NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINES

Treatment and Secondary Prophylaxis of Venous Thrombosis in Patients with Malignant Disease

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

Scope of the guideline:
This protocol is for use in patients who have active cancer and/or are receiving active treatment for cancer.

Recommendations

- Patients with active malignancy and/or receiving systemic anti-cancer therapy (SACT)/radiotherapy who are diagnosed with venous thromboembolism (VTE) including deep vein thrombosis (DVT) and/or pulmonary embolism (PE) should be started on a therapeutic dose of apixaban or dalteparin.

- Dalteparin should be used for patients who are enrolled in a clinical trial where concomitant treatment with direct oral anticoagulant (DOAC) is contraindicated.

Key considerations:

- Patients with gastro-intestinal malignancies (upper gastro-intestinal and colorectal) and genitourinary cancers have an increased risk of upper gastrointestinal bleeding with edoxaban and rivaroxaban.

- DOACs are substrates for P-glycoprotein and cytochrome P enzymes (e.g. CYP3A4) and can interact with a variety of SACT, notably novel biologicals/targeted therapies (tyrosine kinase inhibitors, anti-hormonal agents etc.). Whilst the pivotal trials of DOACs (Caravaggio, Hokusai) have included patients on active anti-cancer treatment, the representation of patients on targeted therapy is low (<10%), and the pharmacokinetic interactions between SACT and DOACs need to be considered.

- Consideration has to be given to the commonly used DOACs in primary and secondary care, to ensure compliance and interchangeability between DOACs. Apixaban and edoxaban are the commonly used DOACs in NHS Greater Glasgow and Clyde for treatment of venous thromboembolism (VTE), and stroke prevention in atrial fibrillation, respectively.

- Other DOACs namely edoxaban may be considered in patients where compliance with twice daily dosing of apixaban is a concern after careful discussion between patient and physician about the risks and benefits due to increased incidence of gastrointestinal bleeding.

Review of current evidence:

Patients with active cancer and/or receiving active treatment for cancer (i.e. SACT, radiotherapy) who are diagnosed with a venous thromboembolism (VTE), are most effectively treated with Low Molecular Weight Heparin (LMWH), rather than warfarin on the basis of the evidence from the CLOT study that demonstrated that dalteparin was more effective than warfarin in reducing the risk of recurrent thromboembolism (9% v 17%, HR 0.48, P = 0.002) with no difference in major or minor bleeding (Lee AY et al). Dalteparin was therefore the treatment of choice when a patient with cancer and/or receiving active treatment for cancer is diagnosed with a VTE. There is now evidence from randomized control trials comparing DOACs against dalteparin. The key evidence is summarized below:

The Caravaggio study compared apixaban to dalteparin in patients, with a primary outcome of recurrent VTE and a principal safety outcome of major bleeding. Apixaban was non- inferior to dalteparin for the treatment of venous thromboembolism (P<0.001 for non-inferiority) without a statistically significant increased risk of major bleeding with apixaban vs dalteparin (3.8 vs 4.0% [P=0.6]).
There was no statistically significant increased risk of major bleeding with apixaban, with incidence of major bleed occurring in 22 patients (3.8%) in the apixaban group and in 23 patients (4.0%) in the dalteparin group (hazard ratio, 0.82; 95% CI, 0.40 to 1.69; P=0.60).

The HOKUSAI VTE Cancer trial (Raskob et al) compared edoxaban to dalteparin for the treatment of VTE in patients with active cancer. Treatment was continued for a minimum of 6 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding at 12 months. Overall, edoxaban was non-inferior to dalteparin, with the rate of recurrent VTE numerically lower with edoxaban than with dalteparin (7.9% vs. 11.3%, P = 0.09). However, the rate of major bleeding was significantly higher with edoxaban (6.9% vs. 4.0%, P = 0.04), a difference driven largely by excess in upper gastrointestinal bleeding in patients with gastrointestinal (GI) cancers. Subsequent sub-group analysis of patients with gastro-intestinal cancers demonstrated that edoxaban was associated with a 7.9% higher risk of clinically relevant major bleeding compared to dalteparin (Mulder et al). This increased bleeding risk was only observed with upper GI tract haemorrhage.

