CHAPTER 2
BLOOD AND BLOOD FORMING ORGANS

2.1 ANAEMIA

DESCRIPTION
Defined as a reduction in the absolute number of circulating red blood cells and most commonly diagnosed when the haemoglobin (Hb) concentration falls below the reference range for age and sex (Hb reference range males 13.0–17.0 g/dL; females 12.0–15.0 g/dL). The clinical features depend on the severity of anaemia, the rate at which it developed and the oxygen demands of the patient.

Anaemia can be classified according to the mean corpuscular volume (MCV) of the red blood cell (RBC) into macrocytic anaemia (MCV >100 fL), microcytic anaemia (MCV <80 fL), or normocytic anaemia (MCV 80–100 fL).

2.1.1 ANAEMIA, IRON DEFICIENCY
D50.0-1/D50.8-9

DESCRIPTION
Anaemia due to iron deficiency. Common causes of iron deficiency are chronic blood loss, poor iron absorption or poor nutritional intake.

Investigations
» Low MCV and low MCH (mean corpuscular hemoglobin <26 pg) – note that these are often normal in early stages.
» Full blood count (FBC) and peripheral smear: Hypochromic (low MCH) microcytic anaemia, and pencil cells often reported.
» Confirm with low ferritin.
» Investigate for cause of iron deficiency.
» Consider upper and lower gastrointestinal endoscopies in high risk patients (all males and postmenopausal female patients) and patients not responding to treatment.

GENERAL MEASURES
» Identify and treat the underlying cause.
» Dietary adjustment if this is the underlying cause.

MEDICINE TREATMENT
Iron supplementation for treatment:
Oral iron preparation
- Ferrous sulfate compound BPC (dried), oral, 170 mg (± 55 mg elemental iron) 12 hourly. *LoE:IIIb*[i]

OR
- Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) 12 hourly.

- Do not ingest with tea, antacids or calcium supplements/milk.
- Doses should be taken on an empty stomach, but if gastrointestinal side effects occur, doses may be taken with meals.
- Continue with treatment for 3 months once Hb has normalised to replace iron stores.
- If daily iron is poorly tolerated (e.g. epigastric pain, nausea, vomiting and constipation), administer oral iron on alternate days with meals.

LoE:IIIb[ii]

Monitor patient response after one month of treatment: Hb should rise by at least 2 g/dL in the adherent patient without ongoing blood loss.

Consider the following if there is failure to respond to iron therapy:
» non-adherence,
» continued blood loss,
» alternate diagnosis,
» malabsorption, or
» mixed deficiency; concurrent folate or vitamin B_{12} deficiency.

Consult a specialist for further workup and/or intravenous iron supplementation if patient is not responding to oral iron supplementation despite adherence and no ongoing losses.

Parenteral iron preparation
Parenteral iron is seldomly required and may very rarely be associated with anaphylaxis. Hypotensive episodes may occur if the injection is administered too rapidly. *LoE:IVb*[iii]

Parenteral iron is only indicated in the following scenarios:
» oral iron is ineffective (defined as lack of response after three months of oral iron therapy);
» oral iron is not tolerated.
» oral iron is not expected to be effective, e.g. malabsorption, patients on haemodialysis and erythropoietin therapy; or
» iron deficiency anaemia from 36 weeks of pregnancy;

In people who require repeated therapy, the intravenous route is preferred.
Note: Use in consultation with a specialist.

The total iron dose to be administered is determined by haemoglobin and body weight (advisable to also reference product information):

$$0.66 \times Body\ weight\ (kg) \times (100 - \frac{(Hb\ \times 100)}{14.8})$$

- Iron, IV, e.g.:
- Iron sucrose, slow IV infusion, 200 mg in 200 mL sodium chloride 0.9%, over 30 minutes.
  - This preparation can be administered to a maximum frequency of 3 times a week until the total calculated iron dose has been given.
  - Test dose is not required, however, caution is advised with every dose of IV iron, even if previously well tolerated.
  - An initial total dose of 600 mg (administered in three divided doses) is usually adequate to raise the Hb to acceptable levels.

OR *LoE:IVb*[iv]

- Low molecular weight iron dextran, slow IV infusion, 100–200 mg, diluted in 100 mL 0.9% sodium chloride or 5% glucose solution.
  - Maximum infusion rate: 100 mL over 30 minutes (200 ml per hour).
  - Administer 2–3 times per week until calculated total iron requirements have been given.
  - If patient requires rapid delivery of iron to replenish iron stores, iron dextran may be administered as a total dose infusion up to a total replacement dose of 20 mg/kg body weight. Dilute dose in 500 mL 0.9% sodium chloride or 5% glucose solution and give over 4–6 hours.
  - Test dose is not required, however, caution is needed with every dose of IV iron, even if previously well tolerated.

LoE:IIIb[v]

Resuscitation equipment should be readily available to manage anaphylaxis.

Red cell concentrate transfusion

Indicated in patients with:

» severe anaemia leading to cardiac failure or severe dyspnoea;
» active, ongoing bleeding; or
» where correction of anaemia is required prior to performing an urgent invasive procedure or surgery.

Iron supplementation for prophylaxis:

O99.0/D50.0-1/D50.8-9/Z29.2

For example during pregnancy:

- Ferrous sulfate compound BPC (dried), oral, 170 mg (± 55 mg elemental iron) daily. *LoE:IIIb*[vi]

OR

- Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) daily.

Note:

» Do not ingest oral iron with tea, antacids or calcium supplements/milk.
» Doses should be taken on an empty stomach, but if gastrointestinal side effects occur, doses should be taken with meals.

If daily iron is poorly tolerated:
» Features of intolerance: epigastric pain, nausea, vomiting, and/or constipation.
» Oral iron preparations may be prescribed on alternate days. If still poorly tolerated, dosing may be modified and taken once weekly (See table below for dosing).

Iron preparation	Alternate day dosing	Once weekly dosing
Ferrous sulphate compound BPC (dried)	170 mg (±55 mg elemental iron), once on alternate days	340 mg (±110 mg elemental iron), once weekly
Ferrous fumarate	200 mg (±65 mg elemental iron), once on alternate days	400 mg (±130 mg elemental iron), once weekly

Table 2.1: Alternative oral iron supplementation dosing regimens

LoE:IIb[vii]

REFERRAL/CONSULTATION
» Ongoing anaemia despite reported adherence and optimal therapy.

2.1.2 ANAEMIA, MEGALOBLASTIC
D51.0-2/D51.2/D51.8-9/D52.0-1/D52.8-9/D53.1/D53.8-9

DESCRIPTION
» Anaemia caused by a deficiency of folate and/or vitamin B_{12}.
» Note that several medicines can cause macrocytic anaemia (e.g. hydroxyurea, methotrexate, zidovudine, azathioprine, valproic acid, and phenytoin) without deficiencies of folate and/or vitamin B_{12}.
» Clinical manifestations of vitamin B_{12} deficiency are mainly neurological – peripheral neuropathy, dementia and subacute combined degeneration of the spinal cord.

Investigations
» Elevated MCV (>100 fl) and MCH (>34 pg).
» Pancytopaenia in severe cases.
» FBC and peripheral smear: oval macrocytes, hypersegmentation of neutrophils, thrombocytopenia with giant platelets.
» Decreased serum vitamin B_{12} and/or red blood cell folate.
» Intrinsic factor antibodies, and/ or anti-parietal cell antibodies are found in pernicious anaemia.

GENERAL MEASURES
» Counsel on dietary modifications to ensure adequate intake of folate and vitamin B_{12} (especially important in vegetarians and malnourished patients).

» Identify and treat the underlying cause, e.g. antibiotics for bacterial intestinal overgrowth.
» Chronic metformin use can lead to vitamin B_{12} deficiency by interfering with absorption. Maintain a low threshold for clinical features of vitamin B12 deficiency in patients on metformin, and check serum levels if clinically indicated.

MEDICINE TREATMENT

» Start with folic acid and vitamin B_{12} supplementation after taking blood samples for RBC folate and serum vitamin B_{12} levels.
» Monitor serum potassium and replace if necessary.
» Adjust management according to results.

CAUTION

Give vitamin B_{12} and folic acid together until the test results are available, as giving folic acid alone in patients with a vitamin B_{12} deficiency may precipitate a permanent neurological deficit.

Folic acid deficiency

- Folic acid, oral, 5 mg daily until Hb returns to normal (see reference ranges in Section 2.1).

Note: Prolonged treatment may be required for malabsorption states.

Vitamin B_{12} deficiency

For uncomplicated pernicious anemia:

- Vitamin B_{12}, IM, 1 mg on alternate days for 1–2 weeks.
  - Followed by 1 mg weekly until blood count is normal.
  - Lifelong maintenance dose: 1 mg monthly.

For serious complications from deficiency:

- Vitamin B_{12} IM, 1 mg daily for 1 week.
  - Followed by 1 mg weekly for 1 month.
  - Lifelong maintenance dose: 1 mg monthly.

LoE:IVb[viii]

Note:

» Response to treatment is associated with an increase in energy, strength and improvement in sense of well-being.
» Reticulocytosis begins 3–5 days after therapy and peaks at about day 7.
» Anaemia normally corrects within 1–2 months. The white cell count and platelets normalise in 7–10 days. As there is an increase in red blood cell production, iron and folic acid supplementation is also recommended until Hb has normalised.
» Monitor for hypokalaemia in the first few days of therapy (See Section 7.2.2: Hypokalaemia for management).

Consider the following in the event of response failure:
» Co-existing folate and/or iron deficiency,
» Other causes of macrocytosis:
  - Myelodysplasia,
  - Hypothyroidism,
  - Chronic alcohol use,
» Drug-induced, e.g. hydroxyurea, methotrexate, zidovudine, azathioprine, valproic acid and phenytoin.

Prophylaxis: O99.0/Z49.1/Z29.2
Vitamin B_{12} prophylaxis:
Vitamin B_{12} is indicated for patients after total gastrectomy or ileal resection:
- Vitamin B_{12}, IM, 1 mg every second month for life.

Folic acid prophylaxis:
Indications:
» Chronic inherited or acquired haemolytic anaemias, e.g. sickle cell anaemia, thalassaemia
» Myeloproliferative disorders
» Exfoliative skin disorders
» Increased demands, e.g. pregnancy, chronic haemodialysis
- Folic acid, oral, 5 mg daily.

2.1.3 ANAEMIA, CHRONIC DISORDER
D63.0/D63.8

DESCRIPTION
Anaemia due to chronic inflammation. This is characteristically a normochromic normocytic anaemia. Common causes of anaemia of chronic disorder include:
» Malignancy, e.g. haematological or solid tumours.
» Autoimmune disorders, e.g. rheumatoid arthritis.
» Chronic infections, e.g. HIV and TB.
» Chronic kidney disease.

GENERAL MEASURES
» Investigate and treat the underlying condition.
» Transfusion is seldom necessary.
» Do not treat with iron, folic acid or vitamin B_{12} unless there is a documented deficiency (note that diagnosing iron deficiency is difficult in chronic disorders as ferritin increases and serum iron decreases due to the acute phase response). A transferrin saturation level less than 20% usually indicates a combination of iron deficiency anaemia and anaemia of chronic disease.

2.1.4 ANAEMIA, HAEMOLYTIC

D55.0-3/D55.8-9/D56.0-4/D56.8-9/D58.0-2/D58.8-9/D59.0-6/D59.8-9

DESCRIPTION

Anaemia due to destruction of red blood cells. Destruction may be due to:

» Extracellular factors such as auto-immunity or mechanical factors, e.g. disseminated intravascular coagulation (DIC), hypersplenism, mechanical heart valves.
» Abnormalities of the cell membrane, e.g. hereditary spherocytosis.
» Enzymes, e.g. G6PD deficiency.
» Haemoglobin abnormalities, e.g. sickle cell anaemia, thalassaemia.
» Thrombotic thrombocytopaenic purpura: TTP is a life-threatening emergency. Refer immediately to a specialist unit for plasma infusion or exchange (see Section 2.6: Thrombotic thrombocytopenic purpura-Haemolytic uraemic syndrome).

Investigations

» Evidence of haemolysis: anaemia, reticulocytosis, decreased haptoglobin, increased lactate dehydrogenase (LDH) and unconjugated hyperbilirubinaemia.
» FBC and peripheral smear: spherocytes often reported.
» Coombs' test (direct antiglobulin) is usually positive with autoimmune haemolysis.
» HIV status.

GENERAL MEASURES

» Treat the underlying cause.
» Do not transfuse prior to conducting appropriate investigations unless anaemia requires immediate intervention.
» In situations of life-threatening anaemia, transfuse the most compatible unit of red blood cells and get specialist advice urgently. Coombs-positive haemolytic anaemia may be technically difficult to cross match.
» Efficacy of transfusion is limited by the shortened red cell survival due to haemolysis.
» In G6PD deficiency, avoid drugs known to cause haemolysis, such as aspirin, sulphonamides (including co-trimoxazole), dapsone, methylene blue, and primaquine.
» In patients with cold agglutinins, all transfusions must be given through a blood warmer to avoid cold-induced haemolysis.

MEDICINE TREATMENT

Because of high red cell turnover, supplement with:

- Folic acid, oral, 5 mg daily.

Autoimmune haemolytic anaemia
Treat under specialist supervision.

- Prednisone, oral. *LoE:IIb*[ix]
  - Initial dose: 1 mg/kg daily, until Hb is stable and >10 g/dL.
  - Taper slowly and monitor Hb at least once weekly. (Refer to Appendix II for an example of a dose reduction regimen).
  - Glucocorticoids should be tapered slowly upon normalization of the haemoglobin and LDH. The patient should be monitored for recurrence following cessation of treatment.
  - As these conditions can often be life-threatening, specialist advice should be sought as early as possible after diagnosis.

REFERRAL/CONSULTATION

Indications of inadequate response:

» Haemolysis remains severe after 3 weeks of prednisone dosed at 1 mg/kg.
» Remission cannot be maintained on low doses of prednisone.
» The patient has intolerable adverse effects or contraindications to glucocorticoids.

Refer to specialist for second-line treatment:

» Immunosuppresive therapy – For specialist initiation.
» Splenectomy: Requires vaccination – see Chapter 11: Surgical prophylaxis.

LoE:IIIb[x]

2.1.5 ANAEMIA, APLASTIC

D60.0-1/D60.8-9/D61.0-3/D61.8-9

DESCRIPTION

Pancytopenia due to a hypoplastic bone marrow.

Clinical features:

» Pallor
» Petechiae
» Frequent or severe infections
» Purpura
» Bleeding

Pancytopenia in PLHIV B23.2 + (D61.2/D61.9)
Most common causes include:

» Direct effect of HIV.
» Medication (e.g. carbamazepine, valproic acid, phenytoin or pure red cell aplasia with emtricitabine and lamividine).
» Secondary opportunistic infections.
» Malignancies and nutritional deficiencies.

Many cases are idiopathic.

Investigations
» FBC and peripheral smear, Vitamin B_{12}, and red cell folate.
» Appropriate investigation to exclude opportunistic infections.
» Bone marrow trephine and aspiration in selected patients: where no other cause is found, in patients with persistent pancytopaenia, or to exclude infiltration with opportunistic infections, malignancies.

MEDICINE TREATMENT
If neutropenic and febrile, see Section 2.2: Febrile neutropenia.

REFERRAL
» Discuss all cases of suspected aplastic anaemia with a specialist. (if necessary, stabilise patient with blood products in preparation for transport after consultation with an expert).

2.1.6 ANAEMIA, SICKLE CELL
D57.0-3/D57.8

DESCRIPTION
Sickle cell disease (SCD) is a genetic, inherited condition resulting in abnormal red blood cells. Homozygous SCD is the commonest and most severe form, characterised by recurrent vaso-occlusive episodes ("sickle crises") and chronic haemolytic anaemia. Adults develop hyposplenism, predisposing them to infection with encapsulated bacteria. Heterozygous SCD includes Haemoglobin S-C disease/HbSC, causing milder sickle cell disease, and sickle cell trait/HbS, who are generally asymptomatic.

VASO-OCCLUSIVE EPISODES
Vaso-occlusion can involve any part of the body, especially bone. Episodes may be triggered by dehydration, infection, stress or menstruation. The most common presentation is with acute episodes of pain that vary in severity, in the affected areas.

Investigations
» The diagnosis is suspected from the history, peripheral blood examination, and/or screening tests for sickling.
» Diagnosis is confirmed on haemoglobin electrophoresis.

GENERAL MEASURES
Severe vaso-occlusive episodes
» Keep well hydrated with intravenous fluids.
» Transfusion is only indicated for episodes with severe anaemia – discuss with a specialist.

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. *LoE:IIIb*[xi]

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

In renal failure (eGFR <30 mL/minute), the recommended prophylactic dose of enoxaparin is 20 mg daily. *LoE:IVb*[xiii]

Analgesia

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

Chronic management

All patients:

- Folic acid, oral, 5 mg daily.
- Vaccination against infections due to pneumococci and haemophilus influenza type b.

Management of severe vaso-occlusive episodes:

» Indications for treatment:
  - frequent painful vaso-occlusive episodes,
  - severe vaso-occlusive episodes (e.g. acute chest syndrome, stroke)
  - severe symptomatic anemia.

» Hydroxyurea is the mainstay of therapy in severe disease – Refer for specialist initiation.

REFERRAL

» All patients, for chronic management in a specialised centre.

» Vaso-occlusive episodes should be managed in consultation with a specialist.

2.2 FEBRILE NEUTROPENIA

D70

DESCRIPTION

Febrile neutropenia is conventionally defined as an absolute neutrophil count of <0.5 x 10^9/L with a temperature of greater than 38°C for >1 hour or a single temperature of 38.3°C, but any neutropaenic patient showing clinical signs of sepsis should be investigated.

Note:

» **This is a medical emergency:** A minor infection may progress rapidly, with patients developing features of severe sepsis (multi-organ failure and/or hypotension). It is crucial to monitor and treat patients for signs and symptoms of infection.

» **Cultures should be obtained for appropriate microbiological testing prior to starting empirical antimicrobial therapy.**

» It is critical to recognise neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly to reduce the risk of severe sepsis and mortality.

LoE:IVb[xiv]

GENERAL MEASURES

» Treat the underlying cause of neutropenia, if applicable.

» Withdraw any medication that may cause neutropenia, e.g. carbimazole, clozapine, co-trimoxazole, penicillins, carbamazepine, valproate.

» Consider removing central IV line. Once culture results are available, adjust treatment to the most appropriate narrow spectrum agent.

MEDICINE TREATMENT

For patients with febrile neutropenia within 48 hours of admission:

- Ceftriaxone, IV, 1 g daily.

AND

- Gentamicin, IV, 6 mg/kg daily (see Appendix II for guidance on prescribing).

<u>If IV line, and skin infection is suspected as the cause:</u>

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).

For patients with febrile neutropenia that develop after 48 hours of admission:

There is an increased risk of a hospital acquired infection. The choice of antibiotic will depend on local susceptibility patterns.

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.

OR
Regimen 2:
- Piperacillin/tazobactam, IV, 4.5 g 6 hourly.

AND *LoE:IVb*[xv]
- Amikacin, IV, 15 mg/kg daily. (See Appendix II, for individual dosing and monitoring for response and toxicity). *LoE:IIIb*[xvi]

OR
Regimen 3:
- Cefepime, IV, 2 g 12 hourly. *LoE:IVb*[xvii]

If no response to antibiotics after 5–7 days: (In discussion with a Clinical Haematologist or Infectious Disease specialist)
ADD:
- Amphotericin B, IV, 1 mg/kg daily in dextrose 5% over 4 hours.
  - Ensure adequate hydration to minimise nephrotoxicity (See Appendix II for preventing, monitoring and management of toxicity).

Duration of therapy:
» If neutrophil count increases to $>0.5 \times 10^9$/L, continue for 2 days after fever has settled.
» If neutrophil count remains $\leq 0.5 \times 10^9$/L, continue for 7 days after fever has settled.

REFERRAL/CONSULTATION
» All cases – consult with haematologist/oncologist.

2.3 MYELODYSPLASTIC SYNDROMES
D46.0-7/D46.9

DESCRIPTION
A group of disorders characterised by refractory cytopaenias due to bone marrow failure. There is a risk of disease progression to acute leukaemia.

Investigations
» Evidence of cytopenia, with normal vitamin B_{12} and folate levels, and often substantial morphological dysplasia on the peripheral smear.

» Bone marrow examination confirms dysplasia of the blood elements and the presence of cytogenetic abnormalities.

GENERAL MEASURES

» Transfusion should ideally be with leucodepleted red cells to delay sensitisation, as these patients require frequent transfusions.
» Bone marrow transplantation can be curative in selected patients.
» If neutropenic and febrile, see Section 2.2: Febrile neutropenia.

REFERRAL

» All patients for further investigation and management.

2.4 BLEEDING DISORDERS

GENERAL PRINCIPLES

A bleeding tendency may result from:
» a coagulation defect (congenital/acquired),
» a vessel wall defect, or
» a platelet defect (quantitative/qualitative).

A careful and detailed history, thorough examination and review of relevant laboratory investigations will allow differentiation between these three categories, as the management of each of these groups differs significantly.

Screening tests include: FBC, prothrombin time (PT) and activated partial thromboplastin time (aPTT; if prolonged, mixing studies are required).

Patients with a chronic bleeding tendency should be advised to wear a medic alert bracelet which clearly mentions the type of disorder he/she suffers from, e.g. severe Haemophilia A, Factor VIII <1%, no inhibitors.

2.4.1 HAEMOPHILIA A AND B

D66.7/D66.8

DESCRIPTION

Haemophilia A and B are lifelong chronic bleeding disorders caused by a lack of clotting factor VIII and clotting factor IX, due to mutations in the Factor VIII and Factor IX genes respectively. Acute bleeding presentation depends on the severity of the condition (see classification below). Bleeding can occur into any tissue, but intraarticular bleeds are the clinical hallmark of haemophilia.

Haemophilia complications include haemarthrosis that may lead to chronic arthropathy, intracranial haemorrhage, soft tissue and muscle haematomas. In a known person with haemophilia, pain/tingling in a joint suggests early-onset bleeding.

Early consultation and regular follow-up with a haematologist or clinician with expertise in managing such patients is advisable. All patients diagnosed with haemophilia should attend a designated specialised Haemophilia Treatment Centre with a dedicated multi-disciplinary health care team at least annually for adults. The details of available Haemophilia Treatment Centres can be accessed at: https://haemophilia.org.za/haemophilia-treatment-centres-htcs/. All patients diagnosed with haemophilia should be enrolled in the South African Bleeding Disorders Registry (access relevant co-ordinators at: https://haemophilia.org.za/haemophilia-nurses-office/)

Those eligible for prophylaxis with factor VIII or IX (see below) may receive factor replacement therapy at a healthcare facility twice a week. Where appropriate, home-based care can be considered.

Haemophilia severity classification

Class	Clotting factor	Factor level	Signs
Mild	VIII or IX	> 5 – <40%	Occasional bleeds, usually after trauma or surgery.
Moderate	VIII or IX	1–5%	Less frequent bleeds than severe; usually post trauma/surgery/dental extraction. Some patients may, however, display a severe bleeding phenotype.
Severe	VIII or IX	< 1%	Spontaneous bleeds, particularly joint and muscle.

Table 2.2: Classification of haemophilia severity
(Adapted from White et.al. Journal of Thrombosis *and* Haemostasis*. 2001)*[xviii]

DIAGNOSTIC CRITERIA

Clinical

» Major bleeds:
  - central nervous system (CNS) – intracranial
  - severe injury
  - muscle compartment (e.g. forearm and calf)
  - gastrointestinal tract
  - neck/throat (airway)
  - advanced joint and soft tissue
  - hip and ilio-psoas muscle

» Minor bleeds:
  - early joint bleed
  - soft tissue
  - mouth and gum
  - muscle
  - epistaxis
  - haematuria

» Pain/tingling in a joint of a patient with haemophilia suggests bleeding.

Investigations

Baseline

» Normal white cell count and platelets; may have anaemia due to blood loss or iron deficiency.
» Normal INR
» Prolonged activated partial thromboplastin time (aPTT)
» APTT correction studies
» Factor VIII or IX plasma levels < 50%
» HIV, hepatitis B, and hepatitis C testing if status not known

Non-responders to factor replacement or those previously diagnosed with inhibitors

» Inhibitor screen (Bethesda or Nijmegen assays)

GENERAL MEASURES

» Patient, family and community education
» Enrolment in the South African Bleeding Disorders Registry (access relevant co-ordinators at*: https://haemophilia.org.za/haemophilia-nurses-office/)*
» MedicAlert bracelet (or similar)
» Dental care (see below for management of tooth extraction)
» Avoid contact sport

Exercise great caution when taking blood specimens (no arterial samples).
Taking blood from femoral veins is contra-indicated.
Do not insert or use central lines unless done as part of life-saving efforts.
Do not aspirate joints.
Avoid IM injections.
Avoid aspirin and other NSAIDs.

MEDICINE TREATMENT

Treatment approaches are divided into two main categories: prophylaxis and on demand (episodic) treatment following a bleed.

Prophylaxis

Prophylaxis aims to prevent the number of bleeds and prevent or delay the development of joint arthropathy and other sequelae. Primary and secondary prophylaxis can be considered in consultation with a Haemophilia Treatment Centre.

In consultation with a Haemophilia Treatment Centre, prophylaxis is sometimes needed in patients presenting with a target joint.

Treatment on Demand (Episodic treatment)

Episodic treatment for bleeding episodes is referred to as on demand therapy (i.e. the use of factor replacement therapy when bleeding occurs).

Home treatment
Haemophilia Treatment Centres promote home treatment of bleeds. Patients or caregivers must be educated on the storage, reconstitution and administration of clotting factor concentrate and provided with a supply of clotting factor concentrate to be kept at home for use in case of a bleed and/or for prophylaxis. Clotting factor concentrate use and bleeding episodes are monitored through an appropriate chart (or bleeding diary), which can be reviewed at consultations and medication collection.

ACUTE MANAGEMENT OF BLEEDS

For pain (as required):
Refer to section 26.2.1 Medical conditions associated with severe pain and section 12.4.2: Postoperative pain in the recovery room.

Do not use NSAIDs, including aspirin.

For bleeding episodes
Emergency treatment while awaiting transfer, if indicated.
If serious bleeding in a known patient with haemophilia, and no factor is available:

- Lyophilised plasma (FDP), IV, 15 mL/kg over 20-30 minutes. Lyophilised plasma contains a minimum of 0.4 units/mL of each coagulation factor.

OR *LoE:IIIb*[xix]

- Fresh Frozen Plasma (FFP), IV, 15 mL/kg over 20-30 minutes.

Acute joint bleeds – Infuse intravenous factor concentrate first (refer to Section 2.4.1.1 or Section 2.4.1.2 below for dosing guidance) with the following adjunctive measures:

» Apply ice packs: 5 minutes on and 10 minutes off.
» Rest the affected joint/limb until pain-free and there is no further swelling.
» Avoid weight-bearing.
» Splint. Do not use circumferential casts.
» **Do not** aspirate affected joints.
» Do not request an X-ray of the affected joint unless there is a strong suspicion of fracture.

Give clotting factor concentrate until the patient is pain-free and the joint's range of motion is normal. Administration should be 12 hourly (for Haemophilia A) for major bleeds but may be daily for minor bleeds.

For mucous membrane bleeds

- Tranexamic acid, oral, 1 - 1.5 g (15 - 25 mg/kg) 6-8 hourly.

For dental extraction/male circumcision/minor surgical procedures
Check that inhibitors are absent.
Admit for the procedure and post-procedure care and observation in a facility with experience in haemophilia management.
Haemophilia A:

- Factor VIII, intravenous, 40 units/kg, immediately before extraction.

AND

- Tranexamic acid, oral, 25 mg/kg/dose 6–8 hourly, starting 2 hours before the procedure and continued for 5 days post-procedure.

Haemophilia B:

- Factor IX/factor IX complex, intravenous, 40 units/kg, immediately before extraction.

Ideally, elective surgery should be performed at a tertiary/quaternary centre in consultation with a clinical haematologist.
In emergencies, treat it as a major bleed and consult the local Haemophilia Treatment Centre as soon as feasible.

2.4.1.1 HAEMOPHILIA A - FACTOR VIII DEFICIENCY (NO INHIBITORS)

D66

PROPHYLAXIS

Prophylaxis (primary and secondary) should be considered for patients with severe haemophilia A (<1% factor activity) who can access the health facility twice weekly for infusions; or have indwelling venous catheters or are candidates for home-based care.

Primary prophylaxis: Prophylaxis started in the absence of documented joint disease/damage.
Secondary prophylaxis: Prophylaxis initiated after joint damage has occurred.

- Factor VIII, intravenous 25 units/kg, twice weekly.
  - The clotting factor should be rounded to the nearest full vial to avoid wastage.
  - Proposed rounded dosing (see table below)

Factor VIII dosing table				
Age in years	**Average weight (kgs)**	**IU required per dose**	**Rounded dose (IU)**	**Available products**
>12 (adults)	50	1250	1300	2 x 500IU plus 1 x 300IU
>12 (adults)	60	1500	1500	3 x 500IU
>12 (adults)	70	1750	1800	3 x 500IU plus 1 x 300IU

TREATMENT ON DEMAND

Minor bleeds:

Bleeds into the muscle or soft tissue, mouth or gums, epistaxis, painless haematuria and early joint bleeds.

- Factor VIII, intravenous, 20 - 40 units/kg.
  - If there is evidence of ongoing bleeding after 12 hours, consult with local haemophilia treatment centre.

Major bleeds:

Advanced muscle or joint bleeds result from severe injury or bleeds that affect the central nervous system, gastrointestinal system, neck or throat, hip or iliopsoas muscle, or forearm compartment.

LoE: III[xx]

- Factor VIII, intravenous, 40 - 50 unit/kg.
  - Use all the contents of the appropriate volume ampoule.
  - All of these patients need hospitalisation.
  - Discuss all patients promptly with the local Haemophilia Treatment Centre.

Intracranial bleeds (*paediatrics and adults*)

- Factor VIII, intravenous, 40 – 50 units/kg 6 hourly.
  - Decrease frequency of dosing if the trough factor level is > 50%, if possible.

2.4.1.2 HAEMOPHILIA B - FACTOR IX DEFICIENCY (NO INHIBITORS)

D67

PROPHYLAXIS

Prophylaxis (primary and secondary) should be considered for patients with severe haemophilia B (<1% factor activity) who can access the health facility twice weekly for infusions; or have indwelling venous catheters or are candidates for home-based care.

Primary prophylaxis: Prophylaxis started in the absence of documented joint disease/damage.
Secondary prophylaxis: Prophylaxis initiated after joint damage has occurred.

- Factor IX, intravenous 25 units/kg, twice weekly.

TREATMENT ON DEMAND

Minor bleeds

Bleeds into the muscle or soft tissue, mouth or gums, epistaxis, painless haematuria and early joint bleeds.

- Factor IX/factor IX complex, intravenous, 40 units/kg immediately as a single dose.
  - If there is evidence of ongoing bleeding after 12 hours, consult with local haemophilia treatment centre.

Major bleeds
Major muscle or joint bleeds result from severe injury or bleeds that affect the central nervous system, gastrointestinal system, neck or throat, hip or iliopsoas muscle, or forearm compartment.

- Factor IX/factor IX complex, intravenous, 60 units/kg. *LoE: III*[xxi]
  - All these patients need hospitalisation.

Discuss all patients promptly with the local Haemophilia Treatment Centre to plan ongoing treatment and factor replacement.

2.4.1.3 HAEMOPHILIA WITH INHIBITORS

Refer for assessment and planning with a haematologist.

REFERRAL
» All cases with **suspected** or established haemophilia (prolonged PTT and normal INR), for assessment, genetic counselling and planning of management, to a Haemophilia Treatment Centre.

2.4.2 VON WILLEBRAND DISEASE
D68.0

DESCRIPTION
Von Willebrand disease is the most common congenital bleeding disorder and is due to reduced amounts or abnormal forms of von Willebrand factor.

DIAGNOSTIC CRITERIA
Clinical
» Recurrent epistaxis, prolonged bleeding from lacerations, easy bruising or gum bleeds.
Investigations
» Reduction in one or more of the following:
- von Willebrand factor antigen,
- Ristocetin co-factor or collagen binding activity,
- factor VIII coagulant activity.

GENERAL AND SUPPORTIVE MEASURES
» Apply pressure to the bleeding site.
» For tooth socket bleeds, bite down on a piece of gauze.

Caution
Avoid aspirin and other NSAIDs.

MEDICINE TREATMENT

Mild bleeding

Such as epistaxis and menorrhagia.

- Antifibrinolytics, e.g.:
- Tranexamic acid, oral, 1 g 6-8 hourly.

Recurrent menorrhagia can also be treated effectively with oral contraceptives. See section 5.2: Uterine bleeding, abnormal.

More severe mucous membrane bleeding

Consult a local haemophilia treatment centre.

During surgery or after major trauma, patients should receive:

- Factor VIII (Factor VIIII-containing von Willebrand factor VIII), IV, 30 IU/kg/dose given every 12 hours.
  - Continue for 48–72 hours to ensure optimal haemostasis.
  - For major surgical procedures, use for 7–10 days. *LoE: IVb*

REFERRAL

» All suspected cases of von Willebrand disease to a Haemophilia Treatment Centre for assessment.
» Symptomatic thrombocytopenia.

2.5 IMMUNE THROMBOCYTOPENIA (ITP)

D69.3

DESCRIPTION

A common bleeding disorder due to immune-mediated destruction of platelets. Clinically apparent associated conditions, drugs (e.g. penicillins, cephalosporins, quinine, rifampicin and heparin), or other agents that may cause thrombocytopenia must be excluded before a diagnosis of ITP can be considered. Patients with suspected ITP should be tested for SLE and for HIV infection.

Investigations:

» Thrombocytopenia with normal white cell count and red cell indices (however, anaemia may be present due to blood loss).
» Peripheral blood smear to exclude RBC fragments. Smear may show large platelets.
» Do INR and aPTT, both of which should be normal in ITP.
» If there is poor response to treatment, to do a bone marrow aspirate and biopsy.

GENERAL MEASURES

» Avoid:
  – medication that affects platelet function, e.g. NSAIDs and aspirin,
  – platelet transfusions, unless there are life-threatening bleeds,

- unnecessary treatment of asymptomatic patients with mild to moderate thrombocytopenia (platelet count >30 x 10^9/L).
- dental procedures in acute phase, and
- intramuscular injections.

» Reassure the patient that resolution usually occurs in acute ITP.
» Medic alert bracelet.
» Platelet transfusions may be given if surgery is required or in life-threatening bleeding: discuss with haematologist.
» Goal of treatment is to reduce the risk of bleeding rather than to normalise the platelet count.

MEDICINE TREATMENT

Acute ITP

- Prednisone, oral, 1 mg/kg daily until platelet count has normalised.
  - Taper slowly and monitor platelet count. (Refer to Appendix II for an example of a dose reduction regimen).
  - Although prednisone is also indicated for HIV-associated immune thrombocytopenia, it is important that these patients should be fast-tracked for antiretroviral therapy (ART) – See Section 10.1: Antiretroviral therapy.

LoE:IIIb[xxii]

Acute life-threatening bleeding and surgery

- Platelet transfusion, intravenous, 1 unit immediately.
  - Platelet transfusions are only indicated in acute active bleeding uncontrolled by other means or before procedures.
  - In an adult, 1 unit of platelets (preferably single donor, leucocyte depleted) is usually sufficient to control the bleeding initially.
  - Platelet transfusions have limited benefit in this condition as platelets are rapidly destroyed by the immune system.
- Methylprednisolone acetate 1 g, IV, daily for 3 days. *LoE:IIIb*[xxiii]

REFERRAL

» All cases not responding to steroids that require second line treatment - Consult haematologist.
» All PLHIV who are not responding to ART - Consult haematologist

2.6 THROMBOTIC THROMBOCYTOPENIC PURPURA-HAEMOLYTIC URAEMIC SYNDROME (TTP-HUS)

D59.3 + (M31.1)

DESCRIPTION

» Acute syndromes with abnormalities in multiple organ systems and evidence of micro-angiopathic haemolytic anaemia and thrombocytopenia.

» This condition presents with varying combinations of the following (only some of which may be present):
  – Microangiopathic haemolytic anaemia and thrombocytopenia, often with purpura but not usually severe bleeding,
  – acute renal insufficiency,
  – neurologic abnormalities, and/or
  – fever.
» Note: The presence of fragments and low platelets is enough to consider the diagnosis.
» Microangiopathic haemolytic anaemia is defined as non-immune haemolysis with prominent RBC fragmentation (schistocytes) observed on the peripheral blood smear along with thrombocytopaenia.
» TTP-HUS is often associated with HIV infection and all patients should be tested for HIV.
» TTP-HUS should be distinguished from disseminated intravascular coagulation (DIC) and severe pre-eclampsia where, in the latter, the coagulation profile (PT/PTT) is also deranged.

MEDICINE TREATMENT

» **This is a medical emergency.**
» In HIV-associated thrombotic thrombocytopenia, start combination antiretroviral therapy urgently.
» Platelet transfusions may be associated with increased morbidity and mortality. Use of platelet transfusions should be discussed with a specialist.

Transfusion of plasma products:

- Lyophilised plasma, IV infusion, 30 mL/kg/day in 3–4 divided doses.

OR

- Fresh frozen plasma, IV infusion, 30 mL/kg/day in 3–4 divided doses.

LoE:IIIb[xxiv]

REFERRAL

» All patients – discuss with a haematologist urgently.

2.7 ACQUIRED COAGULATION DEFECTS

2.7.1 DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

D65/D68.2/D68.8

DESCRIPTION

DIC is a complication of an underlying condition and is characterised by widespread activation of the clotting cascade which leads to consumption of clotting factors and platelets with generalized bleeding. No single diagnostic test, but the combination of a prolonged INR and PTT, presence of

thrombocytopenia, decreased fibrinogen and increased D-dimer is highly suggestive of the diagnosis.

GENERAL MEASURES

» Identify and treat the underlying cause.
» If the patient is bleeding, replace haemostatic factors with cryoprecipitate or FFP/lyophilised plasma.
» If the patient is not actively bleeding and platelet count >20 x 10^9/L, then platelet transfusion is not necessary.

MEDICINE TREATMENT

For severe thrombocytopaenia (<20 x 10^9/L) and/or active bleeding:

- Platelet transfusion (apheresis single donor or pooled random donor), IV, 1 unit, immediately.
  - In chronic DIC, or in the absence of bleeding, platelet transfusions should not be given merely to correct the thrombocytopenia.

For hypofibrinogenaemia:

- Cryoprecipitate, IV, 1 unit/10 kg.

For depletion of other coagulation factors:

- Lyophilised plasma, IV, 15 mL/kg as initial dose.
  - Volume: ±200 mL/unit.

OR

- Fresh frozen plasma, IV, 15 mL/kg as initial dose. *LoE:IIIb*[xxv]
  - Volume: ±280 mL/unit.

» Repeat replacement therapy 8 hourly or less frequently, with adjustment according to the clinical picture and laboratory parameters.
» Monitor response with frequent estimation of the platelet count and coagulation screening tests.

2.8 VENOUS THROMBO-EMBOLISM

I26.0/I26.9/I80.0-3/I80.8-9/I81/I82.0-3

DESCRIPTION

Venous thromboembolism (VTE) can occur at different sites, ranging from calf deep venous thrombosis (DVT) to pulmonary thrombo-embolism (PE). For VTE in pregnancy, see Section 2.8.3: VTE during pregnancy and the puerperium.

Differential diagnosis includes:

» cellulitis
» superficial thrombophlebitis
» lymphoedema
» chronic venous insufficiency
» ruptured popliteal (Baker's) cyst
» calf muscle pull or tear
» internal derangement of the knee

Diagnosis is primarily clinical and confirmed with imaging studies, e.g. Duplex Doppler.

GENERAL MEASURES

Strategies for prevention include:

» lifestyle modifications (e.g. prevention of obesity and inactivity)
» avoiding dehydration
» avoiding cigarette smoking
» maintaining normal blood pressure,
» mechanical measures like vascular compression stockings and intermittent pneumatic compression boots.

LoE:IIIb[xxvi]

Acute management

Thrombolytic therapy may be indicated in patients with confirmed early pulmonary embolism where haemodynamic stability cannot be achieved: Discuss with a specialist.

2.8.1 VENOUS THROMBO-EMBOLISM – PROPHYLAXIS

MEDICINE TREATMENT

Risk Assessement

Risk assessment is essential, and treatment needs to be individualised. Risk factors for VTE can be divided into predisposing factors (i.e. patient characteristics) and exposing factors (i.e. underlying medical conditions, nature of surgical intervention).

Predisposing risk factors	
Thrombophilia	Advanced age (>60 years)
History of VTE	Chronic cardiac insufficiency
Malignancy	Obesity (BMI > 30 kg/m^2)
Drugs, e.g. TB treatment, thalidomide	Oestrogen therapy
HIV infection	Nephrotic syndrome
Auto-immune disease	Varicose veins

Exposing risk factors		
Risk level	**Surgical patients**	**Medical patients**
Low VTE risk	» Surgery lasting <30 minutes » Injuries without or with only minor soft-tissue trauma » No or only minor additional predisposing risk factors	» Infection or acute inflammatory diseases without bed rest » Central venous catheters » No or only minor additional predisposing risk factors

Moderate VTE risk	» Surgical procedures of longer duration » Immobilisation of lower limb with plaster cast » Lower limb arthroscopic procedures » No or only minor additional predisposing risk factors	» Acute cardiac insufficiency (NYHA III/IV) » Acute decompensated COPD without ventilation » Infection or acute inflammatory diseases with bed rest » Malignant disease » No or only minor additional predisposing risk factors
High VTE risk	» Major surgical procedures for malignancy » Multiple trauma or severe trauma of the spine, vertebra or lower limbs » Major orthopaedic surgery, e.g. hip or knee replacement » Major surgical procedure in cardiothoracic and/or pelvic region	» Stroke with paralysis » Acute decompensated COPD with ventilation » Sepsis » ICU patients » Other conditions associated with debilitating illness

Table 2.3: VTE risk assessment in surgical and non-surgical patients
Modified from Source: Jacobson BF, Louw S, Büller H, Mer M, de Jong PR, Rowji P, Schapkaitz E, Adler D, Beeton A, Hsu HC, Wessels P, Haas S; South African Society of Thrombosis and Haemostasis. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013 Feb 15;103(4 Pt 2):261-7. https://www.ncbi.nlm.nih.gov/pubmed/23547704

For patients hospitalised due to medical illnesses at high risk of VTE:

- Rivaroxaban, oral, 10 mg daily while hospitalised. *LoE:Ib*[xxvii]

For patients hospitalised due to medical illnesses and in whom rivaroxaban is contraindicated (see summary table below):

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.
  - In morbid obesity, dosing of LMWH should be individualised, in discussion with a specialist.
  - Renal impairment (eGFR <30 mL/min): adjust dose to 20 mg daily.

OR *LoE:IVb*[xxviii]

- Unfractionated heparin, SC, 5 000 units 12 hourly.
  - Dose adjustment is generally not required for renal impairment.
  - Monitor for bleeding complications. *LoE:IIIb*[xxix]

For orthopaedic surgical patients with trauma-related i) operative extremity fractures or ii) operative and non-operative pelvic and acetabular fractures:

Low to moderate risk of VTE:

- Aspirin, oral, 150 mg daily. *LoE:IIb*[xxx]

- Initiate aspirin >12 hours post-operatively and continue for 14 days or until mobilisation.
- In patients with non-operative pelvic and acetabular fractures, prophylaxis can be continued for up to 35 days. If clinically appropriate (i.e. in the absence of clear evidence of VTE risk), discontinuation prior to 35 days, on discharge from hospital should be considered.

LoE:III

High risk of VTE:

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.
  - In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist.
  - Renal impairment (eGFR <30 mL/min): adjust dose to 20 mg daily.
  - In patients with non-operative pelvic and acetabular fractures, prophylaxis can be continued for up to 35 days. In the absence of clear evidence of VTE risk or on earlier discharge from hospital, discontinuation prior to 35 days should be considered.

For elective total hip arthroplasty:

- Rivaroxaban, oral, 10 mg daily.
  - Initated 6–10 hours post-surgery for duration of admission or a maximum of 10 days.

Following rivaroxaban, prescribe aspirin:

- Aspirin, oral, 150 mg daily for 28 days on discharge from hospital.

For elective total knee arthroplasty:

Total duration of prophylactic therapy: 14 days

- Rivaroxaban, oral, 10 mg daily.
  - Initiate anticoagulation 6–10 hours post-surgery for the duration of hospital admission for a minimum of 2 days and a maximum of 7 days.

Following rivaroxaban, prescribe aspirin:

- Aspirin, oral 150 mg daily.
  - Treat with aspirin for remainder of VTE prophylaxis period, i.e. 14 days in total including days on rivaroxaban.

LoE:Ib[xxxi]

For i) other surgical patients, or ii) orthopaedic surgical patients with a contraindication to aspirin or rivaroxaban:

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.
  - In morbid obesity, dosing of LMWH should be individualised, in discussion with a specialist.
  - Renal impairment (eGFR <30 mL/min): adjust dose to 20 mg daily.

OR

LoE:IVb[xxxii]

- Unfractionated heparin, SC, 5 000 units 12 hourly.
  - Dose adjustment generally not required for renal impairment.

LoE:IIIb[xxxiii]

- Monitor for bleeding complications.

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	<u>Low to moderate risk of VTE:</u> Aspirin, oral, 150 mg daily. <u>High risk of VTE:</u> Enoxaparin, SC, 40 mg daily.	From >12 hours post-operatively, for 14 days or until mobilisation.
	Trauma-related **non-operative** pelvic and acetabular fractures	<u>Low-moderate risk of VTE:</u> Aspirin, oral, 150 mg daily. <u>High risk of VTE:</u> 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

Although the risk of bleeding is small, prophylaxis should only be used under exceptional circumstances in patients with the following conditions:

» Active bleeding or high risk of active bleeding (eg. severe liver disease; peptic ulcer disease).
» Intraocular, intracranial or spinal surgery.
» Patients requiring lumbar puncture or spinal/epidural anaesthesia within 24 hours of rivaroxaban dose, within 12 hours of enoxaparin when used as prophylaxis, or within 24 hours of enoxaparin when used at therapeutic doses. For timing of anticoagulants – See Section 12.7.1: Anticoagulants and spinal or epidural blocks.
» Renal insufficiency: Rivaroxaban not recommended if eGFR<30ml/min; enoxaparin requires renal dose adjustment.
» Coagulopathy
» Uncontrolled hypertension
» Concomitant anticoagulations or antiplatelet therapy

Additional contraindications to rivaroxaban not covered above:

Patient populations	Comorbidities	Drug interactions
Pregnancy Lactation Minors (<18 years of age) Patient weight >120 kg or BMI >40 kg/m^2 Age >65 years†	Known rivaroxaban hypersensitivity Antiphospholipid syndrome (persistent, triple positive) Previous bronchiectasis, pulmonary cavitation, or pulmonary haemorrhage Active malignancy‡	Drugs that ↑rivaroxaban: Ketoconazole, Ritonavir Drugs that ↓rivaroxaban: Phenytoin, carbamazepine, rifampicin, St. John's Wort

Table 2.5: Contraindications to rivaroxaban
†Insufficient evidence in this patient population.
‡Exception: Patients receiving extended prophylaxis after gynaecological or colorectal malignancies.

2.8.2 VENOUS THROMBO-EMBOLISM – ACUTE TREATMENT

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.

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

» 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.

LoE:IVb

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

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. *LoE:IIIb*[xli]
Patient with any **ONE** of the following high risk factors: » Emergency Caesarean section » BMI > 40 kg/m^2 » Prolonged hospital stay » Intravenous drug user	VTE prophylaxis for a minimum of 5 days post delivery (or longer duration if still admitted in hospital)

Indications	Duration of therapy
Patient with any of the following intermediate risk factors: » Age > 35 years of age » BMI 35-40 kg/m^2 » 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. *LoE:IIb*[xlii]
  - Body weight ≥100 kg: 60 mg daily.
  - For post-partum prophylaxis, start 6–12 hours after delivery.

LoE:IIIb[xliii]

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.

LoE:IIIb[xliv]

- 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: *LoE:IIIb*[xlv]

- Low molecular weight heparin, e.g.
- Enoxaparin SC, 1 mg/kg every 12 hours. *LoE:IIIb*[xlvi]
  - 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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SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
ADULT HOSPITAL CHAPTER 2: BBFO
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-4 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

All reviews and costing reports may be accessed at: https://www.health.gov.za/nhi-edp-stgs-eml/
Note that the associated EML chapter has been subjected to subsequent clinical editing. These editorial amendments may not be reflected in the report below.

A: MEDICINE AMENDMENTS

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/ RETAINED
2.1.1 Anaemia, iron deficiency	Parenteral iron	Directions for use amended
	Low molecular weight iron dextran, parenteral	Directions for use amended
2.1.2 Anaemia, megaloblastic	Vitamin B12 deficiency & chronic metformin use	Guidance clarified
- vitamin B_{12} deficiency	Vitamin B_{12}, parenteral	Directions for use amended
2.1.5 Anaemia, aplastic	Pancytopaenia in PLHIV	Editorial amendments
2.1.6 Anaemia, sickle cell	Description	Editorial amendments
	Enoxaparin – renal impairment	Dose amended
	Chronic management - vaccination	Guidance clarified
2.2 Febrile neutropenia	General measures	Editorial amendments
	Filgrastim, parenteral	Not added
	Vancomycin, IV	Dose amended
	Imipenem/cilastatin	Dose amended
	Piperacillin/tazobactam	Dose amended
2.4. Bleeding disorders	Haemophilia sub-committee convened for integration of care pathway	Extensive review of Paediatric and adult STGs
2.4.1 Haemophilia A and B	Description, diagnostic criteria and investigations	Amended
For mucous membrane bleeds	Tranexamic acid	Dose amended
Dental extraction/male circumcision/minor surgical procedures	Tranexamic acid	New guidance added
	Factor VIII and Factor IX	Dose retained
2.4.1.1 Haemophilia A - Factor VIII Deficiency (No inhibitors) *Prophylaxis*	Factor VIII	Added
	Factor VIII	Not added as a therapeutic class
	Coagulation factor VIII (complex)	Retained, but not included in factor VIII therapeutic class
	Human Coagulation Factor VIII (purified)	Not added as a member of the factor VIII therapeutic class
	Recombinant Factor VIII (purified)	Not added as a member of the factor VIII therapeutic class
	Factor VIII	Dose retained
Treatment on demand for acute bleeding episodes	Minor bleeds – factor VIII	Dose retained
	Major bleeds – factor VIII	Dose retained
	Intracranial bleeds – trough factor level	Amended
2.4.1.2 Haemophilia B/Factor IX Deficiency	Factor IX prophylaxis	Added
	Factor IX complex	Added
	Factor IX	Not added as a therapeutic class
	Coagulation factor IX (complex)	Retained, but not included in factor VIII therapeutic class
	Human Coagulation Factor IX (purified)	Not added as a member of the factor VIII therapeutic class

2.4.1.3 Haemophilia with inhibitors	Referral	Amended
2.4.2 Von Willebrand's Disease	Von Willebrand factor VIII concentrate (Coagulation factor VIII) (complex)	Retained
2.5 Immune thrombocytopaenia (ITP)	Medicine treatment	Editorial amendments
2.8 Venous thrombo-embolism	Bemiparin, parenteral	Not added as a member of the LMWH therapeutic class
2.8.1 Venous thrombo-embolism - prophylaxis	Risk assessment – pre-disposing factors	Added
	Risk assessment – models for assessing VTE risk	Deleted
	Risk assessment – exposing risk factors	Amended
	DOACs, oral	Added
	Aspirin	Added
	Enoxaparin, parenteral use	Amended
2.8.2 Venous thrombo-embolism – acute treatment	DOACs, oral	Added
2.8.3 VTE during pregnancy and the puerperium	Low molecular weight heparin	New STG added
Appendix II - Prescribing information for specific medicines	Warfarin oral	Amended

2.1.1 ANAEMIA, IRON DEFICIENCY

Parenteral iron: *Directions for use amended*

The STG text was updated to include the following formula to calculate total dose of parenteral iron, aligned with the SAMF (2022):

The total iron dose to be administered is determined by haemoglobin and body weight (advisable to also reference product information):

$$0.66 \times Body\ weight\ (kg) \times (100 - \frac{(Hb\ \times 100)}{14.8})$$

Level of Evidence: IVb Guidelines[1]

Low molecular weight iron dextran: *Directions for use amended*

Directions for use was expanded as follows and requirement for test dose administration removed. Aligned with SAMF (2022) as tabulated below:

AMENDED FROM:	**AMENDED TO:**
Low molecular weight iron dextran, administered as a single dose. ○ Determine total dose of iron required (total dose up to 20 mg/kg body weight). ○ **Note:** Start with test dose - 25 mg in 100 ml sodium chloride 0.9%, infused over 15 minutes and observe the patient for 1 hour. ○ If there is no adverse drug reaction, administer the remaining dose in 500 mL of sodium chloride 0.9%, 0.9% over 4-6 hours. Observe the patient for 1 hour after the infusion.	Low molecular weight iron dextran, slow IV infusion, 100–200 mg, diluted in 100 mL 0.9% sodium chloride or 5% glucose solution. ○ Maximum infusion rate: 100 mL over 30 minutes (200 ml per hour). ○ Administer 2–3 times per week until calculated total iron requirements have been given. ○ If patient requires rapid delivery of iron to replenish iron stores, iron dextran may be administered as a total dose infusion up to a total replacement dose of 20 mg/kg body weight. Dilute dose in 500 mL 0.9% sodium chloride or 5% glucose solution and give over 4–6 hours. ○ Test dose is not required, however, caution is needed with every dose of IV iron, even if previously well tolerated.

Level of Evidence: IVb Guidelines[2]

[1] SAMF, 2022 edition

[2] SAMF, 2022 edition

2.1.2 ANAEMIA, MEGALOBLASTIC

General Measures

Vitamin B12 deficiency in patients on chronic metformin therapy: *Guidance clarified*

Guidance on monitoring for vitamin B12 deficiency in patients on chronic metformin therapy has been amended as tabulated below:

AMENDED FROM:	**AMENDED TO:**
» Chronic metformin use can lead to vitamin B_{12} deficiency by interfering with absorption.	» Chronic metformin use can lead to vitamin B_{12} deficiency by interfering with absorption. Maintain a low threshold for clinical features of vitamin B12 deficiency in patients on metformin, and check serum levels if clinically indicated.

Vitamin B_{12} deficiency

Vitamin B_{12}, IM: *directions for use amended*

Amended to align with the British National Formulary (2020) and the SAMF (2022), as tabulated below:

AMENDED FROM:	**AMENDED TO:**
• Vitamin B_{12}, IM. o 1 mg daily for 5 days, then weekly for a further 3 doses o Follow with 1 mg every second month for life in patients with pernicious anaemia.	For uncomplicated pernicious anemia: • Vitamin B_{12}, IM, 1 mg on alternate days for 1–2 weeks. o Followed by 1 mg weekly until blood count is normal. o Lifelong maintenance dose: 1 mg monthly. For serious complications from deficiency: • Vitamin B_{12} IM, 1 mg daily for 1 week. o Followed by 1 mg weekly for 1 month. o Lifelong maintenance dose: 1 mg monthly.

Level of Evidence: IVb Guidelines[3,4]

2.1.5 ANAEMIA, APLASTIC

Pancytopaenia in HIV positive patients

Common causes – medication: *Editorial amendment*

Guidance on medication as a common cause of pancytopenia in PLHIV has been amended as tabulated below:

AMENDED FROM:	**AMENDED TO:**
Pancytopenia in HIV positive patients B23.2 + (D61.2/D61.9) Most common causes include: » Direct effect of HIV. » Medication (e.g. emtricitabine, lamivudine, carbamazepine, valproic acid, phenytoin). » Secondary opportunistic infections. » Malignancies and nutritional deficiencies. Many cases are idiopathic.	**Pancytopenia in PLHIV** B23.2 + (D61.2/D61.9) Most common causes include: » Direct effect of HIV. » Medication (e.g. carbamazepine, valproic acid, phenytoin or pure red cell aplasia with emtricitabine and lamividine). » Secondary opportunistic infections. » Malignancies and nutritional deficiencies. Many cases are idiopathic.

2.1.6 ANAEMIA, SICKLE CELL

Description – *Editorial amendment*

The description of sickle cell anaemia[5] was amended as tabulated below:

[3] Joint Formulary Committee. British National Formulary. 80. London: BMJ Group and Pharmaceutical Press; 2020.

