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 seldom 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, valproate, 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 B_{12} 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: Anaemia).

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, valproate 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.

LoE:IIb[ix]

- Prednisone, oral.
  - 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, valprote , 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. W

AND

- Gentamicin, IV, 6 mg/kg daily. A (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. W 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. W

OR

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

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. W

AND LoE:IVb[xv]

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

OR

Regimen 3:

- Cefepime, IV, 2 g 12 hourly. W 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:IIb[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 succinate 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.

<u>High risk of VTE:</u> *LoE:III*

- 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. *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. *LoE:IIIb*[xxxiii]
  - Dose adjustment generally not required for renal impairment.

- 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	Low to moderate risk of VTE: Aspirin, oral, 150 mg daily. High risk of VTE: Enoxaparin, SC, 40 mg daily.	From >12 hours post-operatively, for 14 days or until mobilisation.
	Trauma-related **non-operative** pelvic and acetabular fractures	Low-moderate risk of VTE: Aspirin, oral, 150 mg daily. High risk of VTE: Enoxaparin, SC, 40 mg daily.	From admission up to 35 days.
Other Surgical	Other major surgery	Enoxaparin, SC, 40 mg daily. **OR** Unfractionated heparin, SC, 5 000 units 12 hourly.	While hospitalised.

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

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*[xii]
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.: *LoE:IIIb*[xlvi]
- 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.

References:

[i] Ferrous sulfate/fumarate, oral: Reveiz L, Gyte GM, Cuervo LG, Casasbuenas A. Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD003094. https://www.ncbi.nlm.nih.gov/pubmed/21975735

Ferrous sulfate/fumarate, oral : Rimon E, Kagansky N, Kagansky M, Mechnick L, Mashiah T, Namir M, Levy S. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. Am J Med. 2005 Oct;118(10):1142-7. https://www.ncbi.nlm.nih.gov/pubmed/16194646

Ferrous sulfate/fumarate, oral (duration of therapy): Alleyne M, Horne MK, Miller JL. Individualized treatment for iron-deficiency anemia in adults. Am J Med. 2008 Nov;121(11):943-8. http://www.ncbi.nlm.nih.gov/pubmed/18954837

Ferrous sulfate/fumarate, oral: South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[ii] Ferrous sulfate/fumarate, oral (alternate day dosing – treatment of anaemia): Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, Melse-Boonstra A, Brittenham G, Swinkels DW, Zimmermann MB. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015 Oct 22;126(17):1981-9. https://www.ncbi.nlm.nih.gov/pubmed/26289639

Ferrous sulfate/fumarate, oral (alternate day dosing – treatment of anaemia: Stoffel NU, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, Moretti D, Zimmermann MB. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol. 2017 Nov;4(11):e524-e533. https://www.ncbi.nlm.nih.gov/pubmed/29032957

[iii] Parenteral iron (hypotensive side-effect): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[iv] Parenteral iron (directions for use): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[v] Low molecular weight iron dextran: Atalay H, Solak Y, Acar K, Govec N, Turk S. Safety profiles of total dose infusion of low-molecular-weight iron dextran and high-dose iron sucrose in renal patients. Hemodial Int. 2011 Jul;15(3):374-8. http://www.ncbi.nlm.nih.gov/pubmed/21564503

Low molecular weight iron dextran: Solak Y, Atalay H, Guney I, Turkmen K, Kaya E, Turk S. Comparison of adverse-event profiles of intravenous low-molecular-weight iron dextran and iron sucrose in peritoneal dialysis patients. Ren Fail. 2011;33(3):307-11. http://www.ncbi.nlm.nih.gov/pubmed/21401355

[vi] Iron prophylaxis (pregnancy): Tunkyi K, Moodley J. Prevalence of anaemia in pregnancy in a regional health facility in South Africa. S Afr Med J. 2015;106(1):101-4. https://www.ncbi.nlm.nih.gov/pubmed/26792317

[vii] Iron prophylaxis (pregnancy): National Department of Health: Affordable Medicines, EDP-Primary Health Care level. Medicine Review: Intermittent iron supplementation in pregnancy: 6 November 2017. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Iron prophylaxis (pregnancy): Pena-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. The Cochrane database of systematic reviews. 2015(10):CD009997. https://www.ncbi.nlm.nih.gov/pubmed/26482110

[viii] Vitamin B_{12}, IM (dosing for uncomplicated pernicious anaemia): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Vitamin B_{12}, IM (dosing for uncomplicated pernicious anaemia): Joint Formulary Committee. British National Formulary. 80. London: BMJ Group and Pharmaceutical Press; 2020.

[ix] Prednisone: Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011 Apr 21;117(16):4190-207. http://www.ncbi.nlm.nih.gov/pubmed/21325604

[x] Immunosuppresive therapy (e.g. Azathioprine): Hitzig WH, Massimo L. Treatment of autoimmune hemolytic anemia in children with azathioprine (imuran). Blood. 1966 Dec;28(6):840-50. http://www.ncbi.nlm.nih.gov/pubmed/5959475

Immunosuppresive therapy (e.g. Azathioprine): Worlledge SM, Brain MC, Cooper AC, Hobbs JR, Dacie JV. Immmunosuppressive drugs in the treatment of autoimmune haemolytic anaemia. Proc R Soc Med. 1968 Dec 12;61(12):1312-5. http://www.ncbi.nlm.nih.gov/pubmed/4177973

[xi] Heparin, SC: Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988 May 5;318(18):1162-73. https://www.ncbi.nlm.nih.gov/pubmed/3283548

Low molecular weight heparin (first line option - treatment): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Cost-effectiveness and budget impact analyses: Fondaparinux for the treatment of venous thromboembolism in hospitalised patients in the South African public health system, April 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xii] Low molecular weight heparin (morbid obesity): Lalama JT, Feeney ME, Vandiver JW, Beavers KD, Walter LN, McClintic JR. Assessing an enoxaparin dosing protocol in morbidly obese patients. J Thromb Thrombolysis. 2015 May;39(4):516-21. http://www.ncbi.nlm.nih.gov/pubmed/25087072

Low molecular weight heparin (morbid obesity): Spinler SA, Inverso SM, Cohen M, Goodman SG, Stringer KA, Antman EM; ESSENCE and TIMI 11B Investigators. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J. 2003 Jul;146(1):33-41. http://www.ncbi.nlm.nih.gov/pubmed/12851605

Low molecular weight heparin (morbid obesity): Thompson-Moore NR, Wanat MA, Putney DR, Liebl PH, Chandler WL, Muntz JE. Evaluation and Pharmacokinetics of Treatment Dose Enoxaparin in Hospitalized Patients With Morbid Obesity. Clin Appl Thromb Hemost. 2015 Sep;21(6):513-20. http://www.ncbi.nlm.nih.gov/pubmed/25601898

Low molecular weight heparin (morbid obesity): Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. Am J Hematol. 2012 Jul;87(7):740-3. http://www.ncbi.nlm.nih.gov/pubmed/22565589

[xiii] Low molecular weight heparin (renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xiv] Neutropaenia – urgent empiric management: Wein L, Wein S, Haas SJ, Shaw J, Krum H. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of Americaa. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):427-31. https://www.ncbi.nlm.nih.gov/pubmed/21205990

Neutropaenia – urgent empiric management: National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections, 2018 http://www.nccn.org

[xv] Piperacillin/taxobactam dose: Stanford Hospital and Clinics (SHC). SHC-Extended-Infusion-Piperacillin-Tazobactam.pdf (stanford.edu)

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

[xvi] Piperacillin/taxobactam and amikacin: Nau R, Kinzig-Schippers M, Sörgel F, Schinschke S, Rössing R, Müller C, Kolenda H, Prange HW. Kinetics of piperacillin and tazobactam in ventricular cerebrospinal fluid of hydrocephalic patients.Antimicrob Agents Chemother. 1997 May;41(5):987-91.http://www.ncbi.nlm.nih.gov/pubmed/9145857

Piperacillin/taxobactam and amikacin: NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.

[xvii] Cefipime, IV (2 g): NICD AMR surveillance for ESKAPE, 1 January 2016 to 31 December 2016.

Cefipime, IV (2 g): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[xviii] G C White 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J0; Factor VIII and Factor IX Subcommittee. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 2001 Mar;85(3):560.

[xix] Lyophilised plasma: Bindi ML, Miccoli M, Marietta M, Meacci L, Esposito M, Bisà M, Mozzo R, Mazzoni A, Baggiani A, Scatena F, Filipponi F, Biancofiore G. Solvent detergent vs. fresh frozen plasma in cirrhotic patients undergoing liver transplant surgery: a prospective randomized control study. Vox Sang. 2013 Aug;105(2):137-43. http://www.ncbi.nlm.nih.gov/pubmed/23448618

Lyophilised plasma: Lerner RG, Nelson J, Sorcia E, Grima K, Kancherla RR, Zarou-Naimo CM, Pehta JC. Evaluation of solvent/detergent-treated plasma in patients with a prolonged prothrombin time. Vox Sang. 2000;79(3):161-7. http://www.ncbi.nlm.nih.gov/pubmed/11111235

Lyophilised plasma: Williamson LM, Llewelyn CA, Fisher NC, Allain JP, Bellamy MC, Baglin TP, Freeman J, Klinck JR, Ala FA, Smith N, Neuberger J, Wreghitt TG. A randomized trial of solvent/detergent-treated and standard fresh-frozen plasma in the coagulopathy of liver disease and liver transplantation. Transfusion. 1999 Nov-Dec;39(11-12):1227-34. http://www.ncbi.nlm.nih.gov/pubmed/10604250

Lyophilised plasma: Huisman EL, de Silva SU, de Peuter MA. Economic evaluation of pooled solvent/detergent treated plasma versus single donor fresh-frozen plasma in patients receiving plasma transfusions in the United States. Transfus Apher Sci. 2014 Aug;51(1):17-24. http://www.ncbi.nlm.nih.gov/pubmed/25151097

Lyophilised plasma: National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Price comparison analysis, updated: Fresh frozen plasma vs lyophilised plasma, September 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xx] Factor VIII: World Federation of Haemophilia. 2012. Guidelines for Management of Haemophilia. http://www1.wfh.org/publication/files/pdf-1472.pdf

