AH CH 2: Blood and Blood Forming Organs

National Department of Health

Affordable Medicines Directorate
Essential Drugs Programme

Primary Healthcare Level Standard Treatment Guidelines – 2020-4 Review cycle
Adult Hospital Level Standard Treatment Guidelines – 2020-4 Review cycle

Evidence

Please access the National Essential Medicines List Committee (NEMLC) report for detailed evidence (including rationale, references and costings) informing decision-making on medicine addition, amendments and deletions:

NHI Website: https://www.health.gov.za/nhi-edp-stgs-eml
Knowledge Hub: www.knowledgehub.health.gov.za/e-library

Disclaimer

This presentation is an implementation tool and should be used alongside the most recently published STGs available on the Knowledge Hub. This information does not supersede or replace the STGs.

AH CH 2: Blood and Blood Forming Organs

SCAN ME

Presentation Outline

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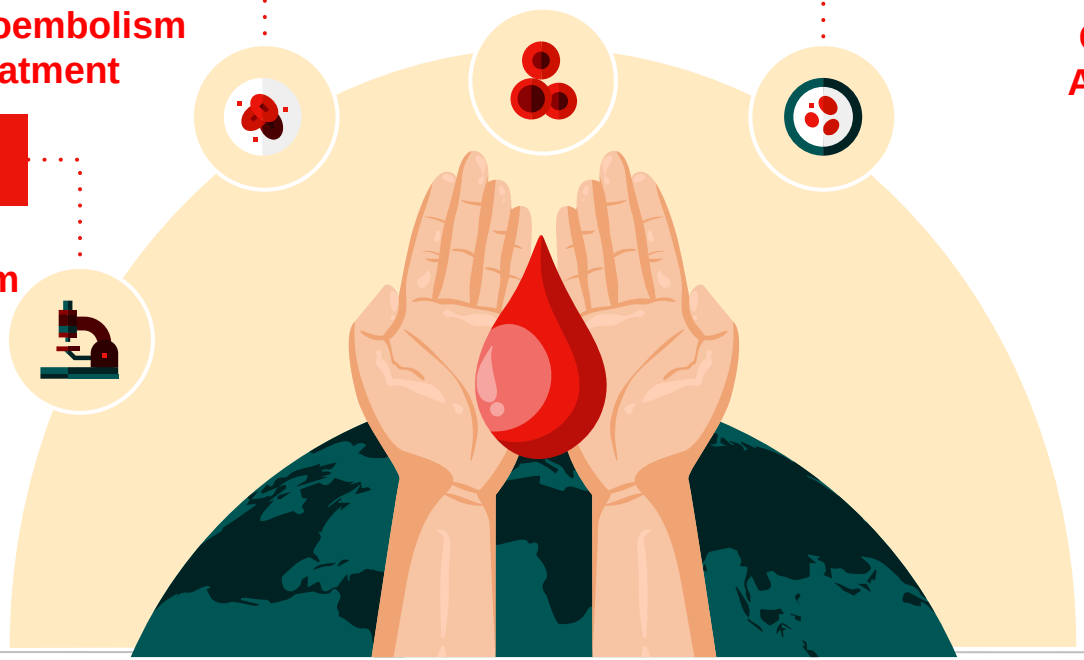

Venous Thromboembolism - Prophylaxis

STG Amendments: AH CH 2 Blood and Blood Forming Organs

The table below is a summary of the guidance for VTE prophylaxis:

	At risk population	VTE prophylaxis	Duration
Medical	Hospitalised patients with debilitating illness	Rivaroxaban, oral, 10 mg daily.	While hospitalised.
Orthopaedic Surgical	Total hip arthroplasty	Rivaroxaban, oral, 10 mg daily **followed by** aspirin, oral, 150 mg daily.	Rivaroxaban: From 6-10 hours post-op, for up to 10 days (or less if hospitalised <10 days). Aspirin: For 28 days on hospital discharge.
Orthopaedic Surgical	Total knee arthroplasty	Rivaroxaban, oral, 10 mg daily for 2-7 days, **followed by** aspirin, oral, 150 mg.	Rivaroxaban: From 6-10 hours post-op, for at least 2 days (max 7 days). Aspirin: Treat for remainder of VTE prophylaxis period, i.e. 14 days in total including days on rivaroxaban.
	Trauma-related **operative**: i) extremity fractures ii) pelvic and acetabular fractures	Low to moderate risk of VTE: Aspirin, oral, 150 mg daily. High risk of VTE: Enoxaparin, SC, 40 mg daily.	From >12 hours post-operatively, for 14 days or until mobilisation.
	Trauma-related **non-operative** pelvic and acetabular fractures	Low-moderate risk of VTE: Aspirin, oral, 150 mg daily. High risk of VTE: Enoxaparin, SC, 40 mg daily.	From admission up to 35 days.
Other Surgical	Other major surgery	Enoxaparin, SC, 40 mg daily. **OR** Unfractionated heparin, SC, 5 000 units 12 hourly.	While hospitalised.