[4] SAMF, 2022 edition

[5] Kato, G., Piel, F., Reid, C. *et al.* Sickle cell disease. *Nat Rev Dis Primers* **4**, 18010 (2018). https://doi.org/10.1038/nrdp.2018.10

AMENDED FROM:	AMENDED TO:
Homozygous sickle cell anaemia (HbSS). Individuals with sickle cell trait have <50% HbS and are generally asymptomatic. Milder sickle cell disease occurs in individuals with HbSC. The disease is characterised by recurrent acute vaso-occlusive episodes ("sickle crises") and chronic haemolytic anaemia. Adults develop hyposplenism, predisposing them to infection with encapsulated bacteria.	Sickle cell disease (SCD) is a genetic, inherited condition resulting in abnormal red blood cells. Homozygous SCD is the commonest and most severe form, characterised by recurrent vaso-occlusive episodes ("sickle crises") and chronic haemolytic anaemia. Adults develop hyposplenism, predisposing them to infection with encapsulated bacteria. Heterozygous SCD includes Haemoglobin S-C disease/HbSC, causing milder sickle cell disease, and sickle cell trait/HbS, who are generally asymptomatic.

Enoxaparin – renal impairment: *Dose amended*

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 FROM:	AMENDED TO:
MEDICINE TREATMENT (SEVERE VASO-OCCLUSIVE EPISODES) Use of Oxygen to maintain adequate saturation. To prevent venous thromboembolism: ▪ Low molecular weight heparin, e.g.: • Enoxaparin, SC, 40 mg daily. In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist. In renal failure (eGFR <30 mL/minute), the recommended dose of LMWH is 1 mg/kg daily. **OR** Unfractionated heparin, SC, 5 000 units 12 hourly. **Analgesia** Refer to chapter 12: Anaesthesiology, pain and intensive care	**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.

Chronic management – vaccination: *Guidance clarified*

Guidance on vaccination requirements for patients with aplastic anaemia has been clarified to include vaccination against pneumococci and haemophilus influenza type b. The cross reference to Section 9.2 Adult vaccination has been removed, as no longer relevant.

AMENDED FROM:	AMENDED TO:
MEDICINE TREATMENT (CHRONIC MANAGEMENT) All patients: • Folic acid, oral, 5 mg daily. • Vaccination against infections due to pneumococci and haemophilus (see section 9.2: Adult vaccination).	**Chronic management** All patients: • Folic acid, oral, 5 mg daily. • Vaccination against infections due to pneumococci and haemophilus influenza type b.

2.2 FEBRILE NEUTROPENIA

General measures: *Editorial amendment*

Examples of drugs that may cause neutropenia and that should be withdrawn have been added as tabulated below:

AMENDED FROM	AMENDED TO:
GENERAL MEASURES » Treat the underlying cause of neutropenia, if applicable. » Withdraw any medication that may cause neutropenia.	**GENERAL MEASURES** » Treat the underlying cause of neutropenia, if applicable. » Withdraw any medication that may cause neutropenia, e.g. carbimazole, clozapine, co-trimoxazole, penicillins, carbamazepine, valproate.

Filgrastim, parenteral: *Not added*

Currently, Granulocyte colony-stimulating factor (GCSF) is listed on the T&Q EML for febrile neutropenia[6], and the PHC/Adult Hospital Level Committee deliberated on whether filgrastim should be included on Adult Hospital Level EML for use at regional hospitals for patients with neutropenic sepsis. The PHC/Adult Hospital Level Committee acknowledged that access to GCSF could minimise referrals to tertiary hospitals of patients referred solely for GCSF in-hospital administration and monitoring of cell counts and may improve equity and access. However, concerns were raised on the risks if a life-threatening diagnosis is missed. Therefore, the PHC/Adult Hospital Level Committee recommended that GCSF not be included on the EML for regional hospital level of care, as management requires subspecialist intervention (clinical haematologist/ oncologist) to ensure that risk is averted.

A T&Q medicine review was conducted in 2008[7]. However, a more updated 2014 Cochrane review[8] of 15 RCTs (n=1533) of GCSF used with antibiotics in febrile neutropenia showed that compared to antibiotics alone:

- Overall mortality was not improved: HR 0.74; 95% CI 0.47 to 1.16; p=0.19; 13 RCTs; n=1335; *low quality evidence*
- Infection-related mortality was not improved: HR 0.75;95% CI 0.47 to 1.20; p=0.23; 10 RCTs; n=897; *low quality evidence*
- Less participants hospitalized for more than 10 days: RR 0.65; 95% CI 0.44 to 0.95; p=0.03; 8 RCTs; n=1221; *low quality evidence*
- Participants had faster neutrophil recovery: RR 0.52; 95% CI 0.34 to 0.81; p=0.004; 5 RCTs; n=794 participants; *moderate quality evidence*
- Participants had shorter duration of neutropenia: SMD-1.70; 95% CI -2.65 to -0.76; p=0.0004; 9 RCTs; n=1135; *moderate quality evidence.*
- Participants had a faster recovery from fever: SMD -0.49;95% CI -0.90 to -0.09; p=0.02; 9 RCTs; n=966 participants; *moderate quality evidence*
- Participants had a shorter duration of antibiotic therapy: SMD -1.50; 95% CI -2.83 to -0.18; p=0.03; 3 RCTs; 457 participants; *low quality evidence*
- No significant difference in the incidence of DVT: RR 1.68; 95% CI 0.72 to 3.93; p=0.23; 4 RCTs; n=389; *low quality evidence*
- Higher incidence of bone or joint pain or flu-like symptoms: RR 1.59 (95% CI 1.04 to 2.42) p=0.03; 6 RCTs; n=622; *low quality evidence*

Overall, the methodological quality of studies was assessed as moderate to low across different outcomes, and the quality of evidence was downgraded mainly due to inconsistency and imprecision of results.

Vancomycin, IV : *Dose amended*

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. The dose range of 25-30mg/kg, is in line with the dose recommendation in the SAMF[9], and has been applied to allow for dose rounding to the nearest 250mg vial. Amendments are tabulated below:

AMENDED FROM:	**AMENDED TO:**
If IV line, skin infection is suspected as the cause::	If IV line, and skin infection is suspected as the cause:
ADD:	**ADD:**
• Vancomycin, IV, 30 mg/kg as a loading dose. Follow with 20 mg/kg/dose 12 hourly. (See Appendix II for guidance on prescribing and monitoring).	• 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).

Imipenem/cilastatin, IV: *Dose amended*

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-

[6] T & Q EML, July 2021

[7] National Department of Health: Affordable Medicines, Tertiary & Quatenary Level. Medicine Review: Filgrastim for febrile neutropenia, 19 November 2008 [on file at NDoH]

[8] Mhaskar R, Clark OA, Lyman G, Engel Ayer Botrel T, Morganti Paladini L, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. Cochrane Database Syst Rev. 2014 Oct 30;2014(10):CD003039. https://pubmed.ncbi.nlm.nih.gov/25356786/

[9] The South African Medicines Formulary (SAMF). 2022, 14th Edition.

associated pneumonia (VAP), as tabulated below. Furthermore, the recommendation to preferentially consider meropenem over imipenem/cilastatin has been removed as there are reports of seizures occurring with both options. In a meta-analysis conducted by Cannon et al[10], the authors concluded that while the absolute risk of seizures with carbapenems was increased in patients receiving carbapenem versus non-carbapenem antibiotics, in the head to head comparison between imipenem versus meropenem, there was no statistically significant difference in seizure risk.

AMENDED FROM:	**AMENDED TO:**
Regimen 1: ▪ Carbapenem with activity against Pseudomonas, e.g.: • Meropenem, IV, 1 g 8 hourly. **OR** • Imipenem/cilastatin, IV, 500/500 mg 6 hourly. ○ Do not use imipenem/cilastatin in patients with central nervous system disorders or history of seizures. For patients with known epilepsy – use meropenem. **Note**: Ertapenem is not recommended as it is not effective for *Pseudomonas* species, which are important pathogens in this setting.	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.

Piperacillin/tazobactam, IV: *Dose amended*

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[11] and Stanford guidelines[12].

Level of Evidence: IVb Guidelines

2.4. BLEEDING DISORDERS

General

The NEMLC convened a Haemophilia Sub-Committee (21 November 2022) with representatives from all respective Expert Review Committees (ERCs) to comprehensively review data and budget impact of the clotting factors, by-passing agents as well as monoclonal antibodies for the management of Haemophilia A. The outcomes from the work of the Haematology Sub-Committee involved the separation of the STGs into different sub-categories, namely: Section 2.4.1.1 Haemophilia A – factor VIII deficiency (no inhibitors), section 2.4.1.2 Haemophilia B – factor IX deficiency (no inhibitors), section 2.4.1.3 Haemophilia with inhibitors, with a clear separation of Von Willebrand's disease into Section 2.4.2 as detailed below.

The Paediatric and Adult Hospital Level STGs and EML for Haemophilia have been aligned to each other in terms of descriptions, diagnosis, treatment and referral, with the objective of ensuring the continuity of care as patients' transition from paediatric to adult healthcare services, while optimizing available resources. The STGs for the management of bleeding disorders have undergone extensive editorial review and treatment approaches have been divided into two main categories: prophylaxis and on demand (episodic) treatment following a bleed.

While considerable effort has been applied with reviewing the available literature and undertaking relevant cost analyses, the Haemophilia Sub-Committee acknowledges the lack of a national high quality data repository/patient registry as a significant limitation to comprehensively achieving this objective. STGs have been kept separately for paediatrics and adults to facilitate inclusion in the relevant Paediatric and Adult Hospital EML chapters.

[10] Cannon JP, Lee TA, Clark NM, Setlak P, Grim SA. The risk of seizures among the carbapenems: a meta-analysis. J Antimicrob Chemother. 2014 Aug;69(8):2043-55. doi: 10.1093/jac/dku111. Epub 2014 Apr 16. PMID: 24744302.

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

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

2.4.1 HAEMOPHILIA A AND B

Description, diagnostic criteria and investigations: *Amended*

Extensive editorial amendments were made to the STG for improved diagnosis and general management. Amendments to the STG are as tabulated below:

AMENDED FROM:

2.4.1 HAEMOPHILIA A AND B, VON WILLEBRAND'S DISEASE

D66/D67/D68.0

DESCRIPTION

Haemophilia A, haemophilia B and von Willebrand's disease are chronic bleeding disorders caused, respectively, by a lack of clotting factor VIII, clotting factor IX and von Willebrand factor (VWF, a carrier protein for factor VIII). Presentation depends on severity of the condition (see classification below).

Complications include haemarthrosis with later chronic arthropathy, intracranial haemorrhage, soft tissue and muscle haematomas. Pain/tingling in a joint suggests bleeding into the joint in a known haemophiliac.

Early consultation with a haematologist or a clinician with expertise in the handling of such patients is advisable. Clinicians should make contact with their local haemophilia centre which may be identified at: http://www.haemophilia.org.za/centres.html

All patients diagnosed with haemophilia should at least annually attend a specialised Haemophilia Treatment Centre with a dedicated multi-disciplinary health care team as guided by the local Haemophilia Treatment Centre.

Subclassification (factor VIII and IX deficiency):

CLASS	CLOTTING FACTOR	% OF NORMAL	SIGNS
Mild	VIII or IX	>5–<40%	Occasional bleeds
Moderate	VIII or IX	1–5%	Less frequent bleeding associated with trauma, surgery or dental work
Severe	VIII or IX	<1%	Traumatic or spontaneous bleeds

AMENDED TO:

2.4.1 HAEMOPHILIA A AND B

D66.7/D66.8

DESCRIPTION

Haemophilia A and B are lifelong chronic bleeding disorders caused by a lack of clotting factor VIII and clotting factor IX, due to mutations in the Factor VIII and Factor IX genes respectively. Acute bleeding presentation depends on the severity of the condition (see classification below). Bleeding can occur into any tissue, but intraarticular bleeds are the clinical hallmark of haemophilia.

Haemophilia complications include haemarthrosis that may lead to chronic arthropathy, intracranial haemorrhage, soft tissue and muscle haematomas. In a known person with haemophilia, pain/tingling in a joint suggests early-onset bleeding.

Early consultation and regular follow-up with a haematologist or clinician with expertise in managing such patients is advisable. All patients diagnosed with haemophilia should attend a designated specialised Haemophilia Treatment Centre with a dedicated multi-disciplinary health care team at least annually for adults. The details of available Haemophilia Treatment Centres can be accessed at: https://haemophilia.org.za/haemophilia-treatment-centres-htcs/. All patients diagnosed with haemophilia should be enrolled in the South African Bleeding Disorders Registry (access relevant co-ordinators at: https://haemophilia.org.za/haemophilia-nurses-office/)

Those eligible for prophylaxis with factor VIII or IX (see below) may receive factor replacement therapy at a healthcare facility twice a week. Where appropriate, home-based care can be considered.

Haemophilia severity classification

Class	Clotting factor	Factor level	Signs
Mild	VIII or IX	> 5 – <40%	Occasional bleeds, usually afte surgery.
Moderate	VIII or IX	1–5%	Less frequent bleeds than sev post trauma/surgery/dental extra Some patients may, however severe bleeding phenotype.
Severe	VIII or IX	< 1%	Spontaneous bleeds, particular muscle.

(Adapted from White et.al. Journal of Thrombosis *and* Haemostasis*. 2001)*

DIAGNOSTIC CRITERIA

Clinical

» Major bleeds:
  - > central nervous system (CNS) – intracranial
  - > severe injury
  - > muscle compartment (e.g. forearm and calf)
  - > gastrointestinal tract
  - > neck/throat (airway)
  - > advanced joint and soft ti
  - > hip and ilio-psoas muscle

» Minor bleeds:
  - > early joint bleed
  - > soft tissue
  - > mouth and gum
  - > muscle
  - > epistaxis
  - > haematuria

» Pain/tingling in a joint of a patient with haemophilia suggests bleeding.

Investigations

Investigations Prolonged partial thromboplastin time (PTT). Factor VIII or factor IX concentration and inhibitor screen.	Baseline » Normal white cell count and platelets; may have anaemia due to blood loss or iron deficiency. » Normal INR » Prolonged activated partial thromboplastin time (aPTT) » APTT correction studies » Factor VIII or IX plasma levels < 50% » HIV, hepatitis B, and hepatitis C testing if status not known Non-responders to factor replacement or those previously diagnosed with inhibitors » Inhibitor screen (Bethesda or Nijmegen assays) **GENERAL MEASURES** » Patient, family and community education » Enrolment in the South African Bleeding Disorders Registry (access relevant co-ordinators at: *https://haemophilia.org.za/haemophilia-nurses-office/)* » MedicAlert bracelet (or similar) » Dental care (see below for management of tooth extraction) » Avoid contact sport Exercise great caution when taking blood specimens (no arterial samples). Taking blood from femoral veins is contra-indicated. Do not insert or use central lines unless done as part of life-saving efforts. Do not aspirate joints. Avoid IM injections. Avoid aspirin and other NSAIDs.

For mucous membrane bleeds

Tranexamic acid*: Dose amended*

An external comment was received proposing that the dose of tranexamic acid for mucous membrane bleeds be amended from 1g to 15 – 25 mg/kg. The Subcommittee proposed that the South African Medicines Formulary[13] dosing be added, which includes both a total dose and a mg/kg dose. The Subcommittee further noted that oral tranexamic acid was available as a 500mg tablet formulation so retaining the dose in a format that could easily be administered would be pragmatic.

The text was amended as detailed below:

AMENDED FROM:

Mucous membrane bleeds in haemophilia A and B:

- Tranexamic acid, oral, 1 g, 6 hourly.

AMENDED TO:

For mucous membrane bleeds

- Tranexamic acid, oral, 1 – 1.5g (15 - 25 mg/kg) 6-8 hourly.

Dental extraction/male circumcision/minor surgical procedures

New guidance: *Added*

Tranexamic acid: *Added*

The STG has been amended to allow for the initiation of tranexamic acid treatment before commencement of dental extraction and other minor surgical procedures. The timing for initiating treatment with tranexamic acid, was included as recommended by the World Federation of Hemophilia, Guidelines for dental treatments of patients with inherited bleeding disorders, i.e. initiation of tranexamic acid, 2 hours prior to procedure.[14] This recommendation is also in line with the South African Medicines Formulary.[15]

[13] South African Medicines Formulary (SAMF). https://samf-app.com/about

[14] World Federation of Hemophilia Dental Committee. Guidelines for Dental Treatment of Patients with inherited bleeding disorders. 2006.

[15] South African Medicines Formulary, 12th Edition. Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town, and Health and Medical Publishing Group. 2016.

An external comment was received proposing that the dose of tranexamic acid for mucous membrane bleeds be amended from 25 mg/kg to 15 – 25 mg/kg. The tranexamic professional information[16] recommends a dose of 25 mg/kg orally 2 hours before the operation, with the same dose given 3 to 4 times daily after the operation. The Subcommittee proposed retaining the dosing guidance as detailed below.

Factor VIII and Factor IX: *Dose retained*

External stakeholder comment was received to amend the dose of factor VIII in haemophilia A and factor IX in haemophilia B from 40 units/kg to 50 units/kg. No supporting evidence was provided for the suggested amendments. The Treatment Guidelines for Haemophilia in South Africa[17] recommends a dose of 20 – 40 units/kg of factor VIII or IX for haemophilia A or B respectively, 30 minutes before surgery. This dose is in line with the current STG recommendations of 40 units/kg. The Subcommittee thus recommended that the dose recommendations for factor VIII and IX be retained.

Extensive revision to the guidance on the management of acute bleeds has been undertaken as tabulated below:

AMENDED FROM:	**AMENDED TO:**
TREATMENT GUIDELINES Treatment approaches are divided into two main categories: prophylaxis and on demand. **Prophylaxis** Secondary prophylaxis is sometimes needed in patients presenting with a target joint in consultation with a Haemophilia Treatment Centre. The aim is to reduce the number of bleeds and prevent or delay development of joint arthropathy. **Treatment on Demand** Episodic treatment for bleeding episodes is referred to as on-demand therapy (i.e. the use of factor replacement therapy after bleeding occurs). **GENERAL MEASURES** » Patient and family education. » Enroll on the Haemophilia registry. » Alert bracelet. » Dental care (discuss management of tooth extraction with local haemophilia centre). » Avoid contact sport. **Acute bleeds into joints** Patients with severe haemophilia should be trained to self-administer their clotting factor concentrate. **Adjunctive management** » Protection (splint but no circumferential casting). » Rest the affected limb until pain free and no weight bearing. » Ice packs may be applied immediately (apply ice, 5 minutes on and 10 minutes off). » Elevation of the affected limb. **MEDICINE TREATMENT** For pain: Refer to chapter 12: Anaesthesiology, pain and intensive care. Exercise great caution when taking blood specimens. Taking blood from femoral veins is absolutely contra-indicated. Do not use central lines for transfusions. Do not do joint aspirations Avoid IM injections. Avoid aspirin and NSAIDS.	**MEDICINE TREATMENT** Treatment approaches are divided into two main categories: prophylaxis and on demand (episodic) treatment following a bleed. **Prophylaxis** Prophylaxis aims to prevent the number of bleeds and prevent or delay the development of joint arthropathy and other sequelae. Primary and secondary prophylaxis can be considered in consultation with a Haemophilia Treatment Centre. In consultation with a Haemophilia Treatment Centre, prophylaxis is sometimes needed in patients presenting with a target joint. **Treatment on Demand (Episodic treatment)** Episodic treatment for bleeding episodes is referred to as on demand therapy (i.e. the use of factor replacement therapy when bleeding occurs). **Home treatment** Haemophilia Treatment Centres promote home treatment of bleeds. Patients or caregivers must be educated on the storage, reconstitution and administration of clotting factor concentrate and provided with a supply of clotting factor concentrate to be kept at home for use in case of a bleed and/or for prophylaxis. Clotting factor concentrate use and bleeding episodes are monitored through an appropriate chart (or bleeding diary), which can be reviewed at consultations and medication collection. **ACUTE MANAGEMENT OF BLEEDS** **For pain (as required):** Refer to section 26.2.1 Medical conditions associated with severe pain and section 12.4.2: Postoperative pain in the recovery room. **Do not use NSAIDs, including aspirin**. **For bleeding episodes** Emergency treatment while awaiting transfer, if indicated. If serious bleeding in a known patient with haemophilia, and no factor is available: • Lyophilised plasma (FDP), IV, 15 mL/kg over 20-30 minutes. Lyophilised plasma contains a minimum of 0.4 units/mL of each coagulation factor. **OR**

[16] Tranexamic Acid Professional Information. Cyclokapron. 2022. https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2022/02/Cyklokapron-PI-approved-09-Jan-2022.pdf

[17] Mahlangu J, Gillham A. Treatment Guidelines for Haemophilia in South Africa. South African Medical Journal, February 2008, 98(2):127 - 138

	• Fresh Frozen Plasma (FFP), IV, 15 mL/kg over 20-30 minutes. **Acute joint bleeds** – Infuse intravenous factor concentrate first (refer to Section 2.4.1.1 or Section 2.4.1.2 below for dosing guidance) with the following adjunctive measures: » Apply ice packs: 5 minutes on and 10 minutes off. » Rest the affected joint/limb until pain-free and there is no further swelling. » Avoid weight-bearing. » Splint. Do not use circumferential casts. » **Do not** aspirate affected joints. » Do not request an X-ray of the affected joint unless there is a strong suspicion of fracture. Give clotting factor concentrate until the patient is pain-free and the joint's range of motion is normal. Administration should be 12 hourly (for Haemophilia A) for major bleeds but may be daily for minor bleeds. **For mucous membrane bleeds** • Tranexamic acid, oral, 1 - 1.5 g (15 - 25 mg/kg) 6-8 hourly. **For dental extraction/male circumcision/minor surgical procedures** Check that inhibitors are absent. Admit for the procedure and post-procedure care and observation in a facility with experience in haemophilia management. <u>Haemophilia A:</u> • Factor VIII, intravenous, 40 units/kg, immediately before extraction. **AND** • Tranexamic acid, oral, 25 mg/kg/dose 6–8 hourly, starting 2 hours before the procedure and continued for 5 days post-procedure. <u>Haemophilia B:</u> • Factor IX/factor IX complex, intravenous, 40 units/kg, immediately before extraction. Ideally, elective surgery should be performed at a tertiary/quaternary centre in consultation with a clinical haematologist. In emergencies, treat it as a major bleed and consult the local Haemophilia Treatment Centre as soon as feasible.

2.4.1.1 HAEMOPHILIA A - FACTOR VIII DEFICIENCY (NO INHIBITORS)

Prophylaxis

<u>Factor VIII prophylaxis</u>: *Added*
<u>Factor VIII:</u> *not added as a therapeutic class*
<u>Coagulation factor VIII (complex):</u> *retained, but not included in factor VIII therapeutic class*
<u>Human Coagulation Factor VIII (purified):</u> *not added as a member of the factor VIII therapeutic class*
<u>Recombinant Factor VIII (purified):</u> *not added as a member of the factor VIII therapeutic class*

Factor VIII prophylaxis: added. See medicine review[18]

SUBCOMMITTEE FOR HAEMAPHILIA RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Rationale: The Committee suggests using intermediate factor VIII prophylaxis for severe haemophilia A patients without inhibitors. There is very low certainty evidence to suggest that low dose and intermediate dose factor VIII prophylaxis therapies are more effective than treatment on-demand for patients with haemophilia A. Basic cost-effectiveness analysis shows low and intermediate dose prophylaxis are potentially more cost-saving than treatment on demand if only considering acquisition costs of factor VIII. Sensitivity scenarios which accounted only for treatment of minor bleeds (and not major or life-threatening bleeds) showed that low and intermediate dose prophylaxis were more effective but more costly than treatment on demand. The analysis did not account for quality of life, mortality, cost of surgeries or long-term complications. Intermediate dose prophylaxis is potentially more effective and may have higher cost savings than low dose prophylaxis.

Level of Evidence: Level 1 – systematic review, very low certainty of evidence for low dose prophylaxis, low certainty of evidence for intermediate.
Review Indicator: Evidence of harm, cost-effectiveness, cost savings, agent price

Factor VIII: *Dose retained*
A stakeholder comment was received proposing to increase the dose and frequency of factor VIII when used for prophylaxis. The inclusion of factor VIII prophylaxis for patients with severe haemophilia without inhibitors was reviewed and approved by NEMLC. The approval was for use in patients with severe haemophilia. Based on the evidence review and cost-effectiveness analysis, intermediate dose prophylaxis was shown to potentially be more effective and have higher cost savings than other dosing strategies when used for prophylaxis, including on demand treatment of bleeds. The Subcommittee thus recommended that the intermediate dose of factor VIII for prophylaxis be retained.

Treatment on demand for acute bleeding episodes
Minor bleeds
Factor VIII: *Dose retained*
A stakeholder comment was received to amend the on demand treatment dose from 20 – 40 units/kg to 50 unit/kg. The South African Treatment Guidelines for Haemophilia recommends 20 - 40 unit/kg, and thus the Subcommittee recommended that the dose range be retained.

Major bleeds
Factor VIII: *Dose retained*
A stakeholder comment was received to amend the on demand treatment dose from 40 - 50 units/kg to 50 unit/kg. The South African Treatment Guidelines for Haemophilia recommend 40 - 50 unit/kg. Furthermore, a dosing range is preferred as it allows for dose rounding to the nearest vial size which assists with minimising wastage. The Subcommittee recommended that the dose range of 40 - 50 units/kg be retained.

Intracranial bleeds – trough factor level: *Amended*
The trough factor level for decreasing the frequency of factor dosing was amended from 60% to 50% in response to an external stakeholder comment. This allows for a more cautious approach.

Extensive revision of the STG was undertaken as tabulated below:

AMENDED FROM:	AMENDED TO:
HAEMOPHILIA WITH NO INHIBITORS The dose of the factor VIII and IX is individualised as it is dependent on body mass, severity of the condition, and the nature and site of the bleeding. **Factor VIII deficiency (with no inhibitor present)**	**2.4.1.1 HAEMOPHILIA A - FACTOR VIII DEFICIENCY (NO INHIBITORS)** D66

[18] Prophylactic Factor VIII compared to on-demand treatment for patients (adults and children) with haemophilia A without inhibitors. July 2023.

Minor bleeds:
Bleeds into the muscle or soft tissue, mouth or gums, epistaxis, painless haematuria and early joint bleeds.

Treatment:
- Factor VIII, intravenous, 25 IU/kg IV, immediately as a single dose.
  - If there is evidence of ongoing bleeding after 12 hours, consult with local haemophilia treatment centre.

Major bleeds:
Advanced muscle or joint bleeds, bleeds resulting from severe injury, or bleeds that affect the central nervous system; gastrointestinal system; neck or throat; hip or iliopsoas; or forearm compartment.

Treatment:
- Factor VIII, intravenous, 50 IU/kg, immediately as a single dose.
  - All of these patients need hospitalisation.
  - Discuss all patients promptly with local haemophilia treatment centre.

PROPHYLAXIS
Prophylaxis (primary and secondary) should be considered for patients with severe haemophilia A (<1% factor activity) who can access the health facility twice weekly for infusions; or have indwelling venous catheters or are candidates for home-based care.

Primary prophylaxis: Prophylaxis started in the absence of documented joint disease/damage.
Secondary prophylaxis: Prophylaxis initiated after joint damage has occurred.

- Factor VIII, intravenous 25 units/kg, twice weekly.
  - The clotting factor should be rounded to the nearest full vial to avoid wastage.
  - Proposed rounded dosing (see table below)

Factor VIII dosing table				
Age in years	**Average weight (kgs)**	**IU required per dose**	**Rounded dose (IU)**	**Available products**
>12 (adults)	50	1250	1300	2 x 500IU plus 1 x 300IU
>12 (adults)	60	1500	1500	3 x 500IU
>12 (adults)	70	1750	1800	3 x 500IU plus 1 x 300IU

MEDICINE TREATMENT
TREATMENT ON DEMAND FOR ACUTE BLEEDING EPISODES
Minor bleeds:
Bleeds into the muscle or soft tissue, mouth or gums, epistaxis, painless haematuria and early joint bleeds.
- Factor VIII, intravenous, 20 - 40 units/kg.
  - If there is evidence of ongoing bleeding after 12 hours, consult with local haemophilia treatment centre.

Major bleeds:
Advanced muscle or joint bleeds result from severe injury or bleeds that affect the central nervous system, gastrointestinal system, neck or throat, hip or iliopsoas muscle, or forearm compartment.
- Factor VIII, intravenous, 40 - 50 unit/kg.
  - Use all the contents of the appropriate volume ampoule.
  - All of these patients need hospitalisation.
  - Discuss all patients promptly with the local Haemophilia Treatment Centre.

Intracranial bleeds (*paediatrics and adults*)
- Factor VIII, intravenous, 40 – 50 units/kg 6 hourly.
  - Decrease frequency of dosing if the trough factor level is > 50%, if possible.

2.4.1.2 HAEMOPHILIA B - FACTOR IX DEFICIENCY (NO INHIBITORS)

Factor IX prophylaxis: *Added*
Factor IX prophylaxis has been included in the EML following the evidence review undertaken and the supporting NEMLC recommendation[19] as tabulated below:

[19] NDoH evidence review. Prophylactic Factor IX compared to on-demand/episodic treatment for patients with severe haemophilia B without inhibitors. Ratified 5 July 2024.

SUBCOMMITTEE FOR HAEMOPHILIA RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

The Haemophilia subcommittee suggests the use of factor IX prophylaxis for patients with severe haemophilia B.

Rationale: There is very limited, low quality evidence available for prophylaxis in the management of haemophilia B. However, the benefit of factor IX prophylaxis compared to on-demand/episodic treatment for haemophilia B patients has been shown in non-randomised controlled trials and recommended in guidelines. The majority of guidelines follow the recommendations for haemophilia A. A cost analysis revealed potential cost-savings for all prophylaxis regimens, with intermediate dose prophylaxis found to be the most cost-saving. Low dose prophylaxis was shown to be less cost saving, but more cost-saving than high dose prophylaxis. The costing model relied on many assumptions including uncertain estimates of the number of patients requiring prophylaxis. Despite these limitations, the potential benefit of prophylaxis is acknowledged and alignment with haemophilia A is considered to be beneficial.

Level of Evidence: Level 2 – nonrandomised trials, low quality
Review Indicator: Evidence of harm, cost-effectiveness, cost savings, agent price
Monitoring and evaluation considerations: Monitoring is compulsory, details regarding implementation to be determined for each relevant Standard Treatment Guidelines

NEMLC RECOMMENDATION 27th May 2024:

The NEMLC accepted the haemophilia subcommittee recommendation for factor IX prophylaxis for patients with severe haemophilia B and the relevant updates to the Adult and Paediatric Hospital Level Standard Treatment Guidelines.

Factor IX complex: *Added*
Reference to factor IX was amended to include factor IX complex to ensure available products are included on the EML and tender processes.

Factor IX: *not added as a therapeutic class*
Coagulation factor IX (complex): *retained, but not included in factor VIII therapeutic class*
Human Coagulation Factor IX (purified): *not added as a member of the factor VIII therapeutic class*

Extensive revision of the STG was undertaken as tabulated below:

AMENDED FROM:	AMENDED TO:

Factor IX deficiency (with no inhibitor present)
Minor bleeds:
Bleeds into the muscle or soft tissue, mouth or gums, epistaxis, painless haematuria and early joint bleeds.
Treatment:
• Factor IX, intravenous, 40 IU/kg immediately as a single dose.
  ○ If there is evidence of ongoing bleeding after 12 hours, consult with local haemophilia treatment centre.
 	
Major bleeds:
Major muscle or joint bleeds, bleeds resulting from severe injury, or bleeds that affect the central nervous system; gastrointestinal system; neck or throat; hip or iliopsoas; or forearm compartment.
 	
Treatment:
• Factor IX, intravenous, 60 IU/kg immediately as a single dose.
  ○ All of these patients need hospitalisation.
	2.4.1.2 HAEMOPHILIA B - FACTOR IX DEFICIENCY (NO INHIBITORS)
	D67
	
	PROPHYLAXIS
	Prophylaxis (primary and secondary) should be considered for patients with severe haemophilia B (<1% factor activity) who can access the health facility twice weekly for infusions; or have indwelling venous catheters or are candidates for home-based care.
	Primary prophylaxis: Prophylaxis started in the absence of documented joint disease/damage.
	Secondary prophylaxis: Prophylaxis initiated after joint damage has occurred.
	
	• Factor IX, intravenous 25 units/kg, twice weekly.
	
	TREATMENT ON DEMAND
	Minor bleeds
	Bleeds into the muscle or soft tissue, mouth or gums,

Discuss all patients promptly with local haemophilia treatment centre to plan ongoing treatment and factor replacement. **Mucous membrane bleeds in haemophilia A and B:** • Tranexamic acid, oral, 1 g, 6 hourly. Ideally elective surgery should be perfomed at a tertiary centre with a consultation with a haematologist. In emergencies, treat as major bleed and consult the local Haemophilia Treatment Centre as soon as feasible. If serious bleeding with known haemophilia, and no factor VIII available: • Lyophilised plasma, IV, 15 mL/kg. **OR** FFP, IV, 15 mL/kg.	epistaxis, painless haematuria and early joint bleeds. • Factor IX/factor IX complex, intravenous, 40 units/kg immediately as a single dose. o If there is evidence of ongoing bleeding after 12 hours, consult with local haemophilia treatment centre. **Major bleeds** Major muscle or joint bleeds result from severe injury or bleeds that affect the central nervous system, gastrointestinal system, neck or throat, hip or iliopsoas muscle, or forearm compartment. • Factor IX/factor IX complex, intravenous, 60 units/kg. o All these patients need hospitalisation. Discuss all patients promptly with the local Haemophilia Treatment Centre to plan ongoing treatment and factor replacement

2.4.1.3 HAEMOPHILIA WITH INHIBITORS

Guidance for referral: *Amended*

Guidance for referral has been amended editorially as detailed below:

AMENDED FROM:	AMENDED TO:
HAEMOPHILIA WITH INHIBITORS Refer for assessment and planning with a haematologist.	**2.4.1.3 HAEMOPHILIA WITH INHIBITORS** Refer for assessment and planning with a haematologist. **REFERRAL** » All cases with **suspected** or established haemophilia (prolonged PTT and normal INR), for assessment, genetic counselling and planning of management, to a Haemophilia Treatment Centre.

2.4.2 VON WILLEBRAND'S DISEASE

Von Willebrand's Disease

Von Willebrand factor VIII concentrate (Coagulation factor VIII) (complex): *Retained*

The management of Von Willibrand's disease has been separated into a dedicated STG and is now covered under Section 2.4.2 with amendments to the chapter as tabulated below:

AMENDED FROM:	AMENDED TO:
VON WILLEBRAND'S DISEASE **Mild bleeding** Such as epistaxis and menorrhagia. Antifibrinolytics, e.g.: Tranexamic acid, oral, 1 g 6 hourly. Recurrent menorrhagia can also be treated effectively with oral contraceptives. See section 5.2: Uterine bleeding, abnormal. **More severe mucous membrane bleeding** Consult a local haemophilia treatment centre. During surgery or after major trauma, patients should receive: Von Willebrand factor VIII concentrate, IV, 30 units/kg/dose given every 12 hours. o Continue for 48–72 hours to ensure optimal haemostasis. o For major surgical procedures, use for 7–10 days. **REFERRAL** » All cases with **suspected** haemophilia (prolonged PTT and normal INR) to a haemophilia treatment centre, for assessment, genetic counselling and planning of management.	**2.4.2 VON WILLEBRAND DISEASE** D68.0 **DESCRIPTION** Von Willebrand disease is the most common congenital bleeding disorder and is due to reduced amounts or abnormal forms of von Willebrand factor. **DIAGNOSTIC CRITERIA** **Clinical** » Recurrent epistaxis, prolonged bleeding from lacerations, easy bruising or gum bleeds. **Investigations** » Reduction in one or more of the following: - von Willebrand factor antigen, - Ristocetin co-factor or collagen binding activity, - factor VIII coagulant activity. **GENERAL AND SUPPORTIVE MEASURES** » Apply pressure to the bleeding site. » For tooth socket bleeds, bite down on a piece of gauze.

» Patients with proven antibodies (inhibitors) against factor VIII or IX. » For further replacement, complex situations and complications in consultation with a haematologist.	**Avoid aspirin and other NSAIDs.** **MEDICINE TREATMENT** **Mild bleeding** Such as epistaxis and menorrhagia. ▪ Antifibrinolytics, e.g.: • Tranexamic acid, oral, 1 g 6-8 hourly. Recurrent menorrhagia can also be treated effectively with oral contraceptives. See section 5.2: Uterine bleeding, abnormal. **More severe mucous membrane bleeding** Consult a local haemophilia treatment centre. During surgery or after major trauma, patients should receive: • Factor VIII (Factor VIIII-containing von Willebrand factor VIII), IV, 30 IU/kg/dose given every 12 hours. o Continue for 48–72 hours to ensure optimal haemostasis. o For major surgical procedures, use for 7–10 days. **REFERRAL** » All suspected cases of von Willebrand disease to a Haemophilia Treatment Centre for assessment. Symptomatic thrombocytopenia

Therapeutic Interchange:

Bid specifications were required for the HP10-2023BIO Supply and Delivery of Small Biological Preparations to the Department of Health for the upcoming tender commencing 1 January 2025 with regards to factor VIII and IX. Previously, human plasma derived factor VIII and IX complex was available from a single supplier (National Bioproducts Institute), however, there are more products on the market (both human plasma derived and synthetic formulations).

Indications:

The characteristics for the various products on the South African market was compared using local registered package inserts:

Product	Indications	Concentration	Pharmacokinetics	Notes
		Factor VIII		
Haemosolvate®	Treatment and prophylaxis of coagulation defects caused by congenital or acquired factor VIII deficiency: Haemophilia A; Acquired or congenital factor VIII deficiency with low levels of factor VIII inhibitor Von Willebrand disease with factor VIII deficiency.	Factor 8: Von Willebrand (1:1) 300 IU: When each vial of the product is reconstituted with the 10 ml Water for Injection, the solution (per vial) will contain factor VIII:C – 300 IU; factor VIII:vWF - > 300 IU; sucrose – £ 0,31 g; protein - not more than 0,15 g, of which not more than 80% is fibrinogen.	The half-life of factor VIII varies between 8 and 20 hours, with an average of 12	The ratio of factor 8 to VWD is sufficient for use in Von Willebrand disease.
Octanate®	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Octanate LV can be used for all age groups. This preparation does not contain von Willebrand factor in pharmacologically effective quantities and is therefore not indicated in von Willebrand's disease.	The product contains approximately 100 IU* per ml human coagulation factor VIII when reconstituted with 5 ml of solvent	Plasma factor VIII activity decreases by a two-phase exponential decay. In the initial phase, distribution between the intravascular and other compartments (body fluids) occurs with a half-life of elimination from the plasma of 3 to 6 hours. In the subsequent slower phase (which probably reflects the consumption of factor VIII), the half-life varies between 8 to 20 hours, with an average of 12 hours. This corresponds to the true biological half-life	The ratio of factor 8 to VWD is **NOT** sufficient for use in Von Willebrand disease.
Kogenate®	Control and prevention of bleeding episodes in adults and children with hemophilia A. Surgical prophylaxis in adults and children with hemophilia A. Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes in children with		This behaviour is similar to that of plasma-derived Factor VIII with a mean terminal half-life of 13 hours (range 11 to 17 hours)	Kogenate FS is **NOT** indicated for the treatment of von Willebrand disease. May be considered as an alternative option for human plasma

Product	Indications	Concentration	Pharmacokinetics	Notes
	hemophilia A and to reduce the risk of joint damage in children without pre-existing joint damage. Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes in adults with hemophilia A. Kogenate FS is not indicated for the treatment of von Willebrand disease.			derived factor VIII for control and prevention of bleeding episodes in adults and children.
Factor IX				
Heamosolvex®	Haemosolvex Factor IX may be used for the treatment of coagulation defects caused by either a congenital or an acquired deficiency of factor IX. Congenital: Haemophilia B Acquired: The treatment of severe bleeding resulting from an overdose of oral coumarin-derivative anticoagulants.	50 IU/ml		Indication for treatment of bleeding in haemophilia B is aligned with the Adult Hospital Level STGs and EML, 2019. Not indicated as a reversal agent for Coumarin toxicity in the Adult Hospital Level STGs and EML, 2019. Contains heparin 10IU/ml as a stabiliser.
Octanine F®	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).	100 IU/ml		Indication for treatment of bleeding in haemophilia B is aligned with the Adult Hospital Level STGs and EML, 2019. Contains heparin 10IU/ml as a stabiliser

Recommendations:

- Von Willebrand factor VIII complex for treatment of bleeds in Von Willebrands Disease (Haemosolvate®)
- Human derived plasma and recombinant factor VIII options for treatment of bleeds for Haemophilia A, includes Haemosolvate®, Octanate®, Kogenate®
- Human derived plasma factor IX, complex and purified formulations options for treatment of bleeds for Haemophilia B, includes Haemosolvex®, Octanine®.

2.5 IMMUNE THROMBOCYTPAENIA (ITP)

Medicine treatment – second line therapy: *Editorial amendment*

Guidance to refer patients requiring second line therapy has been amended and included in the list of referral criteria.

Amendments to the STG are as tabulated below:

AMENDED FROM:	AMENDED TO:
MEDICINE TREATMENT **Acute ITP** Prednisone, oral, 1 mg/kg daily, until platelet count has normalised. o Taper slowly and monitor platelet count. (Refer to Appendix II for an example of a dose reduction regimen). o Although prednisone is also indicated for HIV-associated immune thrombocytopenia it is important that all these patients should be fast-tracked for ART. **Second line therapy** Patients with persistent thrombocytopenia not responding to treatment with glucocorticoids. Treatment with specialist supervision There are other multiple treatments available but are dependent on specialist opinion.	**MEDICINE TREATMENT** **Acute ITP** Prednisone, oral, 1 mg/kg daily until platelet count has normalised. o Taper slowly and monitor platelet count. (Refer to Appendix II for an example of a dose reduction regimen). o Although prednisone is also indicated for HIV-associated immune thrombocytopenia, it is important that these patients should be fast-tracked for antiretroviral therapy (ART) – See Section 10.1: Antiretroviral therapy. **Acute life-threatening bleeding and surgery** • Platelet transfusion, intravenous, 1 unit immediately. o Platelet transfusions are only indicated in acute active bleeding uncontrolled by other means or before procedures.

REFERRAL » All cases not responding to steroids and, in the case of HIV-infected patients, not responding to ART – discuss with haematologist. » Refer for second line treatment. **Acute active life-threatening bleeding and surgery** • Platelet transfusions. Platelet transfusions are only indicated in acute active bleeding uncontrolled by other means or before procedures. In an adult, 1 unit of platelets, preferably single donor, leucocyte depleted platelets, is usually sufficient to control the bleeding initially. Platelet transfusions have limited benefit in this condition as platelets are rapidly destroyed by the immune system. • Methylprednisolone acetate 1 g, IV, daily for 3 days. If the bleeding cannot be controlled, consult with a specialist.	○ In an adult, 1 unit of platelets (preferably single donor, leucocyte depleted) is usually sufficient to control the bleeding initially. ○ Platelet transfusions have limited benefit in this condition as platelets are rapidly destroyed by the immune system. • Methylprednisolone acetate 1 g, IV, daily for 3 days. **REFERRAL** » All cases not responding to steroids that require second line treatment - Consult haematologist. » All PLHIV who are not responding to ART - Consult haematologist

2.8 VENOUS THROMBO-EMBOLISM

Bemiparin, parenteral: not *added as a member of the LMWH therapeutic class*
Bemiparin is not currently registered with SAHPRA, and it was recommended that a review not be completed until such time that there is regulatory approval.

2.8.1 VENOUS THROMBO-EMBOLISM - PROPHYLAXIS

Risk Assessment
Risk assessment – pre-disposing risk factors: *Added*
Risk assessment – models for assessing VTE risk*: Deleted*
Risk assessment – exposing risk factors: *Amended*
A list of pre-disposing risk factors for venous thrombo-embolism[20], has been included in the STG as tabulated below and is separate to exposing risk factors. This table replaces the url links to other risk assessment models that were included in the STG for assessing VTE risk.

'*Other conditions associated with debilitating illness'* has been added as an additional category of medical patients in the high VTE risk group. This Risks Assessment adapted from the publication by Jacobson BF et al[21], has been modified to accommodate for patients hospitalised due to medical illnesses at high risk of VTE.

AMENDED FROM:
MEDICINE TREATMENT
PROPHYLAXIS
Risk Assesement
Risk assessment is essential, and treatment needs to be individualised. Risk factors for VTE can be divided into predisposing factors (i.e. patient characteristics) and exposing factors (i.e. underlying medical conditions, nature of surgical intervention, etc.).

SUBCATEGORIES OF VTE RISK IN SURGICAL AND NON-SURGICAL PATIENTS

	Surgical patients	***Medical patients***

AMENDED TO:
MEDICINE TREATMENT
Risk Assessement
Risk assessment is essential, and treatment needs to be individualised. Risk factors for VTE can be divided into predisposing factors (i.e. patient characteristics) and exposing factors (i.e. underlying medical conditions, nature of surgical intervention).

Predisposing risk factors	
Thrombophilia	Advanced age (>60 years)
History of VTE	Chronic cardiac insufficiency

[20] Jacobson BF, Louw S, Büller H, Mer M, de Jong PR, Rowji P, Schapkaitz E, Adler D, Beeton A, Hsu HC, Wessels P, Haas S; South African Society of Thrombosis and Haemostasis. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013 Feb 15;103(4 Pt 2):261-7. https://www.ncbi.nlm.nih.gov/pubmed/23547704
[21] Jacobson BF, Louw S, Büller H, Mer M, de Jong PR, Rowji P, Schapkaitz E, Adler D, Beeton A, Hsu HC, Wessels P, Haas S; South African Society of Thrombosis and Haemostasis. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013 Feb 15;103(4 Pt 2):261-7. https://www.ncbi.nlm.nih.gov/pubmed/23547704

Low VTE risk	» Surgery lasting <30 minutes » Injuries without or with only minor soft-tissue trauma » No or only minor additional predisposing risk factors	» Infection or acute inflammatory diseases without bed rest » Central venous catheters » No or only minor additional predisposing risk factors
Moderate VTE risk	» Surgical procedures of longer duration » Immobilisation of lower limb with plaster cast » Lower limb arthroscopic procedures. » No or only minor additional predisposing risk factors	» Acute cardiac insufficiency (NYHA III/IV) » Acute decompensated COPD without ventilation » Infection or acute inflammatory diseases with bed rest » Malignant disease » No or only minor additional predisposing risk factors
High VTE risk	» Major surgical procedures for malignancy » Multiple trauma or severe trauma of the spine, vertebra or » lower limbs » Major orthopaedic surgery, e.g. hip or knee replacement » Major surgical procedure of cardiothoracic and pelvic region	» Stroke with paralysis » Acute decompensated COPD with ventilation » Sepsis » ICU patients

Source: Jacobson BF, Louw S, Büller H, Mer M, de Jong PR, Rowji P, Schapkaitz E, Adler D, Beeton A, Hsu HC, Wessels P, Haas S; South African Society of Thrombosis and Haemostasis. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013 Feb 15;103(4 Pt 2):261-7.
https://www.ncbi.nlm.nih.gov/pubmed/23547704

Some risk assesement models for assessing VTE risk:

Model	Url link to tool
Padua Prediction Score	https://www.mdcalc.com/padua-prediction-score-risk-vte
IMPROVE VTE risk score	https://www.outcomes-umassmed.org/IMPROVE/risk_score/vte/index.html
Geneva risk score	https://www.mdcalc.com/geneva-risk-score-venous-thromboembolism-vte-prophylaxis

Malignancy	Obesity (BMI > 30 kg/m^2)
Drugs, e.g. TB treatment, thalidomide	Oestrogen therapy
HIV infection	Nephrotic syndrome
Auto-immune disease	Varicose veins

Exposing risk factors

Risk level	Surgical patients	Medical patients
Low VTE risk	» Surgery lasting <30 minutes » Injuries without or with only minor soft-tissue trauma » No or only minor additional predisposing risk factors	» Infection or acute inflammatory diseases without bed rest » Central venous catheters » No or only minor additional predisposing risk factors
Moderate VTE risk	» Surgical procedures of longer duration » Immobilisation of lower limb with plaster cast » Lower limb arthroscopic procedures » No or only minor additional predisposing risk factors	» Acute cardiac insufficiency (NYHA III/IV) » Acute decompensated COPD without ventilation » Infection or acute inflammatory diseases with bed rest » Malignant disease » No or only minor additional predisposing risk factors
High VTE risk	» Major surgical procedures for malignancy » Multiple trauma or severe trauma of the spine, vertebra or lower limbs » Major orthopaedic surgery, e.g. hip or knee replacement » Major surgical procedure in cardiothoracic and/or pelvic region	» Stroke with paralysis » Acute decompensated COPD with ventilation » Sepsis » ICU patients » Other conditions associated with debilitating illness

Prophylaxis

DOACs, oral: *Added*

Refer to the medicine review: *DOACs for the prevention of VTE in hospitalised adult patients), and the associated budget impact analysis*[22] which may be found at the end of this report or on the NHI webpage. A summary of the recommendation is as follows:

[22] NDoH evidence review. DOACs Prevention of DVT-AdultHospReview_12 Oct 2023_v6.0_final approved

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X
Recommendation: Based on this evidence review, the PHC/Adult Hospital Level Committee recommends that direct oral anticoagulants (DOACs) be used 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. **(Strong: No difference in benefits with trivial increase in major bleeding offset by projected major cost-savings)** *Rationale: There is clear evidence of non-inferiority of DOACs (rivaroxaban and apixaban) compared to LMWH for preventing VTE in the above patient populations. In medically ill, hospitalised, adult patients requiring VTE prophylaxis, there was a trivial increase in major bleeding that does not translate into increased mortality and is offset by major cost-savings. Major cost-savings are specific to rivaroxaban at the current contract price, and this recommendation is therefore specific to rivaroxaban within the DOAC class.* **Level of Evidence:** *Moderate to high certainty* **Review indicator: High quality evidence of a clinically relevant benefit or reduction of harms; new cost data for rivaroxaban, apixaban or LMWH**					
NEMLC RECOMMENDATION (12 October 2023): NEMLC supported the ERC's recommendation on 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).					
Monitoring and evaluation considerations					
Research priorities					

Use of DOACs in patients with renal impairment:

External comment received to include guidance for dosing of rivaroxaban for VTE prophylaxis in patients with renal dysfunction. As the studies evaluated in our review excluded participants with an eGFR< 30mls/min; and the professional information leaflet suggests 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 aeGFR<30ml/min/1.73m^2.

Use of DOACs in obese patients:

External comment received to include guidance on the use of DOACs in obese patients. Due to limited data on the safety and efficacy for the use 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.

Aspirin: *Added*

Refer to the medicine review: Aspirin vs LMWH for the prevention of VTE in surgical patients[23], included below or accessible on the NHI webpage for more details. A summary of the NEMLC recommendation is included below:

[23] NDoH evidence summary. Aspirin vs LMWH prevention of VTE in surgical patients_12 Oct 2023 v1.0_final approved

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				x	
Recommendation: We recommend 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. *Rationale: There is no difference in incidence of death, pulmonary embolism or major bleeding between VTE prophylaxis with aspirin compared with enoxaparin. In addition, the increased risk of DVT with use of aspirin is trivial and does not translate into increased risk of pulmonary embolus or death. The cost incurred by the additional cases of DVT are likely to be far-surpassed by the major cost savings of using aspirin over enoxaparin.* **Level of Evidence: moderate** **Review indicator: New data on the efficacy and/or safety**				
NEMLC RECOMMENDATION (MEETING OF 12 October 2023): NEMLC supported the recommendation pending the editorial amendments as discussed. The EML should include guidance on risk stratification and the STG recommendation for the use of aspirin for VTE prophylaxis should be aligned to the population as specified in the PICO.					
Monitoring and evaluation considerations: A formal cost-analysis maybe performed to quantify the extent of the potential savings.					
Research priorities					

Furthermore, refer to the guideline adaptation of NICE Guideline: "Venous thromboembolism in over 16s" for patients undergoing total hip arthroplasty or total knee arthroplasty requiring venous thromboembolism prophylaxis[24], included at the end of this report or accessible on the NHI webpage. A summary of the NEMLC recommendation is tabulated below:

[24] NDoH evidence summary. Adaptation of NICE Guideline "Venous thromboembolism in over 16s" for patients undergoing total hip arthroplasty or total knee arthroplasty requiring venous thromboembolism prophylaxis. November 2023. Version 1.0_30 Nov 2023_final

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: We recommend 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.

For elective hip arthroplasty, we recommend:

Rivaroxaban 10mg daily initiated 6-10 hours post operatively for 10 days, followed by aspirin 150mg for 28 days on discharge

For elective knee arthroplasty, we recommend:

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: The NEMLC has previously made the recommendation for rivaroxaban over LMWH based on non-inferior efficacy and safety and improved cost-effectiveness of rivaroxaban for VTE prophylaxis. The NICE guideline found that there was no difference in efficacy or safety between aspirin monotherapy in knee arthroplasty or enoxaparin followed by aspirin in hip arthroplasty, compared with low molecular weight heparin monotherapy for VTE prophylaxis. Together with good evidence of efficacy and safety with use of rivaroxaban, NICE suggests any of these three treatment options at the clinician's discretion (aspirin monotherapy/enoxaparin followed by aspirin, enoxaparin monotherapy or rivaroxaban monotherapy). Our adaptation of these guidelines involved replacing the 10 days of enoxaparin preceding aspirin in total hip arthroplasty patients with rivaroxaban for cost-saving reasons, and our choice to use rivaroxaban in the initial post-operative period followed by aspirin in total knee arthroplasty patients was to mitigate the potential bleeding risk associated with aspirin identified in hip arthroplasty patients.

Level of Evidence: adaptation of a high quality guideline based on low certainty evidence
Review indicator: New data on the efficacy and/or safety of aspirin in VTE prophylaxis for arthroplasty patients.

NEMLC RECOMMENDATION (MEETING OF 30 November 2023): NEMLC supports the ERC recommendation as stated above.

Monitoring and evaluation considerations:

Research priorities

Surgical prophylaxis in patients on pre-existing aspirin prophylaxis for CV indications:
External comment received to include guidance on the use of aspirin for surgical patients on pre-existing aspirin prophylaxis for CV-related conditions. The EML recommends the use of aspirin for VTE prophylaxis in orthopaedic surgical patients with trauma-related i) operative extremity fractures or ii) operative or non-operative pelvic and acetabular fractures – these trauma-related fractures present primarily in younger patients in South Africa who are unlikely to be on aspirin prophylaxis. Exceptional cases would need to be managed on a per patient basis.

Enoxaparin, parenteral: *directions for use amended*
Directions for use was amended to include dosing in patients with renal impairment, aligned with SAMF, 2022.
Level of Evidence: IVb Guidelines

STG guidance for VTE prophylaxis and treatment has been separated into Sections 2.8.1 and Section 2.8.2. Updates to the STG for VTE prophylaxis, are as tabulated below:

AMENDED FROM:	**AMENDED TO:**
Prophylactic treatment Prophylaxis is indicated for medical patients with moderate to high risk of VTE (see table above), with restricted mobility during acute illness/ surgical patients. ▪ Low molecular weight heparin, e.g.: • Enoxaparin, SC, 40 mg daily. In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist.	**For patients hospitalised due to medical illnesses at high risk of VTE:** • Rivaroxaban, oral, 10 mg daily while hospitalised. **For patients hospitalised due to medical illnesses and in whom rivaroxaban is contraindicated (see summary table below):** ▪ Low molecular weight heparin, e.g.: • Enoxaparin, SC, 40 mg daily.

In renal failure (eGFR <30 mL/minute), the recommended dose of LMWH is 1 mg/kg daily. **OR** Unfractionated heparin, SC, 5 000 units 12 hourly.	○ In morbid obesity, dosing of LMWH should be individualised, in discussion with a specialist. ○ Renal impairment (eGFR <30 mL/min): adjust dose to 20 mg daily. **OR** Unfractionated heparin, SC, 5 000 units 12 hourly. ○ Dose adjustment is generally not required for renal impairment. ○ Monitor for bleeding complications. **For orthopaedic surgical patients with trauma-related i) operative extremity fractures or ii) operative and non-operative pelvic and acetabular fractures:** <u>Low to moderate risk of VTE:</u> • Aspirin, oral, 150 mg daily. ○ Initiate aspirin >12 hours post-operatively and continue for 14 days or until mobilisation. ○ In patients with non-operative pelvic and acetabular fractures, prophylaxis can be continued for up to 35 days. <u>High risk of VTE:</u> ▪ Low molecular weight heparin, e.g.: • Enoxaparin, SC, 40 mg daily. ○ In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist. ○ Renal impairment (eGFR <30 mL/min): adjust dose to 20 mg daily. ○ In patients with non-operative pelvic and acetabular fractures, prophylaxis can be continued for up to 35 days. In the absence of clear evidence of VTE risk or on earlier discharge from hospital, discontinuation prior to 35 days should be considered. **For elective total hip arthroplasty:** • Rivaroxaban, oral, 10 mg daily. ○ Initated 6–10 hours post-surgery for duration of admission or a maximum of 10 days. <u>Following rivaroxaban, prescribe aspirin:</u> • Aspirin, oral, 150 mg daily for 28 days on discharge from hospital. **For elective total knee arthroplasty:** Total duration of prophylactic therapy: 14 days • Rivaroxaban, oral, 10 mg daily. ○ Initiate anticoagulation 6–10 hours post-surgery for the duration of hospital admission for a minimum of 2 days and a maximum of 7 days. <u>Following rivaroxaban, prescribe aspirin:</u> • Aspirin, oral 150 mg daily. ○ Treat with aspirin for remainder of VTE prophylaxis period, i.e. 14 days in total including days on rivaroxaban. **For i) other surgical patients, or ii) orthopaedic surgical patients with a contraindication to aspirin or rivaroxaban:** ▪ Low molecular weight heparin, e.g.: • Enoxaparin, SC, 40 mg daily. ○ In morbid obesity, dosing of LMWH should be individualised, in discussion with a specialist. ○ Renal impairment (eGFR <30 mL/min): adjust dose to 20 mg daily. **OR** Unfractionated heparin, SC, 5 000 units 12 hourly. ○ Dose adjustment generally not required for renal impairment. ○ Monitor for bleeding complications.