Factor VIII: Mahlangu JN, Gilham A. Guideline for the Treatment of Haemophilia in South Africa. S Afr Med J 2008; 98: 125-140. http://www.samj.org.za/index.php/samj/article/view/336/723

[xxi] Factor IX: World Federation of Haemophilia. 2012. Guidelines for Management of Haemophilia. http://www1.wfh.org/publication/files/pdf-1472.pdf

Factor IX: Mahlangu JN, Gilham A. Guideline for the Treatment of Haemophilia in South Africa. S Afr Med J 2008; 98: 125-140. http://www.samj.org.za/index.php/samj/article/view/336/723

[xxii] Prednisone, oral: Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, Chong BH, Cines DB, Gernsheimer TB, Godeau B, Grainger J, Greer I, Hunt BJ, Imbach PA, Lyons G, McMillan R, Rodeghiero F, Sanz MA, Tarantino M, Watson S, Young J, Kuter DJ. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010 Jan 14;115(2):168-86. https://www.ncbi.nlm.nih.gov/pubmed/9846889

Prednisone, oral: Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011 Apr 21;117(16):4190-207. https://www.ncbi.nlm.nih.gov/pubmed/21325604

[xxiii] Methylprednisolone, IV: Alpdogan O, Budak-Alpdogan T, Ratip S, Firatli-Tuglular T, Tanriverdi S, Karti S, Bayik M, Akoglu T. Efficacy of high-dose methylprednisolone as a first-line therapy in adult patients with idiopathic thrombocytopenic purpura. Br J Haematol. 1998 Dec;103(4):1061-3. http://www.ncbi.nlm.nih.gov/pubmed/9886319

[xxiv] Lyophilised plasma: Bindi ML, Miccoli M, Marietta M, Meacci L, Esposito M, Bisà M, Mozzo R, Mazzoni A, Baggiani A, Scatena F, Filipponi F, Biancofiore G. Solvent detergent vs. fresh frozen plasma in cirrhotic patients undergoing liver transplant surgery: a prospective randomized control study. Vox Sang. 2013 Aug;105(2):137-43. http://www.ncbi.nlm.nih.gov/pubmed/23448618

Lyophilised plasma: Lerner RG, Nelson J, Sorcia E, Grima K, Kancherla RR, Zarou-Naimo CM, Pehta JC. Evaluation of solvent/detergent-treated plasma in patients with a prolonged prothrombin time. Vox Sang. 2000;79(3):161-7. http://www.ncbi.nlm.nih.gov/pubmed/11111235

Lyophilised plasma: Williamson LM, Llewelyn CA, Fisher NC, Allain JP, Bellamy MC, Baglin TP, Freeman J, Klinck JR,

Ala FA, Smith N, Neuberger J, Wreghitt TG. A randomized trial of solvent/detergent-treated and standard fresh-frozen plasma in the coagulopathy of liver disease and liver transplantation. Transfusion. 1999 Nov-Dec;39(11-12):1227-34. http://www.ncbi.nlm.nih.gov/pubmed/10604250

Lyophilised plasma: Huisman EL, de Silva SU, de Peuter MA. Economic evaluation of pooled solvent/detergent treated plasma versus single donor fresh-frozen plasma in patients receiving plasma transfusions in the United States. Transfus Apher Sci. 2014 Aug;51(1):17-24. http://www.ncbi.nlm.nih.gov/pubmed/25151097

Lyophilised plasma: National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Price comparison analysis, updated: Fresh frozen plasma vs lyophilised plasma, September 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxv] Lyophilised plasma: Bindi ML, Miccoli M, Marietta M, Meacci L, Esposito M, Bisà M, Mozzo R, Mazzoni A, Baggiani A, Scatena F, Filipponi F, Biancofiore G. Solvent detergent vs. fresh frozen plasma in cirrhotic patients undergoing liver transplant surgery: a prospective randomized control study. Vox Sang. 2013 Aug;105(2):137-43. http://www.ncbi.nlm.nih.gov/pubmed/23448618

Lyophilised plasma: Lerner RG, Nelson J, Sorcia E, Grima K, Kancherla RR, Zarou-Naimo CM, Pehta JC. Evaluation of solvent/detergent-treated plasma in patients with a prolonged prothrombin time. Vox Sang. 2000;79(3):161-7. http://www.ncbi.nlm.nih.gov/pubmed/11111235

Lyophilised plasma: Williamson LM, Llewelyn CA, Fisher NC, Allain JP, Bellamy MC, Baglin TP, Freeman J, Klinck JR, Ala FA, Smith N, Neuberger J, Wreghitt TG. A randomized trial of solvent/detergent-treated and standard fresh-frozen plasma in the coagulopathy of liver disease and liver transplantation. Transfusion. 1999 Nov-Dec;39(11-12):1227-34. http://www.ncbi.nlm.nih.gov/pubmed/10604250

Lyophilised plasma: Huisman EL, de Silva SU, de Peuter MA. Economic evaluation of pooled solvent/detergent treated plasma versus single donor fresh-frozen plasma in patients receiving plasma transfusions in the United States. Transfus Apher Sci. 2014 Aug;51(1):17-24. http://www.ncbi.nlm.nih.gov/pubmed/25151097

Lyophilised plasma: National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Price comparison analysis, updated: Fresh frozen plasma vs lyophilised plasma, September 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-listhttp://www.health.gov.za/

[xxvi] Non-pharmacological management – VTE prophylaxis: Goldhaber SZ, Turpie AG. Prevention of venous thromboembolism among hospitalized medical patients. Circulation. 2005 Jan 4;111(1):e1-3. https://www.ncbi.nlm.nih.gov/pubmed/15630031

[xxvii] NDoH review. DOACS for prevention of VTE. V6.0_12 October 2023

[xxviii] Low molecular weight heparin (enoxaparin dosing in renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxix] Heparin, SC: Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988 May 5;318(18):1162-73. https://www.ncbi.nlm.nih.gov/pubmed/3283548

Heparin, SC (dosing in renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxx] NDoH review. Aspirin for VTE prophylaxis. V1.0_12 October 2023

[xxxi] NDoH review. DOACS for prevention of VTE. V6.0_12 October 2023

NDoH. Adaptation of NICE Guidance 30 November 2023

[xxxii] Low molecular weight heparin (enoxaparin dosing in renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxiii] Heparin, SC: Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988 May 5;318(18):1162-73. https://www.ncbi.nlm.nih.gov/pubmed/3283548

Heparin, SC (dosing in renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xxxiv] DOACS (treatment of VTE): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review. DOACs: Treatment of DVT&PE_Adults_v6.0_30 November 2023.

[xxxv] Low molecular weight heparin (first line option - treatment): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes, April 2018. http://www.health.gov.za/

Low molecular weight heparin (first line option - treatment): Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. 2017 Apr 21;4:CD007557. https://www.ncbi.nlm.nih.gov/pubmed/28431186

Low molecular weight heparin (first line option - treatment): Wein L, Wein S, Haas SJ, Shaw J, Krum H. Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007 Jul 23;167(14):1476-86. https://www.ncbi.nlm.nih.gov/pubmed/17646601

Low molecular weight heparin (first line option - treatment): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Cost-effectiveness and budget impact analyses: Fondaparinux for prophylaxis of venous thromboembolism in medical and surgical patients in hospitalised patients in the South African public health system, April 2018. http://www.health.gov.za/

[xxxvi] Enoxaparin, SC (dosing for treatment of VTE): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes – Appendix A, April 2018. http://www.health.gov.za/

Low molecular weight heparin (dosing for treatment of VTE): Bhutia S, Wong PF. Once versus twice daily low molecular

weight heparin for the initial treatment of venous thromboembolism. Cochrane database Syst Rev. 2013 Jul;(7):CD003074. https://www.ncbi.nlm.nih.gov/pubmed/23857562

[xxxvii] Low molecular weight heparin (morbid obesity): Lalama JT, Feeney ME, Vandiver JW, Beavers KD, Walter LN, McClintic JR. Assessing an enoxaparin dosing protocol in morbidly obese patients. J Thromb Thrombolysis. 2015 May;39(4):516-21. http://www.ncbi.nlm.nih.gov/pubmed/25087072

Low molecular weight heparin (morbid obesity): Spinler SA, Inverso SM, Cohen M, Goodman SG, Stringer KA, Antman EM; ESSENCE and TIMI 11B Investigators. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J. 2003 Jul;146(1):33-41. http://www.ncbi.nlm.nih.gov/pubmed/12851605

Low molecular weight heparin (morbid obesity): Thompson-Moore NR, Wanat MA, Putney DR, Liebl PH, Chandler WL, Muntz JE. Evaluation and Pharmacokinetics of Treatment Dose Enoxaparin in Hospitalized Patients With Morbid Obesity. Clin Appl Thromb Hemost. 2015 Sep;21(6):513-20. http://www.ncbi.nlm.nih.gov/pubmed/25601898

Low molecular weight heparin (morbid obesity): Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. Am J Hematol. 2012 Jul;87(7):740-3. http://www.ncbi.nlm.nih.gov/pubmed/22565589

[xxxviii] Low molecular weight heparin (renal impairment): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xxxix] Warfarin, oral (directions for use): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[xl] Thrombosis and Embolism during Pregnancy and the Puerperium: Acute Management (Green-top Guideline No. 37b) [Internet]. RCOG. [cited 2022 Nov 1]. Available from: https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/thrombosis-and-embolism-during-pregnancy-and-the-puerperium-acute-management-green-top-guideline-no-37b/

[xli] VTE LMWH prophylaxis (pregnancy): Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb 1;141(2, Supplement):e691S-e736S. https://pubmed.ncbi.nlm.nih.gov/22315276/

[xlii] VTE LMWH prophylaxis – fixed doses (pregnancy): Bistervels IM, Buchmüller A, Wiegers HMG, Ní Áinle F, Tardy B, Donnelly J, 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. https://pubmed.ncbi.nlm.nih.gov/36354038/

[xliii] Enoxaparin (skin reactions): Schindewolf M, Lindhoff-Last E, Ludwig RJ, Boehncke WH. Heparin-induced skin lesions. Lancet. 2012 Nov 24;380(9856):1867-79. doi: 10.1016/S0140-6736(12)60409-7. Epub 2012 May 28. PMID: 22642893.