Table 2.4: Summary of VTE prophylaxis in surgical and non-surgical patients

Refer to the NEMLC report for AH Chapter 2: Blood and Blood Forming Organs, for a full explanation of the amendments made to the STG for prophylaxis of Venous Thromboembolism

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Venous Thromboembolism - Prophylaxis

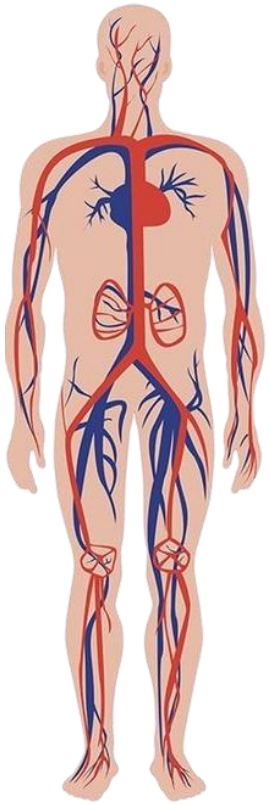
Medicine Review: Direct Oral Anticoagulants (DOACs) for Venous thromboembolism (VTE) prophylaxis in hospitalized, adult patients.

REVIEW

Review conducted of current relevant, high quality practice guidelines and the systematic reviews which informed their recommendations regarding the prevention of VTE – including both deep vein thrombosis (DVT) and pulmonary embolism (PE) - in adult, hospitalised patients at risk.

METHODOLOGY

AGREE II was used to appraise the American Society of Haematology (ASH) 2018 guideline for prophylaxis in medical patients, the ASH 2019 guideline for prophylaxis in surgical patients and National Institute for Health Care Excellence (NICE) 2018 guidelines for VTE prophylaxis. All were found to be of good quality.



RESULTS

Overall, DOACS have similar mortality and VTE outcomes as LMWH when used for the prevention of VTE in medically ill patients and surgical patients who have undergone total hip or total knee arthroplasty procedures. In medically ill patients, the increased risk of major bleeding with DOACs may be considered trivial in the context of major cost savings.

COST ANALYSIS

Rivaroxaban is currently the only DOAC for which a cost-analysis was performed as it is on government contract; at the time of review. Other DOACs are currently more expensive. There are massive projected cost-savings with use of rivaroxaban over enoxaparin and thus this recommendation is specific to rivaroxaban. Other DOACs have been added to the TI database (Refer to the Budget Impact analysis on Rivaroxaban attached to the NEMLC report—see link below)

National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Direct Anticoagulants for venous thromboembolism prophylaxis in hospitalized, adult patients. Direct-Oral-Anticoagulants-DOACS_Prevention-of-DVT-AdultHospReview_Updated-12-Oct-2023_v6.0_final.pdf

National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Budget Impact Analysis: Rivaroxaban – March 2023. Adult-Hospital-Chapter-2-BBFO-with-supporting-NEMLC-report-reviews-2020-4-Version-1.0_23-Sep-2024.pdf

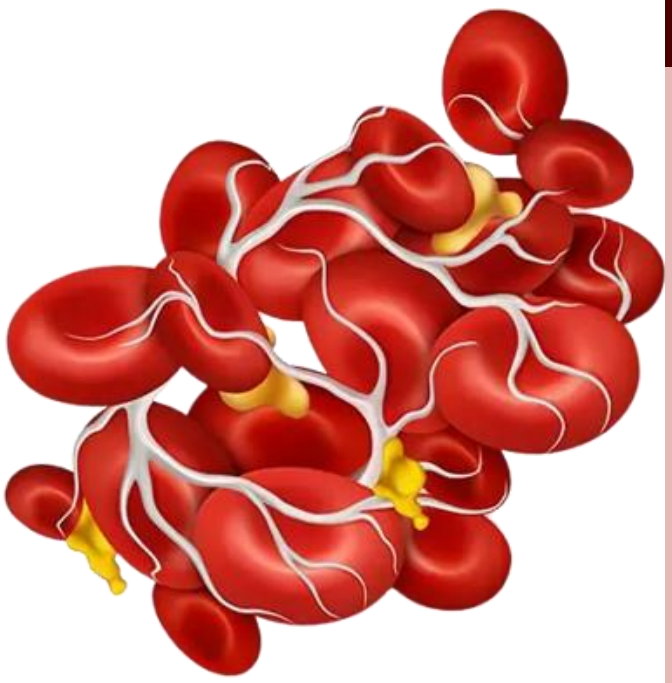
Venous Thromboembolism - Prophylaxis

NEMLC Recommendation

NEMLC recommends the use of direct oral anticoagulants (DOACs) for the prevention of venous thromboembolism (VTE) in medically ill, hospitalised, adult patients and for adult patients who require VTE prophylaxis post total hip or total knee arthroplasty. This recommendation excludes the subset of patients (hospitalised patients with trauma-related operative or non-operative extremity fractures or trauma-related pelvic or acetabular fractures at risk of VTE') in whom aspirin is recommended over LMWH (refer to Evidence summary on aspirin for VTE prophylaxis).

