

**Guideline for the Primary Prophylaxis for Venous Thromboembolism (VTE) in Palliative Patients with Malignancy Whose Treatment is Primarily Palliative**

**Version History**

<b>Version</b>	<b>Date</b>	<b>Summary of Change/Process</b>
1.0	April 2008	Endorsed and approved by Governance Committee
1.1	June 2011	Updated by Anna Lock
1.2	June 2011	Re-circulated to and approved by SPAGG on behalf of the Supportive and Palliative Care NSSG
1.3	June 2011	Reformatted by Lara Barnish
1.4	04 July 2011	With changes by Anna Lock
1.5	20 July 2011	Circulated to and presented at SPAGG
1.5	03.08.11	Presented at the Clinical Governance Sub Group
1.6	31.08.11	With minor amendments from the Sub Group, for the attention of Anna Lock
2.0	31.08.11	With comments from Anna Lock

<b>Date Approved by Network Governance</b>	<b>August 2011</b>
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<b>Date for Review</b>	<b>August 2014</b>
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## 1. Scope of the Guideline

This guideline has been produced to support the care of palliative patients with malignancy admitted to a hospice or hospital. It includes:

- The detection of those that may be at risk from a venous thromboembolism (VTE).
- The prevention of the development of VTE.

## 2. Guideline Background

2.1 VTE is potentially life threatening. Frequently VTEs are asymptomatic, however pulmonary embolism may cause acute and chronic respiratory distress and peripheral deep vein thrombosis (DVT) may be uncomfortable and lead to skin breakdown and ulceration.

2.2 Up to 15% of patients with cancer are thought to develop symptomatic VTE. The risk varies by cancer type, and is especially high among patients with malignant brain tumours and adenocarcinoma of the ovary, pancreas, colon, stomach, lung, prostate, and kidney. Direct alterations to the coagulation cascade caused by the malignancy can cause a hyper-coagulable state which will continue until the end of a patient's life. Specific risk estimates of VTE by cancer type, stage, and treatment approaches are still largely unknown.

2.3 Further increases in risk can be caused by a wide range of factors which have been well described in the general population many of which are common in palliative care patients. The impact of a background of malignancy on the risk stratification is unclear.

2.4 NICE Guidance published in January 2010 highlighted the need for a balanced approach to management of thromboprophylaxis in patients with a palliative diagnosis.

## 3. Guideline Statements

3.1 All patients being admitted to a hospital or hospice, regardless of diagnosis, should have their risk of VTE assessed to decide whether they may benefit from anticoagulation to reduce the risk of symptomatic and life limiting VTE.

3.2 Consideration of primary prophylaxis in palliative care patients for VTE should keep at its centre the focus of high quality symptom control.

3.2.1 There is insufficient evidence to treat all inpatients with advanced cancer with primary prophylaxis for VTE. Decisions should be made on an individual basis with consideration of relative risk and burden of treatment.

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- 3.3 Patient groups who have an evidence based potential benefit from treatment are those who have either had recent major surgery or an acute medical illness from which they are expected to recover (appendix 1).
- 3.4 Other patients who may benefit, but for which there is no clear evidence base:
- i. Recently bed bound due to acute medical illness.
  - ii. New diagnosis of spinal cord compression, expected to recover mobility.
  - iii. Pathological fracture, expected to recover mobility.
- 3.6 The treatment of choice is low molecular weight heparin (LMWH) in a once daily dose. On initiation of therapy, a clinical plan should be documented to review duration and appropriateness of ongoing treatment every 48hrs. The potential risks of low molecular weight heparin are as follows:
- a. Risk of bleeding - Incidence of haemorrhage.
    - Major bleeds: 4% reported.
    - Minor bleeds: 28% reported.
  - b. Risk of subcutaneous bruising.
  - c. Risk of thrombosis despite anticoagulation e.g. heparin induced thrombocytopenia.
  - d. Burden of monitoring when considered necessary.
- 3.7 The duration of treatment with LMWH for patients with cancer is as follows:
- 3.7.1 Immobile patients with acute medical condition: Treatment until the patient achieves full ambulation or for a maximum of 14 days (See the summary of patient characteristics for Clexane).
- 3.7.2 Hip replacement or hip fracture surgery: Treat with LMWH for 28 days post surgery. Fondaparinux, within its licensed indications, may be used as an alternative to LMWH (NICE CG046).
- 3.7.3 Laparotomy, laparoscopy and thoracotomy lasting more than 30 minutes; treat for 14 days or until mobile.
- 3.7.4 Major abdominal or pelvic surgery with residual disease, obesity or a history of previous VTE. This group should have treatment continued for up to 28 days (appendix 2).

