Pan-Birmingham NHS
Cancer Network

Coversheet for Network Site Specific Group Agreed Documentation

This sheet is to accompany all documentation agreed by Pan Birmingham Cancer Network Site Specific Groups. This will assist the Network Governance Committee to endorse the documentation and request implementation.

Document Title	**Guidelines & Evidence: Primary prophylaxis for venous thromboembolism (VTE) in patients with malignancy whose treatment is primarily Palliative.**
Document Date	April 2008
Document Purpose	To aid clinical decision making re: thromboprophylaxis for this cohort of patients by providing additional reference material to support current general guidelines that may be in place within Trusts, or to be the primary resource for specialist palliative areas where there is no current guidance.
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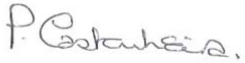
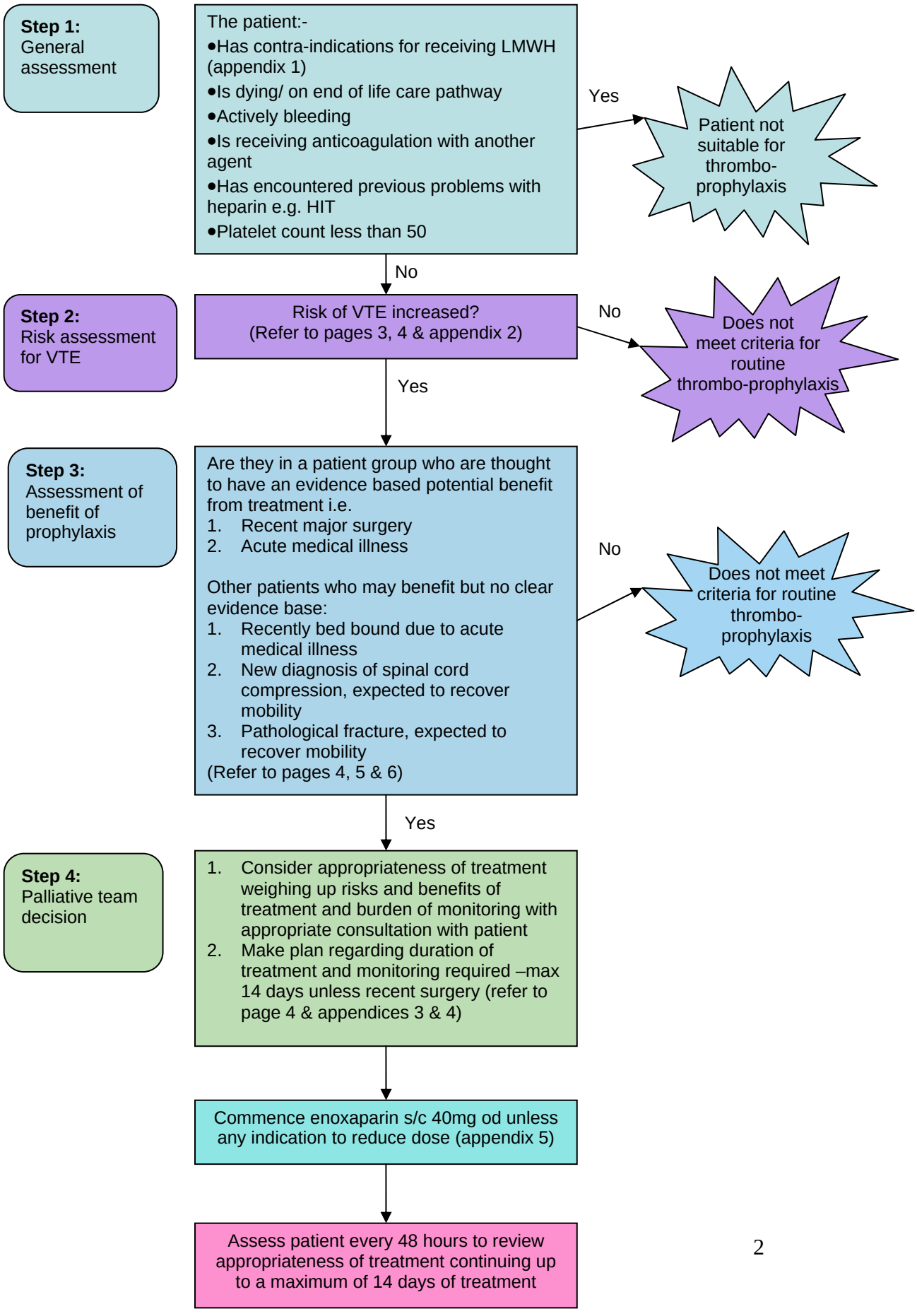
References	As within document
Consultation Process	Approved within Pan Birmingham Palliative Care Network Specialist Palliative Care Audit and Guidelines Group (SPAGG) Consulted with Dr Simon Noble, Consultant in Palliative Care, Gwent Hospital (special interest in VTE prophylaxis in palliative patients) Distributed to palliative colleagues within Pan Birmingham Network for comment Distributed to the following colleagues for further comment:- Dr Will Lester, Consultant Haematologist, UHB & BWH Dr Richard Murrin, Consultant Haematologist, SWBH Dr Nigel Langford, Consultant Physician, SWBH Dr Jonathon Treml, Consultant Geriatrician, UHB Dr Nigel Page, Consultant Geriatrician, SWBH Dr Alistair Main, Consultant Geriatrician, UHB Final sign off at SPAGG meeting April 24th 2008 Confirmation of LMWH choice in region – correspondence with Inderjit Singh, Associate Director of Pharmacy Services, Healthcare Purchasing Consortium (HPC) – within the West Midlands, enoxaparin is the first choice LMWH within Trusts based on cost effectiveness and licensing.
Review Date (must be within two years)	April 2010
Approval Signatures: Specialist Palliative Care Audit & Guidelines Sub Group Chair	
Date Approved by Network Governance Committee	Sept 2008