Venous Thromboembolism - Prophylaxis

Use of DOACs – Other considerations



Renal Impairment

As the studies evaluated in the review excluded participants with an eGFR< 30mls/min; and the professional information leaflet suggests to avoid in this patient population; we recommend that alternatives with demonstrated safety; and documented dose adjustments in renal impairment, such as low molecular weight heparin or unfractionated heparin be considered instead. Guidance has been included in the EML to avoid the use of rivaroxaban in patients with a eGFR <30/ml/min/1.73m^2

Obesity

Due to limited data on the safety and efficacy of rivaroxaban in obese patients for VTE prophylaxis, we do not recommend rivaroxaban in these patients. This guidance will be reviewed as more robust evidence becomes available.

Venous Thromboembolism - Prophylaxis

Updates to the Therapeutic Interchange Database

Section (Description)	Indication	Therapeutic class	INN	strength	unit	formulation
Venous thrombo-embolism	**Prevention of venous thromboembolism - medically ill patients**	**Antithrombotic agent (LMWH)**	**Enoxaparin**	**40**	**mg**	**parenteral**
Venous thrombo-embolism	Prevention of venous thromboembolism - medically ill patients	Antithrombotic agent (LMWH)	Dalteparin	0.2	ml	parenteral
Venous thrombo-embolism	Prevention of venous thromboembolism - medically ill patients	Antithrombotic agent (LMWH)	Nadroparin	0.3	ml	parenteral
Venous thrombo-embolism	Prevention of venous thromboembolism - medically ill patients	Direct oral anticoagulants (DOAC)	Rivaroxaban	10	mg	oral
Venous thrombo-embolism	Prevention of venous thromboembolism - medically ill patients	Direct oral anticoagulants (DOAC)	Apixaban	2.5	mg	oral
~~**Venous thrombo-embolism**~~	**Prevention of venous thromboembolism - surgical patients: low to moderate risk**	~~**Antithrombotic agent (LMWH)**~~	~~**Enoxaparin**~~	~~**40**~~	~~**mg**~~	~~**parenteral**~~
~~Venous thrombo-embolism~~	~~Prevention of venous thromboembolism - surgical patients: low to moderate risk~~	~~Antithrombotic agent (LMWH)~~	~~Dalteparin~~	~~0.2~~	~~ml~~	~~parenteral~~
~~Venous thrombo-embolism~~	~~Prevention of venous thromboembolism - surgical patients: low to moderate risk~~	~~Antithrombotic agent (LMWH)~~	~~Nadroparin~~	~~0.3~~	~~ml~~	~~parenteral~~
Venous thrombo-embolism	**Prevention of venous thromboembolism - surgical patients orthopaedic surgical patients with trauma-related i) operative extremity fractures or ii) operative or non-operative pelvic and acetabular fractures: high risk**	**Antithrombotic agent**	**Enoxaparin**	**40**	**mg**	**parenteral**
Venous thrombo-embolism	**Prevention of venous thromboembolism - surgical patients orthopaedic surgical patients with trauma-related i) operative extremity fractures or ii) operative or non-operative pelvic and acetabular fractures: high risk**	Antithrombotic agent	Dalteparin	0.4	ml	parenteral
Venous thrombo-embolism	**Prevention of venous thromboembolism - surgical patients orthopaedic surgical patients with trauma-related i) operative extremity fractures or ii) operative or non-operative pelvic and acetabular fractures: high risk**	Antithrombotic agent	Nadroparin	0.3	ml	parenteral
Venous thrombo-embolism	**Prevention of venous thromboembolism - surgical patients orthopaedic surgical patients with trauma-related i) operative extremity fractures or ii) operative or non-operative pelvic and acetabular fractures: high risk**	Antithrombotic agent	Fondaparinux	2.5	mg	parenteral
Venous thrombo-embolism	**Prevention of venous thromboembolism -surgical patients elective total hip and knee arthroplasty**	**Antithrombotic agent**	**Enoxaparin**	**40**	**mg**	**parenteral**
Venous thrombo-embolism	**Prevention of venous thromboembolism -surgical patients elective total hip and knee arthroplasty**	Antithrombotic agent	Dalteparin	0.4	ml	parenteral
Venous thrombo-embolism	**Prevention of venous thromboembolism -surgical patients elective total hip and knee arthroplasty**	Antithrombotic agent	Nadroparin	0.3	ml	parenteral
Venous thrombo-embolism	**Prevention of venous thromboembolism -surgical patients elective total hip and knee arthroplasty**	Antithrombotic agent	Fondaparinux	2.5	mg	parenteral
Venous thrombo-embolism	**Prevention of venous thromboembolism -surgical patients elective total hip and knee arthroplasty**	Direct oral anticoagulants (DOAC)	Rivaroxaban	10	mg	oral
Venous thrombo-embolism	**Prevention of venous thromboembolism -surgical patients elective total hip and knee arthroplasty**	Direct oral anticoagulants (DOAC)	Apixaban	2.5	mg	oral