Schindewolf M, Gobst C, Kroll H, et al. Pregnant women have an increased risk for heparin-induced allergic skin reactions—results of a prospective investigation. Vasa 2010; 39: 61–62 (abstract).

[xliv] VTE LMWH prophylaxis – fixed doses (pregnancy): Bistervels IM, Buchmüller A, Wiegers HMG, Ní Áinle F, Tardy B, Donnelly J, 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. https://pubmed.ncbi.nlm.nih.gov/36354038/

Management of DVT prophylaxis in pregnancy: National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Evidence Summary: LMWH for VTE prophylaxis during pregnancy, November 2022. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xlv] Enoxaparin, SC (dosing for treatment of VTE): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes – Appendix A, April 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Low molecular weight heparin (dosing for treatment of VTE): Bhutia S, Wong PF. Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. Cochrane database Syst Rev. 2013 Jul;(7):CD003074. https://www.ncbi.nlm.nih.gov/pubmed/23857562

[xlvi]VTE LMWH acute treatment (pregnancy): Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb 1;141(2, Supplement):e691S-e736S. https://pubmed.ncbi.nlm.nih.gov/22315276/

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. o 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. <u>If serious bleeding with known haemophilia, and no factor VIII available:</u> • 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

<u>Guidance for referral:</u> *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

<u>Von Willebrand factor VIII concentrate (Coagulation factor VIII) (complex):</u> *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. <u>During surgery or after major trauma, patients should receive:</u> 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.

Management of HIT:
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.

2026 STG -updates

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/ RETAINED
2.5 Immune thrombocytopaenia (ITP)	Medicine treatment	Erratum – Methylprednisolone acetate Inj salt corrected

2.5 IMMUNE THROMBOCYTOPAENIA (ITP)

The STG was amended to correct the recommended salt of methylprednisolone for use in ITP. Methylprednisolone succinate is now recommended for IV administration in the treatment of IPT instead of methylprednisolone acetate (contra-indicated for IV usage[30]). See published circular ref: 2026/03/31/EDP/01. The STG has been amended as follows:

[30] Depo-Medrol. Professional Information. Pfizer Laboratories (Pty)Ltd.29 June 2023

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~~ succinate 1 g, IV, daily for 3 days.

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.

References

1. Cardiovascular diseases (CVDs). Accessed September 21, 2021. https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular diseases-(cvds)
2. Cushman M, Tsai AW, White RH, et al. Deep Vein Thrombosis and Pulmonary Embolism in Two Cohorts: The Longitudinal Investigation of Thromboembolism Etiology. Am J Med. 2004;117:19-25. doi:10.1016/j.amjmed.2004.01.018
3. Houghton D, Key NS. Venous Thromboembolism. In: International Encyclopedia of Public Health. Vol 332. ; 2016:330-336. doi:10.1016/B978-0-12-803678-5.00506-3
4. Anderson, D. R., Morgano, G. P., Bennett, C., Dentali, F., Francis, C. W., Garcia, D. A., ... & Dahm, P. (2019). American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood advances*, *3*(23), 3898-3944.
5. National Institute for Health and Care Excellence. *Venous thromboembolism in over 16s.* London: NICE; 2018. p. 19.
6. Samama, C. M., Ravaud, P., Parent, F., Barré, J., Mertl, P., Mismetti, P., & Foto Study Group. (2007). Epidemiology of venous thromboembolism after lower limb arthroplasty: the FOTO study. *Journal of Thrombosis and Haemostasis*, *5*(12), 2360-2367.

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.

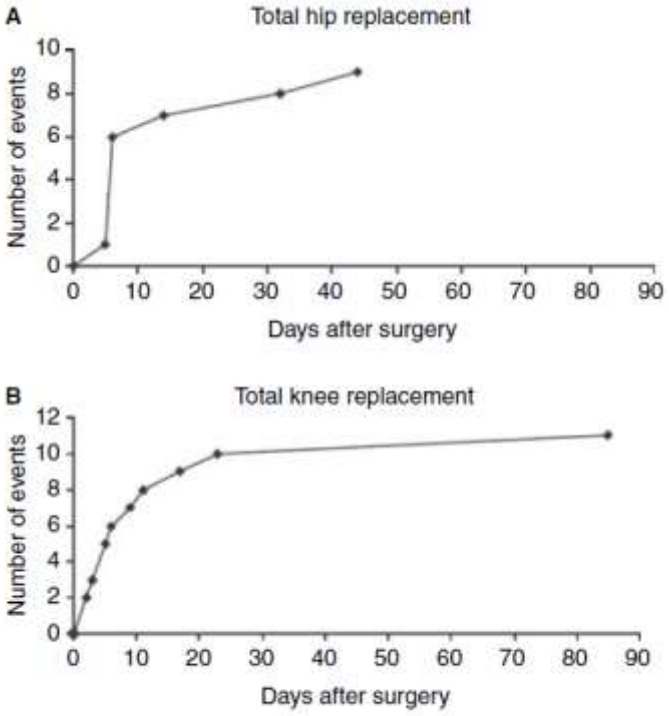

Fig. 1. Time to occurrence of venous thromboembolism after the surgical procedure (day 0).

South African National Essential Medicine List
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)

1. Rocher WD, Page T, Rocher M, Nel D. Venous thromboembolism risk and prophylaxis prescription in surgical patients at a tertiary hospital in Eastern Cape Province, South Africa. South African Medical Journal. 2019 Mar 7;109(3):178-81.
2. Wehmeyer A, Coetzee R, McCartney J. Venous thromboembolism risk assessment and prophylaxis in hospitalised medical patients in the Cape Town metropole, South Africa. S Afr Med J. 2022 Feb 1;112(2):13506. PMID: 35139994.
3. Moodley P, Martinson NA, Joyimbana W, Otwombe KN, Abraham P, Motlhaoleng K, Naidoo VA, Variava E. Venous thromboembolic disease in adults admitted to hospital in a setting with a high burden of HIV and TB. African Journal of Thoracic and Critical Care Medicine. 2021 Sep 1;27(3):99-105.

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.

References:

1. Cardiovascular diseases (CVDs). Accessed September 21, 2021. https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular diseases-(cvds)
2. Cushman M, Tsai AW, White RH, et al. Deep Vein Thrombosis and Pulmonary Embolism in Two Cohorts: The Longitudinal Investigation of Thromboembolism Etiology. Am J Med. 2004;117:19-25. doi:10.1016/j.amjmed.2004.01.018
3. Houghton D, Key NS. Venous Thromboembolism. In: International Encyclopedia of Public Health. Vol 332. ; 2016:330-336. doi:10.1016/B978-0-12-803678-5.00506-3
4. Heit JA, Melton LJ, Lohse CM, et al. Incidence of Venous Thromboembolism in Hospitalized Patients vs Community Residents. Mayo Clinic Proceedings. 2001;76(11):1102-1110. doi:10.4065/76.11.1102
5. National Department of Health. Adult Hospital Level Standard Treatment Guidelines and Essential Medicines List for South Africa, 2019. Accessed November 2021. https://www.knowledgehub.org.za/elibrary/hospital-level-adults-standard-treatment-guidelines-and-essential-medicines-list-2nd
6. van Gorp RH, Schurgers LJ. New insights into the pros and cons of the clinical use of vitamin K antagonists (VKAs) versus direct oral anticoagulants (DOACs). Nutrients. 2015;7(11):9538-9557. doi:10.3390/nu7115479
7. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism. New England Journal of Medicine. 2009;361(24):2342-2352. doi:10.1056/nejmoa0906598
8. Sterne JAC, Bodalia PN, Bryden PA, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: Systematic review, network meta-analysis and cost-effectiveness analysis. Health Technology Assessment. 2017;21(9):1-385. doi:10.3310/hta21090
9. Overview | Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism | Guidance | NICE. Accessed November 13, 2021. https://www.nice.org.uk/guidance/ng89
10. Duggan ST, Scott LJ, Plosker GL. Rivaroxaban: a review of its use for the prevention of venous thromboembolism after total hip or knee replacement surgery. Drugs. 2009 Sep;69:1829-51.
11. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Advances. 2018;2(22):3198-3225. doi:10.1182/BLOODADVANCES.2018022954
12. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, Kahn SR, Rahman M, Rajasekhar A, Rogers FB, Smythe MA. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood advances. 2019 Dec 10;3(23):3898-944.
13. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of Thrombosis and Haemostasis. 2005;3(4):692-694. doi:10.1111/j.1538-7836.2005.01204.x
14. Haac BE, O'Hara NN, Mullins CD, Stein DM, Manson TT, Johal H, Castillo R, O'Toole RV, Slobogean GP. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment. BMJ Open. 2017 Aug 11;7(8):e016676. doi: 10.1136/bmjopen-2017-016676. Erratum in: BMJ Open. 2017 Dec 22;7(12):e016676corr1. PMID: 28801426; PMCID: PMC5629686.

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.

