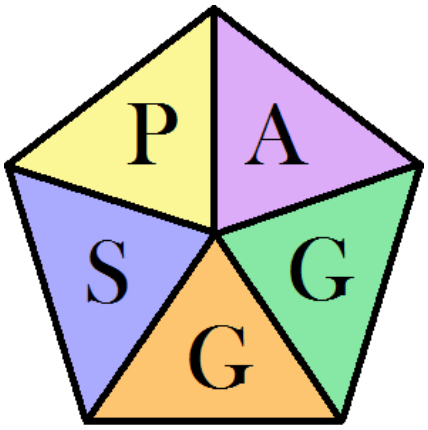

Specialist Palliative Care
Audit and Guidelines Group

Specialist Palliative Care Audit and Guidelines Group (SPAGG)

Clinical Guideline for Primary Prophylaxis for Venous Thromboembolism (VTE) in the palliative care setting

Version 3.2

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Authors	Dr Anna Lock Dr Nadia Khan Dr Laura Holtham
References	1. Ambrus JL, Ambrus CM, Pickren JW. Causes of death in cancer patients. J Med 1975; 6:61-64 2. Kakkar A et al. Low Molecular Weight Heparin, Therapy With Dalteparin, and Survival in Advanced Cancer: The Fragmin Advanced Malignancy Outcome Study (FAMOUS). Journal of Clinical Oncology 2004; 22:10:pp. 1944-1948 3. Kakkar A et al. Low Molecular Weight Heparin and mortality in acutely ill medical patients. NEJM 2001; 365: 2463-2472 4. Kakkar A et al. Low-molecular weight heparin and mortality in acutely ill medical patients. NEJM 2011; 365: 2463-2472. 5. Johnson MJ et al. Primary Thromboprophylaxis in Hospices: The Association Between Risk of Venous Thromboembolism and Development of Symptoms. JPSM 2014; 48: 56–64. 6. McLean S, Ryan K, O'Donnell J et al. Primary thromboprophylaxis in the palliative care setting – a qualitative systematic review. Palliat Med 2010; 24: 386-395. 7. Noble SIR, Nelson A, Finlay G. Factors influencing hospice thromboprophylaxis policy: a qualitative study. Palliat Med 2008; 22: 808-813 8. Noble SIR, Finlay IG. Is long-term low molecular weight hepartin acceptable to palliative care patients in the treatment of cancer related venous thromboembolism? A qualitative study. Palliat Med 2005: 29; 197-201. 9. Noble SIR, Nelson A, Finlay G. Factors influencing hospice thromboprophylaxis policy: a qualitative study. Palliat Med 2008; 22: 808-813. 10. Noble S, Nelson A, Turner C, Finlay I. Acceptability of low molecular weight heparin thromboprophylaxis for inpatients receiving palliative care: qualitative study. BMJ 2006;332(7541):577-80. 11. 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 12. The CLOTS Trials Collaboration. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. The Lancet, volume 373; 9679: 19581965. 13. NICE 2010. Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. CG92. London: National Institute for Health and Care Excellence 14. Department of Health. Report of the independent expert working group on the prevention of venous thromboembolism in hospitalized patients. 15. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):338S-400S. 16. Johnson MJ, Sproule MW, Paul J. The prevalence and associated variables of deep venous thrombosis in patients with advanced cancer. Clinical Oncology 1999; 11:105-110. 17. Rachidi S et al. The use of novel oral anticoagulants for thromboprophylaxis after elective major orthopedic surgery. Expert Rev Hematol. 2013;6(6):677-95 18. White C, Noble SIR, Watson M, Swan F, Allgar VL, Napier E, Nelson A, McAuley J, Doherty J, Lee B, Johnson MJ. Prevalence, symptom burden, and natural history of deep vein thrombosis in people with advanced cancer in specialist palliative care units (HIDDen): a prospective longitudinal observational study. Lancet Haematol 2019;6: e79-88
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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
3.0	Nov 2013	Updated by Nadia Khan and Anna Lock, circulated to SPAGG
3.0	May 2014	Audit of regional practice against v2.0, with outcomes informing v3.0
3.0	Dec 2014	Endorsed and approved by the SPAGG committee
3.1	March 2017	Reviewed by Dr Louisa Nelms, endorsed and approved by SPAGG
3.2	March 2020	With changes from Dr Laura Holtham