The SELECT-D trial compared treatment with rivaroxaban to dalteparin in patients with active cancer and a diagnosis of PE or proximal DVT (Young et al). Rates of recurrent thrombosis were lower in patients treated with rivaroxaban (4 v 11%), with no significant difference in the rate of major bleeding (6 vs. 4%). There was however a significant increased risk of clinically relevant non-major bleeding in patients treated with rivaroxaban (13 v 4%). Furthermore, the rate of major bleeding for patients with gastric or oesophageal cancers was 36% (4/11) with rivaroxaban compared to 5% (1/19) with dalteparin.

Of the three DOACs discussed above, apixaban has not demonstrated an increased risk of bleeding.

Currently available guidelines:

On the basis of the above evidence, ASCO clinical guidelines, published prior to publication of Caravaggio results, recommend the use of LMWH, edoxaban or rivaroxaban for at least 6 months as the preferred treatment for patients with cancer with established VTE to prevent recurrence (Key N et al).
NICE guideline, NG158, recommends DOACs for patients with cancer and LMWH (where DOACs are contraindicated), whilst noting that treating DVT or PE in people with active cancer is an off-label use for most anticoagulants.

Initiation of therapy:
Therapy should be initiated by the healthcare provider diagnosing the VTE e.g. nurse specialist, doctor. Drug initiation, choice of dose and any initial monitoring will be performed by this provider.

Subsequent responsibility for ongoing monitoring and completion of therapy will rest with the doctor managing the patient's cancer, usually the oncologist but possibly a specialist respiratory physician palliative care consultant or GP. This individual should be identified and consulted prior to patient discharge from the acute care team.

Details of the proposed treatment plan should be clarified in the discharge letter to the clinician responsible for on-going care and supervision of anticoagulation therapy.

Initiation of Apixaban

- Initial 10mg twice daily for first 7 days
- Maintenance 5mg twice daily

Initiation of Dalteparin

- Initial therapy for 1st month (sub-cutaneous injection once daily)
  Dalteparin according to table
  It is envisaged that LMWH will be administered by the patient or a carer. Occasionally district nurse support may be required.

Weight range (kg)	Dalteparin daily dose (units) using pre-filled syringe	Syringe colour code
<46	7,500	Green
46-56	10,000	Red
57-68	12,500	Brown
69-82	15,000	Purple
>82	18,000	Grey

- Secondary prophylaxis (after 1st month therapy completed)

Weight range (kg)	Dalteparin daily dose (units) using pre-filled syringe	Syringe colour code
40-45	7,500	Green
46-56	7,500	Green
57-68	10,000	Red
69-82	12,500	Brown
83-98	15,000	Purple
>98	18,000	Grey

Initial monitoring:

- If receiving SACT or radiotherapy, monitor for thrombocytopenia accordingly
- Monitor renal function:
  - If creatinine clearance <50ml/min dose adjust edoxaban accordingly.
  - If creatinine clearance <15ml/min, avoid apixaban and edoxaban - switch patient to dalteparin and monitor anti-Xa level as described below.
- LMWH anti-Xa levels should only be checked if:
  - Calculated creatinine clearance <30ml/min
  - Body weight <35kg or >150kg
  - Target peak anti-Xa level should be 0.5-1.2unit/ml (3-4 hours post-dose) and the sample taken after at least the 3rd dose.

Requirement for dose reduction or treatment cessation:

- See section above (Initial Monitoring) for information related to renal monitoring
- If platelet count <50x10^9/L
    - Use of LMWH, rather than a DOAC, is recommended.
    - During the 1st month of treatment, administer platelet transfusion to maintain platelets ≥50 x10^9/l and continue therapeutic dose LMWH.
    - After the 1st month of treatment, if platelets 25 – 49 x10^9/l reduce LMWH dose to 50% of therapeutic dose.
    - After the 1st month of treatment, if platelets <25 x10^9/l stop anticoagulation temporarily.
- If HIT suspected, all heparin preparations should be discontinued immediately and case discussed with a haematologist.
- If creatinine clearance falls below 30 ml/min use of LMWH is recommended. Check peak anti-Xa level;
    - if >1.0 unit/ml reduce LMWH dose
    - if >1.2 unit/ml consider omitting LMWH for 1-2 days and reassess anti-Xa before restarting.