## 4. Monitoring

- 4.1 Risk of thrombocytopenia
- a. Platelet counts must be measured before the initiation of therapy with LMWH.

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- b. Platelet counts must be rechecked on day 5 to monitor for thrombocytopenia.
- c. If platelet count is significantly reduced (30-50% of initial value) and/or patient develops new thrombosis or skin allergy during treatment, therapy must be discontinued immediately and consideration made of the appropriateness of alternative treatments.

#### 4.2 Renal impairment

- a. Dosage adjustments may be required for renal impairment due to accumulation of LMWH.
- b. Creatinine should be checked weekly.

#### 4.3 Hyperkalemia

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia especially in patients with diabetes mellitus, chronic renal failure, or concomitant administration of potassium sparing drugs. Urea and electrolytes should be checked weekly.

### 5. Indications for consideration of dose reductions

#### 5.1 Renal impairment:

- a. Mild (creatinine clearance 50-80ml/min): no dosage adjustments, careful clinical monitoring is advised.
- b. Moderate (creatinine clearance 30-50ml/min): no dosage adjustments, careful clinical monitoring is advised
- c. Severe (creatinine clearance < 30ml/min): Dose should be reduced to 20mg s/c daily.

#### 5.2 Low body weight:

5.2.1 In low-weight women (< 45kg) and low-weight men (< 57kg), an increase in LMWH exposure has been observed within the prophylactic dosage ranges (non-weight adjusted), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients.

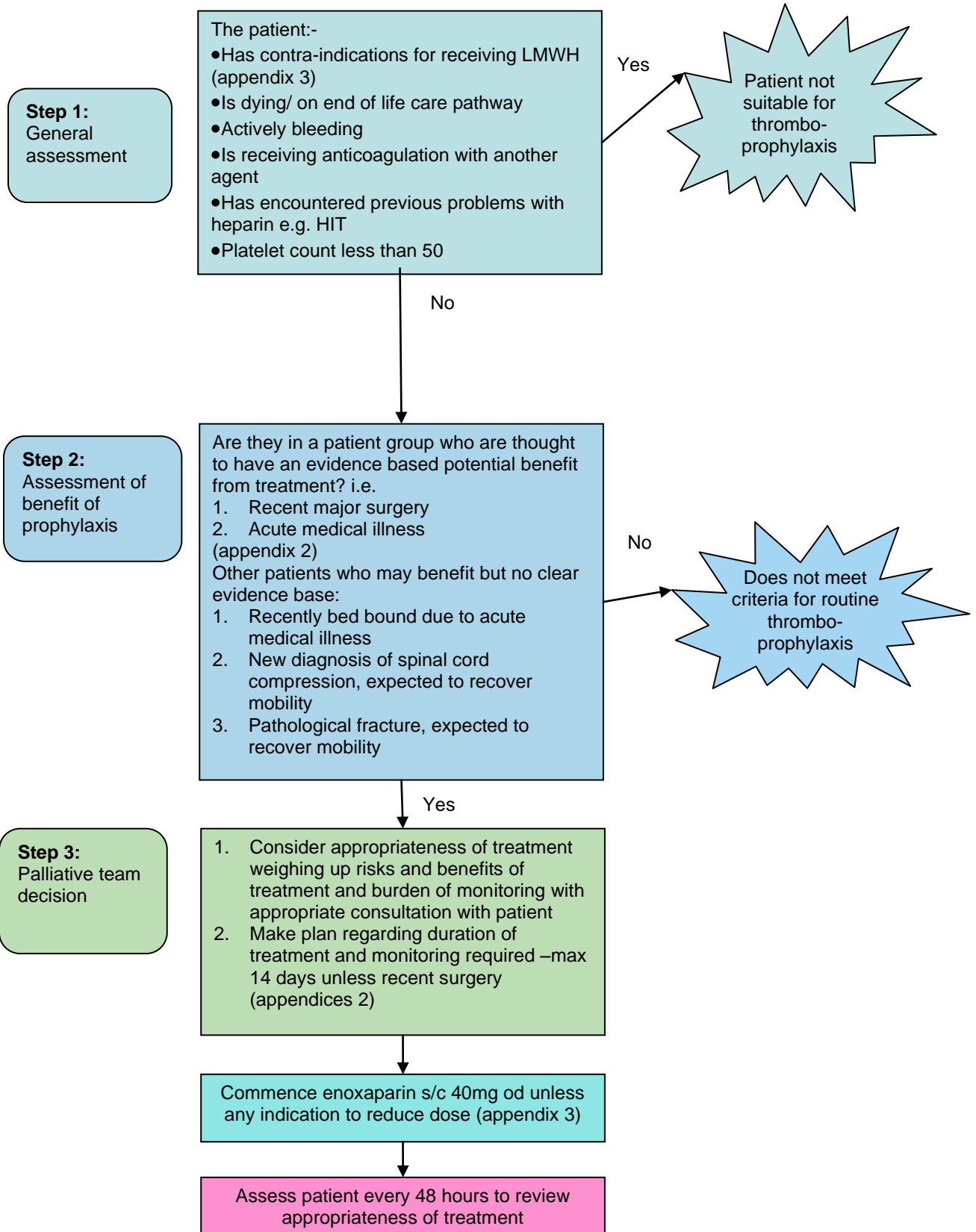
5.2.2 Dose should be reduced to 20mg s/c daily in patients below these weights.