Venous Thromboembolism - Prophylaxis

Medicine Review: Aspirin for VTE Prophylaxis after trauma-related factors

A systematic review was conducted to evaluate the efficacy of aspirin compared with low-molecular weight heparin (LMWH) in adult patients requiring venous thromboembolism (VTE) prophylaxis after trauma-related fractures.

Two relevant trials were identified, Haac 2020 (ADAPT) and O'Toole 2023 (METRC) conducted in USA and Canada, n = 12,540. Both trials tested aspirin (81 mg twice daily) vs enoxaparin (30mg twice daily)

Overall, aspirin is probably no different to enoxaparin ~~for~~:

- mortality RR 1.07 (95% CI 0.71 to 1.59) risk difference (RD) 1 more death (2 fewer to 4 more) per 1000 people treated with aspirin vs enoxaparin
- major bleeding RR 0.96 (0.89 to 1.05) RD 6 fewer per 1000 people (16 fewer to 7 more) treated with aspirin vs enoxaparin, and
- pulmonary emboli RR 0.77 (0.30 to 1.94) RD 4 fewer events (11 fewer to 14 more) per 1000 people treated with aspirin vs enoxaparin **(high certainty evidence).**

However, using aspirin compared to enoxaparin, likely results in a small increase in the risk of developing symptomatic deep vein thrombosis (DVT) RR 1.48 (1.16 to 1.89); RD 8 more per 1000 (3 more to 15 more)

In the South African public sector, enoxaparin is the current recommended medicine for VTE prophylaxis in this patient population. It is costly and administered subcutaneously. Aspirin is extremely cheap, taken orally and is easily accessible in most facilities at every level of care across the country. Using aspirin rather than enoxaparin may lead to major cost-savings and improved access to outpatient VTE prophylaxis, which may reduce duration of hospital stay. There is however, the potential for increased cases of DVT.

Risk stratification may be useful in determining the patient population in whom VTE prophylaxis with aspirin would be a safe choice.

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National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Aspirin for VTE Prophylaxis after trauma related factors..
Evidence-Summary-Aspirin-for-VTE-proph_Fractures_12-Oct-2023-final-approved.pdf

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Venous Thromboembolism - Prophylaxis

NEMLC Recommendation

NEMLC recommends using aspirin as prophylaxis in patients with operative trauma-related extremity fractures for all operative or non-operative hip and acetabular fractures. It must be noted that this recommendation is conditional as it applies only to patients with low to moderate risk of VTE. The studies included are representative of a low to moderate risk population and findings cannot therefore be extrapolated to patients at high risk of VTE. A recommended dose of 150mg of aspirin daily, initiated >12 hours post-operatively and continued for 14 days or until mobilisation is achieved should be given to low-moderate risk patients without contraindications to aspirin, and requiring thromboprophylaxis. In patients with non-operative pelvic and acetabular fractures, prophylaxis can be continued for up to 35 days. VTE risk can be determined by using the Caprini score or risk categories stipulated in the current Standard Treatment Guidelines as detailed for surgical patients

Venous Thromboembolism - Prophylaxis

Medicine Review: Guideline adaptation of NICE Guideline "Venous thromboembolism in over 16s" for patients undergoing total hip arthroplasty or total knee arthroplasty requiring venous thromboembolism (VTE) prophylaxis.

Both the ASH (2019) and NICE (2018) guidelines scored well with AGREE II and both offered multiple pharmacological options for VTE prophylaxis in patients undergoing hip and knee arthroplasty.

The NICE (2018) guideline offers dosing recommendations, specifies duration of therapy and considers the two patient populations separately, detailing distinct regimens for VTE prophylaxis in total hip compared with total knee arthroplasty. These factors made guideline adaptation more practical and are the reasons for choosing NICE over ASH.

The NICE guideline found that the data for aspirin as VTE prophylaxis is of low quality which is in keeping with the reviewers' own literature search. Network meta-analyses were used to compare multiple options for prophylaxis with a separate NMA for each outcome.

Adapted recommendation for total knee arthroplasty:
Rivaroxaban 10mg daily initiated 6-10 hours post operatively for duration of admission for a minimum of 2 to a maximum of 7 days, followed by 150mg aspirin daily on discharge to complete 14 days of VTE prophylaxis in total (rivaroxaban followed by aspirin).
Rationale: Considering the prolonged antiplatelet activity of aspirin together with the poor quality of data informing all guidelines on this matter, it was deemed safer to begin VTE prophylaxis with an anticoagulant other than aspirin in the initial post-operative period. This is to mitigate the potential bleeding risk with aspirin, in alignment with the recommendation for hip arthroplasty patients. The range stipulated in the guideline is to allow for individual variation in clinical course.