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

2. General information

Definitions

DVT	Deep vein thrombosis
LMWH	Low molecular weight heparin
SPC	Specialist palliative care
VTE	Venous thromboembolism

3. Background information

3.1 VTE is potentially life threatening. Frequently VTEs are asymptomatic, however pulmonary embolism may cause acute and chronic respiratory distress and peripheraldeep vein thrombosis may be uncomfortable and lead to skin breakdown and ulceration

3.2 Up to 15% of patients with cancer are thought to develop symptomatic VTE[1]. 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-coaguable state, which will continue until the end of a patient's life. Previous randomised controlled trials have demonstrated that primary thromboprophylaxis can significantly reduce the incidence of VTE in immobile cancer patients[2,3].

3.3 Specific risk estimates of VTE by cancer type, stage, and treatment approaches are still largely unknown. 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 riskstratification is unclear.

3.4 Evidence around VTE in palliative non-cancer patients is lacking and guidelines have largely been based on group consensus and extrapolation of studies evaluating hospitalised acute medical patients. Although several RCTs (MEDENOX, PREVENT, ARTEMIS) have shown treatment with LMWH in hospitalised general medical patients improves survival and reduces VTE, the LIFENOX trial suggests that the use of LMWH with graduated compression stockings, versus graduated compression stockings alone, was not associated in a reduction of mortality from any cause in hospitalised, acute medical patients[4].

3.5 Limited research into primary thromboprophylaxis in the palliative care setting has focused on current practice around thromboprophylaxis in SPC units[5,7], and the acceptability of thromboprophylaxis amongst patients and palliative care professionals[8,9]. No evidence exists to support or refute the routine use of primary thromboprophylaxis in this setting[6].

3.6 Studies of mechanical thromboprophylaxis have been on surgical patients, and not shown to have benefit in medical[11] or stroke[12] patients. Incorrect use of anti-embolism stockings may increase DVT risk, and is less acceptable to palliative care patients than pharmacological measures[10].

3.7 Novel oral anticoagulant agents such as oral rivaroxaban and dabigatran have shown to be an effective method of thromboprophylaxis following elective orthopaedic surgery[17]. However, their role has not been examined in the palliative care setting

3.8 NICE Clinical Guidance 9212 (published in January 2010) highlighted the need for a balanced approach to management of thromboprophylaxis in patients with a palliative diagnosis[13].

4. Guideline statements

4.1 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 (appendix 1).

4.2 Consideration of primary prophylaxis in palliative care patients for VTE should keep at its centre the focus of high quality symptom control, weighed consideration of benefits and burdens, and shared decision-making.

4.2.1 There is insufficient evidence to treat all palliative care 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.

4.3 Consider whether patients may benefit from primary pharmacological prophylaxis, either due to evidence-based potential benefit (appendix 2) and/or the presence of factors contributing to VTE risk (appendix 3).

4.4 Consider the potential risks of primary pharmacological prophylaxis, which include haemorrhage, subcutaneous bruising, heparin-induced thrombocytopenia and burden of monitoring (appendix 4).

4.5 The treatment of choice is low molecular weight heparin (LMWH) in a once daily subcutaneous dose. Dose reductions may be indicated according to renal function and body weight. Novel agents such as oral or subcutaneous agents (fondaparinux/ dagabatrin etc) may be considered if indicated by the clinical context, with further specialist advice if necessary.

4.6 Review decisions about VTE prophylaxis every 48 hours*, taking into account potential risks and benefits, and views of the patient, family and multidisciplinary team[13].

The duration of primary pharmacological prophylaxis, and agents licensed, varies according to indication (appendix 5).

4.7 Consider incorporating the clinical consideration and decision of primary VTE prophylaxis into the documentation process of admission clerking into the inpatient hospice setting (appendix 7).