Although the risk of bleeding is small, in the following patients prophylaxis should only be used under exceptional circumstances:

» active bleeding
» intraocular, intracranial or spinal surgery
» lumbar puncture or spinal/epidural anaesthesia within 12 hours after prophylactic dose or 24 hours of full therapeutic dose, [Timing of anticoagulants for patients receiving anaesthesia: See section 12.8: Spinal (intrathecal) anaesthesia]
» renal insufficiency
» coagulopathy
» uncontrolled hypertension

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	<u>Low to moderate risk of VTE:</u> Aspirin, oral, 150 mg daily. <u>High risk of VTE:</u> Enoxaparin, SC, 40 mg daily.	From >12 hours post-operatively, for 14 days or until mobilisation.
	Trauma-related **non-operative** pelvic and acetabular fractures	<u>Low-moderate risk of VTE:</u> Aspirin, oral, 150 mg daily. <u>High risk of VTE:</u> 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 2.5: Summary of VTE prophylaxis in surgical and non-surgical patients

Although the risk of bleeding is small, prophylaxis should only be used under exceptional circumstances in patients with the following conditions:

» Active bleeding or high risk of active bleeding (eg. severe liver disease; peptic ulcer disease).
» Intraocular, intracranial or spinal surgery.
» Patients requiring lumbar puncture or spinal/epidural anaesthesia within 24 hours of rivaroxaban dose, within 12 hours of enoxaparin when used as prophylaxis, or within 24 hours of enoxaparin when used at therapeutic doses. For timing of anticoagulants – See Section 12.7.1: Anticoagulants and spinal or epidural blocks.
» Renal insufficiency: Rivaroxaban not recommended if eGFR<30ml/min; enoxaparin requires renal dose adjustment.
» Coagulopathy
» Uncontrolled hypertension
» Concomitant anticoagulations or antiplatelet therapy

Additional contraindications to rivaroxaban not covered above:

Patient populations	Comorbidities	Drug interactions
Pregnancy Lactation Minors (<18 years of age) Patient weight >120 kg or BMI >40 kg/m^2 Age >65 years[†]	Known rivaroxaban hypersensitivity Antiphospholipid syndrome (persistent, triple positive) Previous bronchiectasis, pulmonary cavitation, or pulmonary haemorrhage Active malignancy[‡]	Drugs that ↑ rivaroxaban: Ketoconazole, Ritonavir Drugs that ↓ rivaroxaban: Phenytoin, carbamazepine, rifampicin, St. John's Wort

Therapeutic Interchange database

The following updates to the therapeutic interchange database were supported by the Committee:

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

2.8.2 VENOUS THROMBO-EMBOLISM – ACUTE TREATMENT

DOACs, oral: *Added*

Refer to the medicine review: DOACs for the treatment of VTE and the associated budget impact analysis[25], included at the end of this report or alternatively accessible on the NHI webpage. A summary of the NEMLC recommendation is as follows:

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X
Recommendation: Based on this evidence review and the supporting economic analysis, the PHC/Adult Hospital Level Committee 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. (see Table 2 below) **Level of Evidence: Benefit: Moderate certainty ; Safety: High certainty** **Review indicator:** New evidence of harms, change in price of LMWH; rivaroxaban or other DOACs (dabigatran, apixaban)					
NEMLC RECOMMENDATION (30 NOVEMBER 2023): NEMLC ratified the updated ERC recommendation in support of the use of rivaroxaban for the treatment of VTE as stated above.					
Monitoring and evaluation considerations:					
Research priorities:					

The STG for the management of VTE has been re-written in line with the recommendations from the evidence summaries detailed above. The STG has been separated into Section 2.8.1 Venous thromboembolism – prophylaxis and Section 2.8.2 Venous thromboembolism – acute treatment.

AMENDED FROM:

ACUTE TREATMENT

Unfractionated or low molecular weight heparin started simultaneously with_warfarin. After 5 days, heparin may be stopped if a therapeutic INR level has been reached and maintained for at least 24 hours.

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

For proximal deep venous thrombosis and/or pulmonary embolism:

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 1.5 mg/kg daily,
  or
  1 mg/kg 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 dose of LMWH is 1 mg/kg daily.

OR

Unfractionated heparin, SC, 333 units/kg as an initial dose.

- Follow 12 hours later by 250 units/kg/dose 12 hourly.

Units of unfractionated heparin			Volume of heparin in mL (25 000 units/mL)	
Weight (kg)	Loading dose (units)	12 hourly dose (units)	Loading dose (mL)	12 hourly dose (mL)
35 kg	11 000 units	8 750 units	0.44 mL	0.35 mL

AMENDED TO:

MEDICINE TREATMENT

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.

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

» 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,
OR
Enoxaparin, SC, 1 mg/kg 12 hourly.

CAUTION – Enoxaparin

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

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

[25] NDoH evidence summary. DOACS: Treatment of DVT&PE_Adults_v6.0_30 November 2023_final

40 kg	13 000 units	10 000 units	0.52 mL	0.4 mL
45 kg	15 000 units	11 250 units	0.6 mL	0.45 mL
50 kg	17 000 units	12 500 units	0.67 mL	0.5 mL
55 kg	18 000 units	13 750 units	0.73 mL	0.55 mL
60 kg	20 000 units	15 000 units	0.8 mL	0.6 mL
65 kg	22 000 units	16 250 units	0.87 mL	0.65 mL
70 kg	23 000 units	17 500 units	0.93 mL	0.7 mL
75 kg	25 000 units	18 750 units	1 mL	0.75 mL
80 kg	27 000 units	20 000 units	1.07 mL	0.8 mL
85 kg	28 000 units	21 250 units	1.13 mL	0.85 mL
90 kg	30 000 units	22 500 units	1.2 mL	0.9 mL

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.

Follow with:
Warfarin, oral, 5 mg daily.

- INR should be done after 48 hours, then every 1 to 2 days until within the therapeutic range of 2 to 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).
- Continue warfarin for 3 months with regular INR monitoring if there was a precipitating cause that has resolved.
- In patients with a first unprovoked DVT, discuss duration of therapy with a specialist.
- Contraindications for warfarin: first trimester and the last month of pregnancy. In these instances, replace with heparin.
- 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.

Heparin induced thrombocytopenia
A severe immune-mediated drug reaction occurring in 1–5% of patients receiving heparin (more common with unfractionated heparin, but may also occur with low molecular weight heparin) therapy. It presents with thrombocytopenia and thrombosis. Diagnosis needs 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. Confirmation is done by positive antibody testing.
Stop heparin and discuss all patients with a specialist.

REFERRAL/CONSULTATION
Heparin-induced thrombocytopenia.

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.

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).
- 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).
- 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.

<u>Management of HIT:</u>
Stop heparin and discuss all patients with a specialist.

REFERRAL/CONSULTATION
» All patients with heparin induced thrombocytopaenia

Therapeutic Interchange database

The following updates to the therapeutic interchange database were supported by the Committee:

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

2.8.3 VENOUS THROMBOEMBOLISM (VTE) DURING PREGNANCY AND THE PUERPERIUM

New STG added - refer to the text box below: 2.8.1 VTE during pregnancy and the puerperium. For a more detailed review of the evidence refer to the medicine review: *The use of low molecular weight heparins (LMWH) for secondary venous thromboembolism (VTE) prophylaxis during pregnancy and the puerperium and comparative cost analysis of anticoagulants (LMWH/warfarin) as secondary VTE prophylaxis in pregnancy*[26]*,* included at the end of this report or accessible on the NHI webpage. A summary of the NEMLC recommendation is tabulated below:

Conclusion

- 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.

Budget impact analysis:

Refer to the costing analysis report: Comparative cost analysis of anticoagulants (LMWH/warfarin) as secondary VTE prophylaxis in pregnancy, 22 November 2022.

NEMLC RECOMMENDATION – MEETING OF 8 DECEMBER 2022:

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.

Enoxaparin dosing in pregnant patients: External comment received on the recommended doses of enoxaparin for VTE prophylaxis in pregnant patients. The EML recommendation for a prophylactic dose of 40mg daily in pregnant patients weighing less than 100kg and 60mg daily for patients weighing 100kg or more is informed by RCT data from Bistervels 2022.[27] This recommendation is supported by the NEMLC as this two tier weight-based dose band is simpler than the multiple tiers included in the RCOG guidelines[28] (refer to the associated evidence summary[29] for more detailed information).

[26] NDoH evidence summary. LMWH_secondaryVTEprophylaxisInPregnancy_EvidenceSummary_November2022_v0.2_Final

[27] Bistervels IM, Buchmüller A, Wiegers HMG, Ní Áinle F, Tardy B, Donnelly J, et al. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow study): an open-label, multicentre, randomised, controlled trial. Lancet. 2022 Nov 19;400(10365):1777–87.

[28] Royal College of Obstetricians and Gynaecologists (RCOG). Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green Top Guideline No. 37a. April 2015.

[29] NDoH evidence summary. LMWH_secondaryVTEprophylaxisInPregnancy_EvidenceSummary_November2022_v0.2_Final

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/m^2 » 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/m^2 » 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.

APPENDIX II: PRESCRIBING INFORMATION FOR SPECIFIC MEDICINES

Warfarin, oral: *amended*

Interaction with cruciferous vegetables added to STG text, and the following additional editorial amendment was made, aligned with SAMF, 2022 edition:

Frequency of INR monitoring for maintenance of warfarin	
Check INR	
Every 3–5 days	If start/stop an interacting medication, if dose required adjustment by 5–10%; if change in diet, change in activity level or other change that could affect INR
Every 1–2 weeks	Once INR within therapeutic range on 2 consecutive INR checks
Every 4 weeks	If maintained on same stable dose < 6 months and INR stable
Every 6–8 weeks	If maintained on same stable dose ≥ 6 months and INR stable

Warfarin oral: A*mended*

Refer to section 3.3.1.1 Atrial fibrillation of the NEMLC report for the Adult Hospital cardiovascular chapter 3 for updated guidance on management with warfarin.

South African National Department of Health
Brief Report of Rapid Review
Component: Subcommittee for Haemophilia

TITLE: Prophylactic Factor VIII compared to on-demand treatment for patients (adults and children) with haemophilia A without inhibitors

Date: June 2023

UPDATE: This document serves as an update to the medicine review conducted previously, on individuals under the age of 18 years only, which was presented to the NEMLC in October 2022 by the Paediatric Hospital Level Expert Review Committee. The update extends the population group to include both children and adults.

Key findings

- Current South African standard of care for severe haemophilia A patients is treatment of bleeding on-demand with blood factor VIII. A potential alternative is blood factor VIII prophylaxis.
- We conducted a rapid review of systematic reviews, meta-analyses and clinical trials reporting on the efficacy and safety of factor VIII prophylaxis for patients with severe haemophilia A.
- In August 2022, a literature search was conducted using PubMed, Cochrane Database and Epistemonikos. Three systematic reviews were found. One study which most closely matched our PICO and country context was selected for data extraction. **An updated search in February 2023 extending inclusion to patients of all ages found no other studies which matched the PICO question.**
- Most studies included in the systematic review had small samples sizes and overall, the evidence was reported as very low certainty.
- Low dose blood factor VIII prophylaxis (10IU/kg twice weekly) versus on-demand treatment:
  - Total annualised bleeds; 2 RCTs found a significantly smaller number of mean bleeds per annum in the low dose prophylaxis groups (Ratio of means: 0.27, 95% CI 0.17 to 0.43; P < 0.00001; 2 RCTS; n=71; 2 RCTs, n=71, very low quality).
  - Annualised joint bleeds; 2 RCTs found a significantly smaller number of mean joint bleeds per annum in the low dose prophylaxis groups (Ratio of means: 0.17, 95% CI 0.06 to 0.43; P=0.0002; 2 RCTs, n=71, very low quality).
- Intermediate dose blood factor VIII prophylaxis (20-30 IU/Kg twice or thrice weekly) versus on-demand treatment
  - Total annualised bleeds; 4 RCTs found a significantly smaller number of mean bleeds per annum in the intermediate dose prophylaxis groups (Ratio of means: 0.15, 95% CI 0.07 to 0.36; P < 0.00001; 4 RCTs, n=237, very low quality).
  - Annualised joint bleeds; 2 RCTs found a significantly smaller number of mean joint bleeds per annum in the intermediate dose prophylaxis groups (Ratio of means: 0.14 – reduction of 86% in bleeds per annum, 95% CI 0.07 to 0.27; 4 RCTs, n=237, very low quality).
- Adverse events were reported in two studies; one RCT reported no difference in development of inhibitors. Two RCTS reported on central venous access device related infections; one RCT reported more infections in the prophylaxis group however no devices were inserted in the on-demand group and another RCT reported no difference between groups (p values not reported for both RCTs).
- Low and intermediate dose factor VIII prophylaxis are potentially more cost saving than treating bleeds on-demand when considering drug acquisition costs of factor VIII only (base case – intermediate prophylaxis). Scenarios including treatment of minor bleeds only found that low and intermediate dose prophylaxis may be more effective but incrementally more costly than treatment on demand. Intermediate dose factor VIII prophylaxis was estimated to be more cost saving than low dose prophylaxis.
- *See Summary of Findings Table*

SUBCOMMITTEE FOR HAEMAPHILIA RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Rationale: The Committee suggests using intermediate factor VIII prophylaxis for severe haemophilia A patients without inhibitors. There is very low certainty evidence to suggest that low dose and intermediate dose factor VIII prophylaxis therapies are more effective than treatment on-demand for patients with haemophilia A. Basic cost-effectiveness analysis shows low and intermediate dose prophylaxis are potentially more cost-saving than treatment on demand if only considering acquisition costs of factor VIII. Sensitivity scenarios which accounted only for treatment of minor bleeds (and not major or life-threatening bleeds) showed that low and intermediate dose prophylaxis were more effective but more costly than treatment on demand. The analysis did not account for quality of life, mortality, cost of surgeries or long-term complications. Intermediate dose prophylaxis is potentially more effective and may have higher cost savings than low dose prophylaxis.

Level of Evidence: Level 1 – systematic review, very low certainty of evidence for low dose prophylaxis, low certainty of evidence for intermediate.
Review Indicator: Evidence of harm, cost-effectiveness, cost savings, agent price.

(Refer to appendix 1 for the evidence to decision framework)

Monitoring and evaluation considerations	Monitoring is compulsory, details regarding implementation to be determined for each relevant Standard Treatment Guidelines

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NEMLC RECOMMENDATION (20 JULY 2023):

The NEMLC accepted the haemophilia subcommittee recommendation for factor VIII prophylaxis for patients with severe haemophilia A and the relevant updates to the Adult and Paediatric Hospital Level Standard Treatment Guidelines.

Summary of findings Table – From Delgado-Flores et al. (2022)[1]

Low Dose Prophylaxis vs On-Demand Treatment

Table 2. Summary of findings for episodic treatment vs prophylaxis (either low, intermediate, or high dose).

Outcomes (follow-up in months)	of participants (studies)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)
		Risk with Control	Risk with Intervention		
Episodic treatment (control) vs Low-dose prophylaxis (intervention)					
Annualized bleeding rate (12 m)	71 (2 RCTs)	Range of means: 9.4–25.3	Range of means: 2.2–7.7	RM 0.27 (0.17 to 0.43)	⊕◯◯◯ VERY LOW [a,d]
Annualized joint bleeding rate (12 m)	71 (2 RCTs)	Range of means: 5.8–10.3	Range of means: 1.0–1.8	RM 0.17 (0.06 to 0.43)	⊕◯◯◯ VERY LOW [a,d]
Change in the Hemophilia joint health score-2.1 (HJHS-2.1). Range: 0 to 124. Higher score = worst (12 m)	66 (2 RCTs)	• **Verma 2016** Low-dose prophylaxis: median change of 0 points. Episodic treatment: median change of 4.5 points ($p<0.05$). • **Chozie 2019** Low-dose prophylaxis: median change of -1 points. Episodic treatment: median change of 2 points ($p<0.001$).			⊕◯◯◯ VERY LOW [a,d]

Intermediate Dose Prophylaxis vs On-Demand Treatment

Outcomes (follow-up in months)	of participants (studies)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)
		Risk with Control	Risk with Intervention		
Episodic treatment (control) vs Intermediate-dose prophylaxis (intervention)					
Annualized bleeding rate (12.0 to 82.5 m)	237 (4 RCTs)	Range of means: 13.0–57.7	Range of means: 2.5–6.2	RM 0.15 (0.07 to 0.36)	⊕◯◯◯ VERY LOW [a,b,c]
Annualized joint bleeding rate (12.0 to 82.5 m)	237 (4 RCTs)	Range of means: 4.9–43.8	Range of means: 0.6–5.2	RM 0.14 (0.07 to 0.27)	⊕◯◯◯ VERY LOW [a,b,c]
Radiographic findings (49.0 to 82.5 m)	95 (2 RCTs)	413 per 1000	149 per 1000	RR 0.36 (0.18 to 0.71)	⊕◯◯◯ VERY LOW [a,d]

Quality of life (36.0 to 82.5 m)	123 (2 RCTs)	• **Gringeri 2011 (82.5 months):** Score in the "family" dimension of the Haemo-QoL scale was lower (better) in patients with intermediate-dose prophylaxis (mean: 11.3) than in those with episodic treatment (mean 44.0), $p<0.05$.
		• **Manco-Johnson 2017 (36 months):**
		  • Mean change in the score of the Haemo-QoL-A: Intermediate-dose prophylaxis group: 3.98 points. Episodic treatment: 6.00 points ($p = 0.27$).
		  • Mean change in the score of the EQ VAS (higher = better): Intermediate-dose prophylaxis: 10.49 points. Episodic treatment: −1.80 points. No p-value provided.
		  • Mean change in the EQ-5D utility index score (higher = better): Intermediate-dose prophylaxis: 0.06 points. Episodic treatment: −0.01 points. No p-value provided.
					⊕◯◯◯ VERY LOW [a,d]

Adverse events (12.0 to 82.5 m)	154 (3 RCTs)	• **Gringeri 2011:**
		  • Inhibitors developing: 3/21 patients in the prophylaxis group and 2/19 in the episodic group.
		  • CVAD-related infection: 6/20 patient in the prophylaxis group, and 0/19 in the episodic group (no indwelling catheters required).
		• **Manco-Johnson 2007** reported that 6/32 patients had CVAD-related infection in the prophylaxis group and 6/33 in the episodic group.
					⊕◯◯◯ VERY LOW [a,d]

CI: Confidence interval; **yr**: years **RM**: ratio of means; **RR**: Risk ratio; **Haemo-QoL**: Hemophilia quality of life questionnaire for children; **Haemo-QoL-A**: Hemophilia-specific quality of life questionnaire for adults; **EQ VAS**: EuroQol visual analogue scale; **SD**: Standard deviation; **CVAD**: Central venous access device-related infections.

Explanations

[a]. We rated down one level for risk of bias.

[b]. We rated down one level for imprecision due to the small number of participants that presented the outcome (200–400).

[c]. We rated down one level for inconsistency ($I^2 > 70\%$).

[d]. We rated down two levels for imprecision due to the small number of participants that presented the outcome (less than 200)

[e]. We rated down one level for publication bias.

clotting factor VIII resulting in abnormal bleeding. Severe haemophilia A is categorised by a factor VIII

level of less than 1% of normal. Patients with severe haemophilia A can experience spontaneous and/or life-threatening bleeds.[1,2] The current standard of care in the South African public health sector for patients with haemophilia A is treatment with blood factor VIII on demand (for bleeds or pre-surgery)[i]. An alternative is preventive treatment with blood factor prophylaxis which is recommended by in the World Federation of Hemophilia guidelines.[3] Uncontrolled bleeds may lead to mortality and disability leading to lower quality of life and absenteeism[4]. Despite prophylactic factor VIII recommendations in international guidelines, a barrier to implementation in LMICs is affordability. However recent trials conducted in LMICs have been conducted exploring lower doses of Factor VIII prophylaxis[5,6]. The delays in obtaining 'on demand' treatment due to lack of immediate transport capacity to reach health care facilities results in poorer outcomes, increased requirement for factor VIII replacement and the development of inhibitors[7]. The latter is associated with marked increase in cost to treat future bleeds.

This document serves as an update to the medicine review, conducted previously on individuals under the age of 18 years only, which was presented to the NEMLC in October 2022 by the Paediatric Hospital Level Expert Review Committee. The NEMLC recommended that a group be formed to address haemophilia across ages and the levels of care. As such the Haemophilia Subcommittee was established. This medicine review has been updated to include evidence and costing across all ages.

RESEARCH QUESTION

For patients, **of all ages**, with haemophilia A without inhibitors, how effective is Factor VIII prophylaxis compared to treatment of bleeds on demand with Factor VIII? Table 1 outlines the scope of the review.

Table 1. Scope of the technical review

Population 1	Haemophilia A patients **of all ages** without inhibitors (Includes patients who have been previously treated or untreated, patients with mild, moderate or severe haemophilia, patient with or without joint damage, and patients who have or haven't experienced their first bleed)
Intervention/s and comparisons	Intervention: Factor VIII prophylaxis weekly, twice weekly or three times weekly Comparator: Treatment of bleeds on demand with factor VIII
Outcomes	**Efficacy** - Frequency of any bleeds per year - Frequency of minor bleeding episodes per year - Frequency of major bleeding episodes per year - Clotting factor concentrate levels in plasma (mean difference) - Joint assessment (Orthopaedic joint score or clinical joint function or radiological assessment) **Safety** - Mortality - Serious adverse events / effects - Adverse events / effects **Quality of Life** - Quality of life on validated scales (disease-specific where possible)
Study designs	Systematic reviews, Randomised controlled trials

METHODS

A search was conducted in Cochrane Library, PubMed and Epistemonikos databases focusing on systematic reviews of RCTs in 2022. The search strategies for the systematic literature searches are detailed in Appendix 2. Disagreements regarding exclusion and inclusion of studies were handled through discussion (KM, AH, JR). Data from included studies were extracted and analysed (KM & AH). An AMSTAR 2 was conducted independently and in duplicate on the selected systematic review (AH and KM). In addition, both AH and KM reviewed the GRADE of included systematic reviews. Where

[i] Paediatric Hospital Level Standard Treatment Guidelines, Blood and Blood Forming Organs Chapter

multiple eligible SRs were included, we reported evidence from the most relevant, recent and high-quality review or reviews in order to provide evidence across all a priori outcomes. Relevant study data were extracted into a narrative table of results. **The original search strategy was not limited by population thus the search was rerun in February 2023. Search results were reassessed considering the expanded population (KM & JR).**

RESULTS

The search for systematic reviews resulted in 50 articles. After screening, 40 articles were excluded (including five duplicates). Full text review of articles resulted in the exclusion of 7 studies (Appendix 3 shows the excluded studies). **No new studies emerged from the search update**. The three remaining systematic reviews had slightly different PICOs (see Appendix 4). Included and excluded studies in each systematic review were explored for overlaps and gaps. After discussion between the reviewers and members of the Paediatric Hospital Level ERC, it was agreed that the Delgado-Flores *et al*. (2022)[1] systematic review most closely met the medicine review PICO and included trials from LMICs which utilised low dose prophylaxis regimens. In addition, the Delgado-Flores et al study (2022)[1] also included all the relevant studies included in the Iorio *et al*. (2011)[8] and Olasupo *et al*. (2021)[2] reviews. **The studies were re-evaluated during the update and after discussion with the Haemophilia subcommittee it as agreed that Delgado-Flores *et al*. systematic review (2022) still best matched the PICO question.** Data was extracted from the Delgado-Flores et al. (2022)[1] systematic review (see appendix for included studies in Delgado-Flores 2022) and an AMSTAR 2 assessment conducted to assess overall quality.

Internal validity of the systematic reviews

AMSTAR II was used to determine the internal validity of included SRs (Appendix 6). In an effort to reduce duplication of effort in synthesis, we used the most relevant (to the PICO), up-to-date and highest quality SRs, among those, we prioritized reviews using GRADE. Where needed, outcomes were re-GRADED accounting for differencing in contextual/clinical interpretation such as indirectness and imprecision. However, this was deemed not necessary. Delgado-Flores *et al*. 2022 had a low AMSTAR II score (low quality review). However, the review was the most up to date, relevant, and internally valid. As such, meeting the PICO question set out a priori.

Effectiveness of the intervention

The review pooled data from 6 RCTs trials (n=359) comparing factor VIII prophylaxis with treatment on demand. The data were pooled for low (2 RCTs, n=71) and intermediate (4 RCTs, n=237) comparisons. **Comparison of high dose prophylaxis (three times a week) was not included in this medicine review due to feasibility concerns in the South African context.**

Comparison 1: Low dose Factor VIII prophylaxis versus on-demand treatment

The two RCTS included in the meta-analyses for low dose prophylaxis were conducted in LMICs and in children younger than 18 years (mean ages 6.11 and 11.95 years for Verma *et al*. 2016[5] and Chozie et al. 2019[6] respectively).

Outcome 1.1 - Annualised total bleeding rate

The annualised mean bleeding rate in the prophylaxis group of 5.07 (bleeds per annum) was significantly lower compared to the on-demand group at 17.74 (Ratio of means: 0.27 – reduction in 73% in bleeds per annum, 95% CI 0.17 to 0.43; P < 0.00001; 2 RCTS; n=71; low heterogeneity i^2=0%); very low certainty of evidence - rated down one level for risk of bias and two levels for imprecision due to the small number of participants that presented the outcome - less than 200).

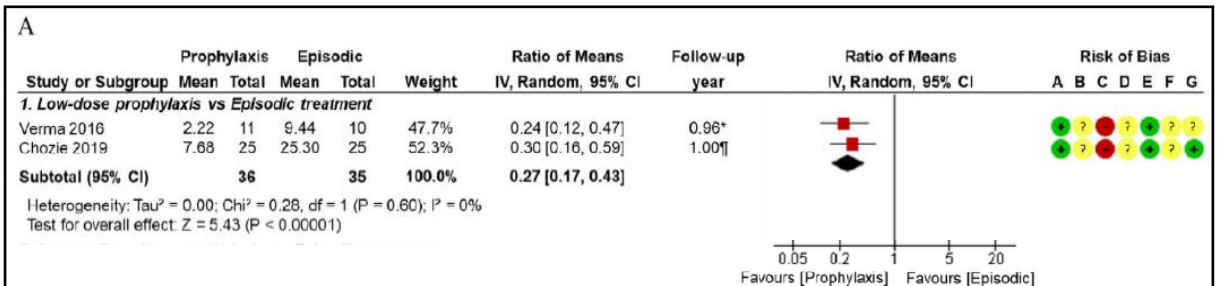


Figure 1: Forest plot from Delgado-Flores et al. 2022[1] – Annualised Bleeding Rate for Low Dose Prophylaxis

Outcome 1. 2 - Annualised joint bleeding rate

The annualised mean joint bleeding rate in the prophylaxis group of 1.11 (bleeds per annum) was significantly lower compared to the on-demand group at 6.66 (Ratio of means: 0.17 – reduction of 83% in bleeds per annum, 95% CI 0.06 to 0.43; P=0.0002; 2 RCTS; n=71; low heterogeneity i^2=0%); very low certainty of evidence - rated down one level for risk of bias and two levels for imprecision due to the small number of participants that presented the outcome - less than 200).

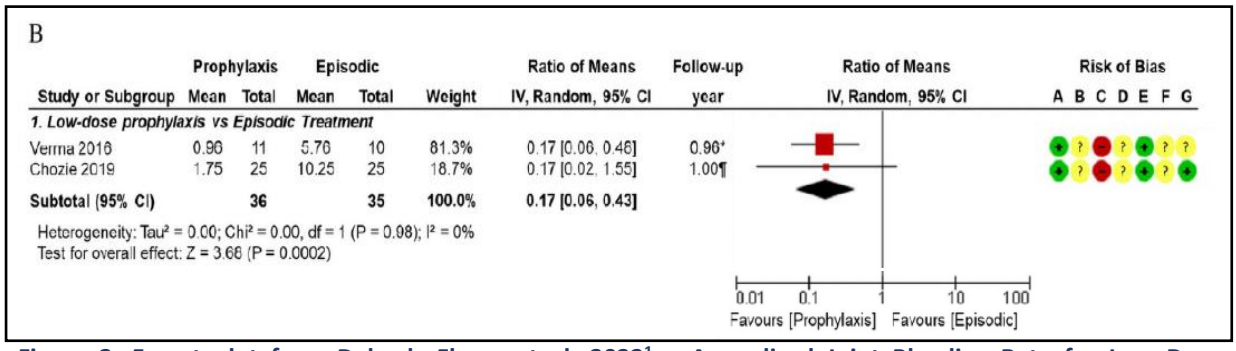


Figure 2: Forest plot from Delgado-Flores et al. 2022[1] – Annualised Joint Bleeding Rate for Low Dose Prophylaxis

Outcome 1.3 - Change in the Haemophilia joint health score-2.1 (HJHS-2.1). Range: 0 to 124. Higher score = worse

Both included RCTs reported a significant difference over a 12-month period. Verma *et al*. 2016[5] showed a median change of 0 points (no worsening) for the low dose prophylactic group compared to a change of 4.5 points (worsening) in the on-demand treatment group (p<0.05). Chozie *et al*. 2019[6] reported a median change of -1 points (improvement of 1 point) in the low-dose prophylaxis group compared to a median change of 2 points (worsening) in the on-demand group (P<0.001); very low certainty of evidence - rated down one level for risk of bias and two levels for imprecision due to the small number of participants that presented the outcome - less than 200).

Comparison 2: Intermediate dose Factor VIII prophylaxis versus on-demand treatment

The four RCTS included in the meta-analyses for intermediate dose prophylaxis were conducted in a range of settings and across different age groups. The mean ages for the RCTs were 1.6 years (Manco-Johnson *et al*. 2007), 4.10 years (Gringeri *et al*. 2011), 29.6 years (Kavakli *et al*. 2015) and 29 years (Manco-Johnson *et al*. 2017).

Outcome 2.1 - Annualised total bleeding rate

The annualised mean bleeding rate in the prophylaxis group of 4.41 (bleeds per annum) was significantly lower compared to the on-demand group at 31.59 bleeds per annum (Ratio of means: 0.15 – reduction of 85% in bleeds per annum, 95% CI 0.07 to 0.36; P < 0.00001; 4 RCTS; n=237; substantial heterogeneity i^2=88%); very low certainty of evidence - rated down one level for risk of bias, one levels for imprecision due to the small number of participants that presented the outcome 200-400, one level for inconsistency).

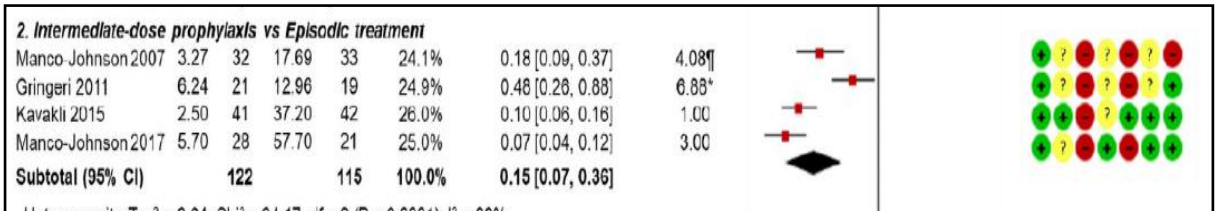


Figure 3: Forest plot from Delgado-Flores et al. 2022[1] – Annualised Bleeding Rate for Intermediate Dose Prophylaxis

Outcome 2.2 – Annualised joint bleeding rate

The annualised mean joint bleeding rate in the prophylaxis group of 2.64 (bleeds per annum) was significantly lower compared to the on-demand group at 22.12 bleeds per annum (Ratio of means: 0.14 – reduction of 86% in bleeds per annum, 95% CI 0.07 to 0.27; 4 RCTS; n=237; substantial heterogeneity i^2=73%); very low certainty of evidence - rated down one level for risk of bias, one levels for imprecision due to the small number of participants that presented the outcome 200-400, one level for inconsistency).

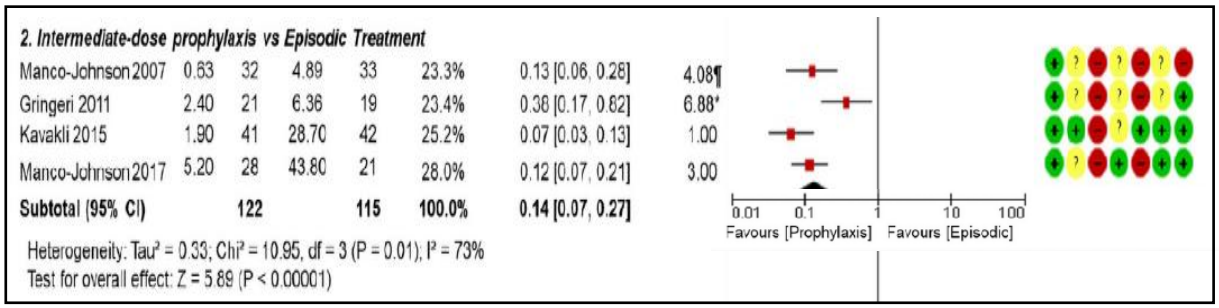


Figure 4: Forest plot from Delgado-Flores et al. 2022[1] – Annualised Joint Bleeding Rate for Intermediate Dose Prophylaxis

Outcome 2.3 – Radiographic findings

There was a significant difference found in radiographic findings between intermediate dose prophylaxis and on-demand treatment. The number of participants with negative radiographic findings was larger in the on-demand treatment groups (19 events) than for intermediate prophylaxis groups (7 events) and was found to be significant (RR 0.36, 95% CI 0.18 to 0.71; 2 RCTS; n=95; low heterogeneity i^2=0%, Chi^2 p=0.52); very low certainty of evidence - rated down one level for risk of bias, one levels for imprecision due to the small number of participants that presented the outcome less than 200, one level for publication bias).

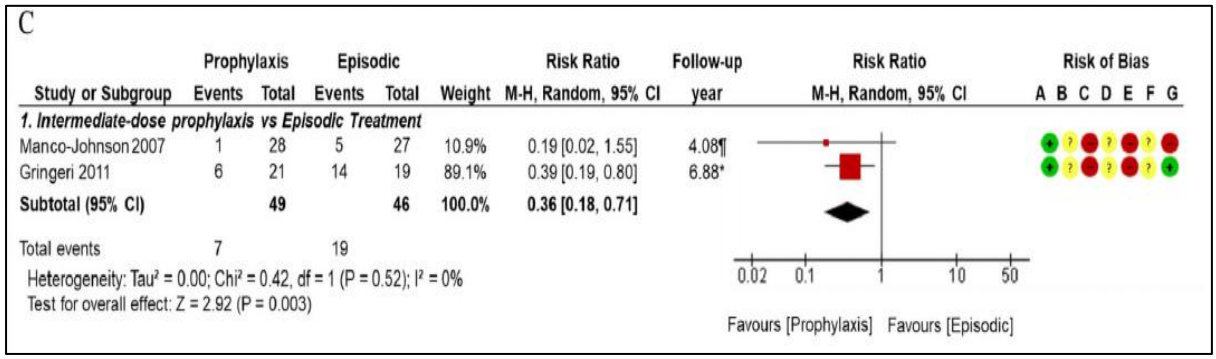


Figure 5: Forest plot from Delgado-Flores et al. 2022[1] – Radiographic Findings for Intermediate Dose Prophylaxis

Adverse events

Two RCTs reported on adverse events but data could not be pooled thus discussed narratively. Gringeri *et al*. (2011)[9] reported three and two patients in the prophylaxis and on-demand treatment groups respectively (no p value reported). A central-venous-access device related infection was reported for 6 out 20 patients. In the Manco-Johnson *et al*. (2007)[10] study an equal number of participants had a central-venous-access device related infection (19% in the prophylaxis group and 18% in the on-demand treatment group). No p values reported for adverse events.

EVIDENCE QUALITY

For the outcomes of interest, the Delgado-Flores 2022 systematic review rated the certainty as very low. Evidence was downgraded for imprecision, inconsistency and risk of bias (open-label trials). See Summary of Findings Table.

COSTING AND BUDGET IMPACT

A costing and budget impact analysis was conducted to investigate the potential budget impact per annum for treating paediatric patients with severe haemophilia A without inhibitors as well as the cost per bleed averted. The analysis was undertaken from the payer perspective and only direct costs to the public health sector are considered. Indirect and societal costs, such as school or work absenteeism, are not included. **Update to costing for adults was inclusion of the total potential population (children and adults), selection of intermediate dose prophylaxis as the base case and accounting for acquisition costs of factor VIII only, and treatment of all bleeds (including severe). Low dose prophylaxis, treatment of minor bleeds only, and inclusion of facility and staff costs are explored in different sensitivity scenarios.**

Population of interest

Population estimates were sourced from the World Federation of Haemophilia, annual global survey[11] and the South Africa Haemophilia Foundation registry data[12]. Uncertainty around population estimates were explored in the sensitivity analysis. A proportion in each age group was assumed to calculate dose estimates for low (10IU twice a week) and intermediate prophylaxis (25IU twice a week). Table 1 shows the number of patients with age group, estimated weights per age group[13] and factor VIII requirements.

Table 3: Average weight, IU requirements and number of patients per age group

Age	Weight (male)	IU required per dose (low)	IU required per week (low)	IU per dose (intermediate)	IU per week (intermediate)	Est. Number of patients
0-1	8	80	160	200	400	23
1-2	11	110	220	275	550	23
2-3	13.5	135	170	337.5	675	23
3-4	15.5	155	310	387.5	775	23
4-5	17.5	175	350	437.5	875	23
5-6	19.5	195	390	487.5	975	23
6-7	22	220	440	550	1100	23
7-8	24	240	480	600	1200	23
8-9	27	270	540	675	1350	23
9-10	30	300	600	750	1500	23
10-11	34	340	680	850	1700	23
11-12	38	380	760	950	1900	23
>12	70	700	1400	1750	3500	640

Costs

Costs for factor VIII products were sourced from the National Department of Health Master Health Product List[14] (contract prices). Proxies for facility and health worker costs for administration of prophylaxis and treatment of bleeds were obtained from the Uniform Patient Fee Schedule (dated April 2023)[15]. Consumables were assumed to be included in the facility costs. Facility and health worker costs were not included in base case but accounted for in sensitivity analysis. It was assumed that administration of prophylaxis would occur at community clinic level. It was assumed that there would no vial sharing but no wastage. Thus in practice patients may receive an intermediate, rather than low dose depending on vial size (sensitivity analysis scenarios). Costs for surgery and complications were not included. Costs for all bleeds (minor, major and life threating bleeds) were included in the base case. Accounting only for minor bleeds was explored in the sensitivity analysis as well as inclusion of facility and staff costs and low dose prophylaxis. Table 1 shows the cost components included in the analyses.

Table 4. Cost point estimates

Item		Value	Reference
Medication			
Haemosolvate® Factor VIII 300 IU 10ml vial		R1 183.67	MHPL 2023 (14)
Haemosolvate® Factor VIII 500 IU		R1 757.73	
Haemosolvate® Factor VIII 1000 IU (2 x 500IU)		R3 515.48	
Health Worker and Facility Costs* (sensitivity analysis)			
Health worker cost for administration of prophylaxis	Nursing Practitioner	R76	UPFS 2023 (15)
Facility cost for administration of prophylaxis	Facility Level 1	R130	
Health worker cost for treatment of minor bleed	Nursing Practitioner	R76	
Facility cost for treatment of minor bleed	Facility Level 1	R130	
Health worker cost for treatment of severe bleeds intensive care	Specialist medical practitioner	R662	
	Nursing Practitioner	R132	
Facility cost for treatment of severe bleed intensive care	Facility Level 3	R7 795	
Health worker cost for treatment of severe bleeds general ward	Specialist medical practitioner	R172	
	Nursing Practitioner	R132	
Facility cost for treatment of severe bleed intensive care	Facility Level 3	R1 155	

Outcomes

Data sourced from the Delgado-Flores systematic review (see 'Effectiveness and safety of the intervention above') was utilised to input into the analysis for estimated total number of bleeds per annum for a patient on intermediate dose factor VIII prophylaxis versus on-demand treatment (as well as low dose effectiveness estimates in sensitivity analysis). Estimates for number of severe bleeds (major and life-threatening) were sourced from literature. Number of days of treatment and hospitalization for bleeds was based on expert opinion of members of the Paediatric Hospital Level ERC. Table 5 shows the point estimates utilised in the analysis. Outcomes for disability, quality of life, surgeries and mortality were not included in the analysis.

Table 5. Outcome point estimates

Item	Value	Reference
No. of minor bleeds per annum per one patient on low dose prophylaxis *sensitivity analysis	5.7	Delgado-Flores et al. 2022 (1) – values

No. of minor bleeds per annum per one on-demand patient (low dose prophylaxis comparison) *sensitivity analysis	17.1	reduced to offset severe bleeds
No. of minor bleeds per annum per one patient on intermediate dose prophylaxis	4.75	
No. of minor bleeds per annum per one on-demand patient (intermediate dose prophylaxis comparison)	30.4	
% of major bleeds that occur in haemophilia A patients as a % of all bleeds	5%	Srivastava et al. 2021[ii] (3)
% of children experiencing a life-threatening bleed annually on low dose prophylaxis	0.5%	Touré et al. 2022[iii] (16)
% of children experiencing a life-threatening bleed annually on-demand treatment (low dose comparison)	1.2%	
% of children experiencing a life-threatening bleed annually on intermediate dose prophylaxis	0.5%	
% of children experiencing a life-threatening bleed annually on-demand treatment (intermediate dose comparison)	2.7%	
No. of days required for treatment of a minor bleed – outpatient	3	Expert opinion (Paediatric Hospital Level ERC)
No. of days required for treatment of a major bleed – inpatient	7	
No. of days required for treatment of an LTB - inpatient	16	

RESULTS

Base Case analysis

Table 6 shows the results of the base case analysis which accounts for **drugs costs only** (at contract price) for **intermediate dose prophylaxis and treatment of all bleeds** (See sensitivity analysis for scenarios including treatment of minor bleeds only, facility and health worker costs, and low dose prophylaxis). The total cost per patient on intermediate dose factor VIII prophylaxis was estimated to be R R561 126 per annum, compared to R684 908 per annum for treating one patient on demand (incremental savings of R123 782 per patient per annum). Total budget impact was an estimated R311 962 320 for 916 patients on low dose factor VIII prophylaxis per annum versus R242 338 176 for 916 patients on demand (incremental impact of R69 624 144). Low dose prophylaxis could potentially avert 11 426 bleeds a year at an estimated incremental cost of R6 094 per bleed averted.

Table 6: Base case analysis results

	Costs per annum				**Benefits per annum**	
	Cost of Prophylaxis	**Treatment of bleeds**	**Total**	**Incremental Cost**	**No. of bleeds**	**No. bleeds averted**
FVIII intermediate dose prophylaxis	R415 680 564	R98 311 240	R513 991 804	-R113 383 948	4 587	24 751
FVII treatment on demand	NA	R627 375 752	R627 375 752		29 338	

[ii] Value was applied equally across low and intermediate effect sizes to obtain number of major bleeds per comparison

[iii] Value for LTB for intermediate cases proportionally increased in line with minor bleeds from low dose values

Cost of providing prophylaxis for 1 patient p/ annum	R561 126	R684 908	-R123 782	ICER – Savings with each bleed	-R 4 581

Sensitivity analysis - Scenarios

Deterministic sensitivity analysis

Ten different scenarios were run in the analysis to explore impact of changing certain variables and assumptions (See table 7 below). Scenarios were also explored for low dose prophylaxis (25IU/kg twice weekly).

Table 7: Scenarios explored in the deterministic sensitivity analysis

Scenario	Type of analysis	Variable and/or assumption changed
Base case intermediate prophylaxis, drug acquisition costs only and all bleeds		
1	Univariate	Base case but **low instead of intermediate dose prophylaxis**
2	Univariate	Base case AND includes treatment of minor bleeds only
3	Multivariate	Base case but low dose AND includes treatment of minor bleeds only
4	Univariate	Base case AND includes facility and health worker costs
5	Multivariate	Base case but **low dose prophylaxis** AND includes facility and health worker costs
6	Multivariate	Base case AND includes treatment of minor bleeds only AND includes facility and health worker costs
7	Multivariate	Base case but **low dose prophylaxis** AND includes treatment of minor bleeds only AND includes facility and health worker costs
8	Univariate	Base case but reduced patient estimates based on consumption data
9	Univariate	Base case but reduced bleeding rate estimates of intervention and control groups by 15%
10	Univariate	Base case but reduced bleeding rate estimates of intervention and control groups by 25%

Scenario 4 resulted in the largest **cost savings** of R152 704 996 per annum (for 916 patients), **savings** of R6 170 per bleed averted. The largest ICER was observed in Scenario 7 with an incremental cost of R82 187 260 (R7 193 per bleed averted). Table 8 outlines the results for each scenario. Scenarios highlighted in green are cost saving. See Appendix 7 for full details.

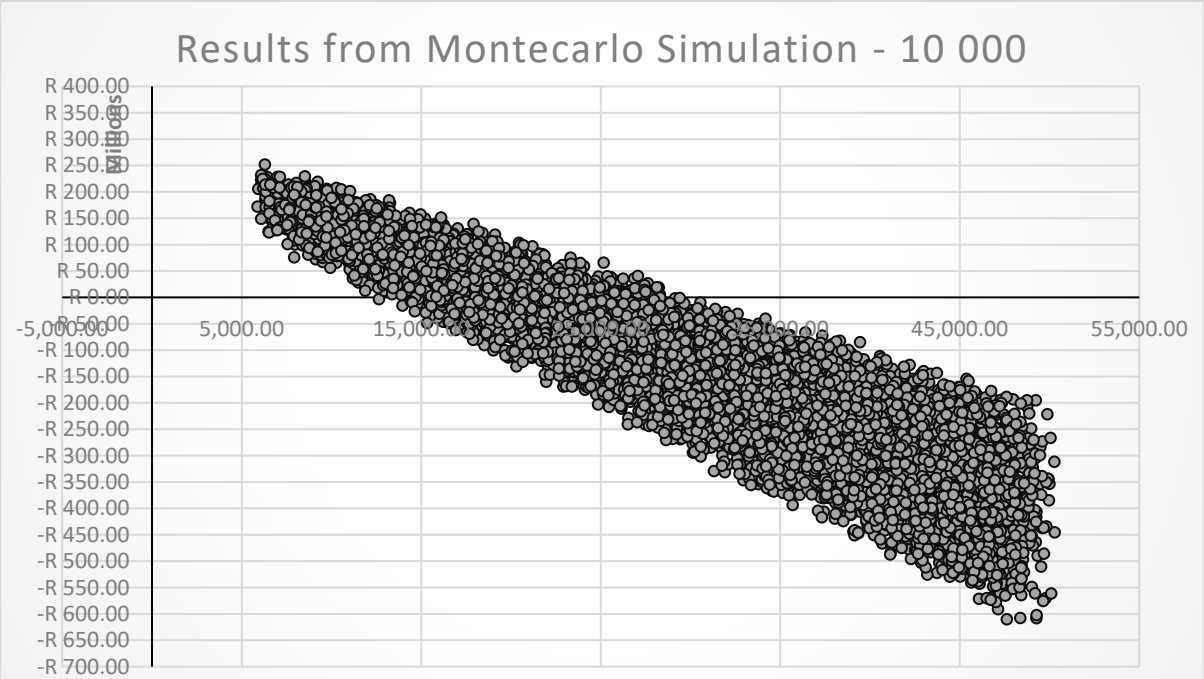
Table 8: Results of the deterministic sensitivity analysis

Scenario	Incremental budget impact	Incremental cost per patient	Number of bleeds averted	Cost per bleed averted
1	-R38 708 300	-R42 258	12 217	-R3 168
2	R57 061 444	R62 294	23 496	R2 429
3	R69 624 144	R76 009	11 426	R6 094
4	-R152 704 996	-R166 709	24 751	-R6 170
5	-R54 143 332	-R59 108	12 217	-R4 432
6	R62 165 300	R67 866	23 496	R2 646
7	R82 187 260	R89 724	11 426	R7 193
8	-R64 836 256	-R70 782	14 456	-R4 485
9	-R35 519 464	-R38 777	21 087	-R1 684
10	R22 849 696	R24 945	18 340	R1 246

Scenarios which included treatment of minor bleeds only (Scenarios 2, 3, 6 and 7) were found to be more costly. Scenarios with intermediate dose prophylaxis were more cost-effective than lose dose prophylaxis scenarios, regardless of whether only minor bleeds were included, or facility and staff costs were included. Reducing annualised bleeding rates of both intervention and control groups by 15% still resulted in an estimated cost savings (Scenario 9). If annualised bleeding rates for both groups reduced by 25% then factor VIII prophylaxis is still estimated to be more beneficial but more costly (Scenario 10).

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was conducted to account for parameter uncertainty, where all model parameters were varied at the same time, using statistical distributions. Distributions were based on confidence intervals in the Delgado-Flores et al. 2022 systematic review for effectiveness estimates and varied by 15% for cost and other estimates, such as number of days treated for major bleeds. A microsimulation was undertaken with 10,000 runs. The results presented in Figure x show that the new intervention (factor VIII prophylaxis) was estimated to be cost saving in 69% of the runs. After 10 000 runs the average cost difference was -R115 605 693 with a benefit difference of 28 113 bleeds resulting in an ICER of means of -R 4 112.



Limitations

Costs for surgeries required for treating major or life threatening bleeds are not included as well as costs for treating long term complications. This costing and budget impact does not look at the impact of mortality, quality of life and disability which a cost utility model would include. Many CEA articles show that prophylaxis is more costly and more effective with the decision on cost-effectiveness based on varied willingness-to-pay thresholds. There is a large variation in CEA results due to lack of standardised approaches (types of costs, perspective, time horizon and model structure).[171819] Lastly the analysis assumes 100% uptake and does not account for current use of factor VIII prophylaxis. Patient number estimates for haemophilia are difficult to source and thus patient numbers may differ in reality to estimates utilised in the model. However, national procurement data shows an average

(last five years) annual spend of R138 130 410 on haemosolvate® products.[iv] Utilising the above base case modelled cost estimate for one patient per annum on demand treatment (R684 908) and the national procurement costs, roughly 200 patients of patients with severe haemophilia are being actively treated for bleeds on demand. Scenarios including facility and staff costs assume that all prophylaxis will be administered at facilities whereas in practice there may be some home-based administration.

DISCUSSION AND CONCLUSION

This medicine review focussed on evidence from the Delgado-Flores 2022[1] systematic review. Two other systematic reviews which were found during the search were Cochrane reviews (Iorio *et al*. 2011[8] and Olasupo *et al.* 2021[2]) concluded in favour of factor VIII prophylaxis over on-demand treatment stating strong evidence (Iorio *et al*. 2011) and low certainty of evidence (Olasupo *et al*. 2021) for some outcomes. However, none of the studies that were included in both reviews, were conducted in LMICs or with lower doses. Affordability is an important consideration thus despite the evidence from Delgado-Flores being of very low certainty (open label trials, small samples and inconsistency), it was agreed that this evidence was the most appropriate and direct. The evidence reported that low dose and intermediate Factor VIII prophylaxis reduced total bleeds by 12 and 27 per annum respectively.

A basic cost effectiveness analysis considered acquisition costs, health worker and facility costs for prophylaxis and treatment of bleeds. For this group of patients, it is estimated that low and intermediate dose factor VIII prophylaxis is incrementally more costly than treating on-demand in the base case (considering acquisition costs and treatment of minor bleeds only). A conservative approach to the base case was selected, however scenarios which included acquisition costs for treatment of major and life-threatening bleeds were cost saving, even after including facility and health worker costs. This was the case for both low and intermediate dose prophylaxis. Intermediate dose prophylaxis was less costly than low dose prophylaxis compared to treatment on demand even after including all bleeding types and facility and staff costs. Costs and effectiveness of surgeries and treatment of long-term complications were not considered and a cost utility analysis incorporating mortality and disability was not undertaken. Due to efficacy and modelled cost estimates in particular, potential cost savings when including treatment of severe bleeds, intermediate dose prophylaxis is suggested over low dose prophylaxis and treatment on demand.

REVIEWERS

Ms Kim MacQuilkan, Mr A Hohlfeld, Dr Jane Riddin, Prof P Jeena, Dr G Reubenson, Mr A Gray
UPDATE: Supported by Haemophilia subcommittee of NEMLC

Author Affiliation and Conflict of Interest Details

- Ms K MacQuilkan (Right to Care, SCTA) has no interests to declare.
- Mr A Hohlfeld (Cochrane South Africa, South African Medical Research Council) has no interests to declare.
- Dr J Riddin (Affordable Medicines Directorate, National Department of Health) has no interests to declare
- Prof P Jeena has no interests to declare
- Dr G Reubenson has no interests to declare
- Mr A Gray – No interests to declare

[iv] RSAPharma data (2020-2022)

APPENDIX 1 - EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [ ] Very low: [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*Low dose prophylaxis vs on-demand treatment* - Very low certainty - 2 RCTs (n=71) ages 1-18 years *Intermediate dose prophylaxis vs on-demand treatment* - Very low certainty 4 RCTs (n=237) ages 1 to 65 years See Summary of Findings Table
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: [X] Moderate: [ ] Small: [ ] None: [ ]	***Low dose prophylaxis vs on-demand*** **Overall annualised bleeding rate** - 2 RCTs, n=71, ratio of means 0.27 (73% reduction in mean bleeds per annum in the prophylaxis group) 95% CI 0.17 to 0.43, p < 0.00001. **Joint annualised bleeding rate** - 2 RCTs, n=71, ratio of means 0.17 (83% reduction in mean bleeds per annum in the prophylaxis group) 95% CI 0.06 to 0.43, p < 0.0002 ***Intermediate dose prophylaxis vs on-demand*** **Overall annualised bleeding rate** - 4 RCTs, n=237, ratio of means 0.14 (86% reduction in the mean bleeds per annum in the prophylaxis group) 95% CI 0.07 to 0.27, p < 0.0001. **Joint annualised bleeding rate** - 4 RCTs, n=71, ratio of means 0.17 (83% reduction in mean bleeds per annum in the prophylaxis group) 95% CI 0.06 to 0.43, p < 0.00001
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [ ] Very low: [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*Intermediate dose prophylaxis vs on-demand treatment* - Very low certainty 4 RCTs (n=237) ages 1 to 65 years *See Summary of findings table*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [X] None: [ ]	*Adverse events not quantitatively analysed however one RCT reported more* central-venous-access device related infections but CVADs not inserted in on-demand group.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [X] Favours control: [ ] Intervention = Control *or* Uncertain: [ ]	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	In the committee's opinion the intervention is feasible, however, where this is not the case on-demand treatment will still be available.
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [X]	BASE CASE: Incremental cost for providing one patient with intermediate-dose prophylaxis per annum = (-)R123 782 (cost-savings) Incremental budget impact per annum for all patients = -R113 383 948 (cost savings) **Cost savings** per bleed = R4 581 **Scenarios including acquisition costs for treatment of minor only are more beneficial but more costly** Intermediate dose prophylaxis provided more cost savings than low dose prophylaxis scenarios. Scenario 1: Low dose prophylaxis Incremental budget impact per annum for all patients = **cost savings** of R38 708 300
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [x] Major: [ ] Uncertain: [ ] **Is the option acceptable to key stakeholders?** Yes: [x] No: [ ] Uncertain: [ ]	

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EQUITY	**Would there be an impact on health inequity?** Yes [x] No [ ] Uncertain [ ]	Where home-based care is not feasible, children in less well-resourced areas may struggle to access prophylactic factor VIII, however, since this can be administered at clinic level inequity should be minimal.