Adapted recommendation for total hip arthroplasty:
Rivaroxaban 10mg daily initiated 6-10 hours post operatively for duration of admission for a maximum of 10 days, followed by aspirin 150mg for 28 days on discharge.
Rationale: LMWH was used in the NICE guideline for the first 10 days. In the evidence to decision, this was to mitigate the bleeding risk with aspirin which is highest in the immediate post-operative period. For our adapted recommendation, LMWH was replaced by rivaroxaban as it has been shown to be noninferior in terms of safety and efficacy and is more cost effective. In all other respects, we have retained the recommendations as included in the NICE guideline

REFERENCE

National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Guideline adaptation of NICE Guideline "Venous thromboembolism in over 16s" for patients undergoing total hip arthroplasty or total knee arthroplasty requiring VTE prophylaxis. Adaptation-of-NICE-Guidance-VTE-Prophylaxis-hip-and-knee-arthroplasty_v1.0_30-Nov-2023-final.pdf

Venous Thromboembolism - Prophylaxis

NEMLC Recommendation

NEMLC recommends using the option of rivaroxaban followed by aspirin for VTE prophylaxis in elective hip and knee arthroplasty patients. This is an adaptation of the 2018 NICE guideline ("Venous thromboembolism in over 16s"). This high quality guideline states that use of aspirin in this patient population is supported by low to very low certainty evidence. For this reason, our recommendation is conditional. The alternative to this prophylaxis regimen would be rivaroxaban for the full duration of prophylaxis

Venous Thromboembolism - Treatment

Medicine Review: Should DOACs be used for the treatment of DVT or PE in hospitalized adult patients?

Review was conducted of current relevant, high quality practice guidelines and the systematic reviews that informed their recommendations. The American Society of Haematology (ASH) 2020 guideline and National Institute for Health Care Excellence (NICE) 2020 guidelines were reviewed and appraised using AGREE II and found to be of good quality. The systematic reviews that informed the guideline recommendations were appraised using AMSTAR and also found to be of good quality.

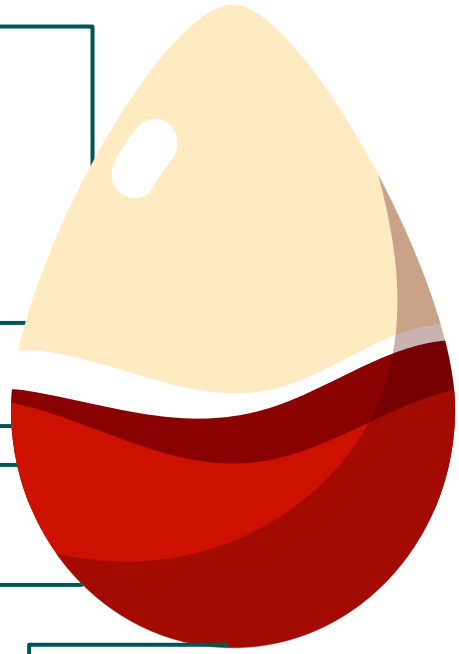
The ASH review reported that there is probably no difference in mortality between direct oral anticoagulants (DOACs) and low molecular weight heparin / vitamin K antagonists (LMWH/VKA), RR, 0.99; (95% CI, 0.85-1.15) with **moderate-certainty evidence**.

The risk of pulmonary embolism and deep vein thrombosis on LMWH/VKA compared to DOACs were similar (RR, 0.97; 95% CI, 0.77- 1.23) and (RR, 0.80; 95% CI, 0.59-1.09), respectively. The quality of evidence was **moderate certainty evidence**

The use of DOACs was associated with a reduction in the risk of major bleeding (RR, 0.63; 95% CI, 0.47-0.84; AR ARR, 6 fewer per 1000 patients; 95% CI, 9 fewer to 3 fewer); NNH = 167 (95% CI, 112 – 334).

Overall DOACS have similar mortality and VTE outcomes as LMWH/VKA. However, there is a potential lower risk of major bleeding with DOACs compared to LMWH/VKA

Based on the most recent **budget impact analysis**, there is a cost saving per patient with the use of rivaroxaban compared to warfarin in the treatment and prevention of recurrent VTE for 3 months following the initial event.



National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Should DOACs be used for the treatment of DVT or PE in hospitalized adult patients. Direct-Oral-Anticoagulants-DOACS_Treatment-of-DVTPE_Adults_v6_30-November-2023_final.pdf

National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Budget Impact Analysis: Rivaroxaban – March 2023. Adult-Hospital-Chapter-2-BBFO-with-supporting-NEMLC-report-reviews-2020-4-Version-1.0_23-Sep-2024.pdf

Venous Thromboembolism - Treatment

NEMLC Recommendation

NEMLC recommends rivaroxaban for the treatment of VTE.
Rationale: There is equivalent efficacy; and probably no difference in mortality between DOACS and vitamin K antagonists (LMWH) in the treatment of venous thromboembolism; **(Moderate certainty evidence)**. DOACS are safer with a lower risk of major bleeding. Rivaroxaban is cheaper at 3 months of therapy.