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



Guidelines & Evidence: Primary prophylaxis for venous thromboembolism (VTE) in patients with malignancy whose treatment is primarily Palliative.

Definition

Primary prophylaxis: Use of anticoagulation in patients to prevent VTE in those who are considered high risk of VTE but have not had previous VTE.

Standard

As part of a holistic assessment all patients should have their risk of VTE assessed to decide whether they may benefit from anticoagulation with low molecular weight heparin, to reduce the risk of symptomatic and life limiting VTE. **These guidelines are aimed at palliative patients admitted to a hospice or hospital.**

Summary

1. Consideration of primary prophylaxis in palliative care patients for VTE should keep at its centre the focus of high quality symptom control.
2. At present there is insufficient evidence to treat all inpatients with advanced cancer with primary prophylaxis for VTE.
3. Decisions should be made on an individual basis with consideration of relative risk and burden of treatment.
4. On initiation of therapy, a clinical plan should be made to review duration and appropriateness of treatment if there is felt to be a sufficient potential benefit from treatment.
5. The treatment of choice is low molecular weight heparin in a once daily dose.
6. There is no evidence to support long term primary prophylaxis in patients with cancer.

Background

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.

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 tumors 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-coaguable 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 (Geerts et al).

Further increases in risk can be caused by a wide range of factors which have been well described in the general population (see appendix 2) many of which are common in palliative care patients. The impact of a background of malignancy on the risk stratification is unclear.

Choice of treatments

Options for prophylaxis include un-fractionated heparin two to three times a day, low molecular weight heparin once daily and graduated elastic compression stockings (GECS – may also be known as TEDs).

The report of the independent working group for preventing VTE in hospital states that mechanical methods of prophylaxis (GECS) have not to date been appropriately evaluated in acutely ill medical patients and thus are not recommended at present. (Department of Health) – however NICE guidance is due in 2009 therefore this guidance will be reviewed once the NICE guidance is issued.

Because of patient acceptability (Noble et al), ease of administration and a lower risk of heparin induced thrombocytopenia the treatment of choice is low molecular weight heparin in a once daily dose.

Potential risks of treatment with low molecular weight Heparin (LMWH)

Prior to decision to treat, consideration of contraindications should be made (see appendix 1).

