal if symptoms persists
  - Massive catheter-related DVT  $\rightarrow$  consider thrombolysis.
- **If catheter not required (no contraindication to anticoagulants)**
  - Remove catheter when clinically appropriate
  - Anticoagulate. **Recommended duration of therapy at least three months**
  - Massive catheter-related DVT  $\rightarrow$  consider thrombolysis.

#### • IVC filter

“Pulmonary embolism while on adequate anticoagulant for DVT” and “New PE while on adequate anticoagulation for PE” are no longer indications for insertion of IVC filter.

#### 4. Miscellaneous

- New algorithm for diagnosis and treatment of heparin-induced thrombocytopenia (HIT) (see full guidelines [NCCN, 2010] for details **HIT-1**)

- Contraindications to prophylactic or therapeutic anticoagulants now include severe liver disease, high risk of falls (head trauma).
- New recommendations for reversing anticoagulation (see full guidelines [NCCN, 2010] for details **VTE-E**).
- Therapeutic anticoagulation failure—recommend insertion of filter to prevent *fatal PE* and consider thrombolysis for high-risk patients (for *submassive or massive PE or massive DVT that is life- or limb-threatening*)—see full guidelines [NCCN, 2010] for details **VTE-H**.

## References

- Donze, J., Le Gal, G., et al. (2008). Prospective validation of the Pulmonary Embolism Severity Scale. *Throm Haemost*, 100, 943–48.
- Khorana, A.A., Kuderer, N.M., et al. (2008). Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*, 111(10), 4902–4907.
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