Venous Thromboembolism - Treatment

STG Amendments: AH CH 2 Blood and Blood Forming Organs

MEDICINE TREATMENT

LoE:Ib[xxxiv]

For proximal deep venous thrombosis and/or pulmonary embolism:

- Rivaroxaban, oral, 15 mg twice daily for 3 weeks, followed by 20 mg once daily for 3 months.

<u>If i) rivaroxaban is contraindicated, or ii) patient is high risk and requires long term anticoagulation (> 6 months), e.g. recurrent VTE:</u>

» Start unfractionated or low molecular weight heparin simultaneously with warfarin.

» After 5 days, heparin may be stopped if an INR within therapeutic range (INR between 2 and 3) has been reached and maintained for at least 24 hours.

» Note: Heparin and warfarin therapy should overlap for at least 5 days.

▪ Low molecular weight heparin, e.g.:

- Enoxaparin, SC, 1.5 mg/kg daily, LoE:I[xxxv]

OR

- Enoxaparin, SC, 1 mg/kg 12 hourly, LoE:I[xxxvi]

CAUTION – Enoxaparin

In morbid obesity, dosing of LMWH should be individualised in discussion with a specialist. LoE:III[xxxvii]

In renal failure (eGFR <30 mL/minute), the recommended treatment dose of enoxaparin is 1 mg/kg daily. LoE:III[xxxviii]

CAUTION – Unfractionated heparin

Evidence indicates that PTT monitoring is not necessary with weight-based dosing of unfractionated heparin. However, in patients with morbid obesity and renal failure (eGFR <30 mL/minute), unfractionated heparin should be used with PTT monitoring to maintain the PTT at 1.5 to 2.5 times the control.

PTT should be taken 4 hours after SC dose.

Venous Thromboembolism - Treatment

Follow with:

- Warfarin, oral, 5 mg daily.
  - Measure INR after 48 hours, then every 1 to 2 days until the INR is within the therapeutic range of 2–3 (refer to initiation dosing tables in the Appendix II).
  - Adjust dose to keep INR within therapeutic range (refer to maintenance dosing tables in Appendix II). LoE:IVb[xxxix]
  - Continue warfarin for 3 months with regular INR monitoring, provided that a precipitating cause that has resolved.
  - In patients with a first-time, unprovoked DVT, discuss duration of therapy with a specialist.
  - All women of reproductive age should be on appropriate contraception (see Primary Health Care STGs and EML, Chapter 7: Family Planning). If a pregnancy is planned, do frequent pregnancy tests and change to enoxaparin once pregnancy is confirmed (see Section 2.8.3: VTE during pregnancy and the puerperium). LoE:IIIb[xl]
  - For all major elective surgery and other elective procedures with a significant bleeding risk, such as neuraxial anaesthesia and lumbar punctures, the INR should be <1.5 (see Section 12.7.1: Anticoagulants and spinal or epidural blocks).
  - Educate patient on signs and symptoms of warfarin toxicity, and on risks associated with drastic dietary changes such as increased consumption of cruciferous vegetables.

Heparin induced thrombocytopenia (HIT)

A severe immune-mediated drug reaction occurring in 1–5% of patients receiving heparin therapy (more common with unfractionated heparin, but may also occur with low molecular weight heparin). It presents with thrombocytopenia and thrombosis. Diagnosis requires a high index of suspicion and should be considered if a patient has a 50% drop in platelet count within 5–10 days after initiating heparin therapy. A positive antibody test confirms the diagnosis.

Management of HIT:

Stop heparin and discuss all patients with a specialist.

REFERRAL/CONSULTATION

» All patients with heparin induced thrombocytopaenia

Venous Thromboembolism - Treatment

Updates to the Therapeutic Interchange Database

Section (Description)	Indication	Therapeutic class	INN	strength	unit	formulation
Venous thrombo-embolism	**Treatment**	Antithrombotic agent (LMWH)	**Enoxaparin**	**1.5**	**mg/kg**	**parenteral**
Venous thrombo-embolism	Treatment	Antithrombotic agent (LMWH)	Enoxaparin	1	mg/kg	parenteral
Venous thrombo-embolism	Treatment	Antithrombotic agent (LMWH)	Dalteparin	100	U/kg	parenteral
Venous thrombo-embolism	Treatment	Antithrombotic agent (LMWH)	Nadroparin	0.01	ml/kg	parenteral
Venous thrombo-embolism	Treatment	Antithrombotic agent	Fondaparinux	7.5	mg	parenteral
Venous thrombo-embolism	Treatment	Direct oral anticoagulants (DOAC)	Rivaroxaban	15	mg	oral
Venous thrombo-embolism	Treatment	Direct oral anticoagulants (DOAC)	Rivaroxaban	20	mg	oral
Venous thrombo-embolism	Treatment	Direct oral anticoagulants (DOAC)	Apixaban	5	mg	oral
Venous thrombo-embolism	Treatment	Direct oral anticoagulants (DOAC)	Dabagatran	150	mg	oral