Duration of therapy:

Patients should receive therapy for a minimum of 6 months and this duration extended if the cancer is not in remission or active cancer treatment is still ongoing. Any decision to shorten or lengthen duration of treatment should be made in discussion between the GP, treating oncologist and the patient.

There is no evidence for the most effective anticoagulant or dose beyond 6 months, and the choice of anticoagulant should be made on bleeding risk, quality of life, patient preference and life expectancy.

VTE recurrence:

If a patient experiences a VTE recurrence ensure there has been no change in the underlying disease process.

If patient's current anticoagulation is:

- ***Apixaban 5mg twice daily or edoxaban***
    - Switch to dalteparin for minimum of 6 months.
- ***Dalteparin***
    - When receiving 75% dose of LMWH, this should be increased to a full therapeutic dose.
- ***Dalteparin***
    - When receiving full therapeutic dose of LMWH, switch to apixaban 10mg twice daily one week and then 5mg twice daily long term.

If symptoms do not improve or worsen after 5-7 days at the higher dose, the DOAC can be changed to dalteparin or an LMWH. Anti-Xa should be checked and the dose increased to aim for a target anti-Xa 1.6-2.0.

Rarely is further imaging required unless there is a significant deterioration in symptoms and the result will alter clinical management.

Drug interactions/cautions:

It is considered good practice to discuss any patients admitted to hospital on SACT with their relevant cancer specialist team.

DOACs are substrates for P-glycoprotein and cytochrome P enzymes (e.g. CYP3A4) and can interact with a variety of Systemic Anti-Cancer Treatments (SACT). When considering potential drug interactions ensure that all medicines (including all SACT) are taken into account - remember that SACT may not appear on Emergency Care Summary. The Cancer Drug Interaction Checker (cancer-druginteractions.org, free access) is a useful source of information in addition to the Summary of Product Characteristics and the BNF. Consideration should be given to the pharmacokinetic profile of the medicines concerned including routes of metabolism and expected half-life.

DOAC Patient Information:

Please refer to GGC medicine webpage for further information on DOAC booklet.
https://ggcmedicines.org.uk/information-for-patients/direct-oral-anticoagulants/

References

Agnes Y.Y. Lee, Mark N Levine, Ross Baker et al. Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer. N Engl J Med 2003; 349:146-153

Giancarlo Agnelli, Cecilia Becattini, Guy Meyer, Andres Muñoz et al., for the Caravaggio Investigators. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. N Engl J Med 2020; 382:1599-1607

N. Key, A. Khorana, M. Kuderer, K. Bohlke et al Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. DOI: 10.1200/JCO.19.01461 Journal of Clinical Oncology 38, no. 5 (February 10, 2020) 496-520.

Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer. 2007;110(10):2339-46.

Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low- molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. The New England journal of medicine. 2003;349(2):146-53.

Li A, Garcia DA, Lyman GH, et al: Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis. Thromb Res 173:158-163, 2019

Mulder FI, van Es N, Kraaijpoel N, Di Nisio M, Carrier M, Garcia D, et al. Efficacy and safety of edoxaban in clinically relevant subgroups: results from the Hokusai VTE Cancer randomized trial. Thrombosis research. 2018;164:S194.

M. Mandala , A. Falanga & F. Roila On behalf of the ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines Annals of Oncology 22 (Supplement 6): vi85– vi92, 2011

Nigel S. Key, Alok A. Khorana, Nicole M. Kuderer, et al Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *Journal of Clinical Oncology* 38, no. 5 (February 10, 2020) 496-520.

Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. The New England journal of medicine. 2018;378(7):615-24.

Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

NICE guideline [NG158] Published: 26 March 2020.https://www.nice.org.uk/guidance/ng158 (accessed 1st May 2021)

Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). Journal of clinical oncology : 2018;36(20):2017-23.