5. Patient information and counselling

Patients should be counselled about the primary prophylaxis for VTE as appropriate. Further information is not covered within this guideline

6. Other issues

6.1 Risk of thrombocytopenia

- Platelet counts must be measured before the initiation of therapy with LMWH.
- Platelet counts should be rechecked on day 7** 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 the appropriateness of alternative treatments.

6.2 Renal impairment

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

6. 3 Hyperkalaemia

- 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.

* although NICE CG9212 suggests decisions about VTE primary prophylaxis in the palliative care setting should be reviewed every 24 hours, for pragmatic purposes e.g. over weekends, it is suggested that review take place at least once every 48 hours.

** Thrombocytopenia can occur at any point between the 5th and 21st day post commencement- the clinical team should be aware that any signs of thrombocytopenia after 5 days post LMWH commencement will warrant a platelet count recheck

7. Indications for consideration of dose reductions

7.1 Renal impairment:

- Mild (creatinine clearance 50-80ml/min): no dosage adjustments, careful clinical monitoring is advised.
- Moderate (creatinine clearance 30-50ml/min): no dosage adjustments, careful clinical monitoring is advised.
- Severe (creatinine clearance < 30ml/min): Dose should be reduced.

7.2 Low body weight:

- 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.
- Dose should be reduced in patients below these weights.

8. Use of thromboprophylaxis at end of life

Patients with an Australia-modified Karnofsky Performance Scale (AKPS) <50 who have been deteriorating over past 12 weeks have a 30% prevalence of femoral VTE with minimal symptoms and no survival difference to those without DVT .[18] Thromboprophylaxis could be stopped in these patients.