****N.B: Refer to the individual product information leaflets for specific dosing guidance.**

NEW STG ADDED

Venous Thromboembolism during Pregnancy and the Puerperium

Evidence Summary: The use of Low Molecular Weight Heparins (LMWH) for secondary venous thromboembolism (VTE) during pregnancy and the puerperium

Normal pregnancy is a hypercoagulable state due to physiological changes in haemostasis and this only returns to a pre-pregnancy state 6-8 weeks after delivery.

The overall incidence of pregnancy-associated VTE is about 200 per 100,000 woman-years; compared to nonpregnant women of childbearing age, the relative risk is increased about fourfold. The risk during the postpartum period is about fivefold higher than the risk during pregnancy.

Warfarin use during weeks 12 to 36 of pregnancy in women requiring VTE prophylaxis for reasons other than mechanical cardiac lesions is not recommended due to concerns for fetal safety.

LMWH is safe for VTE prophylaxis in women with a prior VTE event, and the optimal dose is evidence based.

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National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Evidence Summary. The use of low molecular weight heparins(LMWH) for secondary venous thromboembolism (VTE) prophylaxis during pregnancy and the puerperium.
LMWH_secondaryVTEprophylaxisInPregnancy_EvidenceSummary_November2022_v0.2_final.pdf

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NEW STG ADDED

Venous Thromboembolism during Pregnancy and the Puerperium

NEMLC Recommendation

RECOMMENDED

NEMLC acknowledged the lack of local data for the risk of thrombosis in pregnancy and that no available evidence could be sourced for the risk of mortality, premature births or congenital anomalies associated with warfarin. However, this was likely to be a small patient population. NEMLC recommended that LMWH (e.g. enoxaparin) be recommended for VTE prophylaxis in pregnant women with a prior VTE.

NEW STG ADDED

Venous Thromboembolism during Pregnancy and the Puerperium

New STG: AH CH 2 Blood and Blood Forming Organs

2.8.3 VTE DURING PREGNANCY AND THE PUERPERIUM

O22.2-3/O87.0-1/O87.9/O88.3

DESCRIPTION

The risk of VTE is substantially increased in pregnancy and is an important cause of maternal morbidity and mortality.

MEDICINE TREATMENT

Prophylaxis

Risk Assessement

A risk assessment should be done in pre/early pregnancy and repeated if the woman is admitted to hospital for any reason, during delivery, and immediately post delivery.

The decision to provide VTE prophylaxis will depend on an assessment of the patient's risk for thromboembolism:

Indications	Duration of therapy
Previous VTE episode (DVT or pulmonary embolism)	VTE prophylaxis during pregnancy and for up to 6 weeks post-delivery.
Patient with any **ONE** of the following high risk factors: » Emergency Caesarean section » BMI > 40 kg/m² » Prolonged hospital stay » Intravenous drug user	VTE prophylaxis for a minimum of 5 days post delivery (or longer duration if still admitted in hospital)
Patient with any of the following intermediate risk factors: » Age > 35 years of age » BMI 35-40 kg/m² » Parity ≥ 3 » Smoker » Elective caesarean section » Any surgical procedure in the puerperium » Gross varicose veins » Current systemic infection » Immobility e.g paraplegia, long distance travel » Current pre-eclampsia » Prolonged labour > 24 hours » PPH† > 1 litre or requiring blood transfusion	**One** risk factor: Prevent dehydration and encourage early mobilisation. **Two or more** risk factors: VTE prophylaxis for a minimum of 5 days post delivery (or longer duration if still admitted in hospital).

†Post-partum haemorrhage

Table 2.6: Indications for VTE prophylaxis and duration of therapy

Prophylactic treatment

- Low molecular weight heparin, e.g.
- Enoxaparin, SC:
  - Body weight <100 kg: 40 mg daily.
  - Body weight ≥100 kg: 60 mg daily.
  - For post-partum prophylaxis, start 6–12 hours after delivery.