Additional consideration should be made for all patients of:-

- Risk of bleeding - Incidence of haemorrhage
    - Major bleeds <4% reported,
    - minor bleeds <28% reported.
- Risk of subcutaneous bruising
- Risk of thrombosis despite anticoagulation
- Risk of thrombocytopenia (including heparin induced thrombocytopenia)
- Burden of monitoring when considered necessary (appendix 4)

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 Hospitalized 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
MEDENOX Alikhan et al	579	12.4	14.9	5.5	0.37	<.001	0.22 - 0.63
PREVENT Samama MM et al	3,706	5.1	4.96	2.77	0.55	.0015	0.38 - 0.8
ARTEMIS Cohen et al	849	15.4	10.5	5.6	0.47	.029	0.08 - 0.69

The numbers of patients 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 generalizing 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-coaguable 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 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 receive a LMWH or fondaparinux for 28 days post surgery. For other surgery, patients are administered LMWH or fondaparinux till mobile.

Appendix 1

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

Appendix 2

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 1st degree relative
- Pregnancy or Post-partum
- Spinal injury
- Recent long distance travel
- Previous stroke
- Thrombophilia
- Lymphoedema
- Hickman line in-situ

Stratification of risk factor classification of acutely ill medical inpatients (THRIFT)

N.B. there is no evidence to determine the impact of malignancy on the following factors:

High	Acute illness + prev VTE Acute illness + hypercoaguable state Stroke Acute MI Acute respiratory failure Acute cardiac failure Lower limb paralysis
Moderate	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
Low	Minor trauma or medical illness

Appendix 3

Duration of treatment with enoxaparin for patients with cancer

1. **Immobile patients with acute medical condition**: Treatment until the patient achieves full ambulation or for a maximum of 14 days – whichever is the sooner. (SPC for Clexane).

2. **Hip replacement or hip fracture surgery**: Treat with enoxaparin (or alternative LMWH) for 28 days post surgery. Fondaparinux, within its licensed indications, may be used as an alternative to LMWH (NICE CG046).

3. **Laparotomy, laparoscopy and thoracotomy** lasting more than 30 minutes; treat for 14 days or until mobile – whichever is the sooner.

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 (Lyman et al).

Appendix 4

Monitoring

1. Risk of thrombocytopenia

    - Platelet counts must be measured before the initiation of therapy with enoxaparin sodium or any other LMWH.

    - Recheck platelet count on day 5 to monitor for thrombocytopenia.

    - 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 appropriateness of alternative treatments.

2. Renal impairment

    - Dosage adjustments required for renal impairment due to accumulation of enoxaparin, advised to check creatinine regularly.

Potassium – heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia esp in patients with diabetes mellitus, chronic renal failure, or concomitant administration of potassium sparing drugs, advised to check U&E's regularly (minimum weekly).

Appendix 5

Indications for consideration of dose reductions

1. Renal Impairment

- Mild (creatinine clearance 50-80 ml/min): no dosage adjustments, careful clinical monitoring is advised.

- Moderate (creatinine clearance 30-50 ml/min): no dosage adjustments, careful clinical monitoring is advised

- Severe (creatinine clearance < 30 ml/min): Dose should be reduced to 20mg s/c daily.

2. Low body weight:

In low-weight women (< 45 kg) and low-weight men (< 57 kg), an increase in enoxaparin 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.

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

Appendix 6 Interactions with Other Medicines

It is recommended that agents which affect haemostasis should be discontinued prior to enoxaparin therapy unless their use is essential, such as: systemic salicylates, acetylsalicylic acid, NSAIDs including ketorolac, dextran, and clopidogrel, systemic glucocorticoids, thrombolytics and anticoagulants. If the combination cannot be avoided, enoxaparin should be used with careful clinical and laboratory monitoring.

Appendix 7

Abbreviations used in document

DVT	Deep vein thrombosis
HIT	Heparin Induced Thrombocytopenia
IBD	Inflammatory Bowel Disease
LMWH	Low Molecular Weight Heparin
UFH	Unfractionated heparin
VTE	Venous thromboembolism
MEDENOX	Prophylaxis in Medical Patients with Enoxaparin
PREVENT	Prospective Evaluation of Dalterparin
ARTEMIS	ARixtra for ThromboEmbolism Prevention in a Medical Indications Study

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Approval Date of Network Site Specific Group: 24.04.08

Date Approval by the Clinical Governance Team:

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