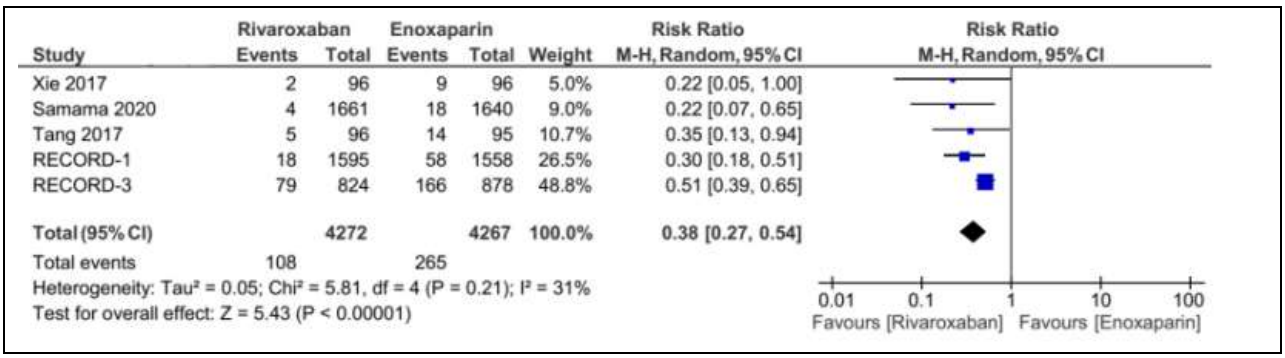
[11] RECORD4 Trial of Rivaroxaban, Published in 2009, Still Turning Heads | tctmd.com accessed 8 Mar 2023

[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)

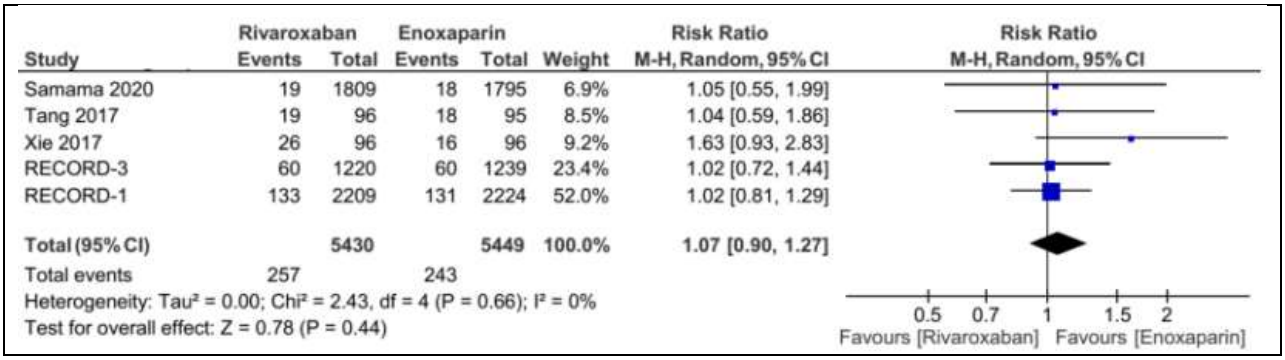
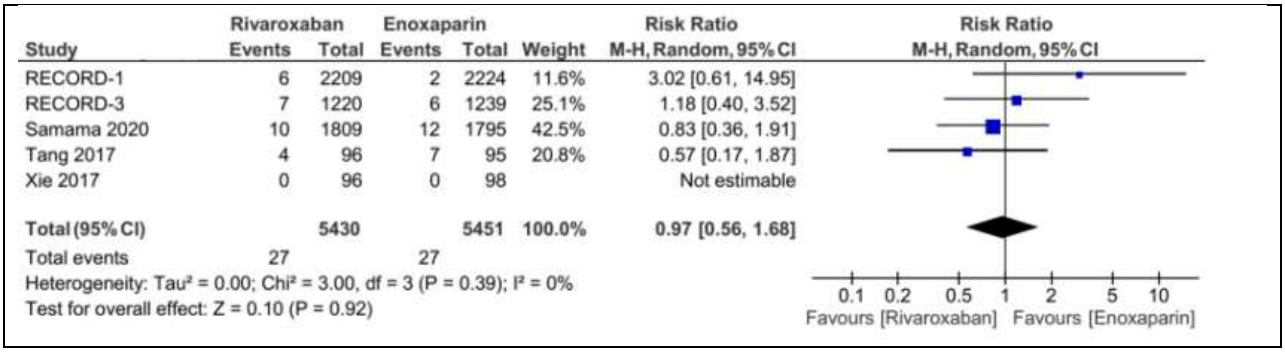


Figure 3: Incidence of major bleeding



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 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)

Veshni Pillay-Fuentes Lorente, Roland van Rensburg, Tamara Kredo, Nqoba Tsabedze, Marc Blockman, Trudy Leong

3. Author affiliation and conflict of interest details

Veshni Pillay-Fuentes Lorente: Stellenbosch University, Tygerberg Hospital; no conflicts of interest to declare.
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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.

References:

1. Cardiovascular diseases (CVDs) [Internet].
2. Cushman M, Tsai AW, White RH, et al. Deep Vein Thrombosis and Pulmonary Embolism in Two Cohorts: The Longitudinal Investigation of Thromboembolism Etiology. Am J Med 2004;117:19–25. https://doi.org/10.1016/j.amjmed.2004.01.018
3. Houghton D, Key NS. Venous Thromboembolism [Internet]. In: International Encyclopedia of Public Health. 2016. page 330–336.https://doi.org/10.1016/B978-0-12-803678-5.00506-3
4. Danwang C, Temgoua MN, Agbor VN, et al. Epidemiology of venous thromboembolism in Africa: a systematic review. J Thromb Haemost 2017;15(9):1770–1781. https://doi.org/10.1111/jth.13769
5. National Department of Health. Standard Treatment Guidelines and Essential Medicines List for South Africa [Internet]. 2019. https://doi.org/10.1128/AAC.03728-14
6. Fda. Coumadin Tablets Label [Internet]. Distribution:1–39.
7. Kahlon P, Nabi S, Arshad A, et al. Warfarin Dosing and Time Required to Reach Therapeutic International Normalized Ratio in Patients with Hypercoagulable Conditions. Turkish J Hematol 2016;33(4):299. https://doi.org/10.4274/TJH.2015.0271
8. van Gorp RH, Schurgers LJ. New insights into the pros and cons of the clinical use of vitamin K antagonists (VKAs) versus direct oral anticoagulants (DOACs) [Internet]. Nutrients2015;7(11):9538–9557. https://doi.org/10.3390/nu7115479
9. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism. N Engl J Med 2009;361(24):2342–2352. https://doi.org/10.1056/nejmoa0906598
10. Favaloro EJ, Pasalic L, Curnow J, et al. Laboratory Monitoring or Measurement of Direct Oral Anticoagulants (DOACs): Advantages, Limitations and Future Challenges. Curr Drug Metab 2017;18(7). https://doi.org/10.2174/1389200218666170417124035
11. Dunois C. Laboratory monitoring of direct oral anticoagulants (Doacs) [Internet]. Biomedicines2021;9(5):445. https://doi.org/10.3390/biomedicines9050445
12. Sessa M, Mascolo A, Callréus T, et al. Direct-acting oral anticoagulants (DOACs) in pregnancy: new insight from VigiBase ®. Sci Rep 2019;9(1). https://doi.org/10.1038/s41598-019-43715-4
13. Lameijer H, Aalberts JJJ, van Veldhuisen DJ, et al. Efficacy and safety of direct oral anticoagulants during pregnancy; a systematic literature review [Internet]. Thromb. Res.2018;169:123–127. https://doi.org/10.1016/j.thromres.2018.07.022
14. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Venous thromboembolism in the context of pregnancy [Internet]. Blood Adv.2018;2(22):3317–3359. https://doi.org/10.1182/bloodadvances.2018024802
15. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium Green-top Guideline No. 37a. 2015;
16. Cohen H, Arachchillage DR, Middeldorp S, et al. Management of direct oral anticoagulants in women of childbearing potential: guidance from the SSC of the ISTH. J Thromb Haemost 2016;14(8):1673–1676. https://doi.org/10.1111/jth.13366
17. Sterne JAC, Bodalia PN, Bryden PA, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: Systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol. Assess. (Rockv).2017;21(9):1–385. https://doi.org/10.3310/hta21090
18. National Institute for Health and Care Excellence. Venous thromboembolic diseases : diagnosis , management and thrombophilia testing. NICE Guidel 2015;(November):12–15.
19. Ortel TL, Neumann I, Ageno W, et al. American society of hematology 2020 guidelines for management of venous thromboembolism: Treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020;4(19):4693–4738. https://doi.org/10.1182/bloodadvances.2020001830
20. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J. Thromb. Haemost.2005;3(4):692–694. https://doi.org/10.1111/j.1538-7836.2005.01204.x
21. Amin A, Jing Y, Trocio J, et al. Evaluation of medical costs associated with use of new oral anticoagulants compared with standard therapy among venous thromboembolism patients. J Med Econ 2014;17(11):763–770. https://doi.org/10.3111/13696998.2014.950670
22. Amin A, Bruno A, Trocio J, et al. Real-World Medical Cost Avoidance When New Oral Anticoagulants are Used Versus Warfarin for Venous Thromboembolism in the United States: http://dx.doi.org/101177/1076029615585991 2015;22(1):5–11. https://doi.org/10.1177/1076029615585991
23. Bamber L, Muston D, McLeod E, et al. Cost-effectiveness analysis of treatment of venous thromboembolism with rivaroxaban compared with combined low molecular weight heparin/vitamin K antagonist. Thromb J 2015;13(1). https://doi.org/10.1186/S12959-015-0051-3
24. Margolis JM, Deitelzweig S, Kline J, et al. Pulmonary Embolism Inpatients Treated With Rivaroxaban Had Shorter Hospital Stays and Lower Costs Compared With Warfarin. Clin Ther 2016;38(11):2496–2503. https://doi.org/10.1016/j.clinthera.2016.09.007
25. Weeda ER, Kohn CG, Peacock WF, et al. Rivaroxaban versus Heparin Bridging to Warfarin Therapy: Impact on Hospital Length of Stay and Treatment Costs for Low-Risk Patients with Pulmonary Embolism. Pharmacother J Hum Pharmacol Drug Ther 2016;36(10):1109–1115. https://doi.org/10.1002/PHAR.1828

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:

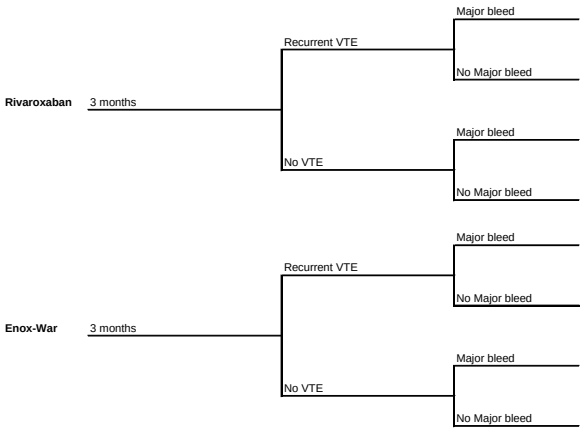

Figure 1. Diagram of decision analysis model for rivaroxaban vs enoxaparin-warfarin

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.