Note:

- Although LMWH related skin reactions are generally rare, they are more common in pregnant women. Monitor injection site for potential skin reactions.
- Women receiving antenatal LMWH should be advised that if they have any vaginal bleeding or once labour begins they should not inject any further LMWH.
- Spinal or epidural anaesthesia should be avoided if possible until at least 12 hours after the previous prophylactic dose of LMWH.
- The use of warfarin for VTE prophylaxis and treatment during pregnancy is not recommended, except in the setting of valvular disease and atrial fibrillation (see section 6.3- Heart disease in pregnancy).
- Women that were either 1) on long-term anticoagulation with warfarin before pregnancy, or 2) require anticoagulation for 6 weeks post delivery can be converted from LMWH to warfarin postpartum when the risk of haemorrhage is reduced, usually 5–7 days after delivery.
  - Note that initiation of warfarin will require continued anticoagulation with LMWH at prophylactic doses (see above) until the INR is within the therapeutic range:
    - Warfarin, oral, 5 mg daily.
    - INR should be done after 48 hours, then every 1 to 2 days until the INR is within the therapeutic range of 2-3 (refer to initiation dosing tables in the Appendix II).
    - Adjust dose to keep INR within therapeutic range (refer to maintenance dosing tables in the Appendix II).
    - Monitor INR at week 1, 2, and 4 (more frequent monitoring may be required if INR is out of therapeutic range).
    - All women of reproductive age should be on appropriate contraception (see chapter PHC STGs and EML, chapter 7: Family Planning). If a pregnancy is planned, do frequent pregnancy tests and change to LMWH once pregnancy is confirmed.
    - For all major elective surgery and other elective procedures with a significant bleeding risk, such as neuraxial anaesthesia and lumbar punctures, the INR should be <1.5.
    - Educate patient on signs and symptoms of warfarin toxicity, and on risks associated with drastic dietary changes such as increased consumption of cruciferous vegetables.
  - Warfarin is safe in breastfeeding

Acute treatment of VTE or pulmonary embolism:

- Low molecular weight heparin, e.g.
- Enoxaparin SC, 1 mg/kg every 12 hours.
  - Discontinue treatment at least 24 hours prior to delivery, if the delivery time is predictable.
  - Continue treatment for 6 weeks post partum, and for at least three months in total.

REFERRAL/CONSULTATION DURING PREGNANCY

- Heparin-induced thrombocytopenia.
- Heritable or acquired thrombophilia.
- Medical comorbidities for consultation with specialist: heart or lung disease, SLE, cancer, inflammatory conditions, nephrotic syndrome, sickle cell disease, anti-phospholipid syndrome.

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Other Notable Chapter Amendments

#1 Anaemia, Sickle Cell

The prophylactic dose of **enoxaparin** in patients with renal failure has been amended in line with the erratum (Reference: 2023/07/14/EDP/03) issued on the 14th July 2023)

AMENDED TO:

MEDICINE TREATMENT

Severe vaso-occlusive episodes

» Maintain adequate saturation with oxygen supplementation.

To prevent venous thromboembolism:

- Low molecular weight heparin (LMWH), e.g.:
- Enoxaparin, SC, 40 mg daily.

OR

Unfractionated heparin, SC, 5 000 units 12 hourly.

In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist.

In renal failure (eGFR <30 mL/minute), the recommended prophylactic dose of enoxaparin is 20 mg daily.

Analgesia

» Control pain adequately – See Section 26.2.1: Medical conditions associated with severe pain.

#2 Febrile Neutropenia

The dose of **vancomycin** for treating suspected line or skin infections in patients who develop febrile neutropenia within 48 hours of admission, has been amended to align with dose recommendations as included in the AH STGs, Section 9.1.1 Intravascular catheter infections and Appendix II: Guidance for prescribing and therapeutic drug monitoring

AMENDED TO:

If IV line, and skin infection is suspected as the cause:

ADD:

- Vancomycin, IV, 25–30 mg/kg as a loading dose. Follow with 15–20 mg/kg/dose 12 hourly. (See Appendix II: guidance on prescribing and monitoring).

#3 Febrile Neutropenia

The dose of **imipenem/cilastatin** for patients with febrile neutropenia developed after 48 hours of admission, has been amended to align with guidance in the AH STG Section 9.1.3 Hospital-acquired pneumonia (HAP) and ventilator associated pneumonia (VAP).

AMENDED TO:

Regimen 1:

- Carbapenem with activity against Pseudomonas, e.g.:
  - Meropenem, IV, 1 g 8 hourly.

OR

  - Imipenem/cilastatin, IV, 1000/1000 mg 8 hourly.

Note: Ertapenem is not recommended as it is not effective for *Pseudomonas* species, which are important pathogens in this setting.

#4 Febrile Neutropenia

The frequency of dosing of **piperacillin/tazobactam**, IV was amended from 4.5g 8 hourly to 4.5g 6 hourly to accommodate for the management of pseudomonas-related infections as recommended in the approved package insert[1] and Stanford guidelines[2].

[1] Package Insert – Tazocin. Pfizer Laboratories (Pty) Ltd. 02 May 2002.

[2] Stanford Hospital and Clinics (SHC). SHC-Extended-Infusion-Piperacillin-Tazobactam.pdf (stanford.edu)

THANK YOU

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