### 6. Interactions with Other Medicines

It is recommended that agents which affect haemostasis should be discontinued prior to LMWH therapy unless their use is essential, such as: systemic salicylates, acetylsalicylic acid, NSAIDs including ketorolac, dextran, and clopidogrel, systemic glucocorticoids, thrombolytics and other

anticoagulants. If the combination cannot be avoided, LMWH should be used with careful clinical and laboratory monitoring.

**Flow chart for consideration of Primary Prophylaxis  
for Venous thrombo-embolism in Palliative patients  
admitted to a Hospice or Hospital**



## Monitoring of the Guideline

Implementation of the guidance will be considered as a topic for audit by the NSSG in 2014.

## References

NICE Jan 2010 Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital

## Bibliography


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- 10 Samama MM et al A comparison of od enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients: Prophylaxis in Medical Patients with Enoxaparin study group. N Engl J Med 341:793-800, 1999
- 11 Summary of Product Characteristics for Clexane. Sanofi-Aventis
- 12 NICE Guidance CG046 – Prevention of venous thromboembolism(deep vein thrombosis and pulmonary embolism) in patients undergoing surgery. April 2007
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**Approval Signatures**

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## Appendix 1 - Factors contributing to risk of venous thromboembolism

- Age >60 years
- Obesity
- Malignancy
- Recent immobility (bed rest over 4 days)
- Recent major surgery
- Previous venous thrombosis
- Medical illness (eg. COPD, MI, CCF or previous stroke)
- Coexisting sepsis
- Inflammatory bowel disease
- Nephrotic syndrome
- Extensive varicose veins
- Family history of VTE including 1<sup>st</sup> degree relative
- Pregnancy or Post-partum
- Spinal injury
- Recent long distance travel
- Previous stroke
- Thrombophilia
- Lymphoedema
- Hickman line in-situ

There is evidence for stratification of risk of VTE in of acutely ill medical inpatients without cancer diagnosis however there is no evidence to determine the impact of malignancy on this stratification.

High risk	<p>Acute illness + prev VTE          Acute illness + hypercoagulable state          Stroke          Acute MI          Acute respiratory failure          Acute cardiac failure          Lower limb paralysis</p>
Moderate risk	<p>Major medical illness; heart/lung disease, Inflammatory Bowel Disease          Sepsis          Malignancy/myeloproliferative disorder          Inflammatory disease          Nephrotic syndrome          Hormonal treatment (e.g. oestrogen therapy, high dose progestogen, tamoxifen, raloxifene)          Major trauma or burns          Fracture or major orthopaedic surgery of pelvis, hip or lower limb</p>
Low risk	<p>Minor trauma or medical illness</p>

## Appendix 2 - Evidence of Efficacy of Prophylaxis

### Group 1: Inpatients with active cancer

The rate of VTE in hospitalised patients with cancer has been found to range from 0.6% to 7.8% (Lyman et al). Treatment with low molecular weight heparin improves survival and reduces VTE in general medical patients hospitalized and therefore bedbound with acute medical conditions such as pneumonia and congestive cardiac failure (Table 1) (Lyman et al).