APPENDIX 2 -SEARCH STRATEGY

PUBMED

#	Query	Search Details	Results
10	#6 AND filter for systematic review and meta-analyses	(("haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]) AND ("Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR "Factor VIII"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])) AND (meta-analysis[Filter] OR systematicreview[Filter])	42
9	#6 AND #5	("haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]) AND ("Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR "Factor VIII"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract]) AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract])	50
8	#6 AND Filter for clinical trials and RCTs	(("haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]) AND ("Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR "Factor VIII"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])	169
7	#6 AND #4	("haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]) AND ("Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR	1 201

		"Factor VIII"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract]) AND (("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))	
6	#1 AND #2 AND #3	("haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]) AND ("Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR "Factor VIII"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])	2 036
5	Systematic reviews	"systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract]	388 961
4	RCTs	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	4 843 051
3	Prophylaxis (intervention)	"prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract]]	1 812 441
2	Factor VIII (intervention & comparator)	"Factor VIII"[Title/Abstract] OR "Factor 8"[Title/Abstract] OR "Factor VIII"[MeSH Terms]	26 891
1	Hemophilia A (population)	"haemophilia A"[Title/Abstract] OR "hemophilia A"[Title/Abstract] OR "hemophilia A"[MeSH Terms]	24 162

COCHRANE

search	Query	Results
#1	MeSH descriptor: [Hemophilia A] explode all trees	**467**
#2	MeSH descriptor: [Factor VIII] explode all trees	**396**
#3	#1 AND #2	**243**
#4	#3 in Cochrane Reviews	**6**

Epistemonikos

(title:((title:("hemophilia A" OR "haemophilia A") OR abstract:("hemophilia A" OR "haemophilia A")) AND (title:("factor VIII" OR "factor 8") OR abstract:("factor VIII" OR "factor 8")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))) OR abstract:((title:("hemophilia A" OR "haemophilia A") OR abstract:("hemophilia A" OR "haemophilia A")) AND (title:("factor VIII" OR "factor 8") OR abstract:("factor VIII" OR "factor 8")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))))

All studies – 445 results
Filtered for RCTs – 17 results
Filtered for systematic reviews & Interventions = 7 results

APPENDIX 3 - Table of excluded studies

No.	Study	Reason for exclusion
1	Sun J, Zhou X, Hu N. Factor VIII replacement prophylaxis in patients with hemophilia A transitioning to adults: a systematic literature review. Orphanet J Rare Dis. 2021 Jun 26;16(1):287. doi: 10.1186/s13023-021-01919-w. PMID: 34174912; PMCID: PMC8236177.	Qualitative synthesis
2	Stobart K, Iorio A, Wu JK. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD003429. doi: 10.1002/14651858.CD003429.pub2. Update in: Cochrane Database Syst Rev. 2006;(2):CD003429. PMID: 15846666.	Earlier review of Iorio et al. 2011 Cochrane review
3	O'Hara J, Sima CS, Frimpter J, Paliargues F, Chu P, Presch I. Long-term outcomes from prophylactic or episodic treatment of haemophilia A: A systematic review. Haemophilia. 2018 Sep;24(5):e301-e311. doi: 10.1111/hae.13546. Epub 2018 Jul 13. PMID: 30004613.	Qualitative synthesis
4	Oldenburg J, Brackmann HH. Prophylaxis in adult patients with severe haemophilia A. Thromb Res. 2014 Nov;134 Suppl 1:S33-7. doi: 10.1016/j.thromres.2013.10.019. Epub 2014 Sep 26. PMID: 25263019.	Qualitative synthesis
5	Makris M. Systematic review of the management of patients with haemophilia A and inhibitors. Blood Coagul Fibrinolysis. 2004 May;15 Suppl 1:S25-7. doi: 10.1097/00001721-200405001-00005. PMID: 15166930.	Incorrect intervention/ comparator
6	van Galen KP, Engelen ET, Mauser-Bunschoten EP, van Es RJ, Schutgens RE. Antifibrinolytic therapy for preventing oral bleeding in patients with haemophilia or Von Willebrand disease undergoing minor oral surgery or dental extractions. Cochrane Database Syst Rev. 2019 Apr 19;4(4):CD011385. doi: 10.1002/14651858.CD011385.pub3. PMID: 31002742; PMCID: PMC6474399.	Incorrect intervention/ comparator
7	Castro HE, Briceño MF, Casas CP, Rueda JD. The history and evolution of the clinical effectiveness of haemophilia type a treatment: a systematic review. Indian J Hematol Blood Transfus. 2014 Mar;30(1):1-11. doi: 10.1007/s12288-012-0209-0. Epub 2012 Nov 4. PMID: 24554812; PMCID: PMC3921319.	Qualitative synthesis

APPENDIX 4: Description of eligible systematic reviews

Study	Date	Population	Intervention	Comparators	Outcomes	Any trials in LMICs
Iorio et al. (Cochrane) [8]	2011	Haemophilia A or B without inhibitors of all ages and severity	Primary and secondary Factor VIII prophylaxis	• prophylaxis versus placebo; • prophylaxis versus on-demand treatment; • prophylaxis versus alternative prophylaxis	1. Number of bleeding episodes or bleeding frequency Secondary outcomes 1. Pain scores 2. Radiologic joint score or radiologic measurements or descriptions of joint damage 3. Orthopedic joint score or clinical joint function 4. QoL 5. Clotting factor concentrate plasma levels 6. Time loss to school or employment 7. Integration into society	None

					8. Scales recording feeling of well-being and global functioning 9. Cost effectiveness, cost benefit, cost utilization, cost minimization 10.Any reported adverse effects or toxicity of clotting factor concentrates will be recorded (e.g. inhibitors, reactions, transmission of infection)"	
Olasupo et al. [2]	2021	Haemophilia A or B without inhibitors any severity. Adults only or if under 18 only if had 1. proven haemophilic arthropathy; or 2. presence of one or more target joint; or 3. previous on-demand treatment.	Secondary Factor VIII prophylaxis	• prophylaxis versus prophylaxis with a different regimen; • prophylaxis versus on-demand treatment; • prophylaxis versus no treatment; • prophylaxis versus placebo."	Primary outcomes 1. Number of joint bleeding episodes or joint bleeding frequency during the trial 2. Orthopedic joint score or clinical joint function 3. QoL on validated scales (disease-specific where possible) Secondary outcomes 1. Number of total bleeding episodes or total bleeding frequency during the trial period 2. Pain scores 3. Radiologic joint score or radiologic measurements or descriptions of joint damage 4. Clotting factor concentrate plasma levels 5. Time loss to school or employment 6. Integration into society (i.e. absenteeism) 7. Scores on scales recording feeling of well-being and global functioning 8. Economic data: cost-effectiveness, cost-benefit, cost-utilisation, cost-minimisation 9. Any reported adverse effects or toxicity of clotting factor concentrates (e.g. inhibitors, reactions, transmission of infection)"	A-Long (Brazil, India, Russia, South Africa); LEOPOLD included SA, PROPEL Malaysia, SPINART (Bulgaria, Romania, Argentina)
Delgado-Flores et al. [1]	2022	Patients with Haemophilia A without inhibitors of all ages and severity (primary and secondary prophylaxis)	Primary and secondary Factor VIII prophylaxis	• Different prophylactic • Episodic • Tailored factor replacement treatments.	1. Annualized bleeding rate (ABR) 2. Annualized joint bleeding rate (AJBR) 3. Radiographic findings 4. Hemophilia joint health score 2.1 (HJHS-2.1) 5. Joint structural changes (using extended magnetic resonance imaging-eMRI) 6. Petterson score 7. Adverse events (AEs) 8. Quality of life	Verma (India); Chozie (Indonesia); LEOPOLD included SA; SPINART (Bulgaria, Romania, Argentina)

Appendix 5: Characteristics of included studies in Delgado-Flores 2022

Table 1. Study and participants' characteristics in the included RCTs.

N	Author (year)	Countries or regions	Population: hemophilia type, age and sex	Factor activity level**	Product: type of clotting factor concentrates and half-life (hours)	Control (n)	Intervention (n)	Follow-up	Fun-ding
Episodic treatment compared with prophylaxis (at low, intermediate, and high doses)									
1	Verma (2016)	India	• Hemophilia A • Age range: 1 to 10 yr (mean: 6.11 yr) • Sex: not mentioned	< 1%	**FVIII concentrate (Hemofil M)** • Plasma-derived, mAb-purified • 15 h	**Episodic (n = 10)** 1. 25 IU/kg or more as early as possible after the joint bleed, 2. 25 IU/kg every 12–24 h until resolution	**Low-dose prophylaxis** (n = 11) • **Weekly dose: 20 IU/kg** (10 IU/kg twice a week)	Median: 0.96 yr	Self-funded
2	Chozie (2019)	Indonesia	• Hemophilia A • Age range: 4 to 18 yr (mean: 11.95 yr) • Sex: not mentioned	< 1%	**FVIII concentrate (Koate-DVI)** • Plasma-derived, chromatography purified • 16 h	**Episodic (n = 25)** • Not specified	**Low-dose prophylaxis (n = 25)** • **Weekly dose: 20 IU/kg** (10 IU/kg twice a week)	Mean: 1 yr	Grifols
3	Manco-Johnson (2007) and Hacker (2007)	United States	• Hemophilia A • Age range: 1 to 2.5 yr (mean: 1.6 yr) • Sex: 100% males	≤ 2%	**FVIII concentrate (Kogenate or Kogenate FS)** • Recombinant • 11 to 15 h	**Episodic (n = 33)** 1. 40 IU/kg at the time of joint hemorrhage. 2. 20 IU at 24 hours and 72 hours after the first dose 3. 20 IU/kg every second day, until 4 weeks.	**Intermediate-dose prophylaxis (n = 32)** • **Weekly dose: 75 IU/kg** (25 IU/kg every second day)	Mean: 4.08 yr	CDC, NIH, Bayer
4	Gringeri (2011)	Italy	• Hemophilia A • Age range: 1 to 7 yr (mean: 4.10 yr) • Sex: not mentioned	< 1%	**FVIII concentrate (Recombinate® until 2003 / Advate® since 2004)** • Both were recombinant • Recombinate: 15 h / Advate: 9 to 12 h • 1° generation / 3° generation	**Episodic (n = 19)** 1. 25 IU/kg or more, possibly within 6 h from the bleeding, 2. Repeated every 12–24 h until complete resolution	**Intermediate-dose prophylaxis (n = 21)** • **Weekly dose: 75 IU/kg** (25 IU/kg three times a week)	Median: 6.88 yr	Baxter
5	Manco-Johnson (2014) and Manco-Johnson (2017)	United States, Bulgaria, Romania and Argentina	• Hemophilia A • Age range: 12 to 50 yr (mean: 29 yr) • Sex: 100% males	< 1%	**FVIII concentrate (Kogenate FS)** • Recombinant • 11 to 15 h	**Episodic (n = 42)** • Not specified	**Intermediate-dose prophylaxis (n = 41)** • **Weekly dose: 75 IU/kg** (25 IU/kg three times a week)	3 yr	Bayer
6	Kavakli (2015)	Europe, South Africa, North America, South America, and Asia	• Hemophilia A • Age range: 12 to 65 yr (mean: 29.6 yr) • Sex: 100% males	< 1%	**FVIII concentrate (BAY 81–8973, Kovaltry)** • Recombinant • 12 to 14 h	**Episodic (n = 21)** • Dependent on the location and severity of the bleed	**Intermediate-dose prophylaxis** (n = 28) • **Weekly dose: 40 to 60 IU/kg** (20–30 IU/kg twice a week) **High-dose prophylaxis (n = 31)** • **Weekly dose: 90 to 120 IU/kg** (30–40 IU/kg three times a week)	1 yr	Bayer

APPENDIX 6 – AMSTAR 2 Results of review of Delgado-Flores 2022

Effects of replacement therapies with clotting factors in patients with hem is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial YesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	Yes
NRSI	Yes Yes Yes Yes

10. Did the review authors report on the sources of funding for the studies included in the review?	Yes Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	Yes
NRSI	Yes Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its **likely impact on the results of the review?**	Yes Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

APPENDIX 7 – Sensitivity Analysis – Deterministic - Scenarios

		Costs				Benefits		Cost/benefit	Per patient		
BASE CASE	Intermediate prophylaxis, includes severe bleeds, factor costs only	Cost for prophylaxis (factor ONLY)	Treatment of bleeds (factor ONLY)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R415 680 564,00	R98 311 240	R513 991 804	-R113 383 947,93	4587,00	24750,80	-R4 581,02	R561 126,42	5,01	-R4 581,02
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R627 375 751,46	R627 375 751		29337,80			R684 908,03	32,03	
									-R123 781,60		
SCENARIO 1	Base case but low dose prophylaxis (assumes no wastage thus accounts for intermediate effects where larger dose can be given	Cost for prophylaxis (factor only)	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Low dose factor VIII prophylaxis	R232 501 950,72	R85 759 160	R318 261 110	-R38 708 299,75	5249,00	12217,40	-R3 168,29	R347 446,63	5,73	-R3 168,29
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R356 969 410,20	R356 969 410		17466,40			R389 704,60	19,07	
									-R42 257,97		
SCENARIO 2	Base case but minor bleeds only, factor only	Cost for prophylaxis (factor only)	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R415 680 564,00	R66 410 948	R482 091 512	R57 061 443,53	4351,00	23496,00	R2 428,56	R526 300,78	4,75	R2 428,56
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R425 030 068,70	R425 030 069		27847,00			R464 006,63	30,40	
									R62 294,15		
SCENARIO 3	Base case but low dose prophylaxis (assumes no wastage thus accounts for intermediate effects where larger dose can be given due to vial size) minor bleeds only	Cost for prophylaxis (factor only)	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Low dose factor VIII prophylaxis	R232 501 950,72	R79 460 369	R311 962 320	R69 624 144,37	5156,00	11426,00	R6 093,48	R340 570,22	5,63	R6 093,48
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R242 338 175,52	R242 338 176		16582,00			R264 561,33	18,10	
									R76 008,89		
SCENARIO 4	Base case, but includes facility/staff costs	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R435 304 948,00	R109 352 602	R544 657 550	-R152 704 995,93	4587,00	24750,80	-R6 169,70	R594 604,31	5,01	-R6 169,70
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R697 362 545,46	R697 362 545		29337,80			R761 312,82	32,03	

SCENARIO 5	Base case but low dose prophylais and includs facility/staff costs	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Low dose factor VIII prophylaxis	R252 126 334,72	R92 282 854	R344 409 188	-R54 143 331,75	5249,00	12217,40	-R4 431,66	R375 992,56	5,73	-R4 431,66
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R398 552 520,20	R398 552 520		17466,40			R435 101,00	19,07	
									-R59 108,44		
SCENARIO 6	Base case but includes administration/facility costs, minor bleeds only	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R435 304 948,00	R69 099 866	R504 404 814	R62 165 299,53	4351,00	23496,00	R2 645,78	R550 660,28	4,75	R2 645,78
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R442 239 514,70	R442 239 515		27847,00			R482 794,23	30,40	
									R67 866,05		
SCENARIO 7	Base case but low dose dose, minor bleeds only and includes administration/facility costs	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Low dose factor VIII prophylaxis	R252 126 334,72	R82 646 777	R334 773 112	R82 187 260,37	5156,00	11426,00	R7 193,00	R365 472,83	5,63	R7 193,00
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R252 585 851,52	R252 585 852		16582,00			R275 748,75	18,10	
									R89 724,08		
SCENARIO 8	Base case with reduced patient estimates (consumption data)	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R240 647 874,48	R56 735 893	R297 383 768	-R64 836 255,98	2679,00	14455,80	-R4 485,14	R324 654,77	2,92	-R4 485,14
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R362 220 023,54	R362 220 024		17134,80			R395 436,71	18,71	
									-R70 781,94		
SCENARIO 9	Base case with reduced estimates for bleeding rates (-25%)	Cost for prophylaxis (factor & administration)	Treatment of bleeds (factor & facility & staff)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benefit	ICER
	Intervention - Intermediate dose factor VIII prophylaxis	R415 680 564,00	R98 311 240	R513 991 804	-R35 519 463,98	4587,00	21086,80	-R1 684,44	R561 126,42	5,01	-R1 684,44
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R549 511 267,51	R549 511 268		25673,80			R599 903,13	28,03	
									-R38 776,71		

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South African National Department of Health
Brief Report of Rapid Review
Component: Subcommittee for Haemophilia

TITLE: Prophylactic Factor IX compared to on-demand/episodic treatment for patients with severe haemophilia B without inhibitors

Date: June 2024

Key findings

- Current South African standard of care for haemophilia B patients is on-demand/episodic treatment for bleeding with blood factor IX. A potential alternative is blood factor IX prophylaxis.
- A search was conducted in PubMed, Cochrane Database and Epistemonikos. No systematic reviews or randomised controlled trials (randomising on-demand vs prophylaxis patients) were found meeting the review criteria. Most studies included had small sample sizes and high risk of bias (due to open-label and patient reported outcomes). Overall, the evidence was determined as low quality, level II evidence.
- **Comparison 1: Standard half-life products (plasma or recombinant) versus on-demand treatment**

  Annualised bleeding rate (2 studies – low quality, n=75):

  - 50 IU twice weekly prophylaxis vs 1st on-demand period = Mean difference of -32.5; 95% CI [-38.5 to -26.6]; P<0.0001; 100 IU once weekly prophylaxis vs on-demand = MD of -30.5; CI [-36.5 to-24.5); P<0.0001). No difference between prophylaxis regimens (P=0.2167) – *1 randomised, 4 period crossover (randomisation of prophylaxis regimens not on-demand) study – use of historic controls, open-label.*
  - Lower mean ABR in the 100 IU once weekly prophylaxis period compared to the preceding on-demand period (Mean ABR 3.6 SD +/- 4.6 vs 32.9 SD +/- 17.4; p<0.0001) – *1 single arm, non-randomised study, use of historic controls, open-label, n=25.*

  Annualised joint bleeding rate (2 studies – low quality, n=75)

  - Joint ABR lower in the 50 IU/kg twice a week prophylaxis (MD 1.9 ± 4.5) and 100 IU/kg once a week prophylaxis (MD 3.6 ± 8.3) compared to the first on-demand period (MD 25.4 ± 19.1) and second on-demand period (MD 24.3 ± 21.5); p values not reported/calculated – *1 randomised, 4 period crossover (randomisation of prophylaxis regimens not on-demand) study – use of historic controls, open-label.*
  - Lower mean joint ABR in the prophylaxis period compared to the preceding on-demand period (Mean ABR 2.1 SD +/- 3.2 vs 27.7 SD +/- 16.9; P value not reported/calculated) – *1 single arm, non-randomised study, use of historic controls, open-label.*

  Safety (2 studies – low quality, n=75): No patient developed a FIX inhibitor during the studies reported. No serious concerns with safety.
- **Comparison 2: Extended half-life products (recombinant) versus on-demand treatment**

  Annualised bleeding rate (3 studies – low quality, n=260):

  - Annualised median bleeding rate higher in the on-demand group (median 15.58, IQR 9.56 to 26.47) compared to the 10 IU/kg prophylaxis (median 2.93, IQR 0.99 to 6.02) and 40 IU/kg prophylaxis (median 1.04, IQR 0.00 to 4.00) groups – 1 *randomised (prophylaxis groups randomised only), single-blind trial, on demand open label, parallel group.*
  - Significant reduction in mean ABR between the weekly dose adjusted (starting 50 IU/kg) prophylaxis (Mean: 3.12, 95% CI [2.46 to 3.95]) and the on-demand (Mean: 18.67, 95% CI [14.01 to 24.89]) groups (83% reduction; p<0.001). Significant reduction in mean ABR between the interval adjusted 100 IU prophylaxis (Mean: 1.4, 95% CI [0.0 to 3.4]) and the on-demand (Mean: 18.67, 95% CI [14.01 to 24.89]) groups (87% reduction; p<0.001) – 1 non-randomised, open-label study, parallel on demand group.

- Significant reduction in total ABR when patients switched from the on-demand treatment (ABR 20.09, 95% CI [16.808 to 24.003]) period to the prophylaxis (ABR 2.22, 95% CI [0.942 to 5.243) period (Median % reduction: 90.94, IQR (81.19 to 100.00); p<0.0001) – non-randomised, open-label, 2 periods, 2 groups.

Annualised joint bleeding rate (1 study – low quality, n=123):

- Lower median joint ABRs in the weekly dose adjusted (starting 50IU/kg) prophylaxis (Median: 1.1, IQR (0.0 to 4.0]) and interval adjusted 100IU/kg prophylaxis (Median: 0.4, IQR (0.0 to 3.2) groups compared to the on-demand (Median: 13.6 IQR (6.1 to 21.6) group; p value not reported/calculated).

Safety (3 studies – low quality, n=260): No patient developed a FIX inhibitor during the studies reported. No serious concerns with safety in two trials. One trial reported one serious adverse event considered related to the product (obstructive clot in urinary collecting system).

➡ The two moderate quality guidelines included recommended factor IX prophylaxis for severe haemophilia B patients.

➡ Low, intermediate and high dose factor IX prophylaxis are potentially more cost saving than treating bleeds on-demand when considering drug acquisition costs of factor IX only (base case – intermediate prophylaxis). Intermediate dose factor IX prophylaxis was estimated to be more cost saving than low dose prophylaxis and high dose prophylaxis. Low dose prophylaxis was more cost saving than high dose prophylaxis. Several limitations are noted related uncertainties in patient estimates, treatment of bleeds in practice, and extrapolation of efficacy estimates from haemophilia A studies.

(Refer to appendix 1 for the evidence to decision framework)

SUBCOMMITTEE FOR HAEMOPHILIA RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

The Haemophilia subcommittee suggests the use of factor IX prophylaxis for patients with severe haemophilia B.

Rationale: There is very limited, low quality evidence available for prophylaxis in the management of haemophilia B. However, the benefit of factor IX prophylaxis compared to on-demand/episodic treatment for haemophilia B patients has been shown in non-randomised controlled trials and recommended in guidelines. The majority of guidelines follow the recommendations for haemophilia A. A cost analysis revealed potential cost-savings for all prophylaxis regimens, with intermediate dose prophylaxis found to be the most cost-saving. Low dose prophylaxis was shown to be less cost saving, but more cost-saving than high dose prophylaxis. The costing model relied on many assumptions including uncertain estimates of the number of patients requiring prophylaxis. Despite these limitations, the potential benefit of prophylaxis is acknowledged and alignment with haemophilia A is considered to be beneficial.

Level of Evidence: Level 2 – nonrandomised trials, low quality
Review Indicator: Evidence of harm, cost-effectiveness, cost savings, agent price
Monitoring and evaluation considerations: Monitoring is compulsory, details regarding implementation to be determined for each relevant Standard Treatment Guidelines

NEMLC RECOMMENDATION 27th June 2024:

The NEMLC accepted the haemophilia subcommittee recommendation for factor IX prophylaxis for patients with severe haemophilia B and the relevant updates to the Adult and Paediatric Hospital Level Standard Treatment Guidelines.

BACKGROUND

A medicine review on factor VIII prophylaxis versus treatment on demand for paediatric patients with severe haemophilia A without inhibitors was completed by the Paediatric Expert Review Committee and presented to the NEMLC in October 2022. The NEMLC recommended that a technical working group be established to review the management of haemophilia across levels of care and for all age groups. Additionally NEMLC recommended that costing analysis be conducted. The haemophilia subcommittee was established comprising NEMLC and ERC members (PHC/Adult Hospital, Paediatric Hospital and Tertiary & Quaternary Hospital Levels). The updated medicine review for factor VIII prophylaxis for patients of all ages with severe Haemophilia A without inhibitors was presented to the NEMLC in July 2023 (See Rapid Medicine Review of Factor VIII Prophylaxis for Haemophilia A[14]. Intermediate dose prophylaxis was approved, subject to the proposed amendments to the Standard Treatment Guidelines (Adult and Paediatric Hospital Level) being presented to the NEMLC. This review explores the evidence for IX prophylaxis for patients with severe haemophilia B without inhibitors.

RESEARCH QUESTION

For patients with haemophilia B without inhibitors, how effective is Factor IX prophylaxis compared to treatment of bleeds on demand with Factor IX? Table 1 outlines the scope of the review.

METHODS

Table 1. PICO for medicine review

Population:	Haemophilia B patients without inhibitors
Intervention:	Intervention: Factor IX prophylaxis (facility-based or home-based) – any dose or frequency*
Comparators:	Comparator: On-demand/Episodic Factor IX for minor or major bleeds (facility-based or home-based)
Outcomes:	**Efficacy** • Frequency of any bleeds per year • Frequency of joint bleeding episodes per year **Safety** • Mortality • Development of inhibitors • Serious adverse events / effects • Adverse events / effects **Quality of Life** • Quality of life on validated scales (disease-specific where possible)
Study designs	Systematic reviews, Randomised controlled trials, observational studies, guidelines

*including human plasma, recombinant, standard and extended half-life products

A search was conducted in Cochrane Library, PubMed and Epistemonikos databases in May 2024. The search strategies are detailed in Appendix 2. A general search for guidelines and HTAs was also conducted in Google Scholar, Google and targeted websites, for example Guidelines International Network (G-I-N), utilising a combination of the search terms such as 'haemophilia', 'Factor IX', and 'prophylaxis'.

Screening and full text review was conducted independently by two reviewers (KM, JR) with disagreements regarding exclusion and inclusion of studies handled through discussion. Data from included studies were extracted and analysed by two reviewers (KM & JR). Guidelines were assessed with the AGREE II[1] tool independently by two reviewers (KM, JR or DF) and included if overall assessment was >5 out of 7.

RESULTS

The search resulted in 874 publications and 96 duplicates were removed. After screening, a further 703 articles were excluded. Full text review of 39 remaining articles resulted in the exclusion of 31 studies (Appendix 3 shows the excluded studies). Data was extracted from the 5 studies (See Table 2 below for Characteristics of the included studies). Two guidelines were included (See Guidelines Section for details). Figure 1 below shows the PRISMA diagram.

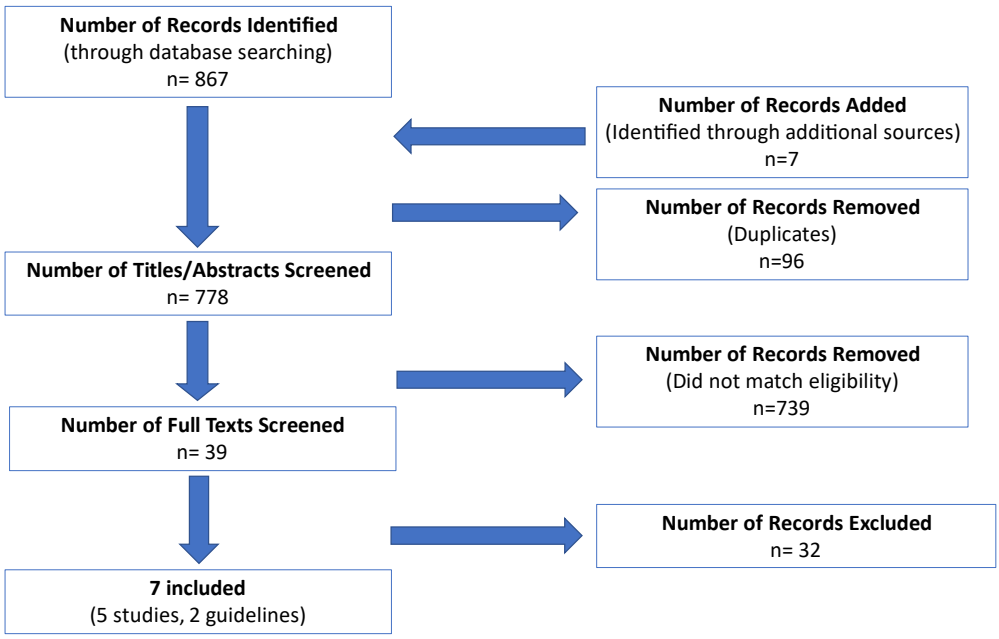

Figure 1: PRISMA diagram for medicine review

Table 2: Characteristics of included studies

Trials						
Study	Date	Study Design	Population	Comparisons	Results	Limitations
Valentino[2]	2014	Phase 4 multicentre randomised, open-label, four-period crossover study (randomization only of prophylaxis groups post on-demand period)	Males with severe or moderately severe Haemophilia B (FIX:C ≤2% and ≥12 bleeding episodes (including ≥6 haemarthrosis episodes) within 12 months of participation Ages 6-65 years, n=50	**Product:** Standard Life Recombinant coagulation factor IX (nonacog alfa) for all groups and periods • Prophylaxis 50IU/kg twice a week (2nd & 4th period) **Vs** On demand treatment (historic control – 1st period) • Prophylaxis 100IU/kg weekly (2nd & 4th period) **Vs** On demand treatment (historic control – 1st period)	Mean ABR • 50 IU twice weekly prophylaxis vs on-demand (Mean difference = -32.5; 95% CI [-38.5 to -26.6]; P<0.0001, n=43 • 100IU once weekly prophylaxis versus on-demand (MD = -30.5; CI [-36.5 to-24.5); P<0.0001, n=44 Safety Most treatment emergent adverse events were mild to moderate *Any adverse event* • On-demand 1st period: 42%; • 50 IU twice weekly prophylaxis: 31.8%; • 100 IU once weekly prophylaxis: 31.8% *Inhibitors:* No patient developed inhibitors during the study	Historic controls; Capturing of bleeds with patient diaries Randomisation for prophylaxis regimens and not on-demand Small number, open label, non-randomised
Kavalki[3]	2016	Open label, non-randomised, 2 period, multicentre trial *Period 1: 26 weeks (on-demand)* *Period 2: 52 weeks (prophylaxis)*	Males with moderately severe to severe haemophilia B (FIX:C ≤2% and ≥12 bleeding episodes (including ≥6 haemarthrosis episodes) within 12 months of participation and >100 exposure days to FIX products. Ages 12-65, n=25	**Product:** Standard Life Recombinant coagulation factor IX (nonacog alfa) for both periods • Prophylaxis 100IU/kg once a week (period 2) **Vs** On demand treatment (period 1)	Mean ABR (+/- SD) On-demand period: 32.9 (17.4) Prophylaxis period: 3.6 (4.6) p < 0.0001 Number of bleeding events On-demand period: 417 Prophylaxis period: 90 Mean joint bleeds (SD) On-demand period: 27.7 (16.9) Prophylaxis period: 2.1 (3.2) Number of patients experiencing joint bleeding events On-demand period: 25 (100%) Prophylaxis period: 12 (48%) Safety Adverse events Most treatment emergent AEs were mild Number of patients with treatment emergent AE	Historic controls; Non-randomised Unclear how data obtained – patient reported? Or at visit? Small number, open label, non-randomised

					On-demand: 16 (64%) Prophylaxis: 24 (96%) Inhibitors and SAE No patient developed a FIX inhibitor or experienced a thrombotic event during the study.	
Collins[4]	2014	Multinational randomised (**prophylaxis groups randomized only**) single-blind trial – prophylaxis groups, on demand parallel group	Moderate or Severe Haemophilia B (FIX activity ≤2 IU/dL) with at least 150 exposure days to any FIX product. Ages 13-70, n=74	**Product:** Recombinant factor IX (nonacog beta pegol) with extended half-life • Prophylaxis 10IU/kg weekly (52 weeks) **Vs** Prophylaxis 40IU/kg weekly (52 weeks) • On-demand group (26 weeks)	Estimated median ABR (IQR) 10 IU/kg prophylaxis: 2.93 (0.99 to 6.02) 40 IU/kg prophylaxis: 1.04 (0.00 to 4.00) On-demand: 15.58 (9.56 to 26.47) Number of patients with bleeds 10 IU/kg prophylaxis: 25/30 40 IU/kg prophylaxis:16/29 On-demand: 14/15 Safety No inhibitor development or thrombotic or hypersensitivity event reported	Allocation into on-demand or prophylaxis not randomised – based on decision of patient and clinician. Open label, non-randomised
Powell[5]	2013	Phase 3, non-randomised, open-label study, parallel group *(allocated based on standard of care at clinical sites by clinician)*	Males with severe haemophilia B (FIX activity ≤2 IU/dL) receiving prophylaxis or had a history of at least 8 bleeding episodes in year before enrolment with at least 100 exposure days to FIX. Ages >12 years, n=123	**Product:** Recombinant factor IX Fc fusion protein (rFIXFc, eftrenonacog alfa) – extended half life • Group 1: rFIXFc weekly dose adjusted prophylaxis (50IU/kg initially) • Group 2: rFIXFc 100IU/kg interval-adjusted prophylaxis (10 days to start) • Group 3: rFIXFc On-demand • Group 4: rFIXFc Treatment in perioperative period	ABR Prophylaxis reduced ABR compared to on demand group 3 for group 1 (83%) and group 2 (87%); p<0.001. Group 1: 3.12, 95% CI [2.46 to 3.95] Group 2: 1.4, 95% CI [0.0 to 3.4] Group 3 (On-demand): 18.67, 95% CI [14.01 to 24.89] Consistent for prespecified subgroup analyses Median ABR for 12 month pre and study result Group 1: 23.0 vs 2.5 Group 2: 25 vs 1.9 Group 3 (on-demand): 18 vs 17.7 Joint ABR Median, IQR Group 1: 1.1, IQR (0.0 to 4.0) Group 2: 0.4, IQR (0.0 to 3.2) Group 3 (On-demand): 13.6, IQR (6.1 to 21.6) Safety Inhibitors	*(groups alloacted based on clinical sites standard of care)* Open label, non-randomised

					One participant had a borderline positive study for inhibitors at the end of the study however were deemed to be transient and low with no clinical effect. <u>Adverse events</u> Across groups, a total of 73.9% had at least 1 adverse event during treatment period - most judged as unrelated to FIX <u>Serious Adverse events</u> 10.9% had at least one serious adverse event, one considered to be related to factor (obstructive clot in urinary collecting system).	
Santagostino[6]	2016	Phase 3, nonrandomised, open-label, multinational trial 2 periods, 2 groups	Severe haemophilia B (FIX activity <2 IU/dL) with at least 150 exposure days to FIX. Males, ages 12-61 years, n=63	Product: Recombinant factor IX Fc fusion protein (rFIXFc) – extended half life <u>Group 1: Period 1 - Prophylaxis / Period 2 - Prophylaxis</u> • Prophylaxis 35-50IU/kg once a week for 26 weeks • Followed by 75IU for 10 or 14 days <u>Group 2: Period 1 - On demand / Period 2 - Prophylaxis</u> • On demand for >/- 26 weeks • Followed by 35-50IU once a week (median 45.1 weeks and *median dose 40.3IU/kg*) *Primary efficacy analysis conducted on group 2	<u>Annualised spontaneous bleeding rate (AsBR)</u> Group 2 (on-demand/prophylaxis) – estimated rate On-demand period: 13.62 95% CI [11.001 to 16.868] Prophylaxis period: 0.55 95% CI [0.233 to 1.322) Median IQR % reduction = 100.00 (90.53 to 100.00); p<0.0001. <u>Total ABR</u> Group 2 (on-demand/prophylaxis) – estimated rate On-demand period: 20.09 95% CI [16.808 to 24.003] Prophylaxis period: 2.22 95% CI [0.942 to 5.243) Median IQR % reduction = 90.94 (81.19 to 100.00); p<0.0001. <u>Safety</u> Inhibitors against FIX were not detected in any patient <u>Adverse events</u> Treatment emergent adverse events were reported in 85.7% of participants. Most were deemed to be of mild of moderate severity and events in 7.9% were considered to be potentially associated with the product (mild to moderate severity). Two patients withdrew after an adverse event (mild to moderate and resolved within the same day without treatment) <u>Serious adverse events.</u> Two patients had an SAE which were deemed unrelated to the product (synovitis and acquired epileptic aphasia)	Unclear on how participants were allocation to groups, only patients who received on demand treatment previously were eligible for on-demand period. Open label, non-randomised

Effectiveness of the intervention

Comparison 1: Prophylaxis versus on-demand/episodic treatment with human plasma or recombinant standard half-life Factor IX (Two trials, n=75).

- *Valentino 2014[2] – randomised, 4 period crossover (randomisation of prophylaxis regimens not on-demand – use of historic controls, open-label, n=50).*
- *Kavalki 2016[3] single arm, non-randomised, historic control, open-label, n=25)*

Outcome 1.1 – Annualised bleeding rate

Valentino 2014 (n=50) reported an annualised mean bleeding rate (ABR) in the 50IU/kg twice a week prophylaxis, and 100IU once weekly prophylaxis regimens of 2.6 and 4.6 respectively, and was significantly lower compared to the first on-demand period of 35.1 ABR (50IU prophylaxis vs on-demand = Mean difference of -32.5; 95% CI [-38.5 to -26.6]; P<0.0001; 100IU vs on-demand = MD of -30.5; CI [-36.5 to-24.5); P<0.0001). Difference between prophylaxis regimens was not significantly different (P=0.2167).

It was found in the trial reported upon by Kavalki 2016 (n=25), that there was lower mean ABR in the prophylaxis period compared to the preceding on-demand period (Mean ABR 3.6 SD +/- 4.6 vs 32.9 SD +/- 17.4; p<0.0001).

Outcome 1.2 – Annualised joint bleeding rate

Valentino 2014 (n=50) reported that the annualised joint bleeding rates were lower in the 50IU/kg twice a week prophylaxis (MD 1.9 ± 4.5) and 100IU/kg once a week prophylaxis (MD 3.6 ± 8.3) compared to the first on-demand period (MD 25.4 ± 19.1) and second on-demand period (MD 24.3 ± 21.5); p values not reported/calculated.

It was found in the trial reported upon by Kavalki 2016 (n=25), that there was lower mean joint ABR in the 100IU once weekly prophylaxis period compared to the preceding on-demand period (Mean ABR 2.1 SD +/- 3.2 vs 27.7 SD +/- 16.9; P value not reported/calculated).

Outcome 1.3 – Safety (Mortality)

This outcome was not reported in the included studies for this comparison

Outcome 1.4 – Safety (Development of inhibitors)

No patient developed a FIX inhibitor during the studies reported by Valentino 2014 and Kavalki 2016.

Outcome 1.5 – Safety (Adverse events)

Majority of the adverse events reported by Valentino 2014 and Kavalki 2016 were considered mild. Valentino 2014 reported that more adverse events occurred during the first on-demand period (42%) compared to the prophylaxis period (31.8% for both the 50IU/kg twice weekly and 100IU/kg once weekly regimens). Kavalki 2016 reported more adverse events in the prophylaxis period (96%) compared to the on-demand period (64%).

Outcome 1.6 – Safety (Serious Adverse events)

Seven serious adverse events deemed to be unrelated to the intervention were reported in by Valentino 2014, occurring five patients (kidney pain, urolithiasis, pneumothorax, accidental injury, severe lower back pain, severe testicular pain, and worsening arthropathy). Kavalki 2016 reported that five patients experienced a serious adverse event with one event (low blood pressure) occurring in the on-demand period deemed to be potentially related to the study drug.

Comparison 2: Prophylaxis versus on-demand/episodic treatment with recombinant extended half-life Factor IX (Three trials, n=260).

- *Collins 2014[4] – randomised (prophylaxis groups randomised only), single-blind trial, on demand open label, parallel group, n=74).*
- *Powell 2013[5] – non-randomised, open-label study, parallel on demand group, n=123)*
- *Santagostino 2016[6] – nonrandomised, open-label, 2 periods, 2 groups, n=63*

Outcome 2.1 - Annualised total bleeding rate

All three trials observed differences in on-demand and prophylaxis treatment. Collins 2014 (n=74) reported that the annualised median bleeding rate was higher in the on-demand group (median 15.58, IQR 9.56 to 26.47) compared to the 10IU/kg prophylaxis (median 2.93, IQR 0.99 to 6.02) and 40IU/kg prophylaxis (median 1.04, IQR 0.00 to 4.00) groups.

Powell 2013 (n=123) found a significant reduction in mean ABR between the weekly dose adjusted (starting 50IU/kg) prophylaxis (Mean: 3.12, 95% CI [2.46 to 3.95]) and the on-demand (Mean: 18.67, 95% CI [14.01 to 24.89]) groups (83% reduction; p<0.001). A significant reduction was also reported in mean ABR between the interval adjusted 100IU prophylaxis (Mean: 1.4, 95% CI [0.0 to 3.4]) and the on-demand (Mean: 18.67, 95% CI [14.01 to 24.89]) groups (87% reduction; p<0.001). Findings were consistent across prespecified subgroup analyses including bleeding trough level of FIX. On comparing the median ABRs 12 months pre study with the study result, larger reductions were observed in the both the weekly dose adjusted (23.0 vs 2.5) group and interval adjusted 100IU/kg prophylaxis (25 vs 1.9) group than in the on-demand group (18 vs 17.7).

Santagostino 2016 (n=63) reported a significant reduction in total ABR when patients switched from the on-demand treatment (est. ABR 20.09, 95% CI [16.808 to 24.003]) period to the prophylaxis (est. ABR 2.22, 95% CI [0.942 to 5.243) period (Median % reduction: 90.94, IQR (81.19 to 100.00); p<0.0001).

Outcome 2.2 – Annualised joint bleeding rate

Powell 2013 (n=123) reported lower median joint ABRs in the weekly dose adjusted (starting 50IU/kg) prophylaxis (Median: 1.1, IQR (0.0 to 4.0]) and interval adjusted 100IU/kg prophylaxis (Median: 0.4, IQR (0.0 to 3.2) groups compared to the on-demand (Median: 13.6 IQR (6.1 to 21.6) group; p value not reported/calculated).

Outcome 2.3 – Safety (Mortality)

This outcome was not reported in the included studies for this comparison

Outcome 2.4 – Safety (Development of inhibitors)

No inhibitor development event was recorded in the trials reported by Collins 2014 and Santagostino 2016. One participant had a borderline positive study for inhibitors at the end of the study reported upon by Powell 2013, however it was deemed to be transient and low with no clinical effect.

Outcome 2.5 – Safety (Adverse events)

Powell 2014 reported that a total of 73.9% of participants had at least one adverse event during treatment period however majority were deemed to be unrelated to FIX. Treatment emergent adverse events were reported in 85.7% of participants as reported by Santagostino 2016. Most were deemed to be of mild of moderate severity. Events in 7.9% of patients were considered to be

potentially associated with the product (mild to moderate severity). Two patients withdrew after an adverse event (mild to moderate and resolved within the same day without treatment)

Outcome 2.6 – Safety (Serious Adverse events)

No thrombotic or hypersensitivity event was recorded in the trial reported by Collins 2014. Powell 2014 reported that 10.9% of participants had at least one serious adverse event, one considered to be related to factor (obstructive clot in urinary collecting system). Two patients had a serious adverse event in the trial reported on by Santagostino 2016, which were both deemed to be unrelated to the product (synovitis and acquired epileptic aphasia)

EVIDENCE QUALITY AND LIMITATIONS

Trials for haemophilia often include both haemophilia A and B patients and with higher proportions of haemophilia A patients. The number of haemophilia B patients included in trials are proportionally low and very few trials focus predominantly on haemophilia B. The search found no RCTs where the on-demand/episodic group and prophylaxis groups were randomised. All trials were open-label and only one trial had a sample size over 100. This condition is however rare, and the feasibility of a patient blinded study is a consideration. Estimates were derived from either parallel comparison to unrandomized groups or results from same individuals either pre-study or at different phases within the same study. Allocation to groups comprising on-demand or prophylaxis components were sometimes unclear or described to be based on clinical practice at the local sites in the trial. Recording of bleeding rates were either not described or recorded by patients in electronic diaries. Overall quality of evidence was considered to be low, level II (non-randomised prospective trials).

GUIDELINES

Five guidelines were assessed with the AGREE II tool (see Appendix x for summary of the assessments). Two guidelines met the eligibility criteria (scoring at least 5 out of 7); conducted by the Malaysian Health Technology Assessment Section (MaHTAS)[7], and the World Federation of Hemophilia (WFH)[15] (See Table 4 below). The paucity of evidence, rare nature of the condition, and design of the studies were cited as limitations for meta-analysis and conducting quality assessments. Recommendations are for haemophilia A and B. Prophylaxis regimens included in the guidelines are summarised in Table 3.

Table 3: Summary of prophylaxis dosing from included guidelines

Prophylaxis Intensity	**WFH 202015**	**MaHTAS[7]**
High-dose prophylaxis	40-60 IU FIX/kg twice per week (>4000 IU/kg per year)	30 - 50 IU/kg twice/week for haemophilia B (preferred)
Intermediate-dose prophylaxis	20-40 IU FIX/kg twice per week (2000-4000 IU/kg per year)	30 - 50 IU/kg once or twice/week
Low-dose prophylaxis (with escalation of dose-intensity; as needed)	10-15 IU FIX/kg twice per week (1000-1500 IU/kg per year)	20 IU/kg once/week

Table 4. Clinical guideline recommendations

Guideline	Recommendations	Strength of evidence	AGREE II
MaHTAS 2018[7]	Prophylaxis should be given to ALL persons with severe haemophilia*. • Primary prophylaxis should start following intracranial haemorrhage, first joint bleed, severe intramuscular bleed or by three years old, whichever comes first. • Malmo protocol** is the preferred prophylactic therapy regimen in haemophilia. *Recommendation for haemophilia A and B; severe classified as <1 IU/dL (<0.01 IU/ml) or <1% of normal *High dose prophylaxis 30 - 50 IU/kg twice/week for haemophilia B	Strength of evidence not provided for overall recommendations, but levels were provided for contributing components were level I and level II-2. Recommendations and evidence were for haemophilia A and B combined.	**Overall assessment score:** 73%, 6 out of 7 **Score for rigour and methodology domain:** 77%
WFH 2020[15]	**Recommendation 6.1.1:** • For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference. • REMARK : Individualizing prophylaxis means that if patients continue to experience bleeds, their prophylaxis regimen should be escalated (in dose/frequency or both) to prevent bleeding. • REMARK : In countries with significant healthcare constraints, the WFH still advocates for the use of prophylaxis over episodic therapy but recognizes that less intensive prophylaxis may be used. **Recommendation 6.2.1:** • For patients with severe phenotype hemophilia A or B, especially children, the WFH recommends regular long-term prophylaxis as the standard of care to prevent hemarthrosis and other spontaneous and breakthrough bleeding, maintain musculoskeletal health, and promote quality of life. When prophylaxis is not feasible, episodic therapy is essential treatment for acute hemorrhages, but it will not prevent long-term joint damage. • REMARK : In the long term, early and regular prophylaxis for children reduces hemarthrosis and other hemophilic bleeding, produces better health and joint outcomes, reduces the number of hospital visits and admissions, and may avert the need for orthopedic interventions, including surgery, in the future. **Recommendation 5.1.1:** • For patients with hemophilia, the WFH does not express a preference for recombinant over plasma-derived clotting factor concentrates. • REMARK : The choice between these classes of product must be made according to local criteria including availability, cost, and patient preferences.	Consensus based recommendations. Guideline developers selected to not assign a strength of evidence through GRADE or other assessment due inability to conduct meta-analysis and nature of the condition. For transparency all recommendations are designated as 'consensus based'. Evidence was acknowledged to be likely low or very low if evaluated.	**Overall assessment score:** 75%, 6 out of 7 **Score for rigour and methodology domain:** 74%

COSTING AND BUDGET IMPACT

A costing and budget impact analysis was conducted to investigate the potential budget impact per annum for treating paediatric patients with severe haemophilia B without inhibitors as well as the cost per bleed averted. The analysis was undertaken from the payer perspective and only direct costs to the public health sector are considered. Indirect and societal costs, such as school or work absenteeism, are not included.

Dosing for prophylaxis regimens and treatment of bleeding events

Several prophylaxis regimens were considered in the analysis, See Table 5. In line with the haemophilia A costing analysis, an intermediate option will be selected for the base case with the twice a week frequency. The high dose and low dose regimens will be explored in the sensitivity analysis. Treatment of bleeds in adults was assumed to be 40IU/kg for minor bleeds and 60IU/kg for major and life threatening bleeds and in paediatrics, 50IU/kg and 65IU/kg for minor and major bleeds respectively.

Table 5: Summary of prophylaxis dosing from included guidelines

Prophylaxis Intensity	Regimen	Sources	Notes
High-dose prophylaxis	50IU/kg **twice a week**	Valentino 2014[2]; WHF 2020[15], MaHTAS 2018[7]	Exact match for trial efficacy estimates; matches high dose for WHF and MaHTAS guidelines
Intermediate-dose prophylaxis	25IU/kg **twice a week**	WHF 2020[15], MaHTAS 2018[7]; Delgado-Flores 2022[13]	WFH and MaHTAS Guideline recommendations for intermediate, efficacy estimates assumed for Haemophilia A intermediate prophylaxis
Low-dose prophylaxis	10IU/kg **twice a week**	WHF 2020[15]; Delgado-Flores 2022[13]	WFH guideline recommendation for low dose, efficacy data from haemophilia A low dose prophylaxis

Population of interest

Population estimates were sourced from the World Federation of Haemophilia, annual global survey[8] and the South Africa Haemophilia Foundation registry data[9]. This provided an estimate of 160 severe haemophilia B patients. An equal proportion in each age group for paediatrics and remainder in adult group was assumed to calculate dose estimates. Table 6 shows the number of patients with age group, estimated weights per age group and factor IX requirements for the base case regimen. There is uncertainty around patients estimates for haemophilia in South Africa and numbers currently treated in the public sector, this be explored in the sensitivity analysis.

Table 6: Average weight, IU requirements and number of patients per age group

Age	Weight (male)	IU per dose (intermediate 25IU/kg)	IU per week (twice a week)	Est. Number of patients
0-1	8	200	400	4
1-2	11	275	550	4
2-3	13.5	337,5	675	4
3-4	15.5	387,5	775	4
4-5	17.5	437,5	875	4
5-6	19.5	487,5	975	4
6-7	22	550	1100	4
7-8	24	600	1200	4
8-9	27	675	1350	4
9-10	30	750	1500	4
10-11	34	850	1700	4

11-12	38	950	1900	4
>12	70	1750	3500	112
			TOTAL	160

Costs

Costs for factor IX products were sourced from the National Department of Health Master Health Product List (contract prices[10]) and the Single Exit Price[11]. Products on contract (haemosolvex ©) will be utilised in the base case and products not on contract (octanine© will be explored in sensitivity analysis). Proxies for facility and health worker costs for administration of prophylaxis and treatment of bleeds were obtained from the Uniform Patient Fee Schedule (dated April 2024)[12]. Consumables were assumed to be included in the facility costs. Facility and health worker costs were not included in base case but accounted for in sensitivity analysis. It was assumed that administration of prophylaxis would occur at community clinic level. It was assumed that there would no vial sharing but no wastage. Costs for surgery and complications were not included. Costs for all bleeds (minor, major and life threating bleeds) were included. Table 7 shows the cost components included in the analyses.

Table 7. Cost point estimates

Item		Value	Reference
Medication Costs			
Haemosolvex® Factor IX complex 500 IU 10ml vial		R2 189.86	MHPL May 2024[10]
Octanine Factor IX 500IU 5ml vial (sensitivity analysis)		R2002.28	SEP May 2024[11]
Health Worker and Facility Costs* (sensitivity analysis only)			
Health worker cost for administration of prophylaxis	Nursing Practitioner	R80	UPFS 2024
Facility cost for administration of prophylaxis	Facility Level 1	R136	
Health worker cost for treatment of minor bleed	Nursing Practitioner	R80	
Facility cost for treatment of minor bleed	Facility Level 1	R136	
Health worker cost for treatment of severe bleeds intensive care	Specialist medical practitioner	R694	
	Nursing Practitioner	R138	
Facility cost for treatment of severe bleed intensive care	Facility Level 3	R9 091	
Health worker cost for treatment of severe bleeds general ward	Specialist medical practitioner	R210	
	Nursing Practitioner	R138	
Facility cost for treatment of severe bleed intensive care	Facility Level 3	R3 341	

Outcomes

Data estimates sourced for Haemophilia B standard half-life products all pertained to high-dose prophylaxis. Thus for the base case (intermediate-dose prophylaxis), estimates for total number of bleeds per annum for each arm were assumed to be same as those utilised for intermediate factor VIII prophylaxis for Haemophilia A intermediate which were sourced from Delgado-Flores 2022[13] (See Rapid Review for Factor VIII Prophylaxis for Haemophilia A)[14]. This was also assumed for low-dose Factor IX prophylaxis; estimates for low-dose factor VIII prophylaxis utilised.

Data sourced from the Valentino 2014[2] (see 'Effectiveness and safety of the intervention above') was utilised to input into the analysis for estimated total number of bleeds per annum for a patient for the high dose factor IX prophylaxis versus on-demand treatment. Estimates for calculating number of severe bleeds (major and life-threatening) as well as number of days of treatment and hospitalization for bleeds were assumed to be the same as those utilised in the haemophilia A costing. Table 8 shows

the point estimates utilised in the analysis. Outcomes for disability, quality of life, surgeries and mortality were not included in the analysis.

Table 8. Outcome point estimates

Item	Value	Reference
No. of minor bleeds per annum per one patient on intermediate dose prophylaxis (25IU/kg twice a week)	4.75	Delgado-Flores 2022 (Haemophilia A[13] - Intermediate-dose) – values reduced to offset severe bleeds
No. of minor bleeds per annum per one on-demand patient	29.45	
% of major bleeds that occur in haemophilia B patients as a % of all bleeds	5%	Srivastava et al. 2021[i 15]
% of children experiencing a life-threatening bleed annually on intermediate-dose prophylaxis	0.5%	Touré et al. 2022[ii 16]
% of children experiencing a life-threatening bleed annually on-demand treatment (intermediate-dose comparison)	2.7%	
No. of days required for treatment of a minor bleed – outpatient	3	Expert opinion (Paediatric Hospital Level ERC) – assumed to be same for Haemophilia B
No. of days required for treatment of a major bleed – inpatient	7	
No. of days required for treatment of an LTB - inpatient	16	
Efficacy for other prophylaxis regimens* (sensitivity analysis only)	Value	Reference
No. of minor bleeds per annum per one patient on high dose prophylaxis (50IU/kg twice a week)	2.85	Valentino 2014[2] – values reduced to offset severe bleeds
No. of minor bleeds per annum per one on-demand patient	33.250	
No. of minor bleeds per annum per one patient on low dose prophylaxis (10IU twice a week)	5.75	Delgado-Flores 2022 (Haemophilia A[13] - low-dose) – values reduced to offset severe bleeds
No. of minor bleeds per annum per one on-demand patient	17.1	

RESULTS

Base Case analysis

Table 9 shows the results of the base case analysis which accounts for **drugs costs only** (at contract price) for **intermediate dose prophylaxis (25IU/kg twice weekly) and treatment of all bleeds** (See sensitivity analysis for scenarios including facility and health worker costs, different prophylaxis regimens and reduction in patient estimates). The total cost per patient on intermediate dose factor IX prophylaxis (25IU/kg twice weekly) was estimated to be R948 998 annum (cost of prophylaxis and treatment of breakthrough bleeds), compared to R1 291 128 per annum for treating one patient on demand (**incremental savings** of R342 130 per patient per annum). Total budget impact was an estimated R151 839 637 for 160 patients on intermediate prophylaxis per annum versus R206 580 443 for 160 patients on demand (incremental cost savings of R54 740 806). Intermediate prophylaxis (25IU/kg twice a week) could potentially avert 4212 bleeds a year; estimated incremental cost of **-R13 265** per bleed averted (**cost saving**).

[i] Value was applied equally across low and intermediate effect sizes to obtain number of major bleeds per comparison

[ii] Value for LTB for intermediate cases proportionally increased in line with minor bleeds from low dose values

Table 9: Base case analysis results

	Costs per annum for all patients				Benefits per annum	
	Cost of Prophylaxis	**Treatment of bleeds**	**Total**	**Incremental Cost**	**No. of bleeds**	**No. bleeds averted**
FIX intermediate dose prophylaxis	R117 516 647	R34 322 990	R151 839 637	-R54 740 806 (cost saving)	842	4212
FIX treatment on demand	NA	R206 580 443	R206 580 443		5054	
Cost per patient per annum					ICER	
Prophylaxis Arm	Prophylaxis	Treatment of bleeds	Total	**Incremental Cost**	ICER – Savings with each bleed averted	
	R734 479	R214 519	R948 998	-R342 130 (cost saving)		
On-demand/ episodic Arm	NA	R1 291 128	R1 291 128		-R12 996 (cost saving)	

Sensitivity analysis - Scenarios

Deterministic sensitivity analysis

Seven different scenarios were run in the analysis to explore impact of changing certain variables and assumptions (See table 10 below).