REFERENCES

1. **Investigators, EINSTEIN-PE.** Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *New England Journal of Medicine.* 2012, Vol. 366, pp. 1287-1297.

2. **Investigators, EINSTEIN.** Oral rivaroxaban for symptomatic venous thromboembolism. *New England Journal of Medicine.* 2010, Vol. 363, 26, pp. 2499-2510.
3. **Prins MH, Lensing AW, Bauersachs R et al.** Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J.* 2013.
4. **van Bellen B, Bamber L, Correa de Carvalho F, Prins M, Wang M, Lensing AW.** Reduction in the length of stay with rivaroxaban as a single-drug regimen for the treatment of deep vein thrombosis and pulmonary embolism. *Curr Med Res Opin.* 2014, Vol. 30, 5, pp. 829-837.
5. **Fernandez M, Hogue S, Preblick R, Kwong WJ.** Review of the cost of venous thromboembolism. *ClinicoEconomics and Outcomes Research.* 2015, Vol. 7, pp. 451-462.
6. **Burness C, Perry C.** Rivaroxaban: a review of its use in the treatment of deep vein thrombosis or pulmonary embolism and the prevention of recurrent venous thromboembolism. *Drugs.* 2014, Vol. 74, pp. 243-262.
7. **Bamber L, Muston D, McLeod E, Guillermin A, Lowin J, Patel R.** Cost-effectiveness analysis of treatment of venous thromboembolism with rivaroxaban compared with combined low molecular weight heparin/vitamin K antagonist. *Thrombosis Journal.* 2015, Vol. 13, p. 20.
8. **B F Jacobson, S Louw, H Büller, M Mer, P R de Jong, P Rowji , E Schapkaitz, D Adler, A Beeton, H-C Hsu, P Wessels, S Haas,.** Venous thromboembolism: Prophylactic and therapeutic practice guideline. *SAMJ.* 2013, Vol. 103, 4, pp. 260-267.
9. MacQuilkin, Wilkinson T, Winch A, Chola L, Rapiti R. Fondaparinux for the **treatment of venous thromboembolism** in hospitalised patients in the South African public health system. South African National Essential Medicines List
Adult Hospital Medication Review Process. January 2019
10. **Awolesi D, Naidoo M, Cassimijee MH.** The profile and frequency of known risk factors or comorbidities for deep vein thrombosis in an urban district hospital in KwaZulu- Natal. S Afr J HIV Med 2016;17(1):a425. https://doi.org/10.4102/sajhivmed.v17i1.425

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 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):
Gayle Tatz, Ntombifuthi Blose, Mashudu Mthethwa, Zahiera Adam, Sumayyah Ebrahim, Tamara Kredo, Marc Blockman

Author affiliation and conflict of interest details
Gayle Tatz (Clinical Pharmacology at the Groote Schuur Hospital, University of Cape Town); NB and MM (Health Systems Research Unit, South African Medical Research Council (SAMRC); TK (Health Systems Research Unit, SAMRC and Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network. ZA (Consultant for Right to Care), no conflicts to declare.

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This review was supported by the SA GRADE Network, which is jointly led and managed by Centre for Evidence Based Health Care (CEBHC), Stellenbosch University and the Health Systems Research Unit, South African Medical Research Council.

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).

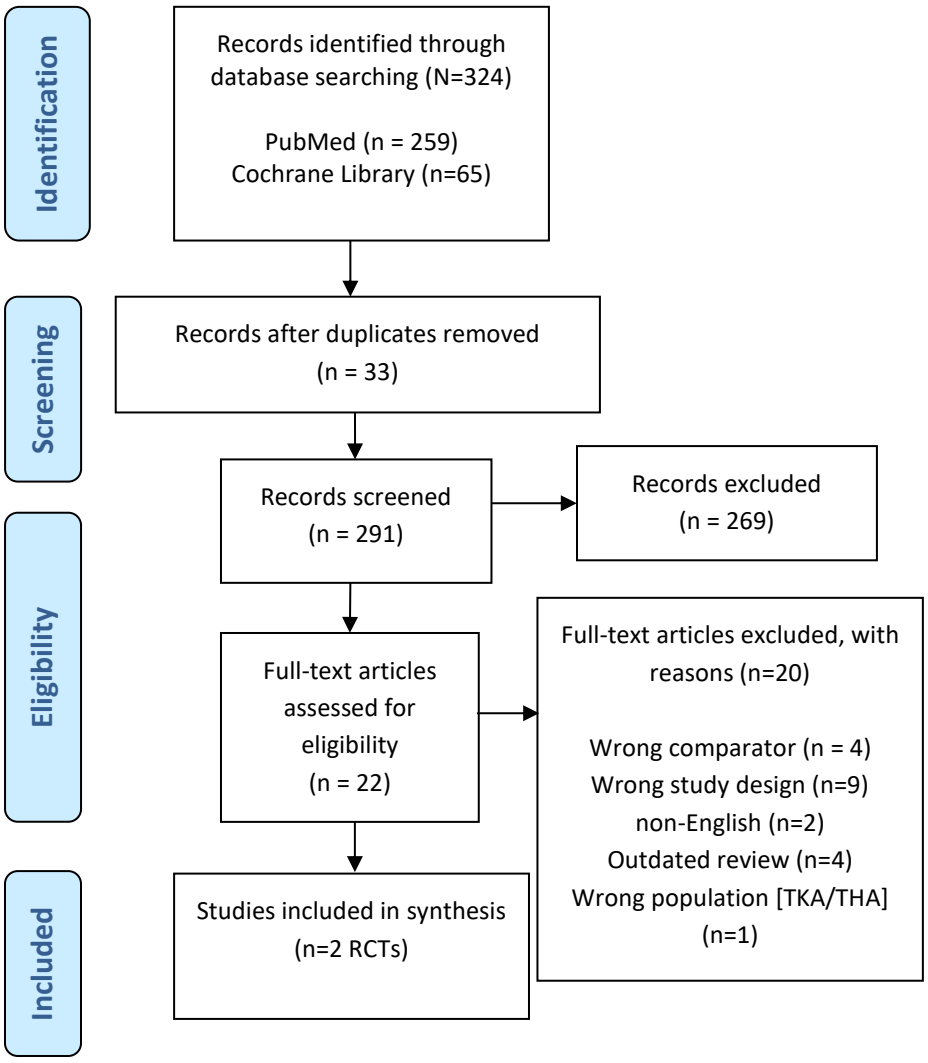


Figure 1: PRISMA flow diagram of included records

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).

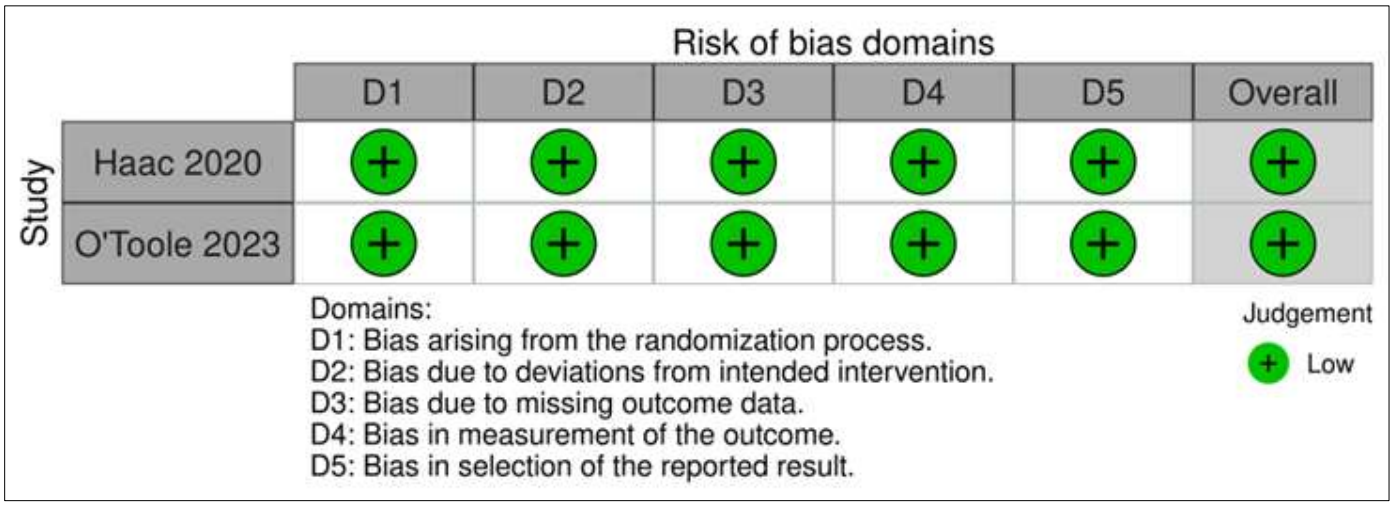


Figure 2: Risk of bias 2.0 of included trials

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).

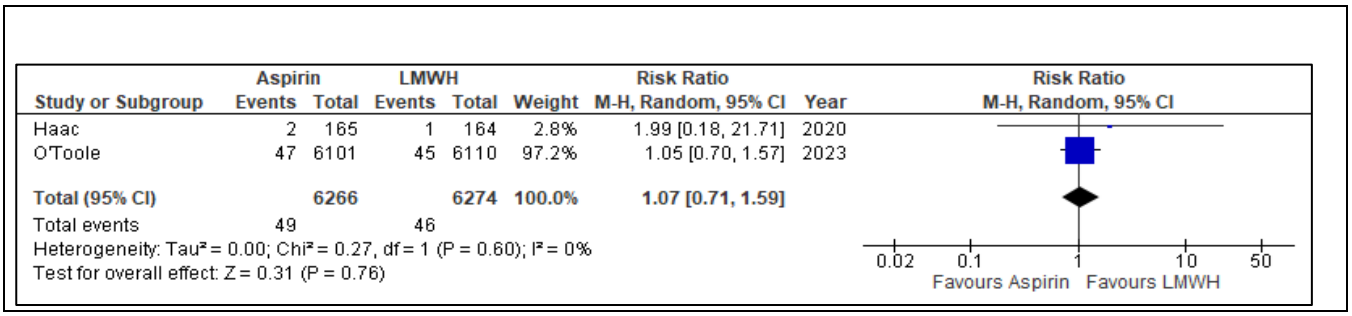


Figure5: Forest plot of Aspirin vs LMWH, outcome: Mortality

- **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).