**Table 1 Trials of Anticoagulants for VTE in Acutely Ill Hospitalised Medical Patients (Lyman et al)**

Study name	Number in Study (N)	% of N with cancer	Placebo events% of N	Treatment events% of N	Relative risk	P	95% ci
<b>MEDENOX</b> Alikhan et al	579	12.4	14.9	5.5	0.37	<.001	0.22 - 0.63
<b>PREVENT</b> Samama MM et al	3,706	5.1	4.96	2.77	0.55	.0015	0.38 - 0.8
<b>ARTEMIS</b> Cohen et al	849	15.4	10.5	5.6	0.47	.029	0.08 - 0.69

The numbers of those in these studies with cancer are small and when subgroup analysis of cancer patients in MEDENOX was undertaken no significant difference in rate of VTE or mortality was found (8/41 VTE in treatment group vs. 3/31 VTE with placebo). There is no data available on the numbers of cancer patients needed to treat to prevent one VTE.

The appropriateness of generalising these studies to palliative cancer patients is uncertain. Many patients are admitted to specialist palliative care units for symptom control with no acute change in medical condition although symptoms such as pain may increase time spent in bed (i.e. immobility). There is no evidence on the efficacy of using thromboprophylaxis within this group.

Unlike general medical patients who may have acute events which increase their risk of VTE temporarily, followed by recovery on treatment, patients with cancer will have a pro-coagulable state which continues to the end of their life. As a consequence it may seem difficult to assess when an individual's risk has reduced sufficiently to stop treatment.

The FAMOUS study (Kakkar A et al) looked at long term anti-coagulation for cancer patients whose main risk factor was a diagnosis of malignancy. They included 385 patients with advanced cancer and randomised them to placebo vs low molecular weight heparin for up to a year, there was no significant difference in symptomatic

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VTE or bleeding in either group. Overall survival also showed no difference although subgroup analysis of those with a better initial prognosis suggested that low molecular weight heparin may have a positive effect on survival.

## **Group 2 - Patients with Cancer Undergoing Surgery**

VTE is a common complication in cancer patients undergoing surgery. The presence of malignant disease doubles the risk for asymptomatic proximal DVT from 10% to 20%, and fatal PE from 1% to 5%. (Lyman et al)

Un-fractionated heparin and low molecular weight heparin have been found to be equally efficacious in preventing VTE in patients undergoing planned curative pelvic or abdominal surgery for cancer. Addition of mechanical prophylaxis such as graduated compression stockings can improve efficacy of treatment.

High risk operations include laparotomy, laparoscopy and thoracotomy lasting more than 30 minutes.

Treatment for a longer period has been found to be more effective in patients undergoing major abdominal or pelvic surgery especially those with residual disease, obesity or a history of previous VTE. This group should have treatment continued for up to 28 days (Lyman et al).

NICE guidance (CG046) states that patients who have undergone hip replacement or hip fracture surgery should have enoxaparin for 28 days post surgery. For other surgery, patients are administered enoxaparin until mobile.

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## **Appendix 3 – Contra-indications to receiving Enoxaparin (Summary of Product Characteristics, Sanofi-Aventis, Clexane®)**

### *Absolute contra-indications*

1. Acute bacterial endocarditis,
2. Active major bleeding and conditions with a high risk of uncontrolled haemorrhage, including recent haemorrhagic stroke.
3. Thrombocytopenia – do not give if platelet count < 50
4. Active gastric or duodenal ulceration
5. Hypersensitivity to either enoxaparin sodium, heparin or its derivatives including other Low Molecular Weight Heparins;
6. Patients receiving heparin for treatment rather than prophylaxis,
7. Within 12 hours of locoregional anaesthesia eg nerve block, epidurals (prophylactic dose) or within 24 hours if treatment dose.

### *Special Warnings and Precautions for use*

1. Severe renal impairment (dose adjust)
2. Severe liver impairment
3. Thrombocytopenia – platelet count <70
4. Use with extreme caution in patients with a history of heparin induced thrombocytopenia (HIT) with or without thrombosis
5. Caution in conditions with increased risk of bleeding i.e.
  - impaired haemostasis
  - history of peptic ulcer
  - recent ischaemic stroke
  - uncontrolled severe arterial hypertension
  - diabetic retinopathy
  - recent neuro- or ophthalmologic surgery
6. Anaemia
7. Major trauma / surgery to brain, eye or spinal cord
8. Spinal and epidural infusions (see notes above in contra-indications)- risk of intra-spinal haematoma

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