Table 10: Scenarios explored in the deterministic sensitivity analysis

Scenario	Type of analysis	Variable and/or assumption changed
Base case intermediate prophylaxis (25IU/kg twice a week), drug acquisition costs only and all bleeds		
1	Univariate	Base case but **low dose (10IU/kg twice a week)** instead of intermediate dose prophylaxis, use of estimates from Haemophilia A low dose (Delgado-Flores 2022)
2	Univariate	Base case but **high dose (50IU/kg twice a week)** instead of intermediate dose prophylaxis, uses estimates from Valentino 2014.
3	Univariate	Base case but **assumes 25% less bleeds in the on-demand/episodic arm**
4	Univariate	Base case **AND includes facility and health worker costs**
5	Univariate	Base case but **utilisation of octanine (SEP)**
6	Multivariate	Base case **low dose (10IU/kg twice a week) AND includes facility and health worker costs**
7	Univariate	Base case **but matching consumption (reducing duration of treatment and number of patients)**

Scenario 4 which was intermediate dose prophylaxis but also included facility and health worker costs was the most cost-effective. Using conservative estimates for efficacy (25% less bleeds in the on-demand/episodic arm was the least cost-effective option but still resulted in cost-savings (Scenario 3). Low dose prophylaxis (scenario 1) was less cost-effective than intermediate dose however still results in an estimated savings of R24 575 923 per annum and was more cost-effective than high dose prophylaxis (scenario 2). The scenario with Octanine© using SEP (scenario 5) shows a slightly lower cost savings than the base case with haemosolvex©, however that is assuming the same product is utilised for prophylaxis and bleeds. Table 11 outlines the results for each scenario and Appendix 4 shows full results for base case and scenarios.

Table 11: Results of the deterministic sensitivity analysis

Scenario	Short name	Incremental budget impact	Incremental cost / patient	No. of bleeds averted	Cost per bleed averted
1	Low Dose	-R24 575 923	-R153 600	2 370	-R10 370 (cost saving)

2	High Dose	-R13 126 459	-R82 040	5380	-R2 440 (cost saving)
3	Lower bleeds in on-demand arm	R5 636 700	-R35 229	3 029	-R1 861 (cost-saving)
4	+ facility and health worker costs	-R61 989 062	-R387 432	4 221	-R14 717 (cost-saving)
5	Octanine SEP	-R50 027 109	-R312 699	4 212	-R11 877 (cost-saving)
6	Low dose + facility and health worker costs	-R26 913 438	-R168 209	2 370	-R11 356 (cost-saving)
7	25% of patients, shorter treatment duration for bleeds	-R5 341 945	-R166 936	1043	-R5 124 (cost-saving)

Limitations

Costs for surgeries required for treating major or life threatening bleeds are not included as well as costs for treating long term complications. This costing and budget impact does not look at the impact of mortality, quality of life and disability which a cost utility model would include. As noted with the haemophilia A rapid review, many CEA articles show that prophylaxis is more costly and more effective with the decision on cost-effectiveness based on varied willingness-to-pay thresholds. There is a large variation in CEA results due to lack of standardised approaches (types of costs, perspective, time horizon and model structure).[17,18,19]

Lastly the base case analysis assumes 100% uptake and does not account for current use of factor IX prophylaxis. Patient number estimates for haemophilia are difficult to source and thus patient numbers may differ in reality to estimates utilised in the model. There may be patients that are not treated for bleeds and/or treated with lower doses or shorter durations. National procurement data shows an average (last five years) annual spend of around R30 million on haemosolvex® products. Utilising the above base case modelled cost estimate for one patient per annum on demand treatment (R1 291 128) and the national procurement costs, roughly 15% of estimated 160 patients with severe haemophilia are being actively treated for bleeds on demand. Sensitivity analysis was conducted which modelled 25% of the patient estimate (32 patients) and decreased duration of treatment for bleeds to attempt to match consumption data (see Scenario 7). Scenarios including facility and staff costs assume that all prophylaxis will be administered at facilities whereas in practice there may be some home-based administration.

DISCUSSION AND CONCLUSION

This review was conducted to explore the efficacy, safety and costs for factor IX prophylaxis for haemophilia B patients compared to episodic/on-demand treatment of bleeds. No RCTs were found which randomised prophylaxis and on-demand patients thus five non-randomised trials were included. Quality of studies were considered low due to high risk of bias from open-label design and patient reported or unclear mechanism for reporting/recording outcomes as well as small sample sizes. The rarity and the nature of the condition is a consideration when assessing feasibility of conducting RCTs and ability to recruit larger samples. The studies showed benefit of factor IX prophylaxis over treatment on-demand in annualised bleeding rate and no concerns were found for safety. Two moderate to high quality guidelines were included which recommended prophylaxis for haemophilia B. Costing was conducted on intermediate-dose prophylaxis 25IU/kg twice weekly and resulting in estimated cost-savings. However patient estimates are very uncertain and as with all the other population groups, there are challenges with matching current expenditure to modelled estimates. Despite the limitations outlined, the potential benefit of the intervention (factor IX prophylaxis) is acknowledged. Furthermore, alignment with recommendations for haemophilia A would be beneficial for implementation.

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- Ms K MacQuilkan (EPiC-SCTA) has no interests to declare.
- Dr J Riddin (Affordable Medicines Directorate, National Department of Health) has no interests to declare

APPENDIX 1 - EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ]	Non-randomised trials, open-label, mechanisms for reporting outcomes not always clear.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [X] Moderate [ ] Small [ ] None [ ]	Comparison 1: Standard half-life recombinant Factor IX prophylaxis vs on-demand <u>Annualised Bleeding Rate (ABR)</u> Valentino 2014: n=50 • 50IU/kg twice a week prophylaxis = 2.6 • 100IU/kg once weekly prophylaxis = 4.6 • On-demand = 35.1 Both prophylaxis groups significantly lower compared to the first on-demand period of 35.1 ABR (50IU prophylaxis vs on-demand = Mean difference of -32.5; 95% CI [-38.5 to -26.6]; P<0.0001; 100IU vs on-demand = MD of -30.5; CI [-36.5 to-24.5); P<0.0001). Difference between prophylaxis regimens was not significantly different (P=0.2167). Kavalki 2016 (n=25) • Lower mean ABR in the prophylaxis period compared to the preceding on-demand period (Mean ABR 3.6 SD +/- 4.6 vs 32.9 SD +/- 17.4; p<0.0001).

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Non-randomised trials, open-label, mechanisms for reporting outcomes not always clear.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	Comparison 1: Standard half-life recombinant Factor IX prophylaxis vs on-demand • Majority of the adverse events reported by Valentino 2014 and Kavalki 2016 were considered mild. • Valentino 2014 reported that more adverse events occurred during the first on-demand period (42%) compared to the prophylaxis period (31.8% for both the 50IU/kg twice weekly and 100IU/kg once weekly regimens). • Kavalki 2016 reported more adverse events in the prophylaxis period (96%) compared to the on-demand period (64%).
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	In the committee's opinion the intervention is feasible, however, where this is not the case on-demand treatment will still be available.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
RESOURCE USE	**How large are the resource requirements?** More intensive: ☐ Less intensive: ☐ Uncertain: ☒ X	BASE CASE: Incremental cost for providing one patient with intermediate-dose prophylaxis per annum = (-)R342 130 (cost-savings) Incremental budget impact per annum for all patients = -R54 740 806 (cost savings) **Cost savings** per bleed = R12 996 Intermediate dose prophylaxis provided more cost savings than low dose and high dose prophylaxis scenarios however low dose provides more cost-savings than high dose. Scenario 1: Low dose prophylaxis Incremental budget impact per annum for all patients = **cost savings** of R24 575 923 Incremental cost per patient = **cost savings** of R153 600
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: ☒ x Major: ☐ Uncertain: ☐ **Is the option acceptable to key stakeholders?** Yes: ☒ x No: ☐ Uncertain: ☐	
EQUITY	**Would there be an impact on health inequity?** Yes: ☒ x No: ☐ Uncertain: ☐	Where home-based care is not feasible, children in less well-resourced areas may struggle to access prophylactic factor IX, however, since this can be administered at clinic level inequity should be minimal.

APPENDIX 2 -SEARCH STRATEGY

PUBMED

#	Query	Search Details	Results
10	#6 AND filter for systematic review and meta-analyses	(("haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]) AND ("Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])) AND (meta-analysis[Filter] OR systematicreview[Filter])	10
9	#6 AND #5	("haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]) AND ("Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract]) AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract])	10
8	#6 AND Filter for clinical trials and RCTs	(("haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]) AND ("Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])	69
7	#6 AND #4	("haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]) AND ("Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract]) AND (("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))	357
6	#1 AND #2 AND #3	("haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]) AND ("Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[MeSH Terms]) AND ("prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract])	581
5	Systematic reviews	"systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract]	434 688
4	RCTs	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	5 082 662
3	Prophylaxis (intervention)	"prophyla*"[Title/Abstract] OR "prevent*"[Title/Abstract]]	1 917279
2	Factor IX (intervention & comparator)	"Factor IX"[Title/Abstract] OR "Factor 9"[Title/Abstract] OR "Factor IX"[MeSH Terms]	8 911
1	Hemophilia B (population)	"haemophilia B"[Title/Abstract] OR "hemophilia B"[Title/Abstract] OR "hemophilia B"[MeSH Terms]	5 792

COCHRANE

search	Query	Results
#1	MeSH descriptor: [Hemophilia B] explode all trees	**196**
#2	MeSH descriptor: [Factor IX] explode all trees	**89**
#3	#1 AND #2	**42**
#4	#3 in Cochrane Reviews	**1**

Epistemonikos

Search String	(title:((title:((title:("hemophilia B" OR "haemophilia B") OR abstract:("hemophilia B" OR "haemophilia B")) AND (title:("factor IX" OR "factor 9") OR abstract:("factor IX" OR "factor 9")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))) OR abstract:((title:("hemophilia B" OR "haemophilia B") OR abstract:("hemophilia B" OR "haemophilia B")) AND (title:("factor IX" OR "factor 9") OR abstract:("factor IX" OR "factor 9")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))))) OR abstract:((title:((title:("hemophilia B" OR "haemophilia B") OR abstract:("hemophilia B" OR "haemophilia B")) AND (title:("factor IX" OR "factor 9") OR abstract:("factor IX" OR "factor 9")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))) OR abstract:((title:("hemophilia B" OR "haemophilia B") OR abstract:("hemophilia B" OR "haemophilia B")) AND (title:("factor IX" OR "factor 9") OR abstract:("factor IX" OR "factor 9")) AND (title:(prophyl*) OR abstract:(prophyl*)) OR (title:(prevent*) OR abstract:(prevent*))))))	
Limits/Filters	All studies	109 results
	Filtered for RCTs	3 results
	Filtered for primary studies	98 results
	Filtered for systematic reviews	6 results

APPENDIX 3 - Table of excluded studies

No.	Study	Reason for exclusion
1	Klukowska A, Laguna P, Svirin P, Shiller E, Vdovin V. Efficacy and safety of OCTANINE F in children with haemophilia B. Haemophilia. 2008 May;14(3):531-8. doi: 10.1111/j.1365-2516.2008.01678.x. Epub 2008 Mar 18. PMID: 18355266.	Incorrect study design
2	Andersson NG, Auerswald G, Barnes C, Carcao M, Dunn AL, Fijnvandraat K, Hoffmann M, Kavakli K, Kenet G, Kobelt R, Kurnik K, Liesner R, Mäkipernaa A, Manco-Johnson MJ, Mancuso ME, Molinari AC, Nolan B, Perez Garrido R, Petrini P, Platokouki HE, Shapiro AD, Wu R, Ljung R. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B - the impact of prophylactic treatment. Br J Haematol. 2017 Oct;179(2):298-307. doi: 10.1111/bjh.14844. Epub 2017 Jul 12. PMID: 28699675.	Incorrect study design
3	Young G, Collins PW, Colberg T, Chuansumrit A, Hanabusa H, Lentz SR, Mahlangu J, Mauser-Bunschoten EP, Négrier C, Oldenburg J, Patiroglu T, Santagostino E, Tehranchi R, Zak M, Karim FA. Nonacog beta pegol (N9-GP) in haemophilia B: A multinational phase III safety and efficacy extension trial (paradigm™4). Thromb Res. 2016 May;141:69-76. doi: 10.1016/j.thromres.2016.02.030. Epub 2016 Mar 2. PMID: 26970716.	Incorrect study design
4	Windyga J, Stasyshyn O, Lissitchkov T, Mamonov V, Serban M, Rusen L, Ploder B, Tangada S. Safety, Immunogenicity, and Hemostatic Efficacy of Nonacog Gamma in Patients With Severe or Moderately Severe Hemophilia B: A Continuation Study. Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620950836. doi: 10.1177/1076029620950836. PMID: 32866032; PMCID: PMC7469725.	Incorrect study design
5	Wu R, Luke KH, Poon MC, Wu X, Zhang N, Zhao L, Su Y, Zhang J. Low dose secondary prophylaxis reduces joint bleeding in severe and moderate haemophilic children: a pilot study in China. Haemophilia. 2011 Jan;17(1):70-4. doi: 10.1111/j.1365-2516.2010.02348.x. PMID: 20579111.	Incorrect population
6	Roy S, De AK. Effect of Prophylactic Management of Hemophilia on Bleeding Episodes. Indian J Hematol Blood Transfus. 2019 Jul;35(3):496-501. doi: 10.1007/s12288-018-1054-6. Epub 2018 Dec 3. PMID: 31388263; PMCID: PMC6646620.	Incorrect population
7	Yang R, Wu R, Sun J, Sun F, Rupon J, Huard F, Korth-Bradley JM, Xu L, Luo B, Liu YC, Rendo P. First open-label, single-arm, prospective study of real-world use of FIX replacement therapy in a predominantly pediatric hemophilia B population in China. Medicine (Baltimore). 2021 May 28;100(21):e26077. doi: 10.1097/MD.0000000000026077. PMID: 34032739; PMCID: PMC8154445.	Incorrect study design
8	Fukutake K, Taki M, Matsushita T, Sakai M, Takata A, Yamaguchi H, Karumori T. Postmarketing safety and effectiveness of recombinant factor IX (nonacog alfa) in Japanese patients with haemophilia B. Haemophilia. 2019 Jul;25(4):e247-e256. doi: 10.1111/hae.13783. Epub 2019 Jun 6. PMID: 31168882; PMCID: PMC6852692.	Incorrect study design
9	Shapiro AD, Kulkarni R, Ragni MV, Chambost H, Mahlangu J, Oldenburg J, Nolan B, Ozelo MC, Foster MC, Willemze A, Barnowski C, Jain N, Winding B, Dumont J, Lethagen S, Barnes C, Pasi KJ. Post hoc longitudinal assessment of the efficacy and safety of recombinant factor IX Fc fusion protein in hemophilia B. Blood Adv. 2023 Jul 11;7(13):3049-3057. doi: 10.1182/bloodadvances.2022009230. PMID: 36848635; PMCID: PMC10331408.	Incorrect study design
10	Windyga J, Lin VW, Epstein JD, Ito D, Xiong Y, Abbuehl BE, Ramirez JH. Improvement in health-related quality of life with recombinant factor IX prophylaxis in severe or moderately severe haemophilia B patients: results from the BAX326 Pivotal Study. Haemophilia. 2014 May;20(3):362-8. doi: 10.1111/hae.12315. Epub 2013 Nov 20. PMID: 24251442	Incorrect study design
11	Windyga J, Lissitchkov T, Stasyshyn O, Mamonov V, Rusen L, Lamas JL, Oh MS, Chapman M, Fritsch S, Pavlova BG, Wong WY, Abbuehl BE. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicentre phase I/III study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) haemophilia B. Haemophilia. 2014 Jan;20(1):15-24. doi: 10.1111/hae.12228. Epub 2013 Jul 9. PMID: 23834666.	Incorrect study design

12	Kavakli K, Nişli G, Aydinok Y, Oztop S, Cetingül N, Aydoğdu S, Yalman O. Prophylactic therapy for hemophilia in a developing country, Turkey. Pediatr Hematol Oncol. 1997 Mar-Apr;14(2):151-9. doi: 10.3109/08880019709030901. PMID: 9089743.	Incorrect population
13	Swedish Council on Health Technology Assessment. Treatment of Hemophilia A and B and von Willebrand Disease: A Systematic Review [Internet]. Stockholm: Swedish Council on Health Technology Assessment (SBU); 2011 May. SBU Assessment No. 208E. PMID: 26153606.	Incorrect study design – narrative summary only
14	Polack B, Calvez T, Chambost H, Rothschild C, Goudemand J, Claeyssens S, Borel-Derlon A, Bardoulat I, Maurel F, Woronoff-Lemsi MC; EQOFIX Study Group. EQOFIX: a combined economic and quality-of-life study of hemophilia B treatments in France. Transfusion. 2015 Jul;55(7):1787-97. doi: 10.1111/trf.13016. Epub 2015 Feb 5. PMID: 25652955.	Incorrect outcome
15	Chowdary P, Kearney S, Regnault A, Hoxer CS, Yee DL. Improvement in health-related quality of life in patients with haemophilia B treated with nonacog beta pegol, a new extended half-life recombinant FIX product. Haemophilia. 2016 Jul;22(4):e267-74. doi: 10.1111/hae.12995. Epub 2016 Jun 28. PMID: 27352908.	Incorrect intervention, comparator
16	Naraine VS, Risebrough NA, Oh P, Blanchette VS, Lee S, Stain AM, Hedden D, Teitel JM, Feldman BM. Health-related quality-of-life treatments for severe haemophilia: utility measurements using the Standard Gamble technique. Haemophilia. 2002 Mar;8(2):112-20. doi: 10.1046/j.1365-2516.2002.00591.x. PMID: 11952846.	Incorrect study design
17	Noone D, O'Mahony B, van Dijk JP, Prihodova L. A survey of the outcome of prophylaxis, on-demand treatment or combined treatment in 18-35-year old men with severe haemophilia in six countries. Haemophilia. 2013 Jan;19(1):44-50. doi: 10.1111/j.1365-2516.2012.02934.x. Epub 2012 Aug 23. PMID: 22913831.	Incorrect study design
18	Funding E, Lowe G, Poulsen LH, Shapiro S, Oldenburg J, Eriksson D, Falk A, Rich C. Real-World Effectiveness of rFIXFc Prophylaxis in Patients with Haemophilia B Switched from Standard Half-Life Therapy in Three European Countries. Adv Ther. 2023 Sep;40(9):3770-3783. doi: 10.1007/s12325-023-02559-1. Epub 2023 Jun 23. PMID: 37351812; PMCID: PMC10427542.	Incorrect study design
19	Ay C, Perschy L, Rejtö J, Kaider A, Pabinger I. Treatment patterns and bleeding outcomes in persons with severe hemophilia A and B in a real-world setting. Ann Hematol. 2020 Dec;99(12):2763-2771. doi: 10.1007/s00277-020-04250-9. Epub 2020 Sep 11. PMID: 32918114; PMCID: PMC7683481.	Incorrect study design
20	Lambert T, Rothschild C, Volot F, Borel-Derlon A, Trossaërt M, Claeyssens-Donadel S, Attal S. A national French noninterventional study to assess the long-term safety and efficacy of reformulated nonacog alfa. Transfusion. 2017 Apr;57(4):1066-1071. doi: 10.1111/trf.13988. Epub 2017 Mar 24. PMID: 28337764.	Incorrect study design
21	Berntorp E, Dolan G, Hay C, Linari S, Santagostino E, Tosetto A, Castaman G, Álvarez-Román MT, Parra Lopez R, Oldenburg J, Albert T, Scholz U, Holmström M, Schved JF, Trossaërt M, Hermans C, Boban A, Ludlam C, Lethagen S. European retrospective study of real-life haemophilia treatment. Haemophilia. 2017 Jan;23(1):105-114. doi: 10.1111/hae.13111. Epub 2016 Oct 20. PMID: 27761962.	Incorrect study design
22	Jackson SC, Yang M, Minuk L, St-Louis J, Sholzberg M, Card R, Iorio A, Poon MC. Patterns of tertiary prophylaxis in Canadian adults with severe and moderately severe haemophilia B. Haemophilia. 2014 May;20(3):e199-204. doi: 10.1111/hae.12391. Epub 2014 Mar 3. PMID: 24589126.	Incorrect study design
23	Saulyte Trakymiene S, Clausen N, Poulsen LH, Ingerslev J, Rageliene L. Progression of haemophilic arthropathy in children: a Lithuanian--Danish comparative study. Haemophilia. 2013 Mar;19(2):212-8. doi: 10.1111/hae.12058. Epub 2012 Nov 20. PMID: 23167920.	Incorrect study design
24	Aznar JA, Marco A, Jiménez-Yuste V, Fernández-Fontecha E, Pérez R, Soto I, Parra R, Moreno M, Mingot ME, Moret A; Spanish Haemophilia Epidemiological Study Working Group. Is on-demand treatment effective in patients with severe haemophilia? Haemophilia. 2012 Sep;18(5):738-42. doi: 10.1111/j.1365-2516.2012.02806.x. Epub 2012 Apr 27. PMID: 22537601.	Incorrect study design

25	Panicker J, Warrier I, Thomas R, Lusher JM. The overall effectiveness of prophylaxis in severe haemophilia. Haemophilia. 2003 May;9(3):272-8. doi: 10.1046/j.1365-2516.2003.00757.x. PMID: 12694517.	Incorrect study design
26	Witmer C, Presley R, Kulkarni R, Soucie JM, Manno CS, Raffini L. Associations between intracranial haemorrhage and prescribed prophylaxis in a large cohort of haemophilia patients in the United States. Br J Haematol. 2011 Jan;152(2):211-6. doi: 10.1111/j.1365-2141.2010.08469.x. Epub 2010 Nov 29. PMID: 21114482.	Incorrect study design
27	Olasupo OO, Lowe MS, Krishan A, Collins P, Iorio A, Matino D. Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B. Cochrane Database Syst Rev. 2021 Aug 18;8(8):CD014201. doi: 10.1002/14651858.CD014201. PMID: 34407214; PMCID: PMC8407508.	Incorrect population
28	Delgado-Flores CJ, García-Gomero D, Salvador-Salvador S, Montes-Alvis J, Herrera-Cunti C, Taype-Rondan A. Effects of replacement therapies with clotting factors in patients with hemophilia: A systematic review and meta-analysis. PLoS One. 2022 Jan 14;17(1):e0262273. doi: 10.1371/journal.pone.0262273. PMID: 35030189; PMCID: PMC8759703.	Incorrect population
29	Hart DP, Matino D, Astermark J, Dolan G, d'Oiron R, Hermans C, Jiménez-Yuste V, Linares A, Matsushita T, McRae S, Ozelo MC, Platton S, Stafford D, Sidonio RF Jr, Tiede A. International consensus recommendations on the management of people with haemophilia B. Ther Adv Hematol. 2022 Apr 2;13:20406207221085202. doi: 10.1177/20406207221085202. PMID: 35392437; PMCID: PMC8980430.	Agree score less than 5 out of 7
30	Guidelines for the management of haemophilia in Australia. Available from: https://www.haemophilia.org.au/news/new-haemophilia-clinical-management-guidelines-2/	Agree score less than 5 out of 7
31	Rayment R, Chalmers E, Forsyth K, Gooding R, Kelly AM, Shapiro S, Talks K, Tunstall O, Biss T; British Society for Haematology. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. Br J Haematol. 2020 Sep;190(5):684-695. doi: 10.1111/bjh.16704. Epub 2020 May 10. PMID: 32390158.	Agree score less than 5 out of 7
32	Oladapo AO, Epstein JD, Williams E, Ito D, Gringeri A, Valentino LA. Health-related quality of life assessment in haemophilia patients on prophylaxis therapy: a systematic review of results from prospective clinical trials. Haemophilia. 2015 Sep;21(5):e344-58. doi: 10.1111/hae.12759. Epub 2015 Jul 17. PMID: 26390060.	AMSTAR critically low, only one relevant trial included for population, narrative

APPENDIX 4 – Full results of base case and scenarios

		Costs				Benefits		Cost/benefit	Per patient			
BASE CASE	Intermediate prophylaxis 25IU twice weekly, factor costs only	Cost for prophylaxis	Treatment of bleeds (factor	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - Intermediate dose factor IX prophylaxis	R117 516 647,04	R34 322 990	R151 839 637	-R54 740 806,36	842,00	4212,00	-R12 996,39	R948 997,73	5,26	-R12 996,39	R734 479,04
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R206 580 443,10	R206 580 443		5054,00			R1 291 127,77	31,59		
									-R342 130,04			
SCENARIO 1	Base case but low dose, factor costs only	Cost for prophylaxis	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - Low dose factor IX prophylaxis	R61 946 759,68	R40 757 674	R102 704 434	-R24 575 922,84	985,00	2370,00	-R10 369,59	R641 902,71	6,16	-R10 369,59	R387 167,25
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R127 280 356,84	R127 280 357		3355,00			R795 502,23	20,97		
									-R153 599,52			
SCENARIO 2	Base case but high dose prophylaxis, factor costs only	Cost for prophylaxis	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - High dose factor IX prophylaxis	R204 970 896,00	R20 768 632	R225 739 528	-R13 126 458,81	506,00	5380,00	-R2 439,86	R1 410 872,05	3,16	-R2 439,86	R1 281 068,10
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R238 865 987,05	R238 865 987		5886,00			R1 492 912,42	36,79		
									-R82 040,37			
SCENARIO 3	Base case but lower effect size - 25% less demand bleeds, factor costs only	Cost for prophylaxis (factor only)	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for all patients	Averted bleeds	ICER	Per patient cost	Per patient benef	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - Intermedite dose factor IX prophylaxis	R117 516 647,04	R34 322 990	R151 839 637	-R5 636 699,64	842,00	3029,00	-R1 860,91	R948 997,73	5,26	-R1 860,91	R734 479,04
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R157 476 336,38	R157 476 336		3871,00			R984 227,10	24,19		
									-R35 229,37			
SCENARIO 4	Base case, but includes facility/staff costs	Cost for prophylaxis	Treatment of bleeds (factor &	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benef	ICER	
	Intervention - Intermediate dose factor IX prophylaxis	R121 110 887,04	R36 516 014	R157 626 901	-R61 989 062,36	842,00	4212,00	-R14 717,25	R985 168,13	5,26	-R14 717,25	
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R219 615 963,10	R219 615 963		5054,00			R1 372 599,77	31,59		
									-R387 431,64			
SCENARIO 5	Base case but octanine at SEP	Cost for prophylaxis	Treatment of bleeds (factor	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - intermediate IX prophylaxis	R107 450 353,92	R31 407 621	R138 857 975	-R50 027 108,54	842,00	4212,00	-R11 877,28	R867 862,35	5,26	-R11 877,28	R671 564,71
	Comparator - Treatment of bleeds on demand factor VIII	R0,00	R188 885 083,80	R188 885 084		5054,00			R1 180 531,77	31,59		
									-R312 669,43			
SCENARIO 6	Base case but low dose includes administration/facility costs	Cost for prophylaxis	Treatment of bleeds (factor &	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	
	Intervention - Low dose factor IX prophylaxis	R65 540 999,68	R43 306 863	R108 847 863	-R26 913 437,84	985,00	2370,00	-R11 355,88	R680 299,14	6,16	-R11 355,88	
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R135 761 300,84	R135 761 301		3355,00			R848 508,13	20,97		
									-R168 208,99			
arios but in narra	HAEM A estimates for intermediate											
SCENARIO 7	Base case but adjusting to match consumption, factor only	Cost for prophylaxis	Treatment of bleeds (factor only)	TOTAL costs	Incremental cost	Total number of annual bleeds for	Averted bleeds	ICER	Per patient cost	Per patient benefi	ICER	PROPHYLAXIS COST ALONE per patient
	Intervention - intermediate dose factor IX prophylaxis	R23 503 329,41	R3 103 470	R26 606 799	-R5 341 944,48	103,20	1042,70	-R5 123,18	R831 462,47	3,23	-R5 123,18	R146 895,81
	Comparator - Treatment of bleeds on demand factor IX	R0,00	R31 948 743,48	R31 948 743		1145,90			R998 398,23	35,81		

References

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South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level of Care Medication Review Process
Component: Blood and blood forming organs

MEDICINE REVIEW

Title: Direct oral anticoagulants (DOACs) for venous thromboembolism (VTE) prophylaxis in hospitalised, adult patients

EXECUTIVE SUMMARY

Date:	2 October 2023
Medicine (INN):	Rivaroxaban
Medicine (ATC):	Antithrombotic agents (B01A, B01AF01, B01AE07, B01AF02)
Indication (ICD10 code):	Z29.2 + (I80.0-3/I80.8-9/I81/I82.0-3/I8.8-9/I26.0/I26.9)
Patient population:	Hospitalised adult patients at risk of venous thromboembolism requiring prophylaxis

Prevalence of condition:

- The majority (77-97%) of hospitalised medical and surgical adult patients in South Africa are at moderate to high risk of venous thromboembolism and require chemoprophylaxis.[1,2]
- The burden of infectious diseases including HIV and TB appear to contribute to this high risk of venous thromboembolism in the South African setting.[3]

Level of Care:	Adult Hospital Level
Prescriber Level:	Medical Doctor
Current standard of Care:	Enoxaparin (LMWH) 40mg by subcutaneous injection given daily
Efficacy and safety estimates:	DOACs vs LMWH

Hospitalised medically ill adult patients

- **no difference in risk of mortality,** RR 0.64 (95% CI 0.21 to 1.98)
- **similar risk of VTE** (DVT: RR 1.03 (95% CI 0.34 to 3.08), PE: RR 1.01 (95% CI, 0.29 to 3.53)
- **small increase in the risk of major bleeding,** 4 vs 2 major bleeds per 1000 patients treated, NNTH 500, RR 1.70; (95% CI, 1.02 to 2.82)

Hospitalised surgical adult patients post total hip or total knee arthroplasty

- **similar risk in mortality**, RR 0.94 (95% CI 0.53 to 1.66)
- **no difference in risk of symptomatic PE,** RR 0.74 (95% CI 0.50 to 1.10)
- **decreased risk of symptomatic DVT**, RR 0.56 (95% CI 0.39 to 0.79)
- **similar risk of major bleeding**, RR 1.03 (95% CI 0.79 to 1.35)
- **no difference in risk of reoperation,** RR 1.43 (95% CI 0.75 to 2.71)

Motivator/reviewer name(s):	Gayle Tatz, Marc Blockman
Secretariat support:	Zahiera Adam
PTC affiliation:	Marc Blockman (Western Cape provincial pharmacy therapeutics committee)

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KEY FINDINGS:

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

- We used AGREE II 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.

HOSPITALISED, ADULT, MEDICALLY ILL PATIENTS:

- For the population of medically ill patients requiring VTE prophylaxis, the ASH 2018 guidelines included 3 randomised controlled trials (RCTs) which our AMSTAR appraisal showed to be of good quality. Two of these three comprised the total evidence for the NICE guidelines and thus the ASH 2018 guideline was summarised and reported as it included an additional RCT. We ran an updated search from 1 January 2019 to 30 September 2023, but found no new trials.

- The ASH review found that in hospitalised, medically ill patients using VTE prophylaxis:
  - There is **no difference in risk of mortality** between direct oral anticoagulants (DOACs) and low molecular weight heparin (LMWH), RR 0.64 (95% CI 0.21 to 1.98) with **high-certainty evidence**
  - There is a **similar risk of VTE** (DVT: RR 1.03 (95% CI 0.34 to 3.08); PE: RR 1.01 (95% CI, 0.29 to 3.53) with **moderate-certainty evidence**.
  - The use of a DOAC was associated with a **small increase in the risk of major bleeding** (RR 1.70; 95% CI, 1.02-2.82). Numbers needed to harm = 500 (95% CI 250-∞) and does not translate into an increased mortality risk. This risk may be considered **trivial in the context of major cost-savings** implicated in the recommendation of use of a DOAC in place of LMWH.

HOSPITALISED, SURGICALLY ILL PATIENTS:

- There is a paucity of evidence which compares outcomes associated with using either LMWH or DOACs for patients undergoing major surgery. The sub-population of surgical patients who have undergone hip or knee arthroplasty however, has been extensively studied.

- The ASH 2019 guideline identified 1 systematic review which included 22 studies that fulfilled their inclusion criteria and an additional 16 studies in their update of the systematic review. All studies were RCTs which involved a patient population who had undergone hip or knee replacement and received thromboprophylaxis with either LMWH or a DOAC.

- The ASH review found that in hospitalised, surgically ill patients who had undergone **total hip or total knee arthroplasty** using DOACS vs LMWH for VTE prophylaxis:
  - There is **similar risk in mortality** between DOACs and LMWH, RR 0.94 (95% CI 0.53 to 1.66) with **moderate-certainty** evidence.
  - There is **no difference in risk of symptomatic PE**, RR 0.74 (95% CI 0.50 to 1.10) with **moderate-certainty** evidence.
  - There is **decreased risk of symptomatic DVT**, RR 0,56 (95% CI 0.39 to 0.79) with **high-certainty** evidence.
  - There is **similar risk of major bleeding**, RR 1.03 (95% CI 0.79 to 1.35) with **high-certainty** evidence.
  - There is **no difference in risk of reoperation**, RR 1.43 (95% CI 0.75 to 2.71) with **moderate-certainty** evidence.

- 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.

- Rivaroxaban is currently the only DOAC for which a cost-analysis has been performed as it is on government contract; and 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**.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X

Recommendation: Based on this evidence review, the PHC/Adult Hospital Level Committee recommends that direct oral anticoagulants (DOACs) be used 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.
(Strong: No difference in benefits with trivial increase in major bleeding offset by projected major cost-savings)

Rationale: There is clear evidence of non-inferiority of DOACs (rivaroxaban and apixaban) compared to LMWH for preventing VTE in the above patient populations. In medically ill, hospitalised, adult patients requiring VTE prophylaxis, there was a trivial increase in major bleeding that does not translate into increased mortality and is offset by major cost-savings. Major cost-savings are specific to rivaroxaban at the current contract price, and this recommendation is therefore specific to rivaroxaban within the DOAC class.
Level of Evidence: *Moderate to high certainty*
Review indicator: High quality evidence of a clinically relevant benefit or reduction of harms; new cost data for rivaroxaban, apixaban or LMWH

NEMLC RECOMMENDATION (12 October 2023): NEMLC supported the ERC's recommendation on 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).

Monitoring and evaluation considerations

Research priorities

NAME OF AUTHOR(S)/MOTIVATOR(S) AND CONFLICT OF INTEREST DECLARATION

Current, updated review: Gayle Tatz[1], Marc Blockman[1]
*The above authors have no conflicts of interest to declare.
(Original Review: Roland van Rensburg[2], Veshni Pillay-Fuentes Lorente[2], Tamara Kredo[3], Nqoba Tsabedze[4], Marc Blockman[1])

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[4]University of the Witwatersrand; Adult Hospital Level Committee, National Department of Health, South Africa; Charlotte Maxeke Johannesburg Academic Hospital

1. Introduction/ Background

Cardiovascular disease remains amongst the top three causes of death globally.[1] Within the causes of cardiovascular related deaths, venous thromboembolism (VTE) has high mortality rates and commonly presents as deep vein thrombosis (DVT) or pulmonary embolism (PE).[1–3] Hospitalised patients are at higher risk of developing VTE.[3] A USA study found that per 10 000 person-years, the average annual age- and sex-adjusted incidence of in-hospital VTE was 960.5 (95% confidence interval, 795.1-1125.9) as compared to 7.1 (95% confidence interval, 6.5-7.6) in community residents.[4] This reflects a 135 times greater risk of VTE when hospitalised.

The current standard of care for VTE prevention is low molecular weight heparin (LMWH).[5] Enoxaparin, a LMWH commonly used in South Africa, acts by binding to antithrombin III, leading to the inhibition of factor Xa. This ultimately leads to the decrease of fibrin formation and/or expansion.

Direct oral anticoagulants (DOACs) have been on the international market since 2008, with dabigatran being the first to be marketed as a direct thrombin inhibitor. Dabigatran etexilate, a prodrug, is converted to an active metabolite dabigatran which binds to thrombin hence altering the clotting cascade. It has a quick onset of action (approximately 2 hours) and could potentially not require concomitant administration of parenteral heparin.[6, 7] However, rivaroxaban was first marketed in 2008, followed by apixaban in 2011. Both drugs are inhibitors of factor Xa and do not require initial administration of parenteral heparin.

DOACs have been considered as an alternate to LMWH in the prevention of VTE, as they are available in oral formulations, increasing ease of administration and decreasing potential complications associated with the parenteral route. Major bleeding is a concern with the administration of both the DOACs and heparins, although the risk is attenuated with prevention compared to treatment doses. Reversal agents for some heparins are readily available and affordable in South Africa, but reversal agents for DOACs are expensive and are not readily available in South Africa.

In South Africa, DOACs have become progressively more affordable and rivaroxaban is currently significantly less costly than enoxaparin dose for dose. Due to the profound cost-savings that could be incurred by using rivaroxaban in place of enoxaparin, it would be important to evaluate the role of DOACs as an alternate therapy, or as a potentially new standard of care for VTE prevention. This evaluation assessed the clinical benefits and harms as well as costs in an evidence-based manner, compared to our current standard practice.

2. Purpose/Objective i.e. PICO question:

Should DOACs be used in favour of LMWH for the prevention of VTE in hospitalised adult patients?

Population – Hospitalised, adult patients at risk of VTE
Intervention – DOACs (rivaroxaban, apixaban and dabigatran)
Comparator – Heparin/LMWH
Outcome - Venous thrombosis (deep vein thrombosis – DVT, and pulmonary embolism – PE), embolic events, mortality, major bleeds
Study design - A review of clinical practice guidelines with high quality systematic reviews.

3. Methods:

Health Technology Assessments (HTAs): We conducted a search in September 2023 for HTAs on the following electronic databases: The International Network of Agencies for Health Technology Assessment (INAHTA), Epistemonikos and Cochrane library, using a simple search with broad search terms.

Guidelines: A search for current, relevant practice guidelines with available systematic reviews that informed them was conducted on the following websites: National Institute for Health Care Excellence (NICE), American Society of Haematology (ASH), American Heart Association (ACA), Canadian Agency for Drugs and Technologies in Health (CADTH) and the Scottish Medicines Consortium (SMC). Terms included were "DOAC, VTE and heparin."

The search and screening of eligible HTAs and guidelines were independently reviewed by two reviewers considering the following factors: most recent, best quality, include most evidence (i.e. relevant trials). All included studies are reported in Table 4 Table of excluded evidence, and the excluded studies are described with reason for exclusion below (Table 1).

Critical appraisal: The identified systematic reviews were assessed using the AMSTAR appraisal tool. Related guidelines were appraised using the AGREE II appraisal tool. For the included evidence, we checked the last search dates and then conducted a comprehensive electronic search in two databases (PubMed and CENTRAL) up to 30 September 2021. The search strategy is reported in Appendix 1. All identified records were screened by title and abstract for eligibility by a single reviewer on the COVIDENCE software. All eligible studies for full text review were evaluated by two reviewers for full data extraction.

Excluded guidelines and their related systematic reviews:

Table 1. Table of excluded evidence

Author, date	Patient Population	Type of document	Reason for exclusion
Sterne JAC, et al (2017)[8]	Hospitalised medically ill adults	HTA	Search only done up until September 2014. The review authors did not explain their selection of the study designs for inclusion in the review, and did not investigate for publication bias
NICE (originally published 2018, updated 2019)[9]	Hospitalised, ill adults	Guideline (with report of systematic reviews of RCTs)	Only included 2 RCTs comparing rivaroxaban and apixaban to LMWH, both of which were included in the ASH guideline.
NICE (originally published 2009, updated 2012)[10]	Hospitalised adults post total hip or knee arthroplasty	Guideline (with report of systematic reviews of RCTs)	Only included 6 RCTs comparing rivaroxaban only to enoxaparin, all of which were included in the ASH guideline.

Evidence synthesis

One HTA was identified but the last search date in the HTA was September 2014. The study was excluded from the review because, 1) the review authors did not explain their selection of the study designs for inclusion in the review, and 2) did not investigate for publication bias. We found four clinical practice guidelines: NICE 2018 guideline for prophylaxis in hospitalised adult patients, the NICE guideline for hospitalised adults undergoing hip or knee arthroplasty, the ASH 2018 guideline for prophylaxis in medical patients and the ASH 2019 guideline for prophylaxis in surgical patients[9-12]. All guidelines' overall quality of evidence as per AGREE II was rated 6/7. They were downgraded for inadequate reporting on stakeholder involvement.

<u>Hospitalised, medically ill, adult patients:</u>

The NICE guideline was excluded since it included only 2 RCTs, both of which were included in the ASH guideline.
The ASH guideline included a systematic review of 3 RCTs and was included in this review. Rivaroxaban and apixaban were assessed; no studies on dabigatran were available. We conducted an updated search from 1 January 2019 to 30 September 2021 for RCTs. Four-hundred and thirty-eight articles were identified, four articles were duplicate publications, and 434 articles were screened by title and abstract. Two articles were selected for full text review. We identified one eligible trial; however, it was the publication of the systematic review and meta-analysis that informed 2018 ASH guidelines, and was therefore already incorporated in the 2018 ASH guideline.

Surgical adult patients undergoing total hip or knee arthroplasty:

The NICE guideline was excluded as it was published in 2009 and last updated in2012. It only included 6 RCTs, all of which were included in the more recent ASH 2019 guideline. The ASH guideline included a total of 22 studies from one systematic review and an additional 16 studies after a search of the literature for more recent studies. All included studies were RCTs. Five studies assessed the effects of dabigatran versus enoxaparin, 15 studies assessed the effects of rivaroxaban versus enoxaparin, 4 studies assessed the effects of apixaban, 5 assessed the effects of darexaban and edoxaban and 4 studies assessed the effects of other DOACs. Thirty-four studies reported on mortality, 33 no nonfatal PEs and 30 on symptomatic DVTs (distal and proximal estimates pooled)

Effectiveness of the intervention: Hospitalised, medically ill, adult patients
Follow up range 10-14 days.

1. *Mortality*

From the available evidence, the use of a DOAC (rivaroxaban or apixaban) instead of LMWH for patients at risk of VTE does not impact mortality at 10 to 14-day follow up. The reported risk ratio (RR) for mortality is 0.64; 95% CI, 0.21-1.98. The anticipated absolute effects demonstrated a risk difference with DOACs to be 0 fewer per 1000 patients (95% CI, 1 fewer to 1 more). The evidence was assessed as high certainty evidence.

2. *Venous thrombosis (DVT and PE), and embolic events*

From the available evidence, the use of a DOAC (rivaroxaban or apixaban) instead of LMWH for patients at risk of VTE does not impact the risk of VTE at 10 to 14-day follow up. The reported RR for the development of DVT is 1.03; 95% CI, 0.34-3.08, and for PE the RR is 1.01; 95% CI, 0.29-3.53. The anticipated absolute effects demonstrated a risk difference with DOACs to be 0 fewer per 1000 patients (95% CI, 1 fewer to 2 more) for DVT, and 0 fewer per 1000 patients (95% CI, 1 fewer to 3 more) for PE. The evidence was assessed as moderate certainty evidence. Embolic events were not reported on.

Harms of the intervention: Hospitalised, medically ill, adult patients
Follow up range 10-14 days.

3. *Major bleeds*

Major bleeds were defined according to the International Society on Thrombosis and Haemostasis (ISTH)[14] as follows: a) Fatal bleeding, and/or b) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra- articular or pericardial, or intramuscular with compartment syndrome, and/or c) Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

From the available evidence, the use of a DOAC (rivaroxaban or apixaban) instead of LMWH for patients at risk of VTE was found to impact the risk of major bleeding at 10 to 14-day follow up. The reported RR for the development of major bleeding is 1.7; 95% CI, 1.02-2.82. The anticipated absolute effects demonstrated a risk difference of 1 more major bleed per 1000 patients administered a DOAC compared to LMWH (95% CI, 0 to 4 more). The absolute risk difference was 0.2% (0.4% with a DOAC compared to 0.2% with LMWH). The numbers needed to harm is therefore 500; i.e. 500 patients need to be treated with a DOAC for 1 patient to experience an additional major bleed, compared to LMWH. The evidence was assessed as high certainty evidence.

Table 2: Summary of findings table: hospitalised, medically ill, adult patients from ASH 2018 guideline.

Author(s): Ignacio Neumann, Juan Jose Yepes-Nuñez, Wojtek Wiercioch, Holger Schünemann

Question: Any DOAC compared to LMWH for VTE prophylaxis in acutely ill hospitalized medical patients

Setting: Inpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	any DOAC	LMWH	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 10 days to 14 days; assessed with: VTE related death)												
3	randomised trials	not serious	not serious	not serious	not serious	none	5/9914 (0.1%)	8/9986 (0.1%)	**RR 0.64** (0.21 to 1.98)	**0 fewer per 1,000** (1 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Pulmonary Embolism – representing the moderate marker state (follow up: range 10 days to 14 days; assessed with: Non-fatal PE)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	11/9911 (0.1%)	11/9984 (0.1%) 0.4% [b]	**RR 1.01** (0.29 to 3.53)	**0 fewer per 1,000** (1 fewer to 3 more) **0 fewer per 1,000** (3 fewer to 10 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Proximal Deep Vein Thrombosis – representing the moderate marker state (follow up: range 10 days to 14 days; assessed with: Symptomatic DVT)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	11/9914 (0.1%)	11/9986 (0.1%) 0.2% [c,d]	**RR 1.03** (0.34 to 3.08)	**0 fewer per 1,000** (1 fewer to 2 more) **0 fewer per 1,000** (1 fewer to 4 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Distal Deep Vein Thrombosis – representing the moderate distal DVT marker state (follow up: range 10 days to 14 days; assessed with: Symptomatic DVT)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	11/9914 (0.1%)	11/9986 (0.1%) 0.6% [c,d]	**RR 1.03** (0.34 to 3.08)	**0 fewer per 1,000** (1 fewer to 2 more) **0 fewer per 1,000** (4 fewer to 12 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Major bleeding (follow up: range 10 days to 14 days)												
3	randomised trials	not serious	not serious	not serious	not serious	none	41/10894 (0.4%)	24/10927 (0.2%) 1.2% [e]	**RR 1.70** (1.02 to 2.82)	**2 more per 1,000** (0 fewer to 4 more) **8 more per 1,000** (0 fewer to 22 more)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Serious Imprecision. The relative estimate of effect is compatible with important harm and important benefit for the intervention that probably crosses the relevant decision threshold.

b. Guijarro (2014) reports on the incidence of PE in acutely ill hospitalized medical patients (n=1,148,301) based on findings from the Spanish National Discharge Database from October 2005 to September 2006 (retrospective database study)
c. Guijarro (2014) reports on the incidence of DVT in acutely ill hospitalized medical patients (n=1,148,301) based on findings from the Spanish National Discharge Database from October 2005 to September 2006 (retrospective database study)
d. We applied the assumption that approximately 20% of symptomatic DVTs are proximal, 80% are distal and 100% of each is of moderate severity.
e. Spencer (2014) reported on incidence rates of major bleeding in older adults based on a community-based study (n=1223) (prospective and retrospective)

Evidence quality:
The quality of evidence for the outcomes of mortality and major bleeding was assessed as high certainty evidence. VTE (DVT and PE) was assessed to be of moderate certainty evidence. The overall quality of the guideline was high and rated 6/7 using the AGREE II tool.

Effectiveness of the intervention: Surgical, adult patients undergoing total hip or knee arthroplasty
Follow up range: 10-35 days.

1. Mortality

There is similar risk in mortality between DOACs and LMWH for patients requiring thromboprophylaxis. The reported risk ratio (RR) for mortality is RR 0.94 (95% CI 0.53 to 1.66). The anticipated absolute effect demonstrated a risk difference with DOACs to be 0 fewer deaths (1 fewer to 1 more) per 1000 patients. The evidence was assessed to be of moderate certainty.

2. Deep Vein Thrombosis

There is a reduction in the risk of symptomatic DVT between patients at risk of VTE who use a DOAC compared with LMWH. The reported RR for the development of DVT is RR 0.56 (95% CI 0.39 to 0.79). The anticipated absolute effect demonstrated a risk difference with DOACs to be 3 fewer per 1000 patients (4 fewer to 1 fewer) for DVT. The evidence was assessed to be of moderate certainty.

3. Pulmonary Embolism

There is no difference in the risk of symptomatic PE between patients at risk of VTE who use a DOAC compared with LMWH. The reported RR for the development of PE is RR 0.74 (95% CI 0.50 to 1.10). The anticipated absolute effect demonstrated a risk difference with DOACs to be 1 fewer (3 fewer to 1 more) per 1000 patients. The evidence was assessed to be of high certainty.

Harms of the intervention: Surgical, adult patients undergoing total hip or knee arthroplasty
Follow up range: 10-35 days.

4. Major bleeds

Major bleeds were defined according to the International Society on Thrombosis and Haemostasis (ISTH)[14] as follows: a) Fatal bleeding, and/or b) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra- articular or pericardial, or intramuscular with compartment syndrome, and/or c) Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

There is similar risk of major bleeding between patients at risk of VTE who use a DOAC compared with LMWH. The reported RR for the development of major bleeding is RR 1.03 (95% CI 0.79 to 1.35). The anticipated absolute effect demonstrated a risk difference with DOACs to be 0 fewer (2 fewer to 3 more) per 1000 patients. The evidence was assessed to be of moderate certainty.

5. Reoperation

There is no difference in the risk of reoperation between patients at risk of VTE who use a DOAC compared with LMWH. The reported RR for the occurrence of reoperation is RR 1.43 (95% CI 0.75 to 2.71). The anticipated absolute effect demonstrated a risk difference with DOACs to be 0 fewer (0 fewer to 2 more) per 1000 patients. The evidence was assessed to be of moderate certainty.

Table 3: Summary of findings Table: hospitalised surgical patients undergoing total hip or knee arthroplasty from ASH 2019 guideline.

Author(s): Ignacio Neumann, Itziar Etxeandia-Ikobaltzeta, Gian Paolo Morgano, Wojtek Wiercioch
Question: DOACs compared to LMWH for patients undergoing total hip or knee arthroplasty
Setting: inpatient
Bibliography: American Society of Hematology 2019 Guidelines for Management of Venous Thromboembolism: Prevention of Venous Thromboembolism in Surgical Hospitalized Patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs	LMWH	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 10 days to 35 days)												
34	randomised trials	not serious	not serious	not serious	serious [b]	none	35/24826 (0.1%)	21/17020 (0.1%)	**RR 0.94** (0.53 to 1.66)	**0 fewer per 1,000** (from 1 fewer to 1 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Symptomatic Pulmonary Embolism - representing the moderate marker state (follow up: range 10 days to 35 days; assessed with: non fatal Symptomatic PE)												
33	randomised trials	not serious [c]	not serious	not serious	serious [b]	none	62/24692 (0.3%)	49/16942 (0.3%)	**RR 0.74** (0.50 to 1.10)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
								0.6% [d]		**1 fewer per 1,000** (from 3 fewer to 1 more)		
Symptomatic Proximal Deep Vein Thrombosis - representing the moderate marker state (follow up: range 10 days to 35 days; assessed with: any Symptomatic DVT)												
30	randomised trials	not serious [c]	not serious	not serious	not serious	none	89/23196 (0.4%)	98/16728 (0.6%)	**RR 0.56** (0.39 to 0.79)	**3 fewer per 1,000** (from 4 fewer to 1 fewer) [f]	⊕⊕⊕⊕ HIGH	CRITICAL
								0.6% [e]		**3 fewer per 1,000** (from 4 fewer to 1 fewer)		
Symptomatic Distal Deep Vein Thrombosis - representing the severe marker state (follow up: range 10 days to 35 days; assessed with: any Symptomatic DVT)												
30	randomised trials	not serious [c]	not serious	not serious	not serious	none	89/23196 (0.4%)	98/16728 (0.6%)	**RR 0.56** (0.39 to 0.79)	**3 fewer per 1,000** (from 4 fewer to 1 fewer) [h]	⊕⊕⊕⊕ HIGH	CRITICAL
								0.0% [g]		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs	LMWH	Relative (95% CI)	Absolute (95% CI)		
Major bleeding (follow up: range 10 days to 35 days)												
32	randomised trials	not serious	not serious [i]	not serious	serious [b]	none	280/27464 (1.0%)	143/18918 (0.8%) 1.0% [j]	**RR 1.03** (0.79 to 1.35)	**0 fewer per 1,000** (from 2 fewer to 3 more) **0 fewer per 1,000** (from 2 fewer to 4 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Reoperation (follow up: range 10 days to 35 days)												
15	randomised trials	not serious	not serious	not serious	serious [b]	none	32/18919 (0.2%)	13/14641 (0.1%)	**RR 1.43** (0.75 to 2.71)	**0 fewer per 1,000** (from 0 fewer to 2 more)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. A sensitivity analysis excluding dose-finding studies was conducted and did not significantly change results in terms of point estimates or confidence intervals. Mortality: 0.94 [0.53, 1.66] I2=0% vs 0.79 [0.40, 1.57] I2=0%; Non Fatal Pulmonary embolism: 0.74 [0.50, 1.10] I2=0% vs 0.91 [0.43, 1.94] I2=35%; Symptomatic DVT: 0.56 [0.39, 0.79] I2 7% vs 0.50 [0.31, 0.81] I2=0%; Major bleeding: 1.03 [0.79, 1.35] I2 21% vs 1.11 [0.80, 1.52] I2=5%.

b. For decision making the certainty range around the effect estimates was felt to cross decision thresholds.

c. There was a considerable proportion of missing outcome data. We conducted a sensitivity analysis assuming that the risk of participants randomized but not counted in the intervention group was 3 times the risk of participants randomized and counted on the analysis. Also we assumed that the risk of participants randomized but not counted in the control group was the same that the risk of participants randomized and counted. Such analysis did not appreciably change the results.

d. The symptomatic PE population event rate of 0.56% was based on data from two retrospective cohort analyses of administrative records of 265,382 patients undergoing total hip or total knee arthroplasty in England and Wales (Jameson 2011, Jameson 2012).

e. The symptomatic proximal DVT rate of 0.588% was derived from data from two retrospective cohort analyses of administrative records of 265,382 patients undergoing total hip or total knee arthroplasty in England and Wales (Jameson 2011, Jameson 2012). The rate was calculated applying the assumption that 75% of all symptomatic DVTs (0.785%) are symptomatic proximal DVTs of moderate severity and considered a critical outcome.

f. The absolute risk difference is based on the study event rate of any symptomatic DVT (5.0%), which consisted of the surrogate composite outcome of any symptomatic proximal or distal DVT. Applying the assumption that only 75% of any symptomatic DVTs are proximal, the calculated absolute risk difference would be 2 fewer per 1,000 (from 3 fewer to fewer) based on an event rate of 0.45%.

g. The symptomatic distal DVT rate of 0.049% was derived from data from two retrospective cohort analyses of administrative records of 265,382 patients undergoing total hip or total knee arthroplasty in England and Wales (Jameson 2011, Jameson 2012). The rate was calculated applying the assumption that 25% of all symptomatic DVTs (0.785%) are symptomatic distal DVTs, of which 25% are assumed to be severe DVTs and considered a critical outcome.

h. The absolute risk difference is based on the study event rate of any symptomatic DVT (0.6%), which consisted of the surrogate composite outcome of any symptomatic proximal or distal DVT. Applying the assumption that only 25% of any symptomatic DVTs are distal, of which 25% are assumed to be severe DVTs and considered a critical outcome, the calculated absolute risk difference would be 0 fewer per 1,000 (from 0 fewer to 0 fewer) based on an event rate of 0.0375%.

i. Some heterogeneity detected (I2=21%), but we did not downgrade.

j. Gerken (2010) reports major bleeding rates of 1% for LMWH.

Table 4: Summary of included guidelines and related systematic review.