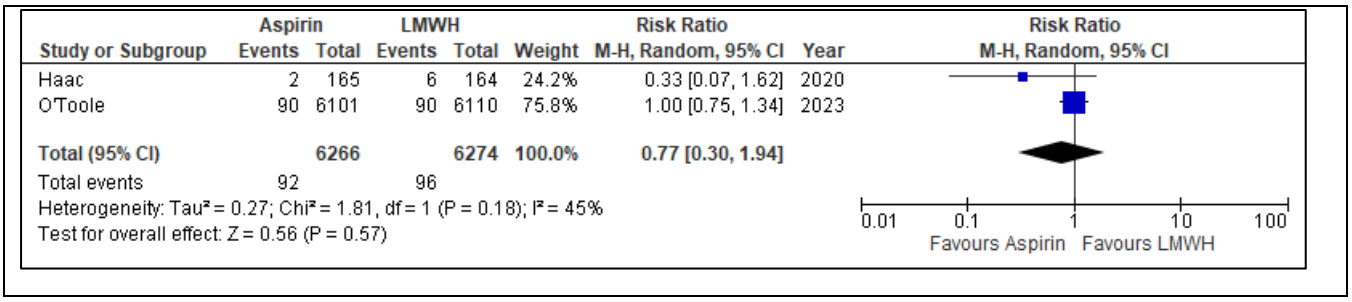


Figure6: Forest plot of Aspirin vs. LMWH, outcome: Pulmonary embolism

- **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).

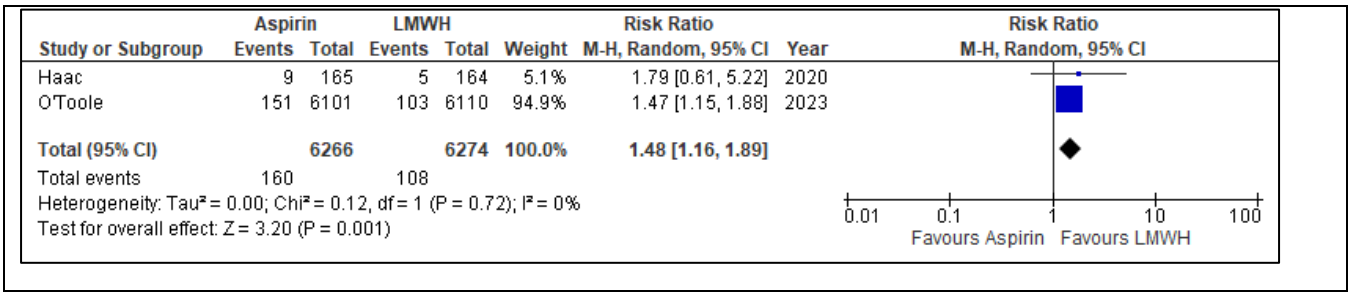


Figure7: Forest plot of Aspirin vs LMWH, outcome: Deep vein thrombosis

- **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).

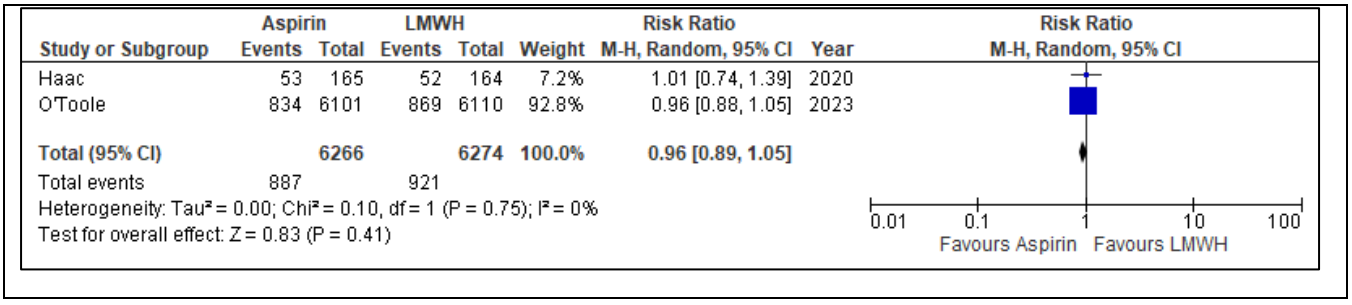


Figure8: Forest plot of Aspirin vs LMWH, outcome: Major bleeding

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.

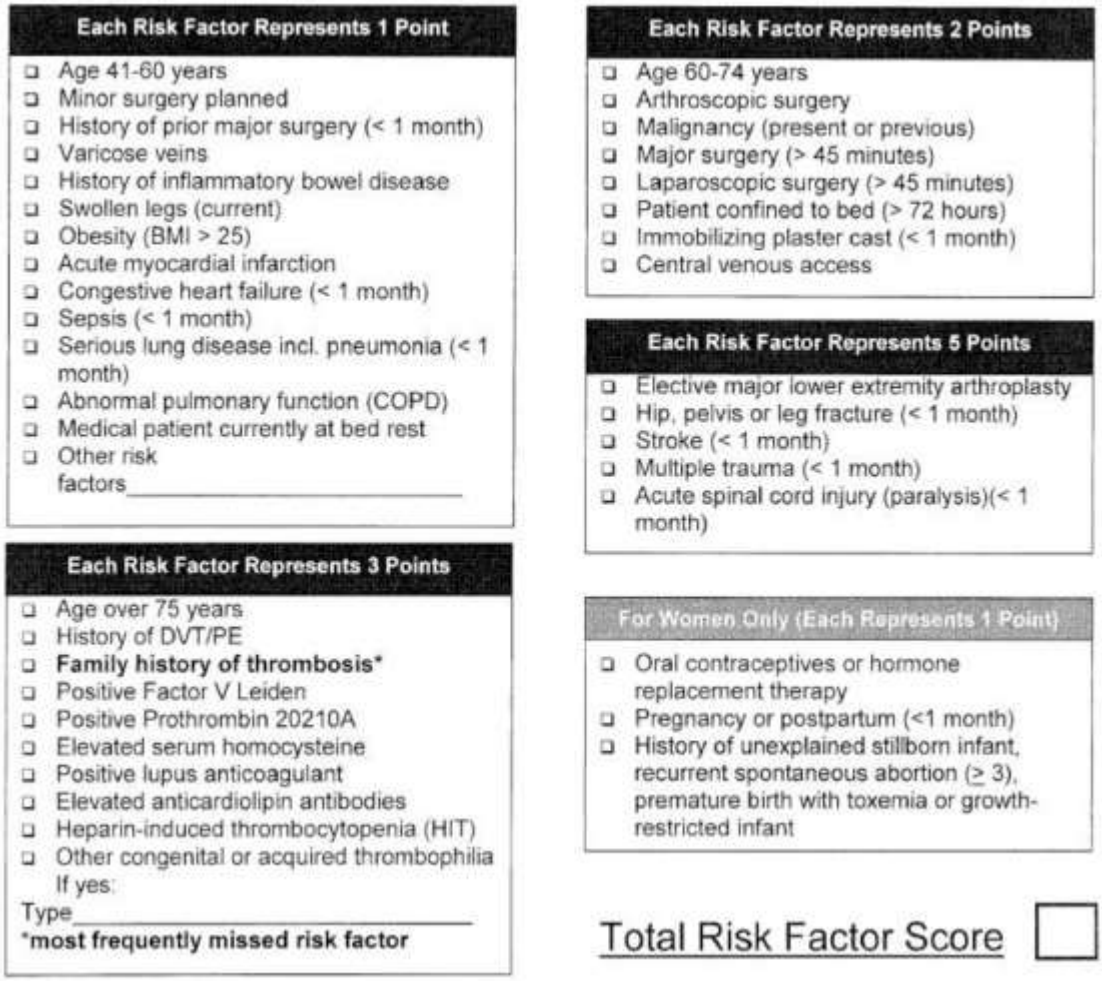
Appendix 4 : Supplementary Tab;e from O'Toole et al (19) (PREVENT CLOT) showing baseline characteristics including risk factors

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.
https://www.ncbi.nlm.nih.gov/pubmed/23547704

References

1. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Archives of internal medicine. 2003;163(14):1711-7.
2. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Archives of internal medicine. 2002;162(11):1245-8.
3. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thrombosis and haemostasis. 2003;90(3):446-55.
4. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. Archives of internal medicine. 1998;158(14):1525-31.
5. Lobastov K, Urbanek T, Stepanov E, Lal B, Caprini J. The thresholds of Caprini score associated with increased risk of venous thromboembolism across different Specialties: a systematic review. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2023 Mar 1;11(2):453.
6. Montinari MR, Minelli S, De Caterina R. The first 3500 years of aspirin history from its roots - A concise summary. Vascular pharmacology. 2019;113:1-8.
7. Gómez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct-acting oral anticoagulants: pharmacology, indications, management, and future perspectives. Eur J Haematol. 2015;95(5):389-404.
8. Agnelli G. Prevention of venous thromboembolism in surgical patients. Circulation. 2004 Dec 14;110(24_suppl_1):IV-4.
9. Wall V, Fleming KI, Tonna JE, Nunez J, Lonardo N, Shipley RW, Nirula R, Pannucci CJ. Anti-factor Xa measurements in acute care surgery patients to examine enoxaparin dose. The American Journal of Surgery. 2018 Aug 1;216(2):222-9.
10. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clinical research ed). 2017;358:j4008.
11. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 205-28.
12. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Completing 'Summary of findings' tables and grading the certainty of the evidence. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 375-402.
13. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Advances. 2019;3(23):3898-944.
14. Jiang Y, Du H, Liu J, Zhou Y. Aspirin combined with mechanical measures to prevent venous thromboembolism after total knee arthroplasty: a randomized controlled trial. Chinese medical journal. 2014;127(12):2201-5.
15. Kulshrestha V, Kumar S. DVT prophylaxis after TKA: routine anticoagulation vs risk screening approach - a randomized study. The Journal of arthroplasty. 2013;28(10):1868-73.
16. Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. The Journal of arthroplasty. 2006;21(6 Suppl 2):139-43.
17. Zou Y, Tian S, Wang Y, Sun K. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2014;25(7):660-4.