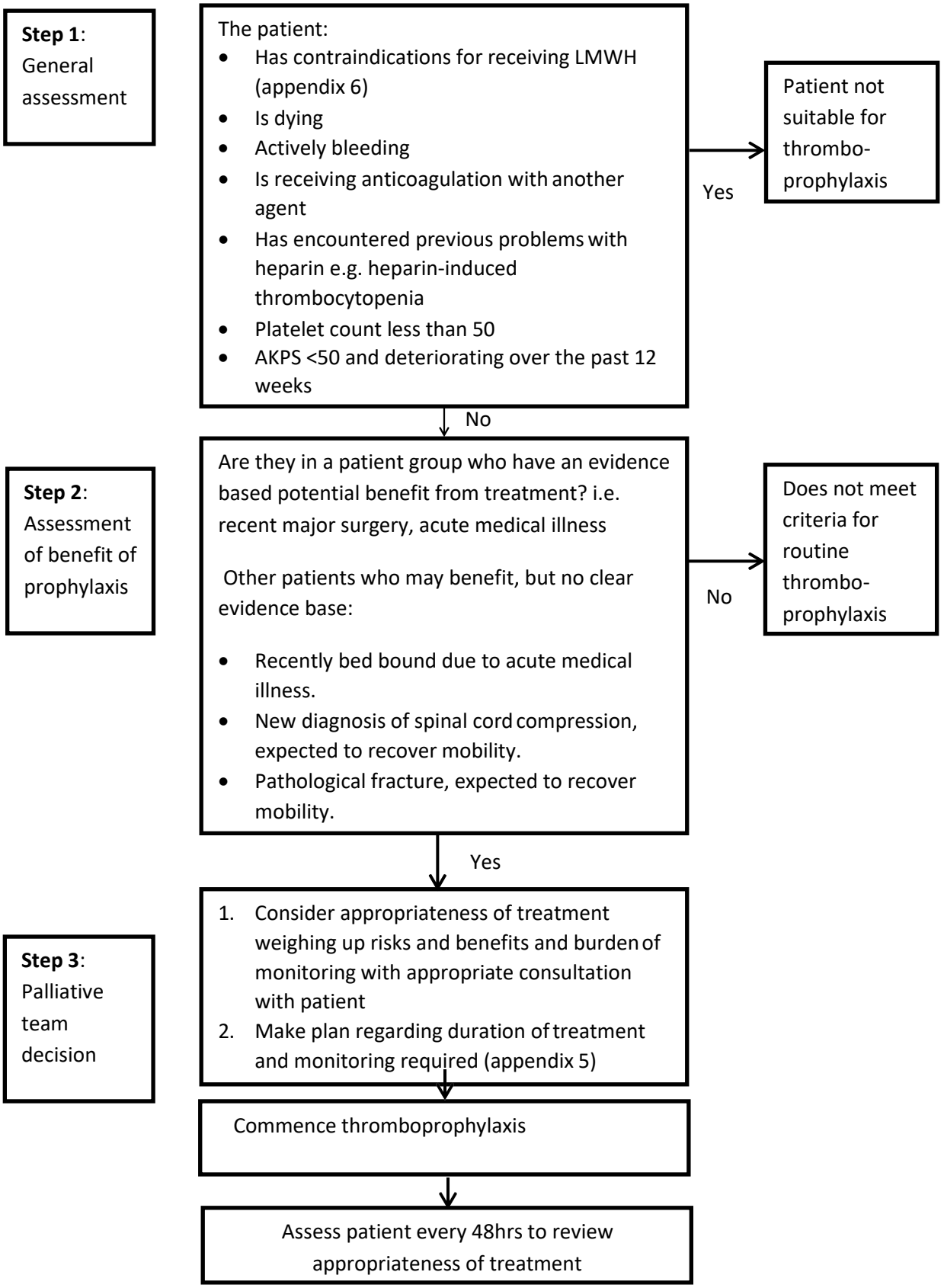
9. Interactions with Other Medicines

It is recommended that agents which affect haemostasis should be discontinued prior to LMWH therapy unless their use is essential, or warranted by the clinical situation where their benefit outweighs the risks, 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.

10. Monitoring of the guideline

Monitoring of guideline implementation locally, and suggested re-audit by SPAGG in 1 years time.

Appendix 1 - Assessment tool for consideration of primary prophylaxis for venous thrombo-embolism in palliative patients admitted to a Hospice or Hospital



Appendix 2

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.

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.

Appendix 3

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

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

High risk

- Acute illness + previous VTE
- Acute illness + hypercoagulable state
- Stroke
- Acute MI
- Acute respiratory failure
- Acute cardiac failure
- Lower limb paralysis

Moderate risk

- 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 risk

- Minor trauma or medical illness

Appendix 4

The potential risks of low molecular weight heparin are as follows:

i. Risk of bleeding - Incidence of haemorrhage.
   a. Major bleeds: 4% reported.
   b. Minor bleeds: 28% reported.
ii. Risk of subcutaneous bruising.
iii. Risk of thrombosis despite anticoagulation e.g. heparin induced thrombocytopenia.
iv. Burden of monitoring when considered necessary.

Appendix 5

The duration of thromboprophylaxis with LMWH for patients with cancer is as follows[13,15]:

i. Immobile patients with acute medical condition: Treatment until the patient achieves full ambulation or for a maximum of 14 days
ii. Hip replacement or hip fracture surgery: Treat with LMWH for 28 days post surgery. Fondaparinux and other novel oral anticoagulants, within their licensed indications, may be used as an alternative to LMWH[17].
iii. Laparotomy, laparoscopy and thoracotomy lasting more than 30 minutes; treat for 14 days or until mobile.
iv. 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 6

Contra-indications to receiving LMWH

- Hypersensitivity to active substance or to any of excipients
- Current or history of immune-mediated heparin-induced thrombocytopenia (type II)
- Active major haemorrhage or conditions predisposing to major haemorrhage
- Septic endocarditis
- In patients receiving heparin for treatment rather than prophylaxis, locoregional anaesthesia in elective surgical procedure is contraindicated because use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis

Special warnings and precautions for use

- Renal impairment with creatinine clearance level <30ml/minute
- Elderly – more likely to have poor renal function
- Caution when performing neuraxial anaesthesia or lumbar puncture – risk of spinal haematoma
- Patients at increased risk of haemorrhage
- Concomitant intramuscular injections should be avoided
- Discontinue use in patients who develop immune-medicated heparin-induced thrombocytopenia
- Avoid in patients at risk of hyperkalaemia. Can suppress adrenal secretion of aldosterone leading to hyperkalaemia
- Not for use in patients with prosthetic heart valves for anticoagulation as treatment failures have been reported