Author, date	Population	Interventions	Outcomes	Appraisal and comments
ASH 2018 guidelines on VTE prophylaxis for medically ill hospitalised patients, Holger J. Schunemann	3 RCTs Approximately 10 000 participants	Intervention (DOAC) rivaroxaban, apixaban and betrixaban Standard course inpatient treatment of 6 to 14 days of the LMWH enoxaparin with an extended treatment of 30 to 42 days of the DOAC	<u>VTE related mortality:</u> RR, 0.64; (95% CI, 0.21-1.98); risk difference, 0 fewer deaths per 1000; (95% CI, 1 fewer to 1 more per 1000); high certainty evidence <u>DVT</u> Symptomatic DVT: RR, 1.03; (95% CI, 0.34-3.08); risk difference, 0 fewer per 1000; (95% CI, 1 fewer to 2 more per 1000); moderate certainty evidence <u>PE</u> Nonfatal PE: RR, 1.01; (95% CI, 0.29-3.53); risk difference, 0 fewer per 1000; (95% CI, 1 fewer to 3 more per 1000); moderate certainty evidence <u>Major bleeding</u> RR, 1.70; (95% CI, 1.02-2.82); risk difference, 1 more per 1000; (95% CI, 0 or 4 more major bleeds); high certainty evidence	Appraisal: AGREE II – 6/7 The points were lost in stakeholder involvement and rigour development. The inclusion criteria was not stated in methods and was stated that it was published in a subsequent article. Recommendation: In acutely ill hospitalised medical patients, the ASH guideline panel recommends using LMWH over DOACs as VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects).
ASH 2019 guidelines on VTE prophylaxis for surgical hospitalised patients	38 RCTs Approximately 24 000 participants	DOACs (rivaroxaban, apixaban, dabigatran, darexaban, edoxaban and other (including betrixaban) Standard dosing of rivaroxaban: 10mg orally daily. Standard dosing of enoxaparin 40mg subcutaneously daily. Duration of treatment was variable and between 10 and 35 days	<u>Mortality:</u> RR 0.94 (95% CI 0.53 to 1.66); risk difference 0 fewer deaths (1 fewer to 1 more) per 1000 patients; moderate certainty evidence. <u>Deep Vein Thrombosis:</u> RR 0.56 (95% CI 0.39 to 0.79); risk difference 3 fewer per 1000 patients (4 fewer to 1 fewer); moderate certainty evidence. <u>Pulmonary Embolism</u> RR 0.74 (95% CI 0.50 to 1.10); risk difference 1 fewer (3 fewer to 1 more) per 1000 patients; high certainty evidence. Major bleeding: RR 1.03 (95% CI 0.79 to 1.35); risk difference 0 fewer (2 fewer to 3 more) per 1000 patients; moderate certainty evidence. <u>Reoperation</u> RR 1.43 (95% CI 0.75 to 2.71), risk difference 0 fewer (0 fewer to 2 more) per 1000 patients; moderate certainty evidence.	Appraisal: AGREE II – 6/7 The points were lost in stakeholder involvement and rigor of development. Recommendation: In patients undergoing total hip or knee arthroplasty in which anticoagulants are used, the ASH guideline panel suggests using DOACs over LMWH (conditional recommendation based on moderate certainty in the evidence of effects)

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Medically ill, hospitalised patients: VTE outcomes (DVT and PE) were assessed as moderate certainty evidence, downgraded for serious imprecision. The outcome of mortality was assessed as high certainty. Overall, an assessment of moderate certainty was made. Surgical patients undergoing total hip or knee arthroplasty: Mortality and DVT outcomes were assessed as moderate certainty evidence, downgraded for serious imprecision. The outcome of pulmonary embolism was assessed as high certainty evidence. Overall, an assessment of moderate certainty was made.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒	Medically ill, hospitalised patients: There was no difference in mortality and similar risk of VTE outcomes with DOAC compared to LMWH use. • Mortality: RR, 0.64 (95% CI 0.21 to 1.98) • DVT: RR 1.03; (95% CI 0.34 to 3.08) • PE: RR 1.01 (95% CI 0.29 to 3.53) Surgical patients undergoing total hip or knee arthroplasty: There was a similar risk in mortality, no difference in risk of PE and decreased risk of DVT with DOAC compared to LMWH use. • Mortality: RR 0.94 (95% CI 0.53 to 1.66) • DVT: RR 0.56 (95% CI 0.39 to 0.79) • PE: RR 0.74 (95% CI 0.50 to 1.10)
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Medically ill, hospitalised patients: The outcome of major bleeding was assessed as high certainty evidence. Surgical patients undergoing total hip or knee arthroplasty: The outcome of major bleeding was assessed as moderate certainty evidence, downgraded for serious imprecision. The outcome of reoperation was assessed as moderate certainty evidence.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☒ None ☐	Medically ill, hospitalised patients: There was a trivial increase in risk of major bleeding with use of DOACs compared with LMWH • Major bleeding: RR 1.70 ((95% CI 1.02 to 2.82); 4 vs 2 major bleeds per 1000 patients = 2 more per 1000 with DOACs (0 more to 4 more); number needed to harm = 500 (95% CI 250 to ∞) Surgical patients undergoing total hip or knee arthroplasty: There was a similar risk of major bleeding and no difference in the risk of reoperation with use of DOACs compared with LMWH. • Major bleeding: RR 1.03 (95% CI 0.79 to 1.35) • Reoperation: RR 1.43 (95% CI 0.75 to 2.71) Overall there was a small increase in risk of harmful outcomes.

<table>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
Favours intervention [ ] Favours control [ ] Intervention = Control [X]</td><td>The intervention is non-inferior to control in terms of risk of VTE and mortality in both medically ill, hospitalised adults and surgical patients undergoing total hip or knee arthroplasty. There is no difference in risk of major bleeding or reoperation in surgical patients undergoing total hip or knee arthroplasty. The increase in risk of major bleeding in medically ill, hospitalised adults, is trivial and may be offset by cost-saving associated with use of the intervention.</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available: n/a</td><td>This is a therapeutic multiple medicine review.</td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [X] Uncertain [ ]

Significant savings to be made in switching from enoxaparin (current standard of care) to rivaroxaban for the prevention of VTE (See Appendix 2 for further detail).</td><td>Price of medicines/ daily dose
*The cost analysis in appendix 2 shows significant cost-saving when using rivaroxaban. Other DOACs are currently more expensive than rivaroxaban and formal cost analysis has not been performed.
<table><tr><th colspan="3">VTE prophylaxis</th></tr><tr><th>Drug</th><th>Price/unit</th><th>Cost per day per patient</th></tr><tr><td>Enoxaparin 40mg OD*</td><td>54.99</td><td>54.99</td></tr><tr><td>Rivaroxaban 10mg OD*</td><td>14.66</td><td>14.66</td></tr><tr><td>Apixaban 2.5mg BD**</td><td>14.75</td><td>29.49</td></tr><tr><td colspan="3">*MHPL – 1 Sep 2023
**SEP database – 14 Aug 2023</td></tr></table></td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [X] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [X]</td><td>No local survey evidence could be sourced. Evidence from North America and Europe suggests that patients prefer oral prophylaxis over injection and were most concerned about the risk of pulmonary embolism.[12]</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [X] No [ ] Uncertain [ ]</td><td>Massive cost-savings of choosing the intervention would impact budget allocation and allow for spending elsewhere to improve health equity.</td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial (v5.0)	18 November 2021	RVR, VPL, TK, NT, MB, TL	DOACs not be used for the prevention of VTE, as there is no clear evidence of superior efficacy compared to LMWH, with an increased signal of harms.
V6.0	26 Sep 2023	GT, MB	Recommendation revised in view of the reduction in price of rivaroxaban and the revised comparative costs and changed in favour of using DOACs over LMWH.

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Appendix 1: Search strategy

Database: **CENTRAL (Issue 9 OF 12, September 2021)**
Date: **30 September 2021**

ID	Search	Hits
#1	[mh "venous thrombosis"] or phlebothrombos*:ti,ab or ("deep vein" next thrombos*):ti,ab or DVT:ti,ab, (Word variations have been searched)	6373
#2	[mh "pulmonary embolism"] or (pulmonary next embolism*):ti,ab or (pulmonary next thrombo*):ti,ab or PE:ti,ab (Word variations have been searched)	7591
#3	[mh "venous thromboembolism"] or (venous next thrombo*):ti,ab or VTE:ti,ab (Word variations have been searched)	6879
#4	#1 or #2 or #3	15555
#5	(oral next anticoagulant*):ti,ab (Word variations have been searched)	2003
#6	[mh dabigatran] or dabigatran:ti,ab'kw or pradaxa:ti,ab,kw or "BIBR 1048":ti,ab,kw (Word variations have been searched)	7591
#7	[mh rivaroxaban] or rivaroxaban:ti,ab,kw or xarelto:ti,ab,kw or "BAY 59 7939":ti,ab,kw or "BAY 597939":ti,ab,kw (Word variations have been searched)	1884
#8	apixaban:ti,ab,kw or eliquis:ti,ab,kw or "BMS 562247":ti,ab,kw or BMS562247:ti,ab,kw (Word variations have been searched)	1027
#9	#5 or #6 or #7 or #8	11019
#10	MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees	2026
#11	[mh heparin] or heparin*:ti,ab,kw or liquaemin:ti,ab,kw or UFH:ti,ab,kw or LMW:ti,ab,kw or LMWH:ti,ab,kw or LMWHS:ti,ab,kw or "low-molecular-weight":ti,ab,kw or dalteparin:ti,ab,kw or enoxaparin:ti,ab,kw or nadroparin:ti,ab,kw or tinzaparin:ti,ab,kw or certoparin:ti,ab,kw or parnaparin:ti,ab,kw or ("vitamin K" next antagonist*):ti,ab,kw	15661
#12	#10 or #11	15661
#13	#4 and #9 and #12	804
#14	#4 and #9 and #12 with Publication Year from 2019 to 2021, in Trials	209

Database: **PubMed**
Date: **30 September 2021**

Search	Query	Results
#14	Search: #11 AND #12 Filters: from 2019/1/1 - 2021/9/30 Sort by: Most Recent	553
#13	Search: #11 AND #12 Sort by: Most Recent	2,081
#12	Search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	4,533,027
#11	Search: #4 AND #9 AND #10 Sort by: Most Recent	3,169
#10	Search: heparin[mh] OR heparin*[tiab] OR heparinic acid[tiab] OR liquaemin[tiab] OR UFH[tiab] OR heparin, low-molecular-weight[mh] OR LMW [tiab] OR LMWH[tiab] OR LMWHS[tiab] OR low-molecular-weight[tiab] OR dalteparin[tiab] OR enoxaparin[tiab] OR nadroparin[tiab] OR tinzaparin[tiab] OR certoparin[tiab] OR parnaparin[tiab] OR vitamin K antagonist*[tiab] Sort by: Most Recent	151,273
#9	Search: #5 OR #6 OR #7 OR #8 Sort by: Most Recent	22,536
#8	Search: apixaban[nm] OR apixaban[tiab] OR eliquis[tiab] OR BMS 562247[tiab] OR BMS562247[tiab] Sort by: Most Recent	4,472
#7	Search: rivaroxaban[mh] OR rivaroxaban[tiab] OR xarelto[tiab] OR BAY 59 7939[tiab] OR BAY 597939[tiab] Sort by: Most Recent	6,858
#6	Search: dabigatran[mh] OR dabigatran[tiab] OR pradaxa[tiab] OR BIBR 1048[tiab] Sort by: Most Recent	5,993
#5	Search: "oral anticoagulant"[tiab] OR "oral anticoagulants"[tiab] Sort by: Most Recent	16,347
#4	Search: #1 OR #2 OR #3 Sort by: Most Recent	172,173
#3	Search: Venous thromboembolism[mh] OR venous thrombo*[tiab] OR VTE[tiab] Sort by: Most Recent	55,557
#2	Search: Pulmonary embolism[mh] OR pulmonary embolism*[tiab] OR pulmonary thrombo*[tiab] OR PE[tiab] Sort by: Most Recent	94,223
#1	Search: Venous thrombosis[mh] OR phlebothrombos*[tiab] OR deep vein thrombos*[tiab] OR DVT[tiab] Sort by: Most Recent	68,272

Appendix 2: BIA Analysis

National Essential Medicines List
Budget impact analysis
Adult Hospital Level
Component: BBFO

Date: 16 March 2023
Medication: Rivaroxaban
Indication: Prophylaxis of venous thromboembolic disease in hospitalised adult patients

1. INTRODUCTION

In January 2023, rivaroxaban was approved on a limited tender due to supply constraints with warfarin. Effective May 2023, rivaroxaban will be available in State on a limited tender as a non-EML medicine at a 52% discount to the SEP[1]. The formulations and approved prices are included in Table 1 below.

Table 1: Formulation and prices of rivaroxaban approved on limited tender[2]

Formulation	Pack size	Tender Price (May 2023)	Price/unit
Rivaroxaban; 10mg; Tablet	30 tablets	R439.66	R14.66
Rivaroxaban; 15mg; Tablet	42 tablets	R615.52	R14.66
Rivaroxaban; 20mg; Tablet	28 tablets	R410.35	R14.66

At these tender prices, the cost per dose of rivaroxaban is considerably less than enoxaparin 40mg (R53.61 per dose[3]), which is on tender for a number of indications, including, for the prevention of venous thromboembolic disease as medical and surgical prophylaxis in adult hospitalised patients. A budget impact analysis has been conducted to determine whether the current recommendation for the use of enoxaparin for the prevention of venous thromboembolic disease in hospitalised adult patients should be retained or whether rivaroxaban should be considered as an alternative.

Note:

1. The use of rivaroxaban for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent venous thromboembolic events (VTE) as well as for the prevention of stroke in atrial fibrillation (AF) have been addressed separately with warfarin as the current standard of care.
2. Evidence [4, 5] suggests that aspirin may be as effective as anticoagulants for the prevention of venous thromboembolism in moderate risk patients post orthopaedic surgery. This applies to prophylaxis of VTE in patients post total knee arthroplasty (TKA) and total hip arthroplasty (THA), as well as patients with trauma-related operative extremity fractures or any pelvic or acetabular fracture (operative or non-operative). Evidence for VTE prophylaxis with aspirin post TKA or THA is of variable quality and difficult to synthesize owing to variability in dosing, duration of therapy, adjunct mechanical measures for VTE prophylaxis and risk stratification to determine which methods of prophylaxis should be utilised. In this patient demographic (post TKA or THA), there is a proportion of patients in whom VTE prophylaxis with aspirin may be non-inferior. A more robust recommendation could be made for low to moderate risk

[1] Database of Medicine Prices Dec 2022. Ixarola 10mg unit price =R30.60 effective 18 Feb 2022.

[2] HP09 contract circular 7 Feb 2023 effective from May 2023

[3] MHPL Mar 2023

[4] Mistry DA, Chandratreya A, Lee PYF. A Systematic Review on the Use of Aspirin in the Prevention of Deep Vein Thrombosis in Major Elective Lower Limb Orthopedic Surgery: An Update from the Past 3 Years. Surg J (N Y). 2017 Dec 29;3(4):e191-e196. doi: 10.1055/s-0037-1615817. PMID: 29302621; PMCID: PMC5747531.

[5] Major Extremity Trauma Research Consortium (METRC); O'Toole RV, Stein DM, O'Hara NN, Frey KP, Taylor TJ, Scharfstein DO, Carlini AR, Sudini K, Degani Y, Slobogean GP, Haut ER, Obremskey W, Firoozabadi R, Bosse MJ, Goldhaber SZ, Marvel D, Castillo RC. Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture. N Engl J Med. 2023 Jan 19;388(3):203-213. doi: 10.1056/NEJMoa2205973. PMID: 36652352.

patients with trauma-related fractures, although not all patients may receive prophylaxis and the duration of prophylaxis is invariably short (3 days). In these patient populations in which patients are at high risk of VTE or where aspirin is not appropriate, rivaroxaban may be considered.

2. LICENSED INDICATIONS

The SAHPRA approved indications for rivaroxaban and enoxaparin for prevention of thromboembolic disease are tabulated below. Comparison to U.S. and UK registered indications also included.

Table 2: Comparative registered indications for enoxaparin and rivaroxaban

MEDICINE	INDICATION	REGULATORY APPROVAL			TREATMENT COST
		S.A.	UK	US	
Rivaroxaban	Prophylaxis of venous thromboembolism after knee or hip surgery: 10 mg once daily, within 6–10 hours after surgery provided that haemostasis has been established. Treatment should be continued for 2 weeks after major knee surgery and for 5 weeks after hip surgery.	Y	Y	Y	Knee R205.24 Hip R513.10
Rivaroxaban	Venous thromboembolism (VTE) prophylaxis in acutely ill hospitalised patients at increased risk for thromboembolic complications but not at high risk of bleeding, 10 mg once daily, can be started during the hospital stay and continued for 31 to 39 days.	N	N	Y	*Variable based on length of stay*
Enoxaparin	Prevention of venous thrombosis after orthopaedic surgery: SC, 40 mg once daily, initiated 12 hours pre-operatively and continued for as long as risk persists (generally for 7–10 days; hip replacement, 3 weeks	Y	Y	Y	Orthopaedic R536.10 Hip R1125.81
Enoxaparin	Prevention of venous thrombosis in medical patients: SC, 40 mg once daily continued until fully ambulatory; minimum duration of therapy, 6 days.	Y	Y	Y	*Variable based on length of stay*

3. SAFETY AND EFFICACY

SURGICAL PROPHYLAXIS

The RECORD 1, 2, 3 and 4 studies were considered by NICE in their consideration for the use of rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults[6]. NICE concluded that rivaroxaban was at least as effective as enoxaparin in preventing VTE, noting an increase in the relative risk of major bleeding. The incidence of treatment-emergent major bleeding was the main safety endpoint in the RECORD trials. The rates of major bleeding as reported for the four studies for rivaroxaban versus enoxaparin is as follows: RECORD 1: 0.3% vs 0.1%, p = 0.178; RECORD 2: 0.1% vs 0.1%, p = 0.98; RECORD 3: 0.6% vs 0.5%, p = 0.77; and RECORD 4: 0.7% vs 0.3%, p = 0.11. An overview of the four studies assessed is included below:

[6] NICE TAG (TA170) rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (April 2009)

3.1 SURGICAL PROPHYLAXIS – HIP

RECORD 1[7] (n=4541) was a multicentre, prospective, double-blind, parallel-group design RCT comparing rivaroxaban with enoxaparin for the prevention of VTE after total hip replacement surgery. Rivaroxaban was administered at a dosage of 10 mg once daily for 35 days starting on the day of surgery. Enoxaparin was administered at a dosage of 40 mg starting 1 day before surgery and for 35 days thereafter. A composite primary endpoint, defined as the composite of deep-vein thrombosis (either symptomatic or detected by bilateral venography if the patient was asymptomatic), nonfatal pulmonary embolism, or death from any cause at 36 days (range, 30 to 42), between rivaroxaban and enoxaparin based on a 'modified' intention to treat (MITT) analysis was reported. The primary endpoint occurred in 1.1% of the rivaroxaban group compared with 3.7% of the enoxaparin group; relative risk reduction (RRR) was 70% (95% confidence interval [CI] 49 to 82, p < 0.001).

RECORD 2[8] (n=2509) was a multicentre, prospective, double-blind, parallel-group design comparing 35 days of prophylaxis with rivaroxaban 10mg OD with 15 days of enoxaparin 40mg OD in patients undergoing total hip surgery. A statistically significant difference in the incidence of the composite primary endpoint (defined as the composite of deep-vein thrombosis (symptomatic or asymptomatic detected by mandatory, bilateral venography), non-fatal pulmonary embolism, and all-cause mortality up to day 30–42), between rivaroxaban and enoxaparin in the MITT analysis was reported; 2.0% in the rivaroxaban group compared with 9.3% in the enoxaparin group (RRR 79%, 95% CI 65 to 87).

3.2 SURGICAL PROPHYLAXIS – KNEE

RECORD 3[9] (n = 2531) was a multicentre, prospective, double-blind, parallel-group design RCTs comparing prophylaxis of rivaroxaban (10mg OD for 10-14 days) with enoxaparin (40mg OD a day before surgery and for 10-14 days thereafter) in patients undergoing total knee replacement surgery. The MITT was reported as a statistically significant difference in the incidence of the composite primary endpoint which was the composite of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE) and all-cause mortality: 9.6% in the rivaroxaban group compared with 18.9% in the enoxaparin group (RRR 49%, 95% CI 35 to 61). Major VTE occurred in 9 (1.0%) patients receiving rivaroxaban compared with 24 (2.6%) patients receiving enoxaparin (RRR 62%, 95% CI 18 to 82; p = 0.02).

RECORD 4[10] (n = 3148) was a multicentre, prospective, double-blind, parallel-group design RCTs comparing enoxaparin 30 mg twice daily starting 1 day before surgery and continuing for 10–14 days thereafter. The composite primary outcome (defined as the composite of any deep-vein thrombosis, non-fatal pulmonary embolism, or death from any cause up to day 17 after surgery), occurred in 6.9% and 10.1% of the rivaroxaban and enoxaparin groups, respectively (p < 0.012), with a lower incidence of major VTE events in the rivaroxaban arm.

SAFETY

The incidence of treatment-emergent bleeding was the main safety endpoint in the RECORD studies which was reported for rivaroxaban and enoxaparin respectively, as follows: RECORD 1: 0.3% vs 0.1%, p = 0.178; RECORD 2: 0.1% vs 0.1%, p = 0.98; RECORD 3: 0.6% vs 0.5%, p = 0.77; and RECORD 4: 0.7% vs 0.3%, p = 0.11.

[7] Eriksson BI, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008 Jun 26;358(26):2765-75. doi: 10.1056/NEJMoa0800374. PMID: 18579811.

[8] Ajay K Kakkar, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial, The Lancet,Volume 372, Issue 9632, 2008, Pages 31-39.

[9] Lassen M, Ageno W, Bandel T, et al. RIVAROXABAN FOR THROMBOPROPHYLAXIS AFTER TOTAL KNEE REPLACEMENT: THE RECORD3 TRIAL. Orthop Procs. 2010;92-B(SUPP_II):289-290. doi:10.1302/0301-620X.92BSUPP_II.0920289d

[10] Turpie AG, et al. RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009 May 16;373(9676):1673-80. doi: 10.1016/S0140-6736(09)60734-0. Epub 2009 May 4. Erratum in: Lancet. 2022 Dec 10;400(10368):2048. PMID: 19411100.

RECENT UPDATES ON RECORD 4:

Recent revelations on the RECORD 4 study[11] indicate that the study was excluded by the FDA as unreliable and that the FDA registration granted in 2011 was based on the results of the RECORD 1, 2 and 3 studies only, which were deemed reliable.

A correction statement was subsequently issued by the RECORD4 Steering Committee and published in the Lancet in Dec 2022[12]. The Committee advised that previous FDA reports from the RECORD 4 study revealed that 1227 of 3148 patients enrolled in RECORD4 might have been randomised postoperatively rather than preoperatively, as stated in the protocol. The FDA concluded that it would need to exclude 652 of the 3148 patients. Furthermore, the Steering Committee also learned that adverse events and serious adverse events had been under-reported at the 9·9% of sites audited for RECORD4 and recommended that the safety data reported in Table 4 of the original paper are inaccurate and should be disregarded. The FDA did not report any concerns regarding the primary efficacy and safety outcomes. The steering committee indicated that they were only made aware of the discrepancies in October 2022.

Note: the dose of enoxaparin used in RECORD 4 was 30mg BD which does not reflect local standard of care.

A more recently published systematic review (SR)[13] comparing the efficacy and safety of rivaroxaban and enoxaparin for thromboprophylaxis in orthopaedic surgery included five RCTS. This SR excluded the following three studies for reasons as specified:

- RECORD 2: Patients were randomised to receive oral rivaroxaban 10 mg once daily for 31–39 days (with placebo injection for 10–14 days; or enoxaparin 40 mg once daily subcutaneously for 10–14 days (with placebo tablet for 31–39 days. This study was excluded as the durations of the intervention drug and comparator drug were not the same as those of the other studies included in the SR (rivaroxaban was given for 39 days)
- RECORD 4: Patients were randomised to receive either oral rivaroxaban 10 mg once daily, beginning 6-8 h after surgery, or subcutaneous enoxaparin 30 mg every 12 h, starting 12-24 h after surgery. This study was excluded as the dose of enoxaparin was 30mg).
- RCT by Kim et al[14]: A prospective study in which patients with an age < 60 years were randomly assigned to three groups (rivaroxaban, enoxaparin, and placebo) and the patients with an age ≥ 60 years were assigned to two groups (rivaroxaban and enoxaparin). All drug regimens started at 12 hours postoperatively and continued for two weeks after surgery. This study was also excluded as the two age groups (<60 and >/=60 years old) were given different regimens.

Authors of the SR concluded that rivaroxaban was superior to enoxaparin as rivaroxaban significantly reduced the incidence of VTE and all-cause mortality based on the obtained risk ratio of 0.38 (95% CI = 0.27–0.54 (Figure 1 below). An AMSTAR assessment was completed to assess the quality of this SR, which was assessed to be of moderate quality.

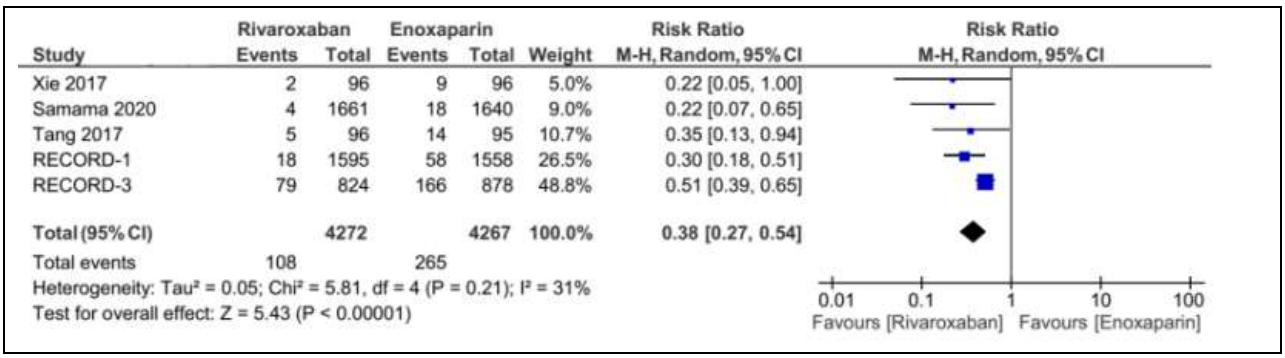
[11] RECORD4 Trial of Rivaroxaban, Published in 2009, Still Turning Heads | tctmd.com accessed 8 Mar 2023

[12] Turpie AA. Revisiting Record 4. The Lancet. Vol 400 December 10, 2022

[13] Rinaldi I, Amin IF, Shufiyani YM, Dewantara IR, Edina BC, Winston K, Nurrobi YAS. Comparison of the Efficacy and Safety of Rivaroxaban and Enoxaparin as Thromboprophylaxis Agents for Orthopedic Surgery-Systematic Review and Meta-Analysis. J Clin Med. 2022 Jul 14;11(14):4070. doi: 10.3390/jcm11144070. PMID: 35887834; PMCID: PMC9315734.

[14] Kim, S.M.; et al. Effect of oral factor Xa inhibitor and low-molecular-weight heparin on surgical complications following total hip arthroplasty. Thromb. Haemost. 2016, 115, 600–607. Available online: https://pubmed.ncbi.nlm.nih. gov/26790579/

Figure 1: Incidence of any VTE and all-cause death



In terms of safety, the authors investigated two factors for clinically relevant bleeding: (1) all bleeding (major and minor hemorrhage), and (2) major bleeding. Major bleeding was defined as bleeding that is potentially lethal to the patient and results in a reduction of Hemoglobin (Hb) by greater or equal than 2 g/dL based on laboratory evidence. The authors concluded that the incidence of any clinically relevant bleeding was not different between rivaroxaban and enoxaparin with a reported risk ratio of 1.07 (95% CI = 0.9–1.27 (Figure 2), including a non-significant difference in major bleeding. (Figure 3).

Figure 2: Incidence of any clinically relevant bleeding (major bleeding and any other clinically relevant bleeding)

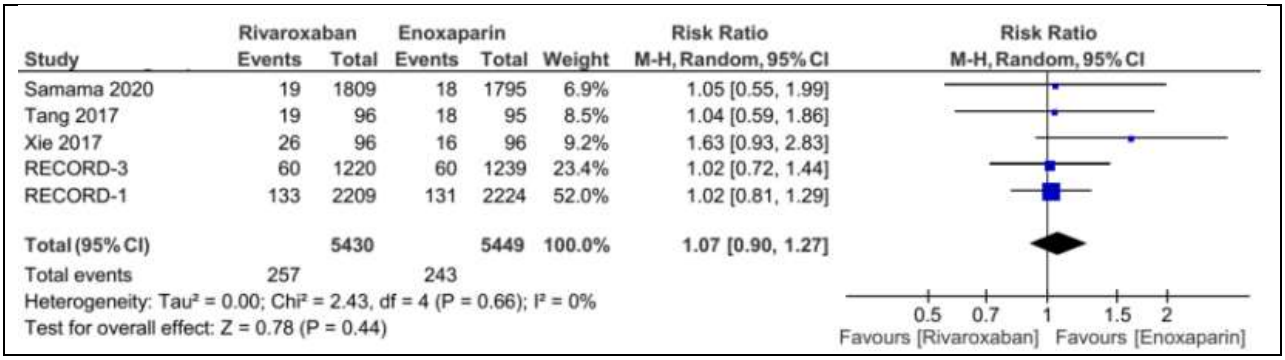
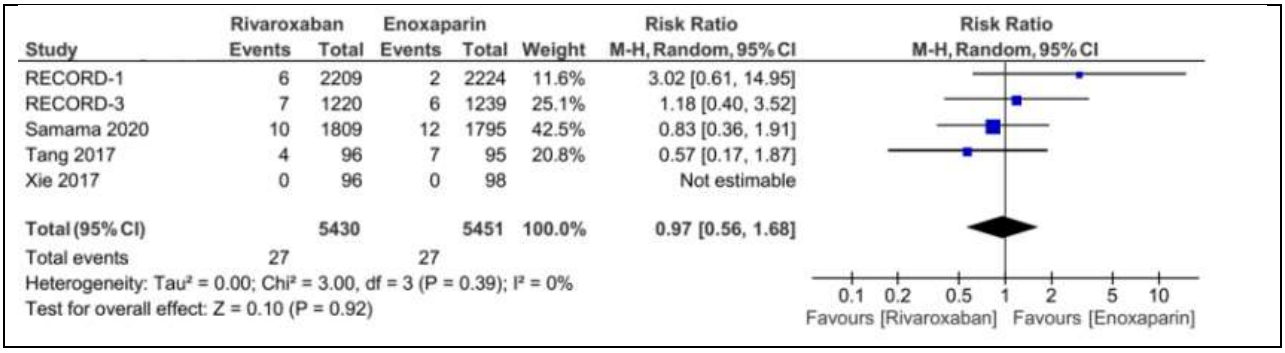


Figure 3: Incidence of major bleeding



3.3 MEDICAL PROPHYLAXIS

Rivaroxaban was approved by the FDA for the prevention of venous thromboembolism (VTE), or blood clots, in hospitalised acutely ill medical patients at risk for thromboembolic complications who are not at high risk of bleeding, in

October 2019. The two pivotal RCTS (the MAGELLAN 2013 and MARINER 2018 studies) included over 20000 acutely ill hospitalised patients.

MAGELLAN (n=8101)[15]: a double-blind RCT in which patients hospitalised for an acute medical illness received either enoxaparin SC, 40 mg once daily, for 10±4 days and oral placebo for 35±4 days or SC placebo for 10±4 days and oral rivaroxaban, 10 mg once daily, for 35±4 days. Primary efficacy outcomes were the composite of asymptomatic proximal or symptomatic venous thromboembolism up to day 10 (non-inferiority test) and up to day 35 (superiority test). The primary efficacy outcome event occurred in 78 of 2938 patients (2.7%) receiving rivaroxaban and 82 of 2993 patients (2.7%) receiving enoxaparin at day 10 (relative risk with rivaroxaban, 0.97; 95% confidence interval [CI], 0.71 to 1.31; P=0.003 for non-inferiority) and in 131 of 2967 patients (4.4%) who received rivaroxaban and 175 of 3057 patients (5.7%) who received enoxaparin followed by placebo at day 35 (relative risk, 0.77; 95% CI, 0.62 to 0.96; P=0.02). The composite of major or clinically relevant non-major bleeding which was a key safety outcome was reported in 111 of 3997 patients (2.8%) in the rivaroxaban group and 49 of 4001 patients (1.2%) in the enoxaparin group at day 10 (relative risk, 2.3; 95% CI, 1.63 to 3.17; P<0.001). For the extended duration, clinically relevant bleeding occurred in 164 of 3997 patients (4.1%) in the group that received extended-duration rivaroxaban as compared with 67 of 4001 patients (1.7%) in the group that received enoxaparin followed by placebo (relative risk, 2.5; 95% CI, 1.85 to 3.25; P<0.001). The authors concluded that rivaroxaban was non-inferior to enoxaparin for standard duration prophylaxis (6-14 days). They also reported a reduced risk of venous thromboembolism with extended duration rivaroxaban (31-39 days). Rivaroxaban was, however, associated with a greater risk of bleeding.

A sub-group analyses of data from the MAGELLAN study identified 5 key factors associated with increased bleeding risk: active cancer, gastrointestinal ulcer, bronchiectasis/pulmonary cavitation, bleeding in the previous 3 months, or concomitant use of dual antiplatelet therapy.

Patients with these risk factors were not eligible for inclusion in the MARINER study conducted subsequently.

MARINER (n=12024)[16]: A double-blind RCT in which medically ill patients at increased risk of VTE (on the basis of a modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score of 4 or higher (scores range from 0 to 10, with higher scores indicating a higher risk of venous thromboembolism) or a score of 2 or 3 plus a plasma d-dimer level of more than twice the upper limit of the normal range (defined according to local laboratory criteria), were given either once-daily rivaroxaban at a dose of 10 mg (with the dose adjusted for renal insufficiency) or placebo for 45 days at hospital discharge. The mean age of study participants was 67.8 years and, with women accounting for 44.5% of the population which was predominantly white (96.5%). For the primary efficacy outcome, which was a composite of symptomatic venous thromboembolism or death due to venous thromboembolism, outcomes were reported in 50 of 6007 patients (0.83%) who were given rivaroxaban and in 66 of 6012 patients (1.10%) who were given placebo (hazard ratio, 0.76; 95% confidence interval [CI], 0.52 to 1.09; P=0.14). The pre-specified secondary outcome of symptomatic nonfatal venous thromboembolism occurred in 0.18% of patients in the rivaroxaban group and 0.42% of patients in the placebo group (hazard ratio, 0.44; 95% CI, 0.22 to 0.89). Major bleeding occurred in 17 of 5982 patients (0.28%) in the rivaroxaban group and in 9 of 5980 patients (0.15%) in the placebo group (hazard ratio, 1.88; 95% CI, 0.84 to 4.23). Important to note though that patients with high risk factors for bleeding such as: active cancer, gastrointestinal ulcer, bronchiectasis/pulmonary cavitation, bleeding in the previous 3 months, or concomitant use of dual antiplatelet therapy, were excluded.

[15] Cohen AT et al. Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Patients. NEJM 7 feb 2013 p513-522.

[16] Spyropoulos AC et al. Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness. NEJM 20 Sep 2018.

3 BUDGET IMPACT

A budget impact assessment was conducted to assess the potential cost savings that could be made in switching from enoxaparin to rivaroxaban for the prevention of thromboembolic disease in hospitalised patients. Utilisation data for Clexane® 40mg for 2021 (Jan-Dec) and 2022 (Jan-Oct) across the provinces was used, and two scenarios are presented, based on an assumed switch rate of 30% and 70% respectively (note however, that rivaroxaban is not currently registered by SAHPRA for medical prophylaxis). Based on the new May 2023 tender prices, rivaroxaban would offer a cost saving of R38.95 for every dose of enoxaparin 40mg administered.

Table 3a: Projected savings with a 30% switch rate from enoxaparin 40mg to rivaroxaban 10mg

ACTUAL QUANTITIES ORDERED			ASSUMED SWITCH RATE 30% WITH RIVAROXABAN		
	ENOXAPARIN 40mg (R53.61 per dose)		RIVAROXABAN	ENOXAPARIN	Projected Saving - ZAR
Period	Pk size=10	Calculated Spend-ZAR			
Jan- Dec 2021	289 237	R 155 059 955.70	R 12 720 643.26	R 108 541 968.99	**R 33797343.45**
Jan-Oct 2022*	213 110	R 114 248 271.00	R 9 372 577.80	R 79 973 789.70	**R 24 901 903.50**

*Data for Nov and Dec not yet reported

Table 3b: Projected savings with a 70% switch rate from enoxaparin 40mg to rivaroxaban 10mg

ACTUAL QUANTITIES ORDERED			ASSUMED SWITCH RATE 70% WITH RIVAROXABAN		
	CLEXANE 40mg (R53.61 per dose)		RIVAROXBAN	CLEXANE	Projected Saving - ZAR
Period	Pk size=10	Calculated Spend-ZAR			
Jan- Dec 2021	289 237	R155 059 955.70	R29 681 500.94	R46 517 986.71	**R 78 860 468.05**
Jan-Oct 2022*	213 110	R114 248 271.00	R21 869 348.20	R34 274 481.30	**R 58 104 441.50**

*Data for Nov and Dec not yet reported

Based on the 2021 (Jan-Dec) utilisation of enoxaparin, the anticipated spend on enoxaparin at the price of R53.61 would be R155.1m and for 2022 (Jan-Oct) R114.2m (includes the COVID-related spend for thromboprophylaxis during 2021). Assuming a 30% switch rate to rivaroxaban, a cost saving of R33.8m would be achieved based on 2021 utilisation and R24.9m for 2022. Similarly, assuming a switch rate of 70% to rivaroxaban, the estimated cost saving would be R78.9m for 2021 and R58.1m for 2022 based on available utilisation data.

We acknowledge that a 100% switch rate will not be feasible as certain patient cohorts will still require enoxaparin. These cohorts include pregnant patients, paediatric patients and surgical patients other than orthopaedic patients undergoing hip or knee arthroplasty.

Note:

- The budget impact is based on medicine costs only and indirect costs related to administration (SC v oral), monitoring and management of adverse effects have not been included.

- The impact of any resultant competitive market dynamics has not been included e.g. any potential cost reduction with enoxaparin or the introduction of generic rivaroxaban, both of which would support further cost savings.
- There is emerging evidence of extended thromboprophylaxis in medically ill patients for up to 45 days following an acute hospitalisation [17], which has not been included in the budget impact analysis. Extended thromboprophylaxis is currently not included on the EML. We do however recognise the risk of scope creep particularly since rivaroxaban is an oral formulation and will be easier for patient self-administration compared to SC administration of enoxaparin. This potential scope creep could negatively impact the projected cost savings.
- Should rivaroxaban be included on the EML for the prophylaxis of thromboembolic disease in hospitalised adult patients there is a potential for scope creep with other indications e.g. atrial fibrillation where the cost effectiveness of rivaroxaban has not been demonstrated when compared to current standard of care.

4 RECOMMENDATION

Based on the approved tender price of R14.66 for rivaroxaban 10mg effective as of May 2023, we recommend a switch from enoxaparin 40mg to rivaroxaban 10mg for prophylaxis of thromboembolic disease in medically ill hospitalised adult patients and surgical, adult, patients undergoing hip or knee arthroplasty, as clinically appropriate.

Extended thromboprophylaxis post-discharge, is not supported in medically ill patients as evidence of safety with regard to bleeding risks has not been demonstrated in patients with additional risk factors for bleeding such as active cancer, gastrointestinal ulcer, bronchiectasis/pulmonary cavitation, bleeding in the previous 3 months, or concomitant use of dual antiplatelet therapy, which were all exclusions in the MARINER study. Thromboprophylaxis in total hip or total knee arthroplasty may however continue post discharge as duration of prophylaxis is recommended for a minimum of 14 days and up until 35 days post surgery.

Report prepared by: Prof M. Blockman and Ms Z.Adam

Conflicts of interest: MB and ZA have no conflicts of interests related to rivaroxaban.

[17] MacDougall K, Spyropoulos AC. New Paradigms of Extended Thromboprophylaxis in Medically Ill Patients. J Clin Med. 2020 Apr 2;9(4):1002. doi: 10.3390/jcm9041002. PMID: 32252423; PMCID: PMC7230788.

South African National Essential Medicine List
Adult Hospital Medication Review Process
Component: Blood and blood forming organs

MEDICINE REVIEW

1. Executive Summary

Date: July 2023
Medicine (INN): Aspirin
Medicine (ATC): B01AC06
Indication (ICD10 code): Z29.2 + (I80.0-3/I80.8-9/I81/I82.0-3/I8.8-9/I26.0/I26.9)
Patient population: Hospitalised patients with trauma-related operative or non-operative extremity fractures or trauma-related pelvic or acetabular fractures at risk of venous thromboembolism
Prevalence of condition: All hospitalised patients at risk with trauma-related operative extremity fractures or either operative or non-operative trauma-related pelvic or acetabular fractures
Prescriber Level: AH
Motivator/reviewer name(s): Prof Marc Blockman, Dr Gayle Tatz, Ms Zahiera Adam
PTC affiliation: WC PTC –Marc Blockman

Key findings

- 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.
- We identified two relevant trials, 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).
- A large proportion of the screened participants in the two trials included in this review, were excluded at the treating clinician's discretion. In most cases, this was likely due to the excluded patients being at higher risk of VTE, although specific reasons were not provided. This data may therefore represent a lower risk population in which prophylaxis with aspirin may perform better.
- 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.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				x	

Recommendation: We recommend 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.

Rationale: There is no difference in incidence of death, pulmonary embolism or major bleeding between VTE prophylaxis with aspirin compared with enoxaparin. In addition, the increased risk of DVT with use of aspirin is trivial and does not translate into increased risk of pulmonary embolus or death. The cost incurred by the additional cases of DVT are likely to be far-surpassed by the major cost savings of using aspirin over enoxaparin.

Level of Evidence: moderate
Review indicator: New data on the efficacy and/or safety

NEMLC RECOMMENDATION (MEETING OF 12 October 2023): NEMLC supported the recommendation pending the editorial amendments as discussed. The EML should include guidance on risk stratification and the STG recommendation for the use of aspirin for VTE prophylaxis should be aligned to the population as specified in the PICO.

Monitoring and evaluation considerations: A formal cost-analysis maybe performed to quantify the extent of the potential savings.

Research priorities

Prospero registration: na

Name of author(s)/motivator(s):
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Author affiliation and conflict of interest details
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INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), are well-known and significant complications that can occur after major surgical procedures. Major surgical procedures are defined as interventions with higher-than-minimal risk, performed in the operating theatre, and requiring specialised training. In the past, before the routine use of effective preventive measures, VTE was a common cause of illness and death following major surgery, resulting in over 50,000 deaths annually in the United States alone (1). The importance of preventive measures to reduce the risk of VTE after major surgery has been acknowledged for many years, although even with the use of preventive measures, surgery still contributes to about 25% of VTE cases(2).

While most surgical procedures involve some risk of VTE, the level of risk varies among different types of surgeries and individual patients. Procedures such as hip and knee arthroplasty, invasive neurosurgical procedures, and major vascular surgeries carry the highest risk of postoperative VTE (3). Certain patient factors increase the risk of thrombosis such as a history of VTE, presence of malignancy and advancing age (4).

Scoring systems like the Caprini score have been developed and validated to assess the risk of postoperative VTE in individual patients undergoing specific surgical procedures, although this scoring system has been studied in many different circumstances including medical patients (4,5). Across board, a Caprini score of 7 or more is associated with a high risk of VTE. (Appendix 5) The South African Standard Treatment Guidelines, Hospital level, adults, 2019 edition, includes risk stratification criteria which may also be used to determine risk. (Appendix 7). Traditionally, postoperative VTE was primarily observed during hospital stays. However, with shorter hospital stays becoming more common, postoperative VTE now often occurs in the days to weeks following discharge from the hospital (4).

The current standard of care for venous thromboembolism (VTE) prophylaxis in patients undergoing surgery for hip or knee arthroplasty and for non-operative trauma-related pelvic and acetabular fractures is low molecular weight heparin (LMWH) e.g. enoxaparin. Recently, randomised controlled trials have suggested that other medications may be used as VTE prophylaxis with non-inferior efficacy and a similar safety profile. These medicines include aspirin, which has been used for multiple other indications for decades, and direct oral anticoagulants (DOACs) which are much newer (6, 7).

Aspirin is a much cheaper medication than any of the currently available DOACs and currently, both aspirin and DOACs (eg. rivaroxaban) are more affordable than enoxaparin. Replacing enoxaparin with aspirin for VTE prophylaxis for patients with operative trauma-related extremity fractures and for non-operative trauma-related pelvic and acetabular fractures, could result in significant cost-savings. The purpose of this review is to investigate the efficacy and safety of such an initiative.

RESEARCH QUESTION

What is the efficacy and safety of *aspirin* compared to *low molecular weight heparin* in adult patients requiring VTE prophylaxis for orthopaedic surgery?

METHODS

We searched guideline clearinghouses such as the National Institute for Health and Care Excellence (NICE), American College of Cardiology (ACC), Canadian Agency for Drugs and Technologies in Health, American Society of Hematology (ASH), Scottish Intercollegiate Guideline Network (SIGN), European Society of Cardiology, and the American College of Chest Physicians (ACCP) on the 15 May 2023 for eligible guidelines. Additionally, we systematically searched PubMed and the Cochrane Library on the 2 June 2023 for eligible systematic reviews and randomised controlled trials (RCTs), published from the year 2019 to June 2023, as guided by the 2019 ASH guideline. Search terms used are found in Appendix 1. Screening of records, and selection of articles was done independently and in duplicate by two reviewers (MM and NB) with conflict resolution by a third reviewer (SE). Data extraction was done by one reviewer (NB) and checked by a second reviewer (MM). The main characteristics of the included study and study outcomes are shown in Appendix 2 and 3.

Review Manager (RevMan) 5 software was used to perform the analyses. We reported risk ratios for dichotomous data with 95% confidence intervals (CI). GRADE was used to assess the overall confidence of the evidence considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness (9). Appendix 3 is a GRADE evidence profile for the comparison of aspirin compared to LMWH. GRADE summary of findings table for this comparison reported in results (Table 3).

Eligibility criteria for review

Table 1: PICO framework

Population	Adult patients requiring VTE prophylaxis for orthopaedic trauma Population: trauma-related operative extremity fracture (proximal to the metatarsals or carpals) OR trauma-related operative or non-operative pelvis or acetabular fracture
Intervention	Aspirin
Control	Low-molecular-weight heparin
Outcomes	1. Mortality 2. Pulmonary embolism 3. Deep vein thrombosis 4. Major bleeding
Study designs	Guidelines, then systematic review of trials and if not found, then clinical trials

RESULTS

Result of search for guidelines

No guidelines identified that were relevant to the population as described in our PICO.

Result of search for systematic reviews and trials

We searched for reviews on aspirin use for arthroplasty or fractures for convenience for a related review. Three hundred and twenty-four potentially eligible records were retrieved from PubMed and the Cochrane Library databases. Of those, three hundred and twenty-two were excluded and two records (Haac 2020 et al., and O'Toole 2022 et al.,) were included in the pooled analysis (Figure 2).

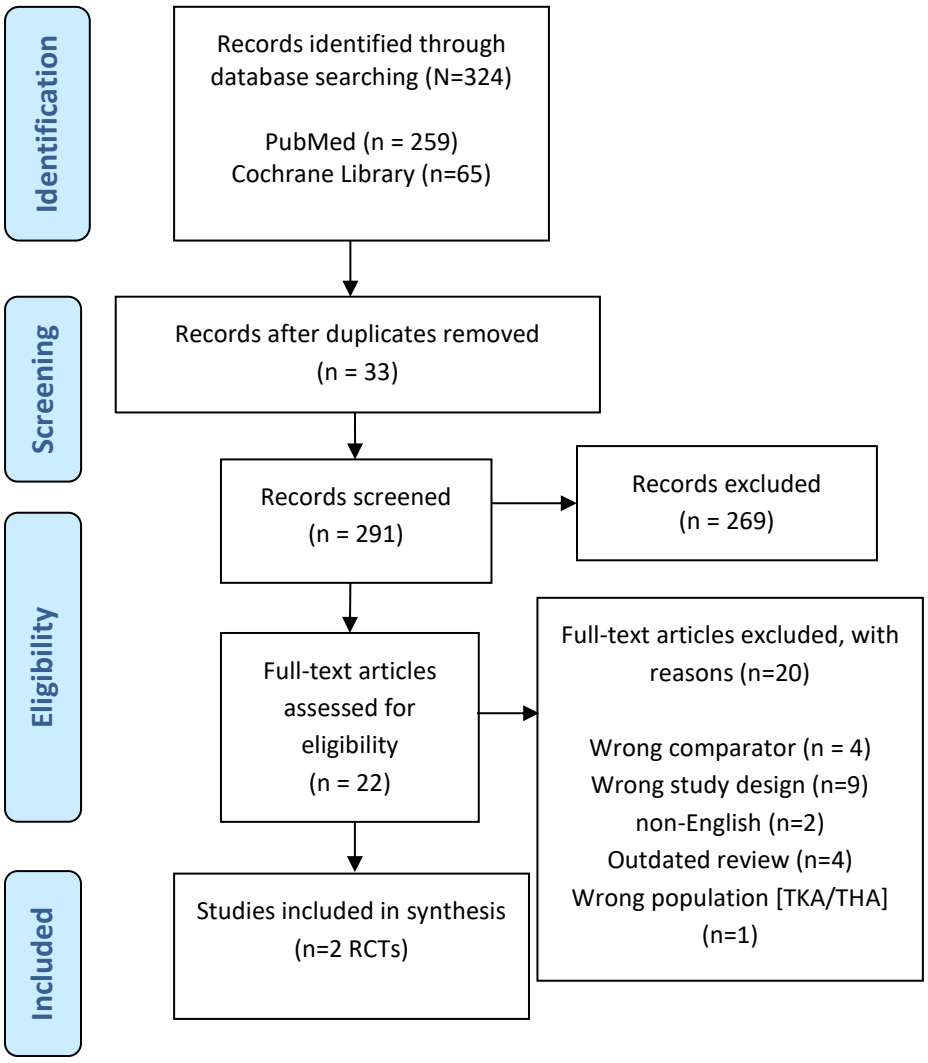


Figure 1: PRISMA flow diagram of included records

DESCRIPTION AND APPRAISALS OF TRIALS

We identified two eligible trials conducted in Canada, and USA which investigated the efficacy and safety of aspirin compared to LMWH for VTE prophylaxis in 12 540 adult patients with trauma-related operative (extremity) fractures or any trauma-related pelvic or acetabular fractures (18-19). In both trials, 81mg oral aspirin was given twice a day in the intervention arm, while 30mg enoxaparin was given subcutaneously twice daily in the control arm. The trials reported on mortality, DVT, PE and major bleeding.

The dose of enoxaparin was the standard in North America where these trials were conducted and is a dose which has been used in many previous studies (8,9) This differs from the dosing in South Africa for prophylaxis of 40mg daily. The dosing of aspirin in this study was given twice daily to match the enoxaparin so that one arm would be no less likely to adhere to their treatment regimen than the other due to dosing frequency.

Our risk of bias assessment showed low risk of bias (Figure 4). We noted lack of blinding in the two trials of both patients and healthcare providers. However, this is unlikely to result in serious risk of bias due to the objective outcomes reported and blinding of outcome assessors (18-19).

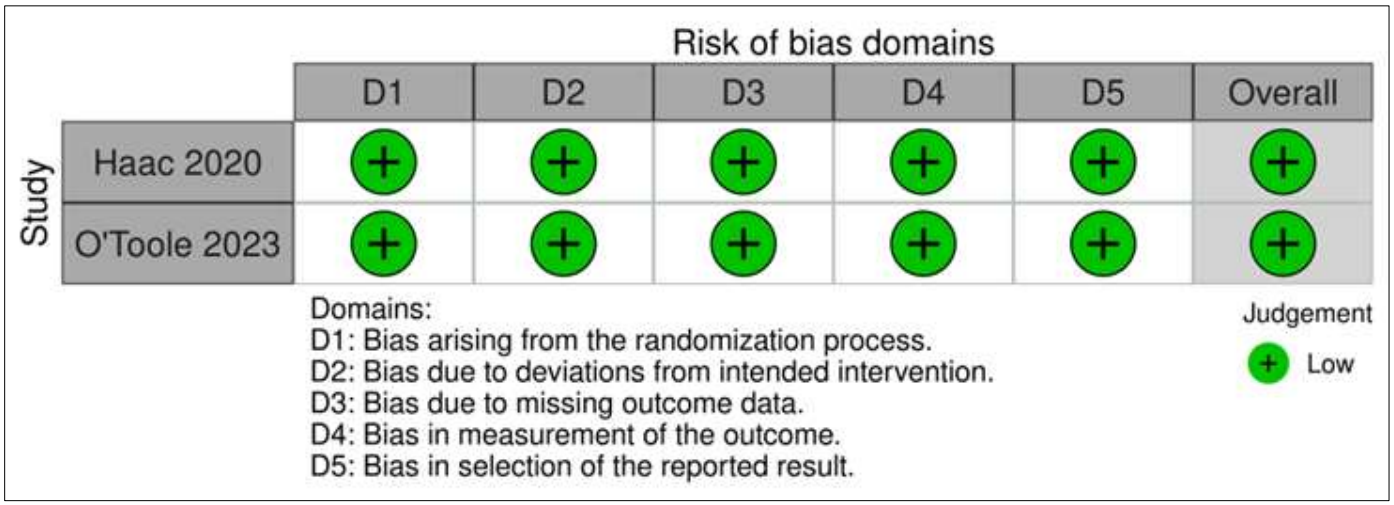


Figure 2: Risk of bias 2.0 of included trials

The O'Toole trial excluded potential participants prior to randomisation at the discretion of the treating clinician without reasons given; this accounted for 11% of excluded participants (Supplementary table S1). The overall total number of potential participants excluded with no reason was 19% (Supplementary table S2). We cannot rule out that this may have excluded higher-risk participants. There is no reason to believe that the higher risk patients who may have been excluded were excluded because of the study arm allocation or that there was selection bias.

Prevalence of risk factors for VTE in the study population showed that 0.7% had a previous VTE, 2.3% had cancer, 8.1% were diabetic and 34.5% were smokers. The average age of the study population was 44.5 years. Other risk factors were not captured in baseline characteristics table and therefore no data were available on the proportion of participants categorised as obese (Appendix 4). Under-representation of the elderly, no data on obesity and other risk factors and few participants with previous VTE, support our concern that this study population may consist of lower risk participants on average, and should therefore only be generalised to those at low to moderate risk of VTE. There were no data available on the risk factors of the patients who had been excluded. There was also no comparison between high-risk subgroups.

EFFECTS OF INTERVENTION

The GRADE Evidence Profile summarises the effects of aspirin compared to LMWH for each of the outcomes with explanation of the GRADE assessment (Appendix 3). Of note, Haac et al 2020 (18) reported composite endpoints of bleeding complications, deep surgical site infection, deep vein thrombosis, pulmonary embolism, and death within 90 days of injury. In the time to event analysis, the trial reported that "the cumulative weighted probability of being event-free at 90-days post-fracture was 97.8% (95% CI, 95.5–1.00%) in the aspirin group and 98.5% (95% CI, 96.6–1.00%) in the LMWH group". For the purposes of this rapid review, we extracted the unweighted outcomes to enable meta-analyses.

Table 2: Summary of findings table of comparison: Aspirin *vs.* LMWH

Aspirin compared to LMWH for VTE

Outcomes (Overall)	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH	Risk difference with Aspirin
Mortality	12540 (2 RCTs)	⨁⨁⨁⨁ High[a]	**RR 1.07** (0.71 to 1.59)	7 per 1,000	**1 more per 1,000** (2 fewer to 4 more)
Pulmonary embolism	12540 (2 RCTs)	⨁⨁⨁⨁ High[a,b]	**RR 0.77** (0.30 to 1.94)	15 per 1,000	**4 fewer per 1,000** (11 fewer to 14 more)
Deep vein thrombosis	12540 (2 RCTs)	⨁⨁⨁⨁ High[a]	**RR 1.48** (1.16 to 1.89)	17 per 1,000	**8 more per 1,000** (3 more to 15 more)
Rate of major bleeding	12540 (2 RCTs)	⨁⨁⨁⨁ High[a]	**RR 0.96** (0.89 to 1.05)	147 per 1,000	**6 fewer per 1,000** (16 fewer to 7 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. The O' Toole trial excluded potential participants prior to randomisation at the discretion of the treating clinician, without reasons given - this accounted for 11% of excluded participants (Supplementary table S1). In addition, overall total number of potential participants excluded with no reason was 19% (supplementary table S2). We can't rule out that this may have excluded higher risk participants, and therefore not fully representative of the patient population in our setting. We noted lack of blinding in both trials, however, this is unlikely to result in serious risk of bias. (O'Toole and Haac trials).
b. We did not downgrade imprecision; however, we noted that the absolute effects ranges from 11 fewer events to 14 more events of pulmonary embolism. A different clinical decision may be made at the extremes of this range.

- **Mortality**

Overall, the Haac 2020 and O'Toole et al., 2023 trials found that there is little difference in mortality when comparing aspirin to LMWH, risk ratio (RR) 1.07 (95% CI 0.72 to 1.59), n=12 540, moderate certainty evidence (Figure 9). There are 7 deaths per 1,000 in the enoxaparin group, with 1 more per 1,000 in the aspirin group (95% CI 2 fewer to 4 more events).