18. Haac BE, O'Hara NN, Manson TT, Slobogean GP, Castillo RC, O'Toole RV, et al. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: A patient-centered randomized controlled trial. PloS one. 2020;15(8):e0235628.
19. O'Toole RV, Stein DM, O'Hara NN, Frey KP, Taylor TJ, Scharfstein DO, et al. Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture. The New England journal of medicine. 2023;388(3):203-13.
20. Sidhu VS, Kelly TL, Pratt N, Graves SE, Buchbinder R, Adie S, et al. Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty: The CRISTAL Randomized Trial. Jama. 2022;328(8):719-27.
21. Farey JE, An VVG, Sidhu V, Karunaratne S, Harris IA. Aspirin versus enoxaparin for the initial prevention of venous thromboembolism following elective arthroplasty of the hip or knee: A systematic review and meta-analysis. Orthopaedics & traumatology, surgery & research : OTSR. 2021;107(1):102606.
22. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, Lake E. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021 Dec 1;160(6):e545-608.
23. (Haac BE, O'Hara NN, Mullins CD, et al. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment [published correction appears in BMJ Open. 2017 Dec 22;7(12):e016676corr1]. *BMJ Open*. 2017;7(8):e016676 10.1136/bmjopen-2017-016676)

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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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).

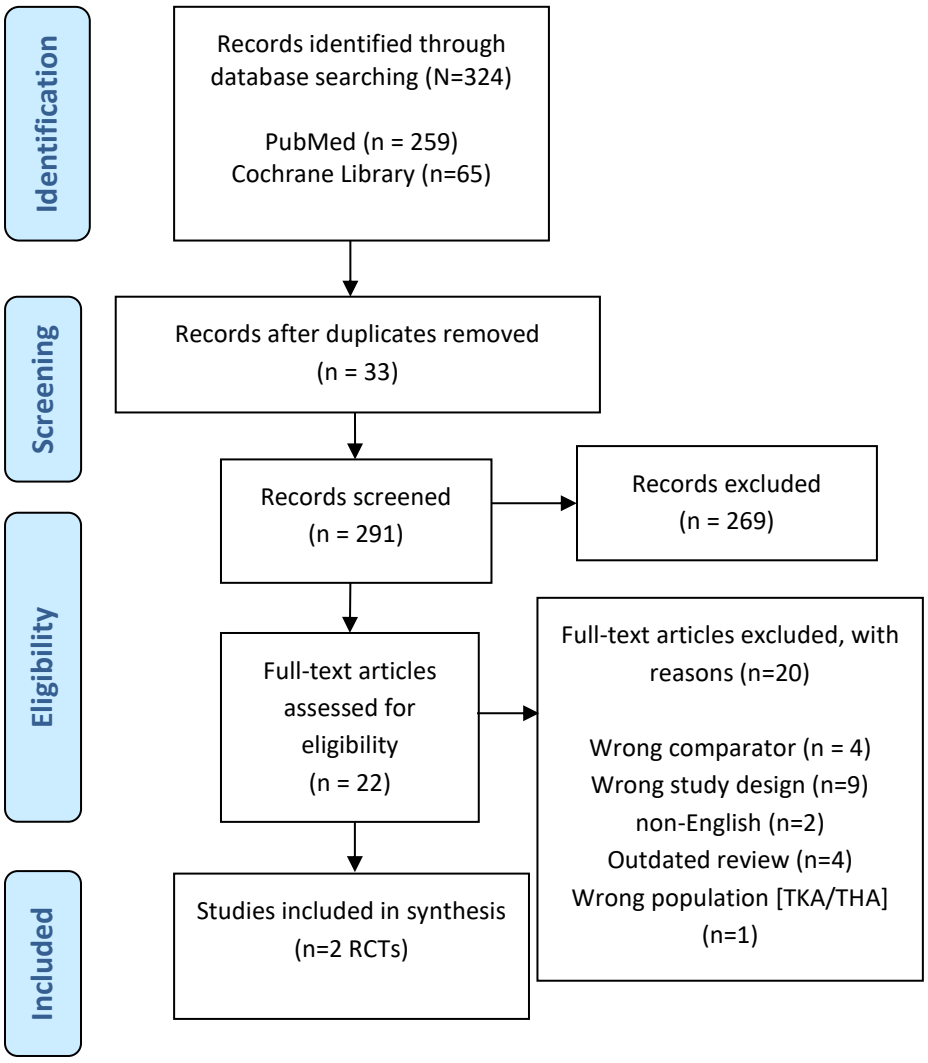


Figure 1: PRISMA flow diagram of included records

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).

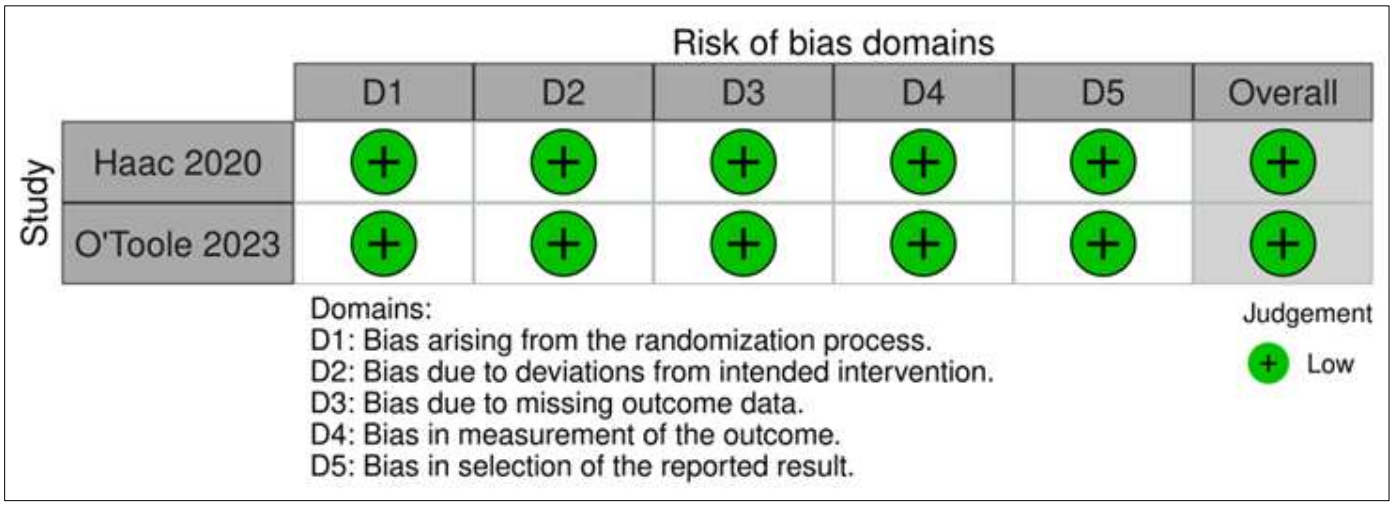


Figure 2: Risk of bias 2.0 of included trials

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).

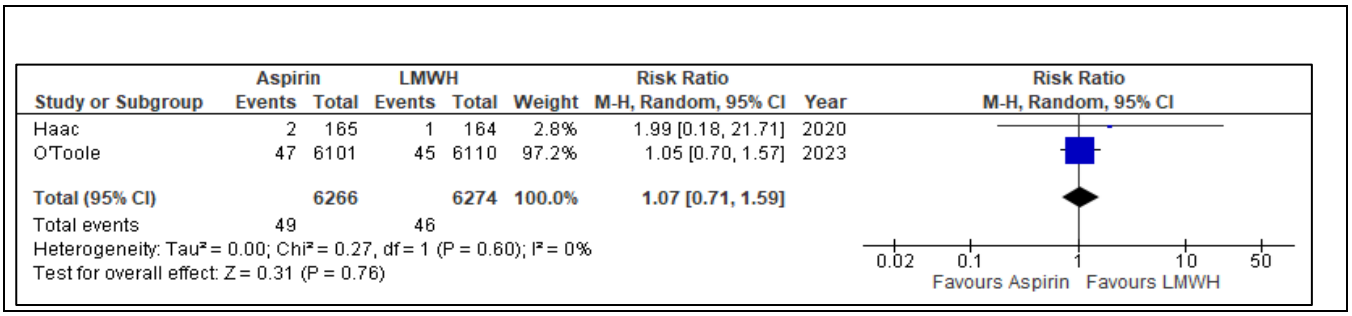


Figure5: Forest plot of Aspirin vs LMWH, outcome: Mortality

- **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).

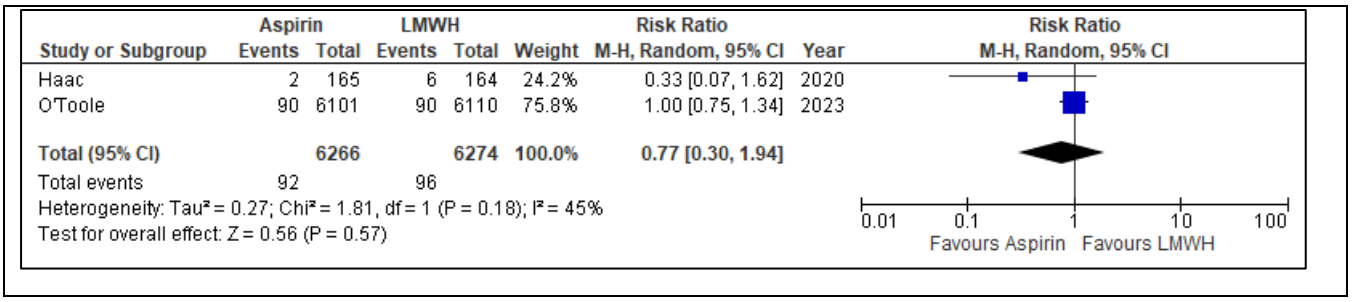


Figure6: Forest plot of Aspirin vs. LMWH, outcome: Pulmonary embolism

- **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).