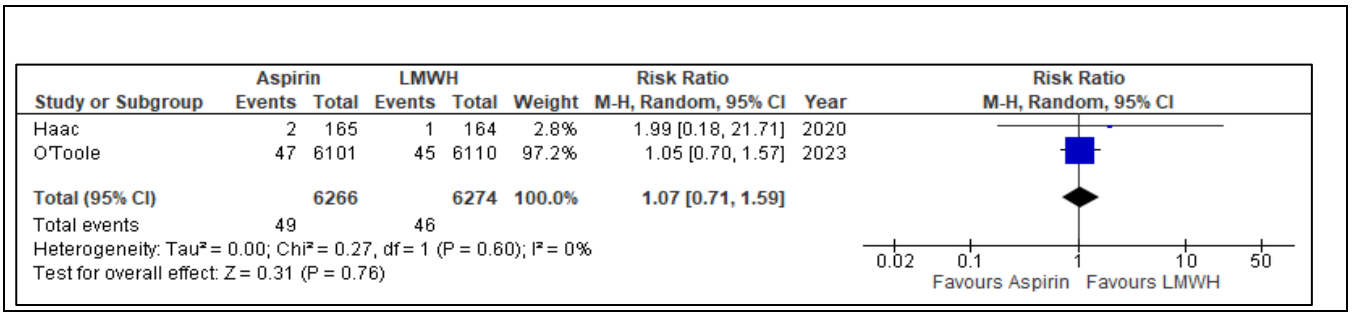


Figure5: Forest plot of Aspirin vs LMWH, outcome: Mortality

- **Pulmonary embolism**

Overall, the Haac, 2020 and O'Toole et al., 2023 trials found that aspirin compared to LMWH probably results in little difference in the risk of development of pulmonary emboli RR 0.77 (95% CI 0.30 to 1.94), n = 12 540, moderate certainty evidence due to imprecision (Figure 10). In the enoxaparin group, there are 15 per 1,000 pulmonary emboli, and there may be 4 fewer events per 1,000 in the aspirin group (95% CI 11 fewer events to 14 more events per 1,000).

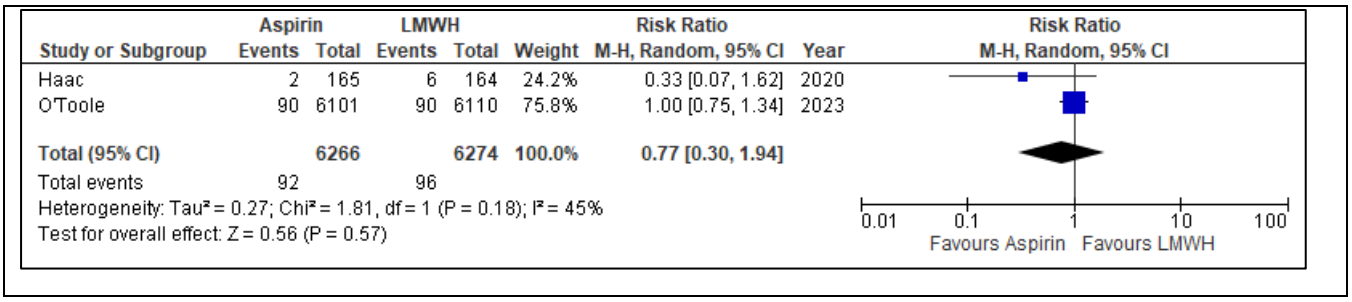


Figure6: Forest plot of Aspirin vs. LMWH, outcome: Pulmonary embolism

- **Symptomatic deep vein thrombosis**

Overall, the Haac, 2020 and O'Toole et al., 2023 trials found that aspirin compared to LMWH results in a small increased risk of DVT, RR 1.48 (95% CI 1.16 to 1.89), n = 12 540, moderate certainty evidence. (Figure 11). There were 17 per 1,000 events of symptomatic DVT in the LMWH group, with 8 more per 1,000 when aspirin given (95% CI 3 more to 15 more). This equated to a difference of 0.80 (95% CI 0.28-1.31) in the intention to treat (ITT) analysis and 0.57 (95% CI 0.08-1.07) in the per protocol (PP) analysis. When looking more closely at the proximal and distal DVT subgroups, there is no significant difference in the proximal DVTs in the ITT analysis; 0.25 (95% CI -0.12;0.62) or PP analysis; 0.04 (95% CI -0.30;0.39) (Appendix 6). The difference in distal DVTs was significant in both analyses (0.58 (95% CI 0.20;0.96) and 0.49 (0.12;0.86) respectively) favouring enoxaparin. In certain settings, risk stratification is used to determine whether distal DVTs will be actively managed with anticoagulation as

patients at low risk of embolization may be managed conservatively with serial ultrasound checks. This is due to their more favourable outcomes with lower rates of complication (22).

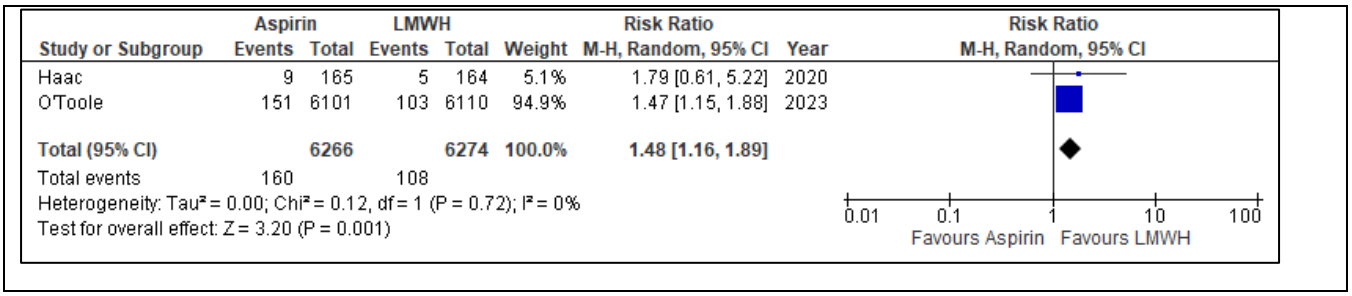


Figure7: Forest plot of Aspirin vs LMWH, outcome: Deep vein thrombosis

- **Rate of major bleeding**

Overall, the Haac, 2020 and O'Toole et al., 2023 trials show that aspirin compared to LMWH results in little or no difference in the rate of major bleeding RR 0.96 (95% CI 0.89 to 1.05), n=12 540, moderate certainty evidence (Figure 12). There are 147 per 1,000 major bleeding events in the LMWH group, with 6 fewer per 1,000 when aspiring given (95% CI 16 fewer to 7 more events).

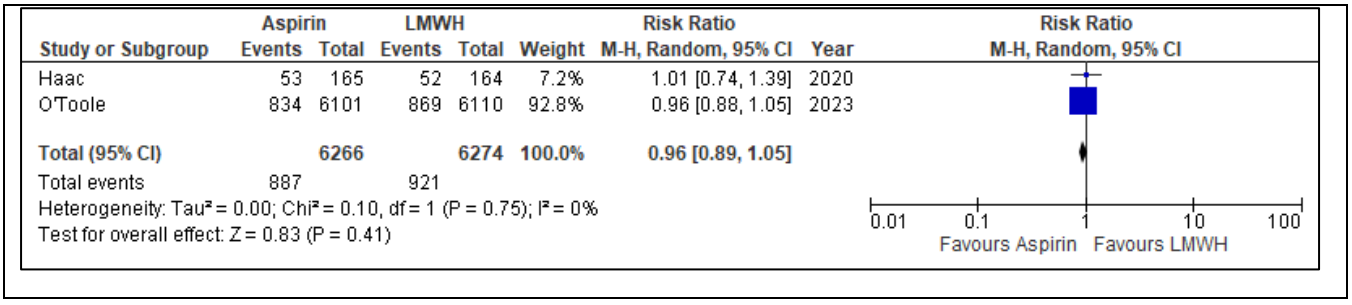


Figure8: Forest plot of Aspirin vs LMWH, outcome: Major bleeding

CONCLUSION

In people requiring venous thromboembolism prophylaxis following trauma-related operative (extremity) fracture and any trauma-related pelvic or acetabular fracture, there is likely little difference in the efficacy of aspirin compared to enoxaparin in terms of mortality, pulmonary embolism and the rate of major bleeding.

However, there is an increase in the risk of symptomatic DVT with aspirin use compared to enoxaparin in this patient population. The absolute risk is small at 8 additional cases of DVT per 1000 patients treated. The excess cases of DVT did not translate into increased risk of pulmonary embolism or death, and therefore aspirin may be a viable option for VTE prophylaxis in this patient population.

The enoxaparin dosing used in these trials (30mg 12hrly) is higher than the South African standard prophylactic dose of 40mg daily. The aspirin dose which we can consider using in South African public sector is 150mg daily, which is very marginally less than the total 162mg daily used in the study. It is possible that the difference in incidence of symptomatic DVT between aspirin and enoxaparin will therefore be less, but we do not have any data using doses of 40mg enoxaparin vs 150mg aspirin.

It is important to note that this study population may have been at low to moderate risk for VTE, as a large proportion (19%) of the screened participants were excluded without reason; 11% of 19% at the clinician's discretion... Some reported characteristics of the study population demonstrated the study prevalence of additional risk factors where 0.7% had a previous VTE, 2.3% had cancer, 8.1% were diabetic and 34.5% were smokers. The average age of the study population was 44.5 years and there were no data available on the proportion of participants categorised as obese. Under-representation of the elderly, no data on obesity prevalence and few participants with previous VTE support our concern that this study population may consist of lower risk participants on average, and should therefore only be generalised to those at low to moderate risk of VTE. There were no data available on the risk factors of the patients who had been excluded. There was also no comparison between high-risk subgroups.

Importantly however, aspirin may provide significant cost savings, increased access to VTE prophylaxis and enable earlier patient discharge from facilities. These potential benefits may still have a big impact, even if used only in the low-risk portion of patients with trauma-related operative (extremity) fractures and any trauma-related hip or acetabular fractures.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality: confident in the evidence* *Moderate quality: mostly confident, but further research may change the effect* *Low quality: some confidence, further research likely to change the effect* *Very low quality: findings indicate uncertain effect*	The certainty of the evidence is moderate. The primary concern was in the O' Toole trial where 19% of excluded patients were excluded for reasons which are unclear. Characteristics of excluded patients are not described. This exclusion may have impacted the overall risk of VTE in the study population but there is no reason to believe that exclusion would have occurred differently between groups and thus risk of selection bias is low. We can only extrapolate these findings to patients at low to moderate risk of VTE for the above reasons. There was lack of blinding, however, the main outcomes of death, pulmonary embolism, deep vein thrombosis and major bleeding are objective and not likely to be affected by performance or detection bias.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ Interventions are similar in efficacy	Death: There are 7 deaths per 1,000 in the enoxaparin group, with 1 more per 1,000 in the aspirin group (95% CI 2 fewer to 4 more events). PE: In the enoxaparin group, there are 15 per 1,000 pulmonary emboli, and there may be 4 fewer events per 1,000 in the aspirin group (95% CI 11 fewer events to 14 more events per 1,000). Bleeding: There are 147 per 1,000 major bleeding events in the LMWH group, with 6 fewer per 1,000 when aspiring given (95% CI 16 fewer to 7 more events).
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	DVT: There were 17 per 1,000 events of symptomatic DVT in the LMWH group, with 8 more per 1,000 when aspirin given (95% CI 3 more to 15 more). We assessed the clinical significance of this finding as trivial as it did not result in an increased risk of DVT complications. PE's and deaths. There is no difference in the risk of PE or death in the aspirin group compared with enoxaparin.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control ~~*or*~~ ~~Uncertain~~ ☒	The balance of effects favours either aspirin or enoxaparin. A dose of 150mg aspirin daily is equivalent to a twice daily dose of 81mg aspirin (162mg per day) as used in the trials included in this review. This is due to the similar daily dose and long half-life of aspirin meaning that plasma concentrations would not be significantly different.

<table>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:</td><td>At the time of this review:
• Enoxaparin is currently included on the EML as the standard of care.
• DOACs especially rivaroxaban are under consideration for inclusion on the EML for this indication but a final decision has not yet been made.</td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td><td>Both medicines are widely available.
Hospital discharge may be more feasible with an oral formulation versus a subcutaneous formulation.
The 300mg scored tablet is currently on tender – tablets would need to be halved for a 150mg dose.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [x] Uncertain [ ]</td><td>Enoxaparin 40mg/ day
Aspirin 150mg/ day (half of 300mg tablet)
Rivaroxaban 10mg/ day
DOACs outside of PICO but included for comparator purposes as currently under review for inclusion on the EML for this indication.
Note: Treatment costs relate to direct medicine costs only i.e. other costs related to length of hospital stay not reflected. In clinical practice duration of therapy is likely to be less than 14 days for the population under consideration.
*MHPL - 1 Sep 2023
**Weighted mean as per tender allocation
<table><tr><th colspan="4">Treatment regimen</th></tr><tr><th>Drug</th><th>Price/unit*</th><th>Duration (days)</th><th>Treatment Cost per patient</th></tr><tr><td>Enoxaparin 40mg OD</td><td>54.99</td><td>14</td><td>769.86</td></tr><tr><td>Rivaroxaban 10mg OD</td><td>14.66</td><td>14</td><td>205.17</td></tr><tr><td>Aspirin 150mg OD**</td><td>0.32</td><td>14</td><td>2.21 - 4.42</td></tr></table>Aspirin treatment cost for 7 days = R2.21. Assuming tender pack size of 14 X 300mg tablets issued per patient then cost = R4.42</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [x] Major [ ] Uncertain [ ]
Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [x]</td><td>Patients have been shown to prefer oral to subcutaneous VTE prophylaxis with a marginal utility of 0.16; 95% CI: 0.11 - 0.21, P<0.0001 (23).</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [ ] Uncertain [x]</td><td>The use of an oral medicine may make earlier discharge more feasible.</td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation
Initial (v1.0)	12 October 2023	GT, NB, MM, ZA, SE, TK, MB	Aspirin to be used as prophylaxis in patients with operative trauma-related extremity fractures for all operative or non-operative hip and acetabular fractures. Recommended for use in patients at low to moderate risk of VTE

APPENDIX

Appendix 1a: Search Strategy PubMed (arthroplasty and fractures)

Search	Query	Results
#4	Search: Filters: from 2019/1/1 - 2023/6/2	259
#3	Search: #1 AND #2	1125
#2	Search: Thromboprophylaxis [tiab] OR Venous Thromboembolism Prophylaxis [tiab] OR VTE prophylaxis [tiab] OR Venous Thromboembolism [Mesh] OR embolism prevention [tiab] OR thrombosis prevention [tiab] OR deep vein thrombosis prevention [tiab] OR venous thrombosis prevention [tiab] OR Venous Thromboembolism prevention [tiab]	32915
#1	Search: Aspirin [Mesh] OR Acetylsalicylic Acid [tiab] OR aloxiprinum [tiab] OR Acylpyrin [tiab] OR Colfarit [tiab] OR disopril [tiab] OR Ecotrin [tiab] OR Easprin [tiab] OR Endosprin [tiab] OR Magnecyl [tiab] OR Micristin [tiab] OR Polopirin [tiab] OR Polopiryna [tiab] OR Solprin [tiab] OR Solupsan [tiab] OR Zorprin [tiab] OR Acetysal [tiab] OR Aspro clear [tiab]	52286

Appendix 1b: Search Strategy Cochrane

Search	Query	Results
#3	Search: #1 AND #2 Filters: from Jan 2019 – June 2023	64
#2	Search: Thromboprophylaxis:ti,ab OR "Venous Thromboembolism Prophylaxis":ti,ab OR VTE next prophylaxis:ti,ab OR [mh "Venous Thromboembolism"] OR embolism next prevention:ti,ab OR thrombosis next prevention:ti,ab OR "deep vein thrombosis" next prevention:ti,ab OR "Venous Thromboembolism" next prevention:ti,ab	2717
#1	Search: [mh Aspirin] OR Acetylsalicylic next Acid:ti,ab OR aloxiprinum:ti,ab OR Acylpyrin:ti,ab OR Colfarit:ti,ab OR disopril:ti,ab OR Ecotrin:ti,ab OR Easprin:ti,ab OR Endosprin:ti,ab OR Magnecyl:ti,ab OR Micristin:ti,ab OR Polopirin:ti,ab OR Polopiryna:ti,ab OR Solprin:ti,ab OR Solupsan:ti,ab OR Zorprin:ti,ab OR Acetysal:ti,ab OR "Aspro clear":ti,ab	8172

Appendix 2: Characteristics of included studies

Citation	Study design	Population	Treatments	Main outcome
Haac BE, O'Hara NN, Manson TT, Slobogean GP, Castillo RC, O'Toole RV, Stein DM, ADAPT Investigators. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: a patient-centered randomized controlled trial. PLoS One. 2020 Aug 3;15(8): e0235628. (ADAPT trial)	Design: 1:1 open label randomized clinical trial Follow up: 90 days Country: Maryland, USA	Sample size: N=329, n= 164 Enoxaparin *vs.* aspirin n=165 Mean (SD) age: 45.4 (20.4) Enoxaparin *vs.* Aspirin 48.0 (18.6) Surgical procedure: Operative extremity fracture, or a pelvis or acetabular fracture	Intervention: enoxaparin at 30-mg, twice daily (oral, rectal, or via any other form of enteral access) Control: aspirin at 81-mg twice daily (oral, rectal, or via any other form of enteral access) Duration of treatment not reported.	1. Mortality 2. Composite DVT 3. Composite PE 4. Composite major bleeding
O'Toole 2023: Major Extremity Trauma Research Consortium (METRC). Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture. New England Journal of Medicine. 2023 Jan 19;388(3):203-13. (PREVENT CLOT Trial)	Design: 1:1 pragmatic, multicenter, randomized, noninferiority trial Follow up: 90 days Country: 21 trauma centers in the United States and Canada	Sample size: N=12 211, Aspirin n=6101, Enoxaparin n=6110 Mean age (±SD) age: 44.6±17.8 years Surgical procedure: Patients who had an extremity fracture operatively or a fracture of the pelvis or acetabulum that was treated operatively or nonoperatively.	Intervention: Aspirin 81 mg twice daily (oral) Control: Enoxaparin at 30mg twice daily (subcutaneous) Duration of treatment not reported.	1. Death from any cause of death Notes: Three grades of cause specific death were used: related to pulmonary embolism, possibly related to pulmonary embolism, and unlikely to be related to pulmonary embolism 2. Pulmonary embolism Notes: Nonfatal pulmonary embolism was also adjudicated by the committee and reported as any, massive, sub-massive, clinically significant, or asymptomatic and in a segmental or subsegmental location 3. DVT Notes: deep-vein thrombosis events were subclassified according to the proximal or distal location. 4.Bleeding events Notes: Bleeding events included symptomatic bleeding into a critical area or organ; bleeding that caused a drop in the hemoglobin level of 20 g per liter or more within a 24-hour period and led to a transfusion of two or more units of whole blood or red cells; or bleeding that led to reoperation

Appendix 3: Evidence profile for aspirin vs LMWH

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	LMWH	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomised trials	not serious[a]	not serious	not serious	not serious	none	49/6266 (0.8%)	46/6274 (0.7%)	**RR 1.07** (0.71 to 1.59)	**1 more per 1,000** (from 2 fewer to 4 more)	⊕⊕⊕⊕ High	CRITICAL
Pulmonary embolism												
2	randomised trials	not serious[a]	not serious	not serious	not serious[b]	none	92/6266 (1.5%)	96/6274 (1.5%)	**RR 0.77** (0.30 to 1.94)	**4 fewer per 1,000** (from 11 fewer to 14 more)	⊕⊕⊕⊕ Moderate	CRITICAL
Deep vein thrombosis												
2	randomised trials	not serious[a]	not serious	not serious	not serious	none	160/6266 (2.6%)	108/6274 (1.7%)	**RR 1.48** (1.16 to 1.89)	**8 more per 1,000** (from 3 more to 15 more)	⊕⊕⊕⊕ High	CRITICAL
Rate of major bleeding												
2	randomised trials	not serious[a]	not serious	not serious	not serious	none	887/6266 (14.2%)	921/6274 (14.7%)	**RR 0.96** (0.89 to 1.05)	**6 fewer per 1,000** (from 16 fewer to 7 more)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. We downgraded for serious risk of bias due to selection bias: The O' Toole trial excluded potential participants prior to randomisation at the discretion of the treating clinician, without reasons given - this accounted for 11% of participants (Supplementary table S1). In addition, overall total number of potential participants excluded with no reason was 19% (supplementary table S2).We can't rule out that this may have excluded higher risk participants, favouring aspirin. We noted lack of blinding of in both trials, however, this is unlikely to result in serious risk of bias. (O'Toole and Haac trials).

b. We did not downgrade imprecision, however, we noted that the absolute effects ranges from 11 fewer events to 14 more events of pulmonary embolism. A different clinical decision may be made at these ranges of the effect estimate.

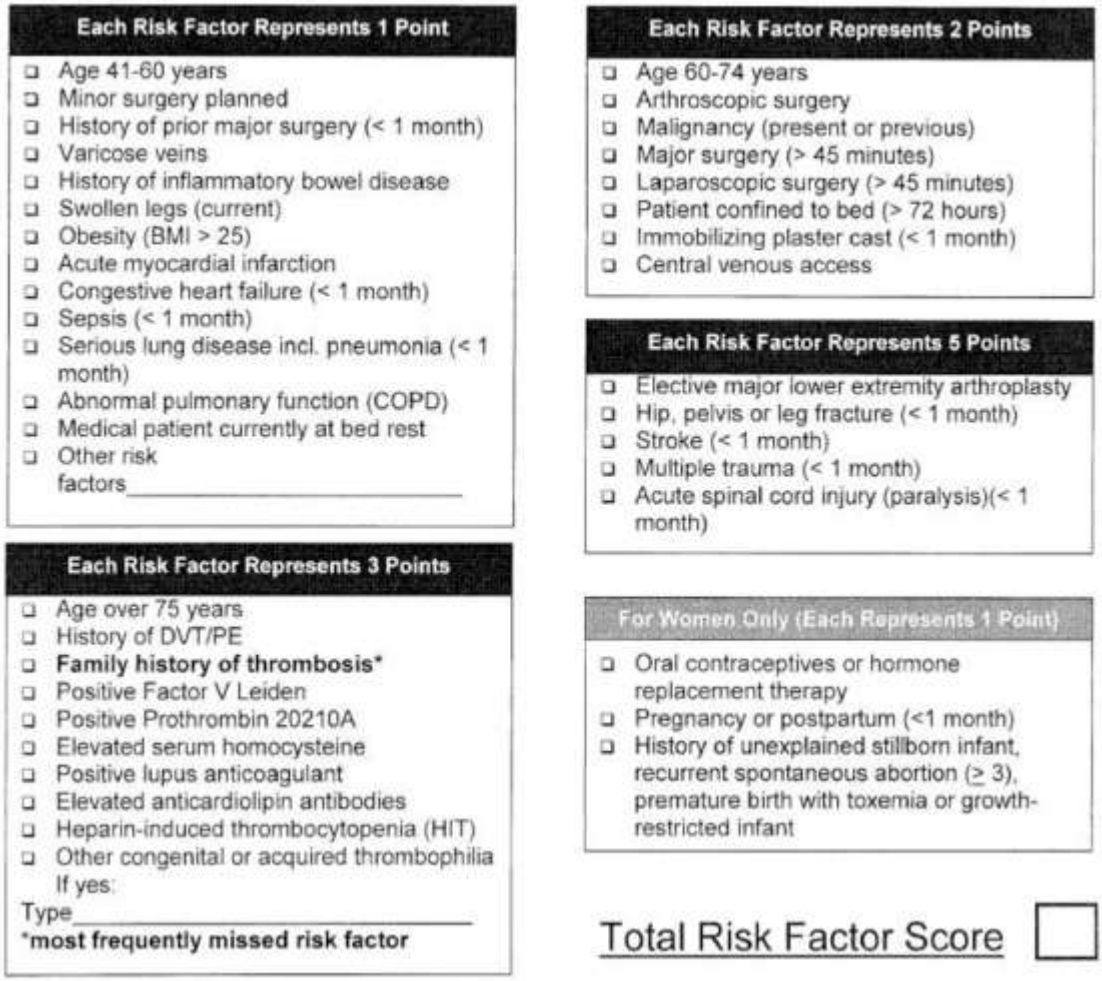
Appendix 4 : Supplementary Tab;e from O'Toole et al (19) (PREVENT CLOT) showing baseline characteristics including risk factors

Table S3. Baseline characteristics of the patients included in the per-protocol analysis*.

Characteristic	Aspirin N = 5505	Low-Molecular-Weight Heparin N = 5170	Overall N = 10,675
Age - years	44.5 ± 18.0	44.7 ± 17.6	44.6 ± 17.8
Male – no. (%)	3435 (62.4%)	3203 (62.0%)	6638 (62.2%)
Body mass index kg/m^2	27.1 (23.5, 31.7)	27.4 (23.7, 32.3)	27.2 (23.6, 32.0)
Race/Ethnicity – no. (%) κ			
Non-Hispanic White	3484 (63.3%)	3301 (63.8%)	6785 (63.6%)
Non-Hispanic Black	1071 (19.5%)	1009 (19.5%)	2080 (19.5%)
Hispanic	707 (12.8%)	627 (12.1%)	1334 (12.5%)
Other	193 (3.5%)	178 (3.4%)	371 (3.5%)
Risk factors – no. (%)			
Previous VTE	36 (0.7%)	35 (0.7%)	71 (0.7%)
Cancer	124 (2.3%)	148 (2.9%)	272 (2.5%)
Diabetes	444 (8.1%)	421 (8.1%)	865 (8.1%)
Smoking status$^{\delta}$			
Never smoked	2699 (49.0%)	2464 (47.7%)	5163 (48.4%)
Former smoker	904 (16.4%)	874 (16.9%)	1778 (16.7%)
Current smoker	1901 (34.5%)	1828 (35.4%)	3729 (34.9%)
Medications prior to injury – no. (%)			
Prior aspirin$^{\phi}$	451 (8.2%)	395 (7.6%)	846 (7.9%)
OCP/Estrogen$^{\Psi}$	100 (1.8%)	93 (1.8%)	193 (1.8%)
Plavix/Other antiplatelet agent$^{\lambda}$	45 (0.8%)	37 (0.7%)	82 (0.8%)
Health insurance – no. (%)$^{\Delta}$	4093 (74.4%)	3909 (75.6%)	8002 (75.0%)
Injury Severity Score [±]	9 (4–10)	9 (4–10)	9 (4–10)
Less than 9	2300 (42.0%)	2221 (43.1%)	4521 (42.5%)
9 to 15	2445 (44.6%)	2203 (42.8%)	4648 (43.7%)
More than 15	734 (13.4%)	724 (14.1%)	1458 (13.7%)
Injury regions – no. (%)[ε]			
Lower extremity	4829 (88.1%)	4513 (87.7%)	9342 (87.9%)
Upper extremity	1495 (27.3%)	1427 (27.7%)	2922 (27.5%)
Abdomen	661 (12.1%)	672 (13.1%)	1333 (12.5%)
Spine	528 (9.6%)	550 (10.7%)	1078 (10.1%)
Thorax	954 (17.4%)	982 (19.1%)	1936 (18.2%)
Neck	51 (0.9%)	61 (1.2%)	112 (1.1%)
Face	729 (13.3%)	752 (14.6%)	1481 (13.9%)
Head	693 (12.6%)	661 (12.8%)	1354 (12.7%)
Lower extremity fracture only	3698 (67.5%)	3431 (66.6%)	7129 (67.1%)
Upper extremity fracture only	650 (11.9%)	635 (12.3%)	1285 (12.1%)
Lower and upper extremity fractures	1131 (20.6%)	1082 (21.0%)	2213 (20.8%)

*Plus – minus values are means ±SD.
VTE venous thromboembolism, OCP oral contraceptive pill, IQR, interquartile range.
κ 1 patient with missing race data. An additional 104 patients refused to provide data.
δ 5 patients with missing smoking status.
ϕ 1 patient with missing prior aspirin data.
Ψ 2 patients with missing OCP/estrogen data.
λ. 1 patient with missing Plavix/other antiplatelet agent data.
Δ 1 patient with missing health insurance data.

Appendix 5: Caprini Risk Assessment Tool



Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Minor surgery planned
- ❑ History of prior major surgery (< 1 month)
- ❑ Varicose veins
- ❑ History of inflammatory bowel disease
- ❑ Swollen legs (current)
- ❑ Obesity (BMI > 25)
- ❑ Acute myocardial infarction
- ❑ Congestive heart failure (< 1 month)
- ❑ Sepsis (< 1 month)
- ❑ Serious lung disease incl. pneumonia (< 1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Medical patient currently at bed rest
- ❑ Other risk factors_____

Each Risk Factor Represents 2 Points

- ❑ Age 60-74 years
- ❑ Arthroscopic surgery
- ❑ Malignancy (present or previous)
- ❑ Major surgery (> 45 minutes)
- ❑ Laparoscopic surgery (> 45 minutes)
- ❑ Patient confined to bed (> 72 hours)
- ❑ Immobilizing plaster cast (< 1 month)
- ❑ Central venous access

Each Risk Factor Represents 3 Points

- ❑ Age over 75 years
- ❑ History of DVT/PE
- ❑ **Family history of thrombosis***
- ❑ Positive Factor V Leiden
- ❑ Positive Prothrombin 20210A
- ❑ Elevated serum homocysteine
- ❑ Positive lupus anticoagulant
- ❑ Elevated anticardiolipin antibodies
- ❑ Heparin-induced thrombocytopenia (HIT)
- ❑ Other congenital or acquired thrombophilia

If yes:

Type_____

***most frequently missed risk factor**

Each Risk Factor Represents 5 Points

- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (< 1 month)
- ❑ Stroke (< 1 month)
- ❑ Multiple trauma (< 1 month)
- ❑ Acute spinal cord injury (paralysis)(< 1 month)

For Women Only (Each Represents 1 Point)

- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

Total Risk Factor Score ☐

Appendix 6: Table 2 from O'Toole et al (19) showing the subgroups of proximal and distal DVTs.

Table 2. Primary and Secondary Outcomes.*

Outcome	Intention-to-Treat Population			Per-Protocol Population		
	Aspirin (N=6101)	Low-Molecular-Weight Heparin (N=6110)	Difference (CI)†	Aspirin (N=5505)	Low-Molecular-Weight Heparin (N=5170)	Difference (CI)†
	no. (% 90-day probability)		*percentage points*	*no. (% 90-day probability)*		*percentage points*
Primary outcome: death from any cause	47 (0.78)	45 (0.73)	0.05 (−0.27 to 0.38)‡	41 (0.75)	38 (0.72)	0.03 (−0.31 to 0.38)
Secondary efficacy outcome§						
Cause-specific death						
Death related to PE	4 (0.07)	5 (0.08)	−0.02 (−0.12 to 0.08)	4 (0.07)	3 (0.06)	0.01 (−0.08 to 0.11)
Death possibly related to PE	18 (0.30)	14 (0.22)	0.08 (−0.10 to 0.27)	14 (0.26)	10 (0.18)	0.08 (−0.10 to 0.26)
Death unlikely to be related to PE	29 (0.49)	31 (0.52)	−0.03 (−0.28 to 0.22)	27 (0.50)	28 (0.55)	−0.05 (−0.33 to 0.23)
PE type						
Any	90 (1.49)	90 (1.49)	0 (−0.43 to 0.43)	50 (0.92)	43 (0.84)	0.08 (−0.17 to 0.54)
Massive	1 (0.02)	3 (0.05)	−0.03 (−0.10 to 0.03)	0 (0.00)	2 (0.04)	−0.04 (−0.09 to 0.02)
Submassive	22 (0.36)	15 (0.25)	0.12 (−0.08 to 0.31)	11 (0.20)	10 (0.20)	0.01 (−0.16 to 0.18)
Clinically significant	61 (1.01)	64 (1.06)	−0.05 (−0.41 to 0.31)	34 (0.62)	26 (0.51)	0.11 (−0.17 to 0.40)
Asymptomatic	3 (0.05)	5 (0.08)	−0.03 (−0.12 to 0.06)	2 (0.04)	2 (0.04)	0 (−0.08 to 0.07)
Segmental	61 (1.01)	59 (0.98)	0.03 (−0.32 to 0.39)	36 (0.66)	26 (0.51)	0.15 (−0.14 to 0.44)
Subsegmental	38 (0.63)	40 (0.66)	−0.03 (−0.32 to 0.25)	23 (0.42)	22 (0.43)	−0.01 (−0.26 to 0.24)
DVT type						
Any	151 (2.51)	103 (1.71)	0.80 (0.28 to 1.31)	109 (2.01)	73 (1.44)	0.57 (0.08 to 1.07)
Proximal	74 (1.23)	59 (0.98)	0.25 (−0.12 to 0.62)	46 (0.85)	41 (0.81)	0.04 (−0.30 to 0.39)
Distal	87 (1.45)	52 (0.86)	0.58 (0.20 to 0.96)	65 (1.20)	36 (0.71)	0.49 (0.12 to 0.86)
Secondary safety outcome						
Bleeding complication	834 (13.72)	869 (14.27)	−0.54 (−1.78 to 0.69)	730 (13.30)	693 (13.44)	−0.14 (−1.43 to 1.16)
Wound complication	8 (0.13)	14 (0.23)	−0.10 (−0.25 to 0.05)	7 (0.13)	10 (0.20)	−0.07 (−0.22 to 0.09)
Infection	103 (1.73)	93 (1.55)	0.18 (−0.28 to 0.64)	100 (1.86)	69 (1.36)	0.50 (0.02 to 0.98)

* Percentages are calculated with the use of treatment-specific 90-day outcome probabilities, as calculated by a Kaplan–Meier estimator for the primary outcome and cumulative-incidence functions for the secondary outcomes, and do not use the group population as the denominator. This method was chosen over simple percentages to reflect the differential follow-up in some patients and for consistency with the treatment-effect estimates. DVT denotes deep-vein thrombosis, and PE pulmonary embolism.

† The confidence intervals are 95% confidence intervals for all the measures except death from any cause, for which 96.2% confidence intervals are shown.

‡ P<0.001 for noninferiority.

§ Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates and confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

Appendix 7: Subcategories of VTE Risk in Surgical and Non-Surgical Patients as per Standard Treatment Guidelines and Essential Medicines List for South Africa. Hospital Level, Adults, 2019 edition

SUBCATEGORIES OF VTE RISK IN SURGICAL AND NON-SURGICAL PATIENTS

	Surgical patients	*Medical patients*
Low VTE risk	» Surgery lasting <30 minutes » Injuries without or with only minor soft-tissue trauma » No or only minor additional predisposing risk factors	» Infection or acute inflammatory diseases without bed rest » Central venous catheters » No or only minor additional predisposing risk factors
Moderate VTE risk	» Surgical procedures of longer duration » Immobilisation of lower limb with plaster cast » Lower limb arthroscopic procedures. » No or only minor additional predisposing risk factors	» Acute cardiac insufficiency (NYHA III/IV) » Acute decompensated COPD without ventilation » Infection or acute inflammatory diseases with bed rest » Malignant disease » No or only minor additional predisposing risk factors
High VTE risk	» Major surgical procedures for malignancy » Multiple trauma or severe trauma of the spine, vertebra or » lower limbs » Major orthopaedic surgery, e.g. hip or knee replacement » Major surgical procedure of cardiothoracic and pelvic region	» Stroke with paralysis » Acute decompensated COPD with ventilation » Sepsis » ICU patients

Source: Jacobson BF, Louw S, Büller H, Mer M, de Jong PR, Rowji P, Schapkaitz E, Adler D, Beeton A, Hsu HC, Wessels P, Haas S; South African Society of Thrombosis and Haemostasis. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013 Feb 15;103(4 Pt 2):261-7.
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South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level of Care Medication Review Process
Component: Blood and blood forming organs

MEDICINE REVIEW

Title: 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

Date: 02 November 2023

INTRODUCTION

The standard of care for venous thromboembolism prophylaxis in patients undergoing total hip and total knee arthroplasty has recently been updated to rivaroxaban 10mg orally daily for 2 weeks duration in total knee replacement patients, and 5 weeks in total hip replacement patients.

This recommendation was recently ratified by the NEMLC as rivaroxaban was found to be non-inferior to LMWH, the previous standard of care, and because of the major projected cost savings in switching from LMWH to rivaroxaban[1].

In the context of the current fiscal crisis in which our health care budget has been severely cut, potential further cost-savings by using even cheaper agents was actively explored, and the option of using aspirin was investigated.

The literature search around aspirin use for this patient population was conducted and yielded few, poor quality data which were difficult to synthesise. Two high quality guidelines however, have made recommendations for use of aspirin in these patients. The NICE[5]and ASH[4] guidelines were appraised and analysed, and although both were found to be of high quality, the NICE guidelines provided more specific recommendations, and explored the hip and knee arthroplasty patient populations separately.

We used the NICE guideline[5] to formulate new recommendations for VTE prophylaxis in arthroplasty patients, incorporating aspirin for part of the duration of prophylaxis.

EXECUTIVE SUMMARY

Guideline for Adaptation: NICE Guideline "Venous thromboembolism in over 16s" (2018)

Patient population: Orthopaedic patients undergoing hip arthroplasty or knee arthroplasty requiring VTE prophylaxis
Level of care: Adult Hospital Level
Prescriber Level: Medical Doctor
Current standard of Care: LMWH recently amended to Rivaroxaban 10mg orally, daily
Motivator/reviewer name(s): Gayle Tatz, Marc Blockman
Secretariat support: Zahiera Adam
PTC affiliation: Marc Blockman (Western Cape provincial pharmacy therapeutics committee)

Adapted Guideline for Total Hip Arthroplasty Patients:

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.

Adapted Guideline for Total Knee Arthroplasty Patients:

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).

[1] NDoH Evidence Review. DOACS for VTE Prophylaxis. 12 October 2023
Adaptation of NICE Guideline "Venous thromboembolism in over 16s" for patients undergoing total hip arthroplasty or total knee arthroplasty requiring venous thromboembolism prophylaxis. November 2023. Version 1.0_30 Nov 2023_final

KEY FINDINGS

- 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.

	NICE Guideline	**Adapted Recommendation**
Total Hip Arthroplasty	Choose any one of: • LMWH for 10 days followed by aspirin (75 or 150 mg) for a further 28 days. • LMWH for 28 days combined with anti-embolism stockings (until discharge). • Rivaroxaban 10mg starting 6-10 hours after surgery for 5 weeks	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.
Total Knee Arthroplasty	Choose any one of: • Aspirin (75 or 150 mg) for 14 days. • LMWH for 14 days combined with anti-embolism stockings until discharge. • Rivaroxaban 10mg starting 6-10 hours after surgery for 2 weeks	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 for the above changes in hip arthroplasty patients:

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 non-inferior 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.

- Rationale for the above changes in knee arthroplasty patients:

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.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: We recommend 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.

For elective hip arthroplasty, we recommend:

Rivaroxaban 10mg daily initiated 6-10 hours post operatively for 10 days, followed by aspirin 150mg for 28 days on discharge

For elective knee arthroplasty, we recommend:

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: The NEMLC has previously made the recommendation for rivaroxaban over LMWH based on non-inferior efficacy and safety and improved cost-effectiveness of rivaroxaban for VTE prophylaxis. The NICE guideline found that there was no difference in efficacy or safety between aspirin monotherapy in knee arthroplasty or enoxaparin followed by aspirin in hip arthroplasty, compared with low molecular weight heparin monotherapy for VTE prophylaxis. Together with good evidence of efficacy and safety with use of rivaroxaban, NICE suggests any of these three treatment options at the clinician's discretion (aspirin monotherapy/enoxaparin followed by aspirin, enoxaparin monotherapy or rivaroxaban monotherapy). Our adaptation of these guidelines involved replacing the 10 days of enoxaparin preceding aspirin in total hip arthroplasty patients with rivaroxaban for cost-saving reasons, and our choice to use rivaroxaban in the initial post-operative period followed by aspirin in total knee arthroplasty patients was to mitigate the potential bleeding risk associated with aspirin identified in hip arthroplasty patients.

Level of Evidence: adaptation of a high quality guideline based on low certainty evidence

Review indicator: New data on the efficacy and/or safety of aspirin in VTE prophylaxis for arthroplasty patients.

NEMLC RECOMMENDATION (MEETING OF 30 November 2023): NEMLC supports the ERC recommendation as stated above.

Monitoring and evaluation considerations:

Research priorities

History

The National Essential Medicines List Committee (NEMLC) of South Africa, recently approved the use of rivaroxaban as venous thromboembolism prophylaxis in patients undergoing total hip and total knee arthroplasty. This has replaced the previous standard of care of low molecular weight heparin (LMWH). The medicine review and budget impact analysis informing this decision showed rivaroxaban to be non-inferior and more cost effective than LMWH.

Many international guidelines have used aspirin for thromboprophylaxis in this patient population, whether it be for the entire duration of prophylaxis post-operatively, or for the latter portion of the duration of prophylaxis. Aspirin is vastly more cost effective than either LMWH or rivaroxaban. A preliminary literature search looking at aspirin vs LMWH for VTE prophylaxis in patients undergoing hip or knee arthroplasty yielded few randomised controlled trials with all studies being of low to very low quality. Considering that two good quality guidelines were available which addressed the question of which agents may be considered for VTE

prophylaxis in patients undergoing hip or knee arthroplasty, we decided to conduct an expedited adaptation of one of the guidelines, to determine how aspirin would fit in as a prophylaxis option for these patients. The place of aspirin use in this guideline will be the focus of the review.

Rationale for selecting the NICE guideline for adaptation

Two good quality guidelines were available for patients requiring venous thromboembolism (VTE) prophylaxis after total hip or knee arthroplasty. These were:

i) the American Society of Haematology (ASH) guideline for the "Prevention of Venous Thromboembolism in Surgical Hospitalized Patients" (2019)[4] and
ii) the National Institute for Health and Care Excellence (NICE) guideline on "Venous thromboembolism in over 16s" (2019)[5].

The reason for choosing the NICE guideline is twofold. Firstly, treatment doses and durations were specified. Secondly, hip arthroplasty compared with knee arthroplasty were explored separately as two different patient populations and were found to have different treatment regimens with very different durations of therapy.

In the ASH guidelines, hip and knee arthroplasty were assessed together as a single patient population and the guideline does not specify dose or duration of treatment. We felt that the two populations (hip arthroplasty vs knee arthroplasty patients) are different in terms of their VTE risk, and that assessing them separately was necessary. Tangible dosing regimens also make adaptation simpler with the fortuitous finding that the aspirin formulations in the United Kingdom where the NICE guidelines are applicable, are similar to what is available in South Africa, further simplifying the process.

In terms of risk difference between patients undergoing total hip and total knee arthroplasty, few epidemiological studies are available. It appears from one of the largest observational cohorts however, that VTE occurs more frequently in total knee arthroplasty patients, but that this occurs most commonly within the first 2 weeks post operatively[6]. In total hip arthroplasty patients, fewer cases of VTE occur and are spread out evenly over 45 days post operatively with 4 out of 5 cases of VTE occurring within 35 days (Appendix 1). This data correlates with the duration of therapy stipulated in the guideline.

A dent in the methodological rigour of the NICE guidelines, was the use of multiple network meta-analyses (NMA) which may have allowed for the differentiation of the guidance for hip compared to knee arthroplasty patients, but was imprecise in many of the outcomes. This was balanced against the benefit of allowing for more nuanced patient care overall.

AGREE II

The NICE Guideline scored well in all 6 domains. A score of less than 30% is generally considered poor. None of the domain scoring fell into this category. The most poorly performing domain was Domain 5: Applicability.

[Domain 1: 83%; Domain 2: 61%; Domain 3: 94%; Domain 4: 89%; Domain 5: 38%; Domain 6: 83%]

NICE Guideline recommendations

The NICE Guideline makes separate recommendations for total hip arthroplasty patients and total knee arthroplasty patients requiring VTE prophylaxis.

Elective hip replacement

1.5.8 Offer VTE prophylaxis to people undergoing elective hip replacement surgery whose risk of VTE outweighs their risk of bleeding. Choose any one of:

- **LMWH[aa] for 10 days followed by aspirin[bb] (75 or 150 mg) for a further 28 days.**
- **LMWH[cc] for 28 days combined with anti-embolism stockings (until discharge).**
- **Rivaroxaban[dd].** Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. [This text is from *Rivaroxaban for the prevention of venous*

thromboembolism after total hip or total knee replacement in adults (NICE technology appraisal guidance 170).] **[2018]** This document suggests using rivaroxaban **10mg starting 6-10 hours after surgery for 5 weeks in elective hip surgery patients.**

1.5.9 Consider one of the following if none of the options in recommendation 1.5.8 can be used:

- Apixaban[ee] is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery. [This text is from Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (NICE technology appraisal guidance 245).]
- Dabigatran etexilate[ff], within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (NICE technology appraisal guidance 157).]

1.5.10 Consider anti-embolism stockings until discharge from hospital if pharmacological interventions are contraindicated in people undergoing elective hip replacement surgery. **[2018]**

aa At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
bb At the time of publication (March 2018), aspirin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
cc At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
dd At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
ee At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
ff At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.

Elective knee replacement

1.5.11 Offer VTE prophylaxis to people undergoing elective knee replacement surgery whose VTE risk outweighs their risk of bleeding. Choose any one of:

- **Aspirin[gg] (75 or 150 mg) for 14 days.**
- **LMWH[hh] for 14 days combined with anti-embolism stockings until discharge.**
- **Rivaroxaban[ii].** Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (NICE technology appraisal guidance 170).] [2018] This document suggests using rivaroxaban **10mg starting 6-10 hours after surgery for 2 weeks in elective knee surgery patients.**

1.5.12 Consider one of the following if none of the options in recommendation 1.5.11 can be used:

- Apixaban[jj] is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery. [This text is from Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (NICE technology appraisal guidance 245).]
- Dabigatran etexilate[kk], within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. [This text is from Dabigatran

etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (NICE technology appraisal guidance 157).]

1.5.13 Consider intermittent pneumatic compression if pharmacological prophylaxis is contraindicated in people undergoing elective knee replacement surgery. Continue until the person is mobile. **[2018]**

gg At the time of publication (March 2018), aspirin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
hh At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
ii At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
jj At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
kk At the time of publication (March 2018), rivaroxaban did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.

NMA and Evidence Quality from the NICE guideline

The evidence to decision was explicit in the NICE guideline. The evidence around aspirin use was generally considered to be poor. This was also the case in the ASH guideline and correlates with our own literature search around aspirin use in this patient population. The evidence regarding rivaroxaban use in patients undergoing total hip and total knee replacement surgery is covered in a separate NDOH review[2] and is not replicated in this document.. The NEMLC recommendation from this review supports the use of rivaroxaban over LMWH in patients undergoing total hip or knee replacement surgery for 5 and 2 weeks post operatively respectively at a dose of 10mg daily. Rivaroxaban's non-inferiority in terms of efficacy and safety, and more affordable cost were cited as the rationale by NEMLC in support of rivaroxaban over LMWH.

A NMA was used to compare different treatment regimens and a different NMA was conducted for each outcome. Interventions included: no VTE prophylaxis, pharmacological and mechanical interventions as single agents, and combination interventions of both pharmacological and mechanical interventions.

Outcomes considered included all-cause mortality, DVT (symptomatic and asymptomatic), pulmonary embolus (PE) and major bleeding. Fewer studies were included in the NICE guideline compared with the ASH guidelines, which is a limitation of the NICE guideline. Importantly, the recommendations in the ASH guideline also includes the use of aspirin as an option for VTE prophylaxis in hip and knee arthroplasty patients, which demonstrates that the final outcome of the NICE guideline was not impacted by the inclusion of fewer studies.

Total Hip Arthroplasty

Table 43 in the NICE guideline (figure 1) depicts the clinical evidence summary for total hip arthroplasty patients comparing a standard dose of dalteparin (5000IU daily) for 5 weeks with dalteparin for 10 days followed by aspirin 81mg daily for 28 days. The GRADE assessment of the quality of the data was low for the outcomes of all-cause mortality, fatal PE, major bleeding, clinically relevant other major bleeding and wound infection. It was very low for the outcome of PE.

There is no DVT outcome included. This has been noted as a limitation of the guideline and this was because it was not included in the DVT NMA. This outcome was not reported as the informing trial using this particular regimen reported only on proximal DVTs and not on symptomatic and asymptomatic DVTs which all of the other trials had reported on. DVT (symptomatic and asymptomatic) outcome was assumed to be the same as that for the outcome "proximal DVT" which was reported in the included trial and there was therefore no reported difference between intervention and comparator.

[2] NDoH Evidence Review. DOACS for VTE Prophylaxis. 12 October 2023
Adaptation of NICE Guideline "Venous thromboembolism in over 16s" for patients undergoing total hip arthroplasty or total knee arthroplasty requiring venous thromboembolism prophylaxis. November 2023. Version 1.0_30 Nov 2023_final

Risk differences were not estimable for all-cause mortality, PE and major bleeding as there were zero events in the intervention arm. The population concerned in the evidence used was a North American population with a mean age of 57.8 years and a male:female ratio of 1.3:1.

Table 43: Clinical evidence summary: LMWH (standard dose; extended duration) versus LMWH (standard dose; standard duration) followed by aspirin (extended duration)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LMWH followed by Aspirin (extended duration)	Risk difference with LMWH (extended duration) (95% CI)
All-cause mortality	785 (1 study) 90 days	LOW[b] due to imprecision	Peto OR 7.12 (0.14 to 358.94)	0 per 1000	-[a]
PE	778 (1 study) 90 days	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 7.1 (0.74 to 68.48)	0 per 1000	-[a]
Fatal PE	785 (1 study) 90 days	LOW[b] due to imprecision	Not estimable4	Not estimable[a]	0 fewer per 1000 (from 0 fewer to 0 more)[d]
Major bleeding	785 (1 study) 90 days	LOW[b] due to imprecision	Peto OR 7.12 (0.14 to 358.94)	0 per 1000	-[a]
Clinically relevant non-major bleeding	785 (1 study) 90 days	LOW[b] due to imprecision	Peto OR 1.88 (0.38 to 9.38)	5 per 1000	5 more per 1000 (from 3 fewer to 4 more)
Wound infection	785 (1 study) 90 days	LOW[b] due to imprecision	RR 0.8 (0.35 to 1.83)	31 per 1000	6 fewer per 1000 (from 20 fewer to 26 more)

a Absolute effect could not be calculated due to zero events in the intervention arm
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
d Zero events in both arms. Risk difference calculated in Review Manager.

Figure 1

Table 63 (figure 2) depicts the clinical evidence summary for total hip arthroplasty patients comparing unfractionated heparin with aspirin. This is included as it was a component of the meta-analysis but as an individual finding, is not relevant to this review.

Table 63: Clinical evidence summary: UFH versus aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aspirin	Risk difference with UFH (95% CI)
DVT (symptomatic and asymptomatic)	37 (1 study) 7 days	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.24 (0.05 to 1.13)	333 per 1000	253 fewer per 1000 (from 317 fewer to 43 more)
PE	37 (1 study) 7 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.10 (0 to 5.16)	83 per 1000	74 fewer per 1000 (from 83 fewer to 236 more)
Fatal PE	37 (1 study) 7 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.76 (0.05 to 11.39)	83 per 1000	20 fewer per 1000 (from 79 fewer to 866 more)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Figure 2

Total Knee Arthroplasty

Table 86 (figure 3) depicts the clinical evidence summary in total knee arthroplasty patients comparing enoxaparin 40mg daily with aspirin 100mg daily as prophylaxis. Only the outcomes of DVT and PE are available although the relative effect between the intervention and comparator for the outcome of PE is not estimable because of the extremely low event rates (zero in both arms). There was very serious imprecision, indirectness and risk of bias surrounding both results and quality of evidence was very low on both counts.

Table 86: Clinical evidence summary: LMWH (standard dose; standard duration) versus aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aspirin	Risk difference with LMWH (standard dose) (95% CI)
DVT (symptomatic and asymptomatic)	222 (1 study) 28 days	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.76 (0.4 to 1.46)	164 per 1000	39 fewer per 1000 (from 98 fewer to 75 more)
PE	222 (1 study) 28 days	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Not estimable[d]	Not estimable[d]	0 fewer per 1000 (from 20 fewer to 20 more)[d]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

d Zero events in both arms of one of the studies included. Risk difference calculated in Review Manager.

Figure 3

Table 113 (figure 4) shows the clinical evidence summary in total knee arthroplasty patients comparing rivaroxaban 10mg daily with aspirin 100mg daily as prophylaxis. The risk difference of PE was once again not estimable due to zero events occurring in both arms and the GRADE was considered very low. The risk of DVT (symptomatic and asymptomatic was low with rivaroxaban compared with aspirin at 134 fewer events per 1000 (134 fewer to 67 fewer) with a high quality of evidence rating on GRADE. It is important to note that not included in the guideline, is the breakdown of symptomatic vs asymptomatic DVTs. There were 2 symptomatic DVTs in the aspirin arm and 0 in the rivaroxaban arm. The committee noted the dose used for aspirin in the evidence represented a non-standard dose for the UK at 100mg per day and they stipulated that clinicians can decide whether to use 75mg or 150mg.

Table 113: Clinical evidence summary: Rivaroxaban versus aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aspirin	Risk difference with Rivaroxaban (95% CI)
DVT (symptomatic and asymptomatic)	212 (1 study) 28 days	HIGH	RR 0.18 (0.05 to 0.59)	164 per 1000	134 fewer per 1000 (from 67 fewer to 155 fewer)
PE	212 (1 study) 28 days	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	Not estimable[b]	Not estimable[b]	0 fewer per 1000 (from 20 fewer to 20 more)[b]

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Zero events in both arms. Risk difference calculated in Review Manager.

c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol

d Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Figure 4

Evidence to Decision: NICE Guideline

Total Hip Arthroplasty

Below is an excerpt justifying the choice of regimen for hip arthroplasty patients.

"The top ranked intervention for the clinical outcomes of PE and major bleeding was a combined pharmacological option of LMWH initially, followed by aspirin. The committee and orthopaedic subgroup discussed the current concerns in regards to the bleeding risk associated with aspirin, especially when used soon after surgery (when bleeding risk is highest). However they agreed that the use of aspirin after a 10-day course of LMWH would take into account the high early bleeding risk whilst providing clinical benefit in terms of the evaluated outcomes of PE and major bleeding. The durations for LMWH (10 days) and aspirin (28 days) are based on the evidence evaluated in the clinical trials."

Total Knee Arthroplasty

The evidence to decision process for use of aspirin in total knee arthroplasty patients for VTE prophylaxis was based on the fact that aspirin appeared to be non-inferior to LMWH and performed neither well nor poorly in

comparison to other interventions. Rivaroxaban was rated highest. The guideline stated that "The inclusion of aspirin and LMWH combined with anti-embolism stockings (until discharge) in the recommendation was primarily based on the results from the economic model (see 'Trade-off between net clinical effects and costs' section for further discussion). The durations of the interventions were based on the durations presented in the relevant clinical trials."

Contextualising within South African Health Care system

The standard of care for VTE prophylaxis is LMWH which has recently (2020-23 review cycle) been changed to rivaroxaban given the non-inferior efficacy, similar safety profile, and cost-effectiveness. While evidence supports a comparable efficacy and safety profile between apixaban and rivaroxaban; based on current pricing, rivaroxaban is the more cost-effective option.

Aspirin has been identified in the NICE guideline discussed, as being an option for both hip and knee arthroplasty patients, the use of which differs between these two groups. In the South African context, we suggest adapting the NICE guideline in the following way:

Total Hip Arthroplasty Patients

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.

Total Knee Arthroplasty Patients

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.

Rationale: Adaptation of NICE Guideline for the EML

Total Hip Arthroplasty Patients

LMWH was used in the NICE guideline for the first 10 days. For the purposes of the EML, we have taken the decision to replace LMWH with rivaroxaban as it has been shown to be non-inferior in terms of safety and efficacy and is more cost effective. In all other respects, our recommendation for the EML is the same as the NICE guideline.

Total Knee Arthroplasty Patients

In the NICE evidence to decision for VTE prophylaxis in patients undergoing total hip arthroplasty, allowance was made for the initial use of LMWH in the immediate post-operative period as bleeding risk with aspirin use was highest at this time. The same consideration was not given for patients undergoing total knee arthroplasty. 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. For the EML guidance, we opted for rivaroxaban as the anticoagulant of choice as it is cheaper than LMWH. With the exception of patients who develop complications post-surgery, patients who have undergone total knee arthroplasties are not expected to remain admitted for prolonged periods and it is reasonable to give rivaroxaban as VTE prophylaxis in hospital, followed by aspirin on discharge. The range stipulated in our recommendation is to allow for individual variation in clinical course.

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Appendices

Appendix 1

From Sumama et al.[6] showing the timing of venous thromboembolic events after total hip and total knee replacement in the first 90 days post-operatively.

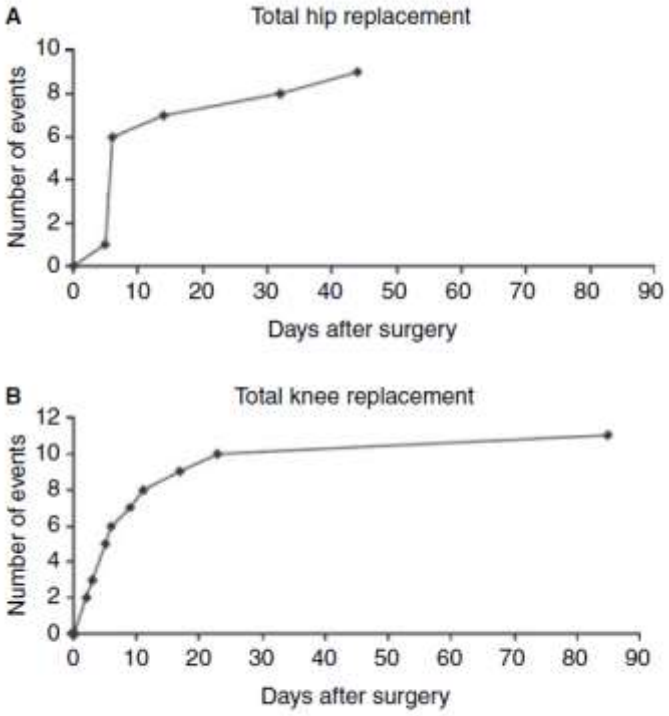

Fig. 1. Time to occurrence of venous thromboembolism after the surgical procedure (day 0).

South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: BBFO

MEDICINE REVIEW

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

Date: 30 November 2021 (original)
Updated: October 2023

Key findings

- We conducted a review of current relevant, high quality practice guidelines and the systematic reviews that informed their recommendations. The American Society of Hematology (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 2020 guideline is summarized and reported in our review as the recommendations were based on a high quality systematic review of 12 randomised controlled trials, which incorporated all of the 8 clinical trials from Health Technology Assessment that informed the NICE guideline.
- The last search in the ASH guideline was January 2019. Therefore, to ensure we did not miss any new data, we conducted an updated search from 1 February 2019 to 30 September 2021, but we found no new trials.
- 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 (refer to Appendix 2 below), 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.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X
Recommendation: Based on this evidence review and the supporting economic analysis, the PHC/Adult Hospital Level Committee 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. (see Table 2 below) **Level of Evidence: Benefit: Moderate certainty ; Safety: High certainty** **Review indicator:** New evidence of harms, change in price of LMWH; rivaroxaban or other DOACs (dabigatran, apixaban)					
NEMLC RECOMMENDATION (30 NOVEMBER 2023): NEMLC ratified the updated ERC recommendation in support of the use of rivaroxaban for the treatment of VTE as stated above.					
Monitoring and evaluation considerations:					
Research priorities:					

1. Executive Summary

Date: Updated 26 October 2023 (Original review: 06 October 2021)
Medicine (INN): Rivaroxaban, dabigatran, apixaban
Medicine (ATC): Antithrombotic agents (B01A)
Indication (ICD10 code): I80.2
Patient population: Hospitalised acutely ill patients with venous thromboembolism
Prevalence of condition: Prevalence of DVT and PE were estimated between 2.4% - 9.6% and 0.14% to 61.5%, respectively (Danwang C, et al. 2017)
Level of Care: Hospital level care
Prescriber Level: Medical doctor, specialist
Current standard of Care: Low molecular weight heparin / vitamin K antagonists (warfarin)
Efficacy estimates: (preferably NNT) Similar mortality (RR, 0.99; 95% CI, 0.85-1.15) and VTE [(PE: RR, 0.97; 95% CI, 0.77- 1.23); (DVT: RR, 0.80; 95% CI, 0.59-1.09)] outcomes**.**
Motivator/reviewer name(s): Veshni Pillay-Fuentes Lorente, Roland van Rensburg, Tamara Kredo, Nqoba Tsabedze, Marc Blockman, Trudy Leong
PTC affiliation:

2. Name of author(s)/motivator(s)

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Tamara Kredo: Cochrane South Africa, South African Medical Research Council and Division of Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University; no conflicts of interest to declare.
Nqoba Tsabedze: University of the Witwatersrand; Adult Hospital Level Committee, National Department of Health, South Africa; Charlotte Maxeke Johannesburg Academic Hospital; declarations include: Servier Laboratories SA (Pty) Ltd - consultancy (To review slide deck on New Hypertension Guideline Management), Novartis SA (Pty)Ltd - Consultancy (To develop a Heart Failure Toolbox. For Management of Acute and Chronic heart failure. Collaboration on a Heart Failure with preserved ejection fraction epidemiological study, Boehringer – Ingelheim, Novonordisk, Eli-Lilly, AstraZeneca, Adcock

Ingram, Pfizer, Merck: Speaker Fees for Webinars & Advisory Board Services, Merck - collaborating on a systematic review of efficacy of Beta Blockers in Black Hypertensives, Wits University – various grants.
Marc Blockman: University of Cape Town, Groote Schuur Hospital, Adult Hospital Level Committee, National Department of Health, South Africa; declaration - University of Cape Town receives various sponsorships from Pharma Industry.
Trudy Leong: Essential Drugs Programme, National Department of Health; no conflicts of interest – assisted with the costing analyses.

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4. Introduction/ Background

Cardiovascular disease remains amongst the top three causes of death globally.[1] Within the causes of cardiovascular related deaths, venous thromboembolism (VTE) has high mortality rates and commonly presents as deep vein thrombosis (DVT) or pulmonary embolism (PE).[1–3] Hospitalised patients are at higher risk of developing VTE.[3] In Africa, the prevalence of DVT and PE were estimated between 2.4% - 9.6% and 0.14% to 61.5%, respectively.[4] The PE mortality rate ranges between 40% - 69.5%.[4]

The current VTE standard of care treatment constitutes the initiation of low molecular weight heparin (LMWH) plus warfarin followed by the cessation of LMWH once the international normalized ratio (INR) is within the therapeutic range (2.0 – 3.0).[5] Enoxaparin, a LMWH commonly used in South Africa, acts by binding to antithrombin III, the antithrombin III-LMWH complex further inhibits factor Xa. This ultimately leads to the decrease of further fibrin formation and/or expansion.

Warfarin, also known as a vitamin K antagonist, binds and inhibits the enzyme, vitamin K epoxide reductase complex 1 (VKORC1).[6] Vitamin K is required for the synthesis of coagulation factors II (half-life 42 to 72 hours), VII (half-life 4 to 6 hours), IX, and X (half-life 27 to 48 hours), as well as anticoagulants, proteins C and S. These clotting factors are biologically activated by the addition of carboxyl groups to key glutamic acid residues within the proteins' structure. In the process, "active" vitamin K is converted to an "inactive" form, which is then reactivated by VKORC1. The inhibition of VKCOR1 by warfarin causes a depletion of functional vitamin K reserves hence reduces synthesis of active vitamin K dependent clotting factors. The prolonged time taken for depletion of circulating clotting factors and the early depletion of anticoagulants, C and S, predisposes patients to a procoagulant state in the initial phase of warfarin therapy. As a result, parenteral administration of LMWH is required during the initial phase of warfarin therapy until therapeutic INR is achieved. The time taken to reach therapeutic INR is approximately 5 to 6 days.[7]

Direct oral anticoagulants (DOACs) have been on the international market since 2008, with dabigatran being the first to be marketed as a direct thrombin inhibitor. Dabigatran etexilate, a prodrug, is converted to an active metabolite dabigatran which binds to thrombin hence altering the clotting cascade. It has a quick onset of action (approximately 2 hours) and could potentially not require concomitant administration of parenteral LMWH.[8] However, the clinical trials evaluating dabigatran compared to warfarin administered pretreatment with a parenteral anticoagulant to all patients hence currently dabigatran is not recommended as monotherapy.[9] Rivaroxaban was first marketed in 2008, followed by apixaban in 2011. Both drugs are inhibitors of factor Xa and do not require initial administration of parenteral heparin.

DOACs have been considered as an alternate to warfarin in treating VTE as they offer potential important benefits over warfarin such as no INR monitoring, thereby reducing clinic visits, and reduced interindividual patient variability. The initial delayed onset of action of warfarin requires the co-administration of parenteral heparins until therapeutic INRs are

reached, making DOACs an attractive option.[8] Throughout warfarin treatment, regular INR monitoring is required, which leads to many more patient visits. This was initially thought not to be necessary with DOACs. However, the lack of laboratory monitoring of DOACs have been challenged, particularly in special populations such as obesity.[10,11] In pregnancy, DOACs are avoided due to limited evidence to establish efficacy and embryo-fetal safety.[12,13] Many guidelines recommend against the use of DOACs in pregnancy.[14–16]

In South Africa, DOACs have historically been more costly than the current standard of care for VTE, however the price at which rivaroxaban is available in the public sector has been reduced. Due to the perceived benefits; and reduced costs for rivaroxaban, it would be important to evaluate the role of DOACs as an alternate therapy, or as a potentially new standard of care for VTE. This evaluation assessed the clinical benefits and harms as well as costs; in an evidence-based manner, compared to our current standard practice.

5. Purpose/Objective i.e. PICO question:

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

Population – Hospitalised adult patients with DVT or PE
Intervention – DOACs (rivaroxaban, apixaban and dabigatran)
Comparator - LMWH plus VKA (warfarin)
Outcome - Mortality, post-thrombotic limb, embolic events (DVT and PE), recurrent DVT, major bleeds
Study design - A review of clinical practice guidelines with high quality systematic reviews.

6. Methods:

Health Technology Assessments (HTAs): We conducted a search in May 2021 for HTAs on the following electronic databases: The International Network of Agencies for Health Technology Assessment (INAHTA), Epistemonikos and Cochrane library, using a simple search with broad search terms.

Guidelines: A search for current, relevant practice guidelines with available systematic reviews that informed them was conducted on the following websites: National Institute for Health Care Excellence (NICE), American Society of Haematology (ASH), American Heart Association (ACA), Canadian Agency for Drugs and Technologies in Health (CADTH) and the Scottish Medicines Consortium (SMC). Terms included were “DOAC, VTE and VKAs.”

The search and screening of eligible HTAs and guidelines were independently reviewed by two reviewers considering the following factors: most recent, best quality, include most evidence (i.e. relevant trials). All included studies are reported in Table 1: Table of excluded evidence, and the excluded studies are described with reason for exclusion below.

Costing data: we sought costing data from the relevant guidelines, reported under ‘other considerations in the results. We did not appraise the quality of the costing analyses. However, a supporting economic analysis was done – refer to the updated health economics report for rivaroxaban for VTE (Appendix 2),

Critical appraisal: The identified systematic reviews were assessed using the AMSTAR appraisal tool. Related guidelines were appraised using the AGREE II appraisal tool. For the included evidence, we checked the last search dates and then conducted a comprehensive electronic search in two databases (PubMed and CENTRAL) up to 30 September 2021. The search strategy is reported in appendix 1. All identified records were screened by title and abstract for eligibility by a single reviewer on the COVIDENCE software. All eligible studies for full text review were evaluated by two reviewers for full data extraction.

Excluded guidelines and their related systematic reviews:

Table 1. Table of excluded evidence

Author, date	*Type of document*	*Reason for exclusion*
Sterne JAC, et al (2017)[17]	HTA	Search only done up until September 2014. The review authors did not explain their selection of the study designs for inclusion in the review, and did not investigate for publication bias
NICE (originally published 2012, updated 2020)[18]	Guideline (with report of systematic reviews of RCTs)	Included 8 RCTs, all of which were included in the ASH guideline.

7. Evidence synthesis

One HTA was identified but the last search date in the HTA was September 2014. The study was excluded from the review because, 1) the review authors did not explain their selection of the study designs for inclusion in the review, and 2) did not investigate for publication bias. We found two clinical practice guidelines: NICE 2020 guidelines and ASH 2020 guidelines.[18,19] Both guidelines' overall quality of evidence as per AGREE II was rated 6/7. They were downgraded for inadequate reporting on stakeholder involvement. The NICE guideline was excluded since it included 8 RCTs which were all included in the ASH guideline.

The ASH guideline included a systematic review of 12 RCTs and was included in this review. The last search date in the ASH guideline was conducted in January 2019. We conducted an updated search from February 2019 to 30 September 2021 for RCTs. Four-hundred and thirty-eight articles were identified, four articles were duplicate publications, and 420 articles were screened by title and abstract. Fourteen articles were selected for full text review. We identified one potentially eligible trial; however, the full text was not found. The abstract reported that the study included 54 participants with spinal cord injury and results are not likely to affect the outcome effect sizes based on the available systematic review.

Effectiveness of the intervention

1. *Mortality:* The use of a DOAC instead of dose-adjusted VKA (warfarin) to maintain INR between 2.0-3.0 for patients with VTE probably does not impact mortality. The reported risk of mortality is RR, 0.99; 95% CI, 0.85-1.15. The anticipated absolute effects demonstrated a risk difference with DOACs to be 0 fewer per 1000 patients (95% CI, 6 fewer to 6 more). The evidence was assessed as moderate certainty evidence.

2. *Post-thrombotic limb:* This outcome was not reported.

3. *Embolic events (DVT and PE), recurrent DVT:* The risk of PE on DOACs compared to LMWH/VKA were similar (RR, 0.97; 95% CI, 0.77- 1.23; ARR, 1 fewer per 1000 patients; 95% CI, 5 fewer to 5 more. The quality of evidence was moderate certainty. DOACS compared to LMWH/VKA likely results in little or no reduction in the risk of DVT (RR, 0.80; 95% CI, 0.59-1.09; ARR, 5 fewer per 1000 patients; 95% CI, 11 fewer to 2 more). The evidence was assessed as moderate certainty evidence.

4. *Major bleeds:* Major bleeds were defined according to the International Society on Thrombosis and Haemostasis (ISTH)[20] as follows: a) Fatal bleeding, and/or b) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra- articular or pericardial, or intramuscular with compartment syndrome, and/or c) Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

   The use of a DOAC was associated with a reduction in the risk of major bleeding (RR, 0.63; 95% CI, 0.47-0.84; ARR, 6 fewer per 1000 patients; 95% CI, 9 fewer to 3 fewer) with high certainty evidence.

   In populations with a high risk for bleeding, the use of a DOAC instead of a VKA may lead to a reduction of 8 fewer bleeding events per 1000 patients (95% CI, 11 fewer to 3 fewer; high-certainty evidence). This was based on a risk of

bleeding of 2.1% in patients treated for 6 months (considered high risk population) with LMWH/VKA. Patients treated with LMWH/VKA for 6 months and longer were considered a high risk population group.

Major bleeding in the DOAC group was reported as 1.1% and 1.7% in the LMWH/VKA group. The numbers needed to harm (NNH) associated with major bleeding is 167. In the high-risk population group (2.1% risk of bleeding) the NNH = 100.

Other considerations

We identified five economic analyses reporting the cost comparisons between using DOACs and LMWH/VKA for treatment of VTE. The reports consistently suggest DOAC use is cost-saving compared with warfarin. One report used hypothetical health plan population [21], the other four analyses were informed by real world data.[22–25]

Fifteen economic analyses compared the cost and effectiveness of DOACs versus VKA on the treatment of VTE. All of them suggest DOACs as cost-effective alternative to LMWH or VKA. The studied DOACs mainly include apixaban, and rivaroxaban. A recent systematic review and cost effectiveness analysis found that at a willingness to pay threshold of £20,000–30,000 per QALY in the UK, DOAC are likely cost-effective.[17]
The health economic analysis for rivaroxaban for the treatment of VTE was conducted from a South African national public sector payer perspective and is included in Appendix 2 below. The incremental cost of treating DVT and PE over a period of 3, 6, and 9 months is shown in table 2.

Table 2. Incremental cost of treating DVT and PE over a period of 3, 6, and 9 months

	0 to 3 months	***0 to 6 months***	***0 to 9months***
Rivaroxaban	*R 10 075*	*R 12 181*	*R 14 214*
Enoxaparin-warfarin	*R 10 739*	*R 11 721*	*R 12 704*
Incremental Cost	*-R 664*	*R 461*	*R 1 510*

Summary of included guideline and related systematic review.

Table 3. Summary of ASH guideline and related systematic review

Author, date	Population	Interventions	Outcomes	Appraisal and comments
Ortel, et al., 2020 American Society of Haematology, 2020 guidelines	Systematic reviews of 12 randomized trials (n = 28 876) Patients with PE or DVT (without cancer)	Initial treatment with LMWH (5-10 days) with dose-adjusted warfarin (INR range, 2.0-3.0) Dabigatran and edoxaban were also administered after an initial treatment of 5 to 10 days with LMWH Rivaroxaban and apixaban were administered without initial parenteral anticoagulants.	Mortality RR, 0.99; 95% CI, 0.85-1.15; ARR, 0 fewer per 1000 patients; 95% CI, 6 fewer to 6 more; moderate certainty evidence Risk of PE RR, 0.97; 95% CI, 0.77-1.23; ARR, 1 fewer per 1000 patients; 95% CI, 5 fewer to 5 more; moderate-certainty evidence Risk of DVT RR, 0.80; 95% CI, 0.59-1.09; ARR, 5 fewer per 1000 patients; 95% CI,	Review: Overall quality of evidence as per AGREE – 6/7 The review search was up to date to January 2019. The review did not include cancer patients. Cost-effectiveness was considered. DOACs was recommended due to cost-effectiveness even though VTE outcomes were not statistically significant. The outcomes were reported as a class effect (DOACs) and in the search strategy all medications within our PICO was incorporated. However, not all the DOACs incorporated in the search strategy is available in South Africa. Recommendation:

		The length of the anticoagulation varied - 3 to 12 months.	11 fewer to 2 more; moderate-certainty evidence), although this was not statistically significant. <u>Risk of major bleeding</u> RR, 0.63; 95% CI, 0.47-0.84; ARR, 6 fewer per 1000 patients; 95% CI, 9 fewer to 3 fewer; high-certainty evidence NNH = 167 (DOAC 1.1% and VKA 1.7%) If considering the VKA 2.1%, then NNH = 100 In populations with a high risk for bleeding, the use of a DOAC instead of a VKA may lead to a reduction of 8 fewer bleeding events per 1000 (95% CI, 11 fewer to 3 fewer; high-certainty evidence	For patients with DVT and/or PE, the ASH guideline panel suggests using DOACs over VKAs (conditional recommendation based on moderate certainty in the evidence of effects). The ASH VTE treatment guideline panel has provided a conditional recommendation for the use of DOACs over VKAs as treatment for patients with a new diagnosis of VTE. Although the evidence supporting a reduced risk for bleeding with the use of a DOAC compared with a VKA was of high certainty, the lack of benefit for the VTE outcomes resulted in the conditional recommendation. *Remarks:* This recommendation may not apply to certain subgroups of patients, such as those with renal insufficiency (creatinine clearance < 30 mL/min), moderate to severe liver disease, or antiphospholipid syndrome.

8. Evidence quality:

The quality of evidence for the outcomes of mortality, pulmonary embolism and deep vein thrombosis was assessed as moderate certainty evidence. Major bleeding was assessed to be of high certainty evidence. The overall quality of the guideline was high and rated 6/7 using the AGREE II tool.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Mortality and VTE outcomes were assessed as moderate certainty evidence.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒	Mortality, and VTE outcomes with DOAC and LMWH/VKA use were similar • Mortality: RR 0.99 (0.85 to 1.15) • PE: RR 0.97 (0.77 to 1.23) • DVT: RR 0.80 (0.59 to 1.09)

QUALITY OF EVIDENCE OF HARM

What is the certainty/quality of evidence?

High	Moderate	Low	Very low
X			

High quality: confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect

Major bleeding outcomes was assessed as high certainty evidence.

EVIDENCE OF HARMS

What is the size of the effect for harmful outcomes?

Large	Moderate	Small	None

DOACS are safer.

There was a reduction in bleeding risk with DOACs.
<u>*Major bleeding:*</u> RR 0.63 (0.47 to 0.84); 6 fewer per 1,000; (9 fewer to 3 fewer)

Absolute risk reduction = 0.6% and in high-risk population = 1%

(Duration of treatment is 3 to 6 months, but most of the RCTs reviewed in the systematic review were of 3 months duration).

BENEFITS & HARMS

Do the desirable effects outweigh the undesirable harms?

Favours intervention	Favours control	Intervention = Control *or* Uncertain
X		

Mortality and VTE outcomes with DOAC and LMWH/VKA use were similar. There was a reduction of bleeding risk with DOACs.

THERAPEUTIC INTERCHANGE

Therapeutic alternatives available: n/a

This is a therapeutic multiple medicine review.

FEASIBILITY

Is implementation of this recommendation feasible?

Yes	No	Uncertain
X		

DOACs are SAHPRA registered for the treatment of VTE.,
INR monitoring is not required with DOACs.

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
	X	

Price of medicines/ treatment course

VTE Treatment			
Drug	**Indication: Treatment of DVT & PE**	**Cost for 3 months treatment**	**Cost for 6 months treatment**
Rivaroxaban	15mg BD for D1-D21 then 20mg OD for D22 onwards	1626.74	2945.72
Dabigatran	300 mg taken orally as 150 mg capsules twice daily following treatment with a parenteral anticoagulant for at least 5 days	4267.58	7901.12
Apixiban	10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily	2801.87	5456.27
Warfarin (excludes INR monitoring costs)	Enoxaparin 1mg/kg 12 hourly for 8 days with warfarin 5mg OD	1372.05	1406.67
Assumption 1 month = 30days			
MHPL 1 Sep 2023			
SEP Database 14 Aug 2023			

<table>
<tr>
<td></td>
<td></td>
<td>NB: Refer to updated health economic analysis for rivaroxaban for treating VTE (March 2023 – See Appendix 2)
<table>
<tr><td></td><td>0 to 3 months</td><td>0 to 6 months</td></tr>
<tr><td>Rivaroxaban</td><td>R 10 075</td><td>R 12 181</td></tr>
<tr><td>Enoxaparin-warfarin</td><td>R 10 739</td><td>R 11 721</td></tr>
<tr><td>Incremental Cost</td><td>-R 664</td><td>R 461</td></tr>
</table>
Other resources:
• Five economic analyses reported the cost comparisons between using DOACs and LMWH/VKA for treatment of VTE. All these reports suggest DOAC use is cost-saving compared with warfarin. Four analyses were based on real world data, whilst the other was a simulated model.
• Fifteen economic analyses compared the cost and effectiveness of DOACs versus VKA on the treatment of VTE. All of them suggest DOACs as cost-effective alternative to LMWH or VKA. The studied DOACs mainly include apixaban, and rivaroxaban.
• A recent systematic review and cost effectiveness analysis found that at willing to pay of £20,000–30,000 per QALY, suggesting that DOAC are likely cost-effective interventions

Given the substantial reduction in price of rivaroxaban and the cost savings in patients treated for up to 3 months, it is recommended that rivaroxaban is included on the EML for the treatment of DVT and PE and the prevention of recurrent VTE.</td>
</tr>
<tr>
<td>VALUES, PREFERENCES, ACCEPTABILITY</td>
<td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td>
<td>No included studies, and the Committee was of the opinion that DOACs are acceptable to prescribers.</td>
</tr>
<tr>
<td>EQUITY</td>
<td>Would there be an impact on health inequity?
Yes [X] No [ ] Uncertain [ ]</td>
<td>Access to INR monitoring is required with warfarin therapy, which is not needed with DOACs.</td>
</tr>
</table>

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	30 November 2021	VPL, RvR, TK, NT, MB, TL	DOACs not recommended for the treatment of VTE, as despite no difference in mortality benefit, yet greater reduction in major bleeding of DOACs compared to current standard of care (LMWH+warfarin), DOACs are currently unaffordable.
V6.0	October 2023	MB, ZA	Based on this evidence review and the supporting economic analysis, the PHC/Adult Hospital Level Committee recommends rivaroxaban for the treatment of VTE.

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Appendix 1: Search strategy

Database: **CENTRAL (Issue 9 OF 12, September 2021)**
Date: **30 September 2021**

ID	Search	Hits
#1	[mh "venous thrombosis"] or phlebothrombos*:ti,ab or ("deep vein" next thrombos*):ti,ab or DVT:ti,ab, (Word variations have been searched)	6373
#2	[mh "pulmonary embolism"] or (pulmonary next embolism*):ti,ab or (pulmonary next thrombo*):ti,ab or PE:ti,ab (Word variations have been searched)	7591
#3	[mh "venous thromboembolism"] or (venous next thrombo*):ti,ab or VTE:ti,ab (Word variations have been searched)	6879
#4	#1 or #2 or #3	15555
#5	(oral next anticoagulant*):ti,ab (Word variations have been searched)	2003
#6	[mh dabigatran] or dabigatran:ti,ab'kw or pradaxa:ti,ab,kw or "BIBR 1048":ti,ab,kw (Word variations have been searched)	7591
#7	[mh rivaroxaban] or rivaroxaban:ti,ab,kw or xarelto:ti,ab,kw or "BAY 59 7939":ti,ab,kw or "BAY 597939":ti,ab,kw (Word variations have been searched)	1884
#8	apixaban:ti,ab,kw or eliquis:ti,ab,kw or "BMS 562247":ti,ab,kw or BMS562247:ti,ab,kw (Word variations have been searched)	1027
#9	#5 or #6 or #7 or #8	11019
#10	MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees	2026
#11	[mh heparin] or heparin*:ti,ab,kw or liquaemin:ti,ab,kw or UFH:ti,ab,kw or LMW:ti,ab,kw or LMWH:ti,ab,kw or LMWHS:ti,ab,kw or "low-molecular-weight":ti,ab,kw or dalteparin:ti,ab,kw or enoxaparin:ti,ab,kw or nadroparin:ti,ab,kw or tinzaparin:ti,ab,kw or certoparin:ti,ab,kw or parnaparin:ti,ab,kw or ("vitamin K" next antagonist*):ti,ab,kw	15661
#12	#10 or #11	15661
#13	#4 and #9 and #12	804
#14	#4 and #9 and #12 with Publication Year from 2019 to 2021, in Trials	209

Database: **PubMed**
Date: **30 September 2021**

Search	Query	Results
#14	Search: #11 AND #12 Filters: from 2019/1/1 - 2021/9/30 Sort by: Most Recent	553
#13	Search: #11 AND #12 Sort by: Most Recent	2,081
#12	Search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	4,533,027
#11	Search: #4 AND #9 AND #10 Sort by: Most Recent	3,169
#10	Search: heparin[mh] OR heparin*[tiab] OR heparinic acid[tiab] OR liquaemin[tiab] OR UFH[tiab] OR heparin, low-molecular-weight[mh] OR LMW [tiab] OR LMWH[tiab] OR LMWHS[tiab] OR low-molecular-weight[tiab] OR dalteparin[tiab] OR enoxaparin[tiab] OR nadroparin[tiab] OR tinzaparin[tiab] OR certoparin[tiab] OR parnaparin[tiab] OR vitamin K antagonist*[tiab] Sort by: Most Recent	151,273
#9	Search: #5 OR #6 OR #7 OR #8 Sort by: Most Recent	22,536
#8	Search: apixaban[nm] OR apixaban[tiab] OR eliquis[tiab] OR BMS 562247[tiab] OR BMS562247[tiab] Sort by: Most Recent	4,472
#7	Search: rivaroxaban[mh] OR rivaroxaban[tiab] OR xarelto[tiab] OR BAY 59 7939[tiab] OR BAY 597939[tiab] Sort by: Most Recent	6,858
#6	Search: dabigatran[mh] OR dabigatran[tiab] OR pradaxa[tiab] OR BIBR 1048[tiab] Sort by: Most Recent	5,993
#5	Search: "oral anticoagulant"[tiab] OR "oral anticoagulants"[tiab] Sort by: Most Recent	16,347
#4	Search: #1 OR #2 OR #3 Sort by: Most Recent	172,173
#3	Search: Venous thromboembolism[mh] OR venous thrombo*[tiab] OR VTE[tiab] Sort by: Most Recent	55,557
#2	Search: Pulmonary embolism[mh] OR pulmonary embolism*[tiab] OR pulmonary thrombo*[tiab] OR PE[tiab] Sort by: Most Recent	94,223
#1	Search: Venous thrombosis[mh] OR phlebothrombos*[tiab] OR deep vein thrombos*[tiab] OR DVT[tiab] Sort by: Most Recent	68,272

Appendix 2: Budget Impact Analysis (BIA)

National Essential Medicines List Pharmacoeconomics and
Budget impact analysis Update
Adult Hospital Level
Component: BBFO

Date: 25 March 2023 (sixth update)
Medication: Rivaroxaban
Indication: Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent venous thromboembolic events (VTE)

INTRODUCTION

A motivation was initially received for rivaroxaban to be added to the EML for the following conditions;

- Post hip and knee surgery prophylaxis
- Treatment of DVT and pulmonary embolism
- Stroke prevention in treatment of non-valvular atrial fibrillation

A pharmacoeconomics decision analysis model was developed in December 2015 to determine the incremental cost for the use of rivaroxaban in the treatment of DVT or PE and the prevention of recurrent VTE compared to standard of care (enoxaparin and warfarin).

The report was reviewed in September 2017 to reflect updated costs, and subsequently updated 8 July 2020, to include a quotation from Bayer of a price 46% lower than SEP. It was further updated to describe costs (including generic Rivaxored® rivaroxaban prices) for 26 November 2021 and then again to describe costs of the clone (Ixarola®) of the originator brand for 17 November 2022 due to a successful patent infringement challenge from Bayer in 2021. Subsequently, Bayer has been awarded a contract based on a substantially reduced price of Xarelto® and the model has been revised to reflect the new pricing available as of January 2023.

PHARMACOECONOMICS MODEL - METHODS

A cost-minimization approach was used but with differences in bleeding rates and hospitalization costs taken into consideration. The perspective was that of a third-party payer – i.e. Department of Health/Government and therefore only direct costs were included. The costs were modeled for initial event, 3, 6 and 9 months and therefore no discounting was required.
A decision tree structure was used as per the figure below:

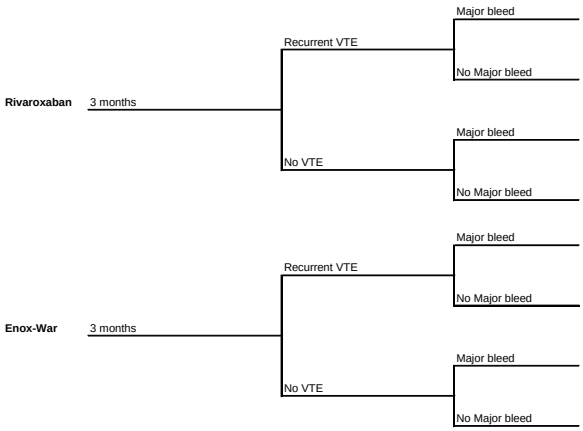

Figure 1. Diagram of decision analysis model for rivaroxaban vs enoxaparin-warfarin

CLINICAL INPUTS AND COSTS

The clinical input variables for the cost-effectiveness analysis were obtained from a number of sources, predominantly the EINSTEIN-DVT and EINSTEIN-PE studies (1) (2) which showed statistically significant non-inferiority in the primary efficacy endpoint (incidence of symptomatic recurrent VTE) in both trials at 3, 6 or 12 months and therefore a base-line event rate of recurrent symptomatic VTE was selected at 2.1%

The risk of first major bleed was significantly reduced with rivaroxaban from 1.7% to 1% in the EINSTEIN pooled analysis (3).

The initial length of stay for treatment was based on 1 day in ICU followed by a general ward stay of 4 days and 5 days for rivaroxaban and enoxaparin and warfarin (enox-war) respectively. Analysis of the EINSTEIN PE and DVT studies shows a reduction in initial length of stay for patients treated with rivaroxaban compared to standard of care (4).

The average length of hospitalization for a recurrent VTE was taken from a review of the cost of VTE (5) in 18 published studies. The length of stay (LOS) varied considerably between countries with ranges from 4.9-7 days and 5.8-7.7 days for DVT and PE respectively in the US. In Germany and Belgium, the length of stay increased to 14-24 days. Therefore, a baseline LOS of 6 days for enoxaparin-warfarin and 5 days for rivaroxaban was selected with a sensitivity analysis.

The unit costs for in-patient admissions and consultations were taken from the UPFS Tariffs from April 2022. The medication costs for rivaroxaban and for enoxaparin-warfarin were obtained from the most recent contract database. INR monitoring costs were obtained from the 2021 NHLS Costing Tables and inflation adjusted to 2022.

The medicine costs used in the model are as follows:

Medicine Costs

Medicine	Strength	Dosage form	Pack	Tender or Quotation Price/pack	Tender or Quotation Price /unit	SEP pack size	SEP (+VAT)	SEP (incl VAT)/unit
Rivaroxaban	15 mg	tab	42	R 615.52	R 14.66	42		
Rivaroxaban	20 mg	tab	28	R 410.35	R 14.66	28		
Warfarin	5 mg	tab	100	R 60.95	R 0.61	100	R 180.09	R 1.08
Enoxaparin	40mg	inj	1	R 53.61	R 53.61	n/a	n/a	n/a

Table 1. Medicine pricing for rivaroxaban, enoxaparin and warfarin

A number of assumptions were made for the model including:

- Hospitalisations included 1 day in ICU or HC followed by the balance of the days in general ward.
- The patient was consulted by an ICU specialist once on the day in ICU followed by general medical consultations in the general ward daily thereafter. Only general ward or no hospital stay was also modelled.
- All patients were treated at a Level 2 facility in terms of costs.
- Both DVT and PE patients were included together in the model even though it is acknowledged that they have different outcomes and prevalence.
- Recurrent VTEs were similar in terms of treatment regardless of whether the patient was on rivaroxaban or enoxaparin-warfarin and therefore accumulated the same costs.
- Efficacy of rivaroxaban and standard of care is the same (proven by non-inferiority) based on EINSTEIN trials and only bleeding outcomes differ (based on pooled EINSTEIN data).
- Only one further event occurred per time period (i.e. only one recurrent VTE regardless of whether in 3, 6, or 9 months).
- All patients were admitted for treatment of first time or recurrent DVT or PE.

RESULTS

At a base case pricing of the updated price for generic rivaroxaban (R 410.35 for 28 x 20mg tablets), the cost difference of treating a patient from the initial event for up to 3 months with rivaroxaban compared to enoxaparin-warfarin would be a cost saving of approximately R663.87. As the treatment duration increases to 9 months, the incremental cost increases to just over R1500. The outcomes of the model were as follows:

	0 to 3 months	***0 to 6 months***	***0 to 9months***
Rivaroxaban	*R 10 075*	*R 12 181*	*R 14 214*
Enoxaparin-warfarin	*R 10 739*	*R 11 721*	*R 12 704*
Incremental Cost	*-R 664*	*R 461*	*R 1 510*

Table 2. Incremental cost of treating DVT and PE over a period of 3, 6, and 9 months

The model was most sensitive to changes in length of stay (LOS) and then the price of rivaroxaban (Table 3). If the LOS was further reduced by 1 day for rivaroxaban, the model became cost-saving at 6 months. If patients did not need an ICU stay when on rivaroxaban, the model remained cost-saving even at 6 and 9 months. However, if both rivaroxaban and enox-war had the same LOS (5 days), then the model was no longer cost-saving at 3 months. If the enox-war arm had no ICU stay then the incremental cost increased quite substantially to R6 374 per patient at 9 months. Changing the efficacy event rate or varying the major bleed rate did not impact the model by much. Changing the LOS of a recurrent VTE did not impact the model as it was assumed to be the same for both arms (rivaroxaban and enox-war).

		Incremental Cost		
Model parameter	**Range**	**3 months**	**6 months**	**9 months**
Event Efficacy (VTE)	*2,10%*	*-R 664*	*R 461*	*R 1 510*
Lower (Riv)	1,75%	-R 701	R 423	R 1 470
Upper (Enox-war)	3,00%	-R 759	R 363	R 1 408
Event Bleed riv	*1%*	*-R 664*	*R 461*	*R 1 510*
Lower	0,5%	-R 728	R 397	R 1 446
No Diff	1,7%	-R 574	R 551	R 1 600
Upper	2,5%	-R 471	R 654	R 1 703
Event Bleed Enox-war	*1,70%*	*-R 664*	*R 461*	*R 1 510*
Lower	1,00%	-R 574	R 551	R 1 600
Upper	3,00%	-R 831	R 294	R 1 343
LOS_Riv	*5*	*-R 664*	*R 461*	*R 1 510*
Lower	4	-R 1 344	-R 219	R 830
Upper	10	R 2 736	R 3 861	R 4 910
No ICU stay	5	-R 5 528	-R 4 403	-R 3 354

LOS_Enox-war	*6*	*-R 664*	*R 461*	*R 1 510*
Lower	5	R 463	R 1 141	R 2 190
Upper	10	-R 4 064	-R 2 939	-R 1 890
No ICU stay	5	R 4 200	R 5 325	R 6 374
Rivaroxaban (per unit)	*14,66*	*-R 664*	*R 461*	*R 1 510*
5% reduction	13,92	-R 746	R 311	R 1 297
10% reduction	13,19	-R 828	R 162	R 1 083
15% reduction	12,46	-R 910	R 12	R 870
20% reduction	11,72	-R 992	-R 137	R 657
25% reduction	10,99	-R 1 074	-R 287	R 444
45% reduction	10,26	-R 1 402	-R 884	-R 409
Enoxaparin price	80mg bd	*-R 252*	*R 872*	*R 1 921*
Major bleed Cost	*6435,35*	*-R 664*	*R 461*	*R 1 510*
Lower	3000	-R 616	R 509	R 1 558
Upper	15000	-R 784	R 341	R 1 390

Table 3. Sensitivity analysis of key parameters for the model at 3, 6, and 9 months

PUBLISHED HEALTH ECONOMICS

There are a number of published cost-effectiveness studies on this subject (6). All used efficacy data from the EINSTEIN DVT and PE studies and reported ICERS as cost/LYG and cost/QALY. Rivaroxaban was found to be dominant (i.e. cost less with greater benefit) in all 3 of the US based studies, as well as in the model submitted by the manufacturer to NICE in the UK. The Evidence Review Group (ERG) of NICE presented their own analysis for DVT and PE and found that for DVT rivaroxaban dominated standard of care in the 3 month treatment arm but showed an ICER of £3,200 and £14,900 for the 6 and 12 month treatment groups respectively. For PE, the ERG produced an ICER of £11,590/QALY for 12 months treatment and £35,909 for lifelong treatment. An analysis carried out in 2015 evaluated the cost-effectiveness of treatment of VTE with rivaroxaban compared to LMWH/WAR for lifelong treatment showed ICERs of £8677 and £7072 for DVT and PE respectively which is below the cost-effectiveness threshold (around £20 000/QALY) for the UK (7).

BUDGET IMPACT ANALYSIS

It is challenging to determine the incidence of DVT and PE as well as rate of recurrence in the South African population. According to South African guidelines, the DVT prevalence appears to be similar in medically ill patients compared to moderate risk surgery patients (around 10-20%) (8) however little information is available as to the actual numbers of DVTs or PE in the total population in order to be able to assess the total and incremental budget impact of treating patients with rivaroxaban compared to standard of care. A previous economic evaluation conducted by MacQuilkin et al (9) on behalf of the NEMLC in 2019 estimated the number of VTEs in South Africa at 3000 based on procurement data from procurement volumes Contract Circular HP06-2017SVP. Other estimates range from 0.1% of the total population (approx. 60 000 per annum) to around 200 000 patients per annum (10). Additional unknown factors include the ratio of patients only requiring 3 months of treatment compared to longer durations or even lifelong treatment as well as the increased risk of VTE in people living with HIV or TB (10).

The total **medicine cost** per patient of treating DVT and PE with rivaroxaban compared to enoxaparin-warfarin (including INR monitoring) is shown in Table 4 below:

Rivaroxaban	**Cost Rx**		**Total Cost (including initial Tx and INR)**
Initial phase (15mg bd x 21 days)	R 615		
3 months (20mg daily)	R 1 025		R 1 641
6 months (20mg daily)	R 2 374		R 2 989
9 months (20mg daily)	R 3 649		R 4 264

Enoxaparin+Warfarin	Cost Rx	INR	
Initial phase (enox 160mg x 8 days)	R 1 716		
Initial phase (warfarin 5mg x 26 days)	R 16	R 335	R 2 066
3 months (5mg daily)	R 1 768	R 447	R 2 215
6 months (5mg daily)	R 1 824	R 614	R 2 438
9 months (5mg daily)	R 1 883	R 782	R 2 665

Table 4. Medicine cost of treating DVT and PE for 3, 6, and 9 months

The medicine cost difference per patient is initial phase R-1 116 (cost saving with rivaroxaban), R -127 (3 months), R1 165 (6 months) and R2 381 (9 months) assuming 6 INR in the initial treatment phase followed by 1 INR per month thereafter.

Making some broad assumptions around number of patients eligible for treatment ranging from 500 up to 100 000 with an increasing uptake of rivaroxaban up to 100%, the possible incremental budget impact shifts from being increasingly cost saving for the 3-month treatment duration to an incremental annual cost of around R150 million at 100% uptake for 100 000 patients receiving 9 months of treatment.

3 months incremental budget impact

Incidence	Uptake					Current SOC
Rivaroxaban	20%	40%	60%	80%	100%	*0%*
Enox-War+INR	80%	60%	40%	20%	0%	*100%*
500	-66 387	-132 775	-199 162	-265 550	-331 937	*5 369 585*
1500	-199 162	-398 325	-597 487	-796 649	-995 812	*16 108 754*
3000	-398 325	-796 649	-1 194 974	-1 593 299	-1 991 623	*32 217 509*
10000	-1 327 749	-2 655 498	-3 983 247	-5 310 996	-6 638 745	*107 391 695*
60000	-7 966 494	-15 932 987	-23 899 481	-31 865 974	-39 832 468	*644 350 173*
100000	-13 277 489	-26 554 978	-39 832 468	-53 109 957	-66 387 446	*1 073 916 955*

9 months incremental budget impact

Incidence	Uptake					Current SOC
Rivaroxaban	20%	40%	60%	80%	100%	*0%*
Enox-War+INR	80%	60%	40%	20%	0%	*100%*
500	150 988	301 975	452 963	603 951	754 939	*6 352 238*
1500	452 963	905 926	1 358 890	1 811 853	2 264 816	*19 056 715*
3000	905 926	1 811 853	2 717 779	3 623 706	4 529 632	*38 113 430*
10000	3 019 755	6 039 510	9 059 265	12 079 020	15 098 775	*127 044 765*
60000	18 118 530	36 237 059	54 355 589	72 474 118	90 592 648	*762 268 593*
100000	30 197 549	60 395 099	90 592 648	120 790 197	150 987 747	*1 270 447 655*

Table 5. Incremental cost (Rands) of treatment for rivaroxaban compared to enoxaparin-warfarin

Assuming a likelihood of around 60% uptake in 10 000 patients per year the incremental savings for 3 months would be in the region of R4 million at 3 months and shifting to just over R9 million at 9 months. However, if an assumption is made that the proportion of patients requiring only 3 months of treatment is 70% and those needing 9 months of treatment is 30% then the incremental impact is a saving of R46 996 pa. If that ratio shifts to 50% 3 months and 50% 9 months then the annual budget impact is R1 692 006.

Incremental cost	2023	2024	2025	2026	2027
Uptake of 10 000pts	60%	60%	60%	60%	60%
70% (3m), 30% (9m)	-46 996	-49 815	-52 804	-55 972	-59 331

50% (3m), 50% (9m)	1 692 006	1 793 526	1 901 138	2 015 206	2 136 119

Table 6. Budget impact at varying proportions of patients requiring 3m and 9m treatment

RECOMMENDATION

There is a cost saving per patient for use of rivaroxaban compared to warfarin in the treatment and prevention of recurrent VTE for 3 months following the initial event, however, as the length of treatment increases then the cost difference increases to an additional cost of up to R1 510 per patient for 9 months of treatment.

The initial budget impact shows a cost saving at 3 months however, the increase in budget could be considerable depending on the number of eligible patients, rate of uptake and proportion of patients requiring short-term compared to longer-term treatment. A more sophisticated model is required to determine the impact of varying more than one parameter at a time. A follow-up study in South Africa should be carried out to assess whether the projected cost savings from reduction in hospital stay and reduction in long-term outcomes (fewer bleeds, possibly fewer recurrent VTEs) materialize. The impact on quality of life of the patient who no longer needs to take warfarin and have regular INR monitoring has not been determined.

Given the substantial reduction in price of rivaroxaban and the cost savings in patients treated for up to 3 months, it is recommended that rivaroxaban is included on the EML for the treatment of DVT and PE and the prevention of recurrent VTE.

There is a risk that if rivaroxaban becomes available on the EML for the treatment of VTE, it will also be used in other clinical indications for anticoagulation, such as atrial fibrillation, where the cost-effectiveness is not proven.

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Model (2015) developed by: Dr J Miot
Affiliation: Health Economics and Epidemiology Research Office (HE²RO), University of Witwatersrand

Report updated by: TD Leong
Affiliation: Secretariat to the NEMLC, Essential Drugs Programme, National Department of Health

Conflicts of interest: JM and TDL have no conflicts of interests related to rivaroxaban.

Version	Date	Reviewer(s)	Conclusion
First	11 December 2015	J Miot	There is an incremental cost per patient for use of rivaroxaban compared to warfarin in the treatment and prevention of recurrent VTE, however, if the price of rivaroxaban is reduced (by 80%), the incremental cost can be neutralized. A price reduction should be negotiated.
Second	10 September 2017	TD Leong	There is an incremental cost per patient for use of rivaroxaban compared to warfarin in the treatment and prevention of recurrent VTE, however, if the price of rivaroxaban is reduced (by 80%), the incremental cost can be neutralized. A price reduction should be negotiated.
Third	15 July 2020	TD Leong	There is an incremental cost per patient for use of rivaroxaban compared to current standard of care in the treatment and prevention of recurrent VTE, however, if the quotation price (provided on 8 July 2020) of rivaroxaban is reduced by a further 30%, the incremental cost can be neutralized. A further price reduction should be negotiated.
Fourth	25 November 2021	TD Leong	There is an incremental cost per patient for use of rivaroxaban compared to current standard of care in the treatment and prevention of recurrent VTE, however, if the SEP of generic rivaroxaban (Rivaxored®) is reduced by a further 25%, the incremental cost can be neutralized. A further price reduction should be negotiated.
Fifth	17 November 2022	J Miot	There is an incremental cost per patient for use of rivaroxaban compared to current standard of care in the treatment and prevention of recurrent VTE, however, if the SEP of generic rivaroxaban (Ixarola®) is reduced by a further 45%, the incremental cost can be neutralized. A further price reduction should be negotiated.
Sixth	25 March 2023	J Miot	There is a cost saving per patient for use of rivaroxaban compared to warfarin in the treatment and prevention of recurrent VTE for 3 months however, the cost difference increases to an additional cost of up to R1 510 per patient for 9 months of treatment.

South African National Essential Medicine List
Adult Hospital Level Medication Review
Component: Obstetrics

EVIDENCE SUMMARY

TITLE: The use of low molecular weight heparins (LMWH) for secondary venous thromboembolism (VTE) prophylaxis during pregnancy and the puerperium.

Date: November 2022

BACKGROUND

- 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.
- There are three indications for anticoagulation during pregnancy:
    1. Mechanical heart valves
    2. Therapeutic, for acute venous thromboembolism (VTE; DVT and pulmonary embolus)
    3. **Prophylactic use to prevent VTE in women with:**
        a. **A previous VTE (requires prophylaxis during pregnancy and 6 weeks post-delivery)**
        b. Other risk factors (requires prophylaxis for 5 days following delivery)
        c. Thrombophilia's (tertiary care)

    NOTE: This evidence summary deals with point **3a** above (the bold/underlined indications); specifically for pregnant women without mechanical heart valves or any cardiac disease requiring prophylactic long-term anticoagulation. The use of warfarin in women with cardiac lesions was the basis of a medicine review (National Department of Health: Essential Drugs Programme. Adult Hospital medicine review: LMWH in pregnant women with mechanical heart valves, January 2020. Available at: https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list) and guidance is included in the Adult Hospital Level STGs and EML, 2019 edition: Obstetrics chapter.

Incidence and risks

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. (1) (2)

Risk stratification can help identify those pregnant women at higher risk for thrombosis, and appropriate prophylaxis can be recommended. The highest risk is in a pregnant woman who had a previous episode of VTE before the index pregnancy- the odds ratio for a repeat VTE in this scenario is 24.8 (17.1-36)](3).

These women requires thromboprophylaxis during pregnancy and for 6 weeks post-delivery, as they are at high risk serious complications and/or death(4). The challenge is the choice of agent:

- Vitamin K antagonists (e.g., warfarin) are known to act as teratogens. Warfarin is contra-indicated in the first trimester, as it is a known teratogenic drug (warfarin embryopathy in about 5% of cases). (EML)
- Warfarin should not be used in the last month of pregnancy/4 weeks prior to scheduled delivery due to the risk of excessive bleeding during labour. (EML)
- In addition, there is a warfarin risk to the fetus after the first trimester- (warfarin fetopathy in about 2-5% of cases), mainly due to cerebral and pulmonary haemorrhage leading to blindness, deafness, mental retardation or death.(5) The immature liver enzyme system and the low levels of vitamin K-dependent clotting factors in the fetus result in higher levels or overdosing of the fetus with oral anticoagulants, leading to haemorrhage. This damage is dose-dependent.(6)

REVIEW QUESTION

In pregnant women requiring prophylactic anticoagulation for VTE prophylaxis during the entire pregnancy (not for any cardiac/valve disease), is LMWH throughout pregnancy safer and/or more effective than switching to warfarin in second trimester and back to LMWH in the later third trimester?

P: pregnant patients requiring prophylactic anticoagulation

I: LMWH

C: LMWH 1st and 3rd trimester, warfarin from weeks 12 to 36

O: Fetal side effects, bleeding complications in the mother

No randomised trial was identified that answers this specific PICO.

SAFETY WARNINGS ON THE USE OF WARFARIN DURING PREGNANCY:

A. CIPLA-WARFARIN (SAPHRA) package insert:

CIPLA-WARFARIN is contra-indicated in the following settings:

- Where there are insufficient laboratory facilities.
- **Pregnancy and in breastfeeding mothers**
- Threatened abortion.
- **Children < 18 years, as safety has not been established.**

PREGNANCY AND LACTATION:

CIPLA-WARFARIN **should be avoided in pregnancy and lactation** as it is a recognised Teratogen. When CIPLA-WARFARIN is given in the first trimester of pregnancy it can cause the foetal warfarin syndrome. CNS or warfarin embryopathy abnormalities may develop following use in any trimester but **appear most likely after use in the second trimester**. Spontaneous abortion and stillbirth have been reported.

CIPLA-WARFARIN is distributed into milk only in its active form; studies in infants who are breast-fed while their mothers were taking CIPLA-WARFARIN did not find any effect on prothrombin time, however, breast-fed infants (especially neonates) are very sensitive to oral anticoagulants because of the low concentrations of vitamin K in breast milk."

B. FDA website (package insert for Coumadin)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s108lbl.pdf

"COUMADIN is contraindicated in women who are pregnant (except in pregnant women with mechanical heart valves, who are at high risk of thromboembolism, and for whom the benefits of COUMADIN may outweigh the risks). COUMADIN can cause fetal harm when administered to a pregnant woman. COUMADIN exposure during pregnancy causes a recognized pattern of major congenital malformations (warfarin embryopathy), fetal haemorrhage, and an increased risk of spontaneous abortion and fetal mortality. Mental retardation, blindness, schizencephaly, microcephaly, hydrocephalus, and other adverse pregnancy outcomes have been reported following warfarin exposure during the second and third trimesters of pregnancy."

C: Society recommendations based on systematic reviews:

i. The Royal College of Obstetricians and gynaecologists (RCOG) guideline (7)

- Warfarin use in pregnancy is restricted to the few situations where heparin is considered unsuitable, e.g., some women with mechanical heart valves.
- LMWHs are the agents of choice for antenatal and postnatal VTE thromboprophylaxis.
- AGREE 2 score assessment of 92%, good quality

The RCOG summarises the odds ratios (ORs) for VTE associated with each risk factor derived from various studies (Table 2). Women with multiple risk factors for VTE, even those with no history of thrombophilia or VTE, were reported to have an increased risk of VTE in pregnancy, especially in the third trimester and postpartum (12). Factors contributing substantially to rates of VTE includes age greater than 35 years, obesity and caesarean section (13).

Table 2: Adjusted odds ratios for risk factors for VTE reported in the RCOG (2015) include (7):

Risk factor	Adjusted odds ratio (95% CI)	Reference
Previous VTE	24.8 (17.1, 36)	13, 14
Emergency caesarean section	2.7 (1.8, 4.1)	15
Age > 35	1.3 (1.0, 1.7)	15
Current smoker	2.7 (1.5, 4.9)	16
Pre-eclampsia	2.9 (2.1, 3.9)	15
Parity ≥3	2.4 (1.8, 3.1)	15
PPH > 1 litre	4.1 (2.3, 7.3)	17

ii. The American College of Obstetricians and gynaecologists (ACOG) guideline (8)

- Neither unfractionated heparin nor low-molecular-weight heparin crosses the placenta and both are considered to be safe in pregnancy.
- Low-molecular-weight heparin is recommended in place of warfarin.
- AGREE 2 score assessment of 75%, moderate quality (this is a practice bulletin).

Why is there a different recommended regimen of anti-coagulation for pregnant women with mechanical cardiac valves?

Pregnant women with a mechanical prosthetic heart valves are at high risk complications due to the hypercoagulable state of pregnancy combined with the inherently thrombogenic mechanical valve. The EML recommends warfarin for prophylaxis in women with mechanical heart valves over LMWH- a medicine review was presented to NEMLC in 2020. The reason stated in this review is warfarin throughout pregnancy (in this specific group of women) was associated with the lowest rate of maternal death, followed by warfarin/LMWH used sequentially. The highest rate of maternal death was in the LMWH group.

There is concern in the literature about the use of LMWH in mechanical heart valves if monitoring with FactorXa is not available or if patients are not fully compliant(9). A 2022 systematic review and meta-analysis on the risk of bleeding complications in women with mechanical heart valves during pregnancy found that a combination of unfractionated heparin (UFH) and vitamin K antagonist (VKA); and single VKA therapy showed the lowest risk of bleeding (8 and 12%). The highest risk of bleeding was found in women receiving a combination of low-molecular-weight-heparin (LMWH) and VKA (33%) or mono-therapy with LMWH (22%).

RECOMMENDATIONS ON DOSE AND SAFETY OF LMWH FOR VTE PROPHYLAXIS IN PREGNANCY:

A. Systematic review and meta-analysis: safety

Jacobson et al 2020 (10) did a systematic review and meta-analysis on the safety and efficacy of enoxaparin use in pregnancy. In the 24 clinical trials selected, not enough information was available to assess efficacy of VTE prophylaxis with a pooled meta-analysis, but they could make a conclusion on safety in pregnancy. Enoxaparin was associated with significantly lower complications than aspirin and reports of thromboembolic events, thrombocytopenia, and congenital malformations were rare.

B: Randomised controlled trials: dose

Bistervels et al 2022 (11) conducted an open-label, randomised, controlled trial in women with a history of objectively confirmed venous thromboembolism and a current pregnancy with gestational age <14 weeks. The aim was to determine the optimal dose of LMWH to prevent recurrent VTE. Randomisation was to either a weight-adjusted dose (as extrapolated form non-pregnant populations) or a fixed low-dose (for enoxaparin 40mg if <100kg or 60mg if >100kg; see alternatives in table below) of LMWH during the remainder of the pregnancy and for 6 weeks post-delivery. Venous thromboembolism occurred in 11 (2%) of 555 women in the weight-adjusted dose group and in 16 (3%) of 555 in the fixed low-dose group (relative risk [RR] 0·69 [95% CI 0·32–1·47]; p=0·33. They conclude that low-dose LMWH for thromboprophylaxis during pregnancy is the appropriate dose for the prevention of pregnancy-related recurrent venous thromboembolism.

Table 2: Therapeutic interchangeable LMWH for DVT prophylaxis in pregnancy

Medicine	Daily dose: <100kg	Daily dose: ≥100kg	Indication	Evidence
Enoxaparin	4000 IU	6000 IU	DVT prophylaxis in pregnancy	Bistervels et al 2022(11)
Dalteparin	5000 IU	7500 IU		
Nadroparin	2850 IU	3800 IU		

Source: Bistervels IM, et al; Highlow Block writing committee; Highlow Investigators. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow study): an open-label, multicentre, randomised, controlled trial. Lancet. 2022 Oct 28:S0140-6736(22)02128-6.

Conclusion

- **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.**

Budget impact analysis

Refer to the costing analysis report: Comparative cost analysis of anticoagulants (LMWH/warfarin) as secondary VTE prophylaxis in pregnancy, 22 November 2022.

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NEMLC RECOMMENDATION – MEETING OF 8 DECEMBER 2022:

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.

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