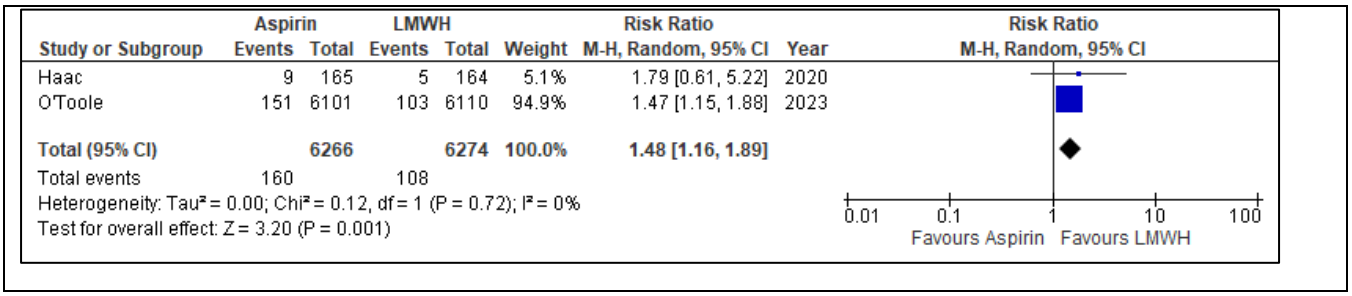


Figure7: Forest plot of Aspirin vs LMWH, outcome: Deep vein thrombosis

- **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).

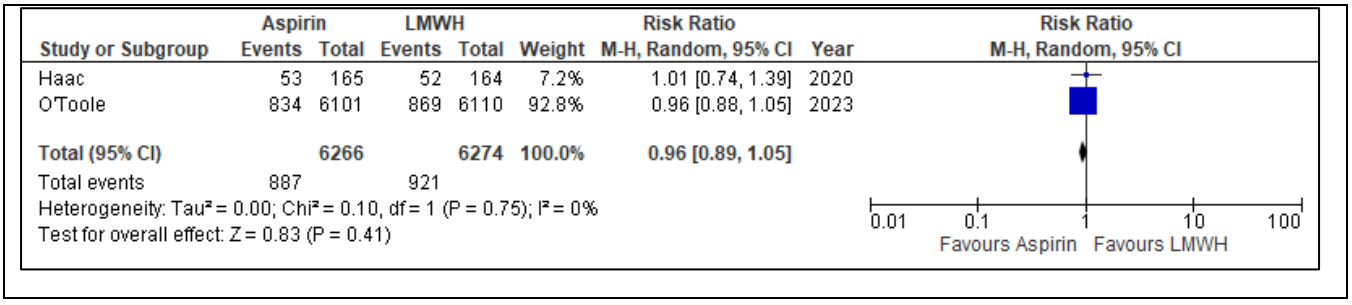


Figure8: Forest plot of Aspirin vs LMWH, outcome: Major bleeding

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.

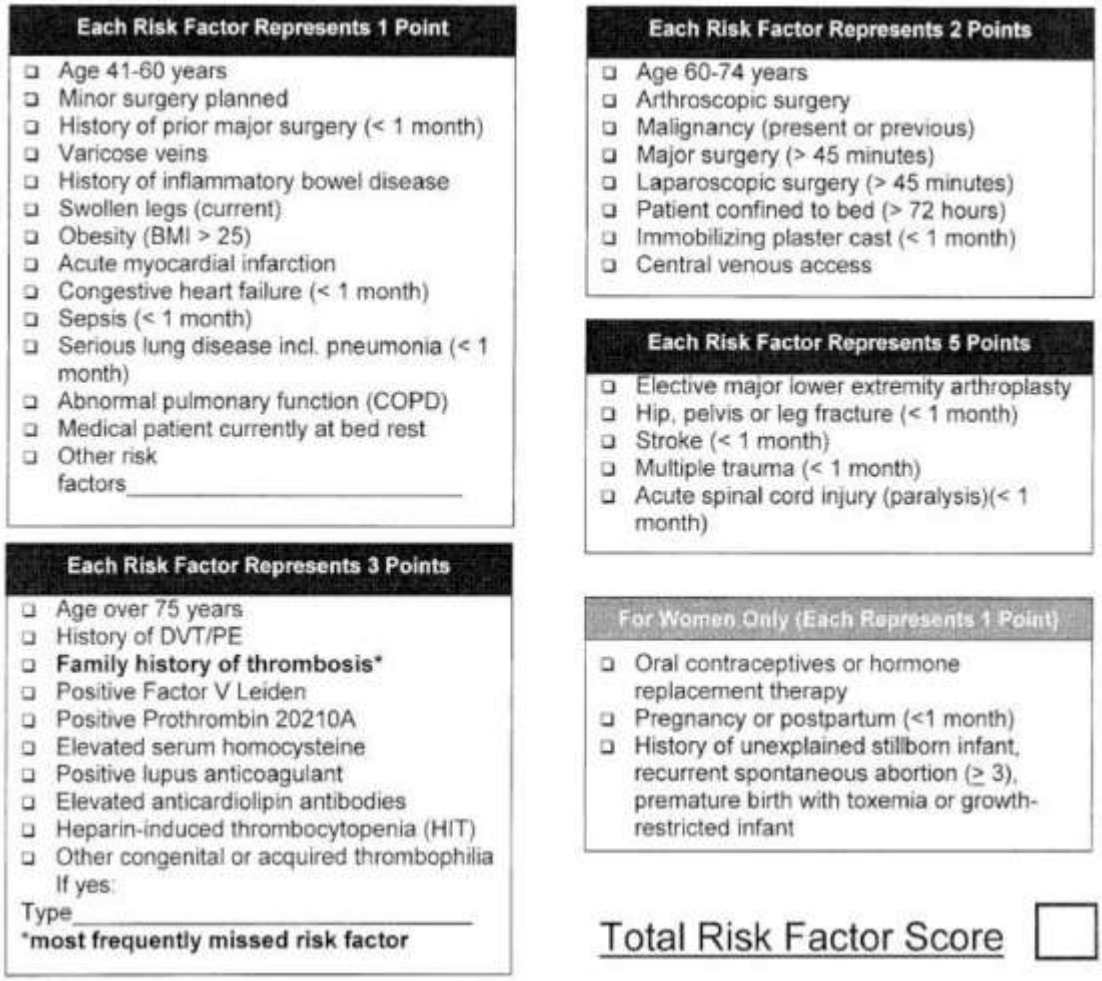
Appendix 4 : Supplementary Tab;e from O'Toole et al (19) (PREVENT CLOT) showing baseline characteristics including risk factors

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.
https://www.ncbi.nlm.nih.gov/pubmed/23547704

References

1. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Archives of internal medicine. 2003;163(14):1711-7.
2. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Archives of internal medicine. 2002;162(11):1245-8.
3. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thrombosis and haemostasis. 2003;90(3):446-55.
4. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. Archives of internal medicine. 1998;158(14):1525-31.
5. Lobastov K, Urbanek T, Stepanov E, Lal B, Caprini J. The thresholds of Caprini score associated with increased risk of venous thromboembolism across different Specialties: a systematic review. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2023 Mar 1;11(2):453.
6. Montinari MR, Minelli S, De Caterina R. The first 3500 years of aspirin history from its roots - A concise summary. Vascular pharmacology. 2019;113:1-8.
7. Gómez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct-acting oral anticoagulants: pharmacology, indications, management, and future perspectives. Eur J Haematol. 2015;95(5):389-404.
8. Agnelli G. Prevention of venous thromboembolism in surgical patients. Circulation. 2004 Dec 14;110(24_suppl_1):IV-4.
9. Wall V, Fleming KI, Tonna JE, Nunez J, Lonardo N, Shipley RW, Nirula R, Pannucci CJ. Anti-factor Xa measurements in acute care surgery patients to examine enoxaparin dose. The American Journal of Surgery. 2018 Aug 1;216(2):222-9.
10. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clinical research ed). 2017;358:j4008.
11. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 205-28.
12. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Completing 'Summary of findings' tables and grading the certainty of the evidence. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 375-402.
13. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Advances. 2019;3(23):3898-944.
14. Jiang Y, Du H, Liu J, Zhou Y. Aspirin combined with mechanical measures to prevent venous thromboembolism after total knee arthroplasty: a randomized controlled trial. Chinese medical journal. 2014;127(12):2201-5.
15. Kulshrestha V, Kumar S. DVT prophylaxis after TKA: routine anticoagulation vs risk screening approach - a randomized study. The Journal of arthroplasty. 2013;28(10):1868-73.
16. Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. The Journal of arthroplasty. 2006;21(6 Suppl 2):139-43.
17. Zou Y, Tian S, Wang Y, Sun K. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2014;25(7):660-4.

18. Haac BE, O'Hara NN, Manson TT, Slobogean GP, Castillo RC, O'Toole RV, et al. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: A patient-centered randomized controlled trial. PloS one. 2020;15(8):e0235628.
19. O'Toole RV, Stein DM, O'Hara NN, Frey KP, Taylor TJ, Scharfstein DO, et al. Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture. The New England journal of medicine. 2023;388(3):203-13.
20. Sidhu VS, Kelly TL, Pratt N, Graves SE, Buchbinder R, Adie S, et al. Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty: The CRISTAL Randomized Trial. Jama. 2022;328(8):719-27.
21. Farey JE, An VVG, Sidhu V, Karunaratne S, Harris IA. Aspirin versus enoxaparin for the initial prevention of venous thromboembolism following elective arthroplasty of the hip or knee: A systematic review and meta-analysis. Orthopaedics & traumatology, surgery & research : OTSR. 2021;107(1):102606.
22. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, Lake E. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021 Dec 1;160(6):e545-608.
23. (Haac BE, O'Hara NN, Mullins CD, et al. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment [published correction appears in BMJ Open. 2017 Dec 22;7(12):e016676corr1]. *BMJ Open*. 2017;7(8):e016676 10.1136/bmjopen-2017-016676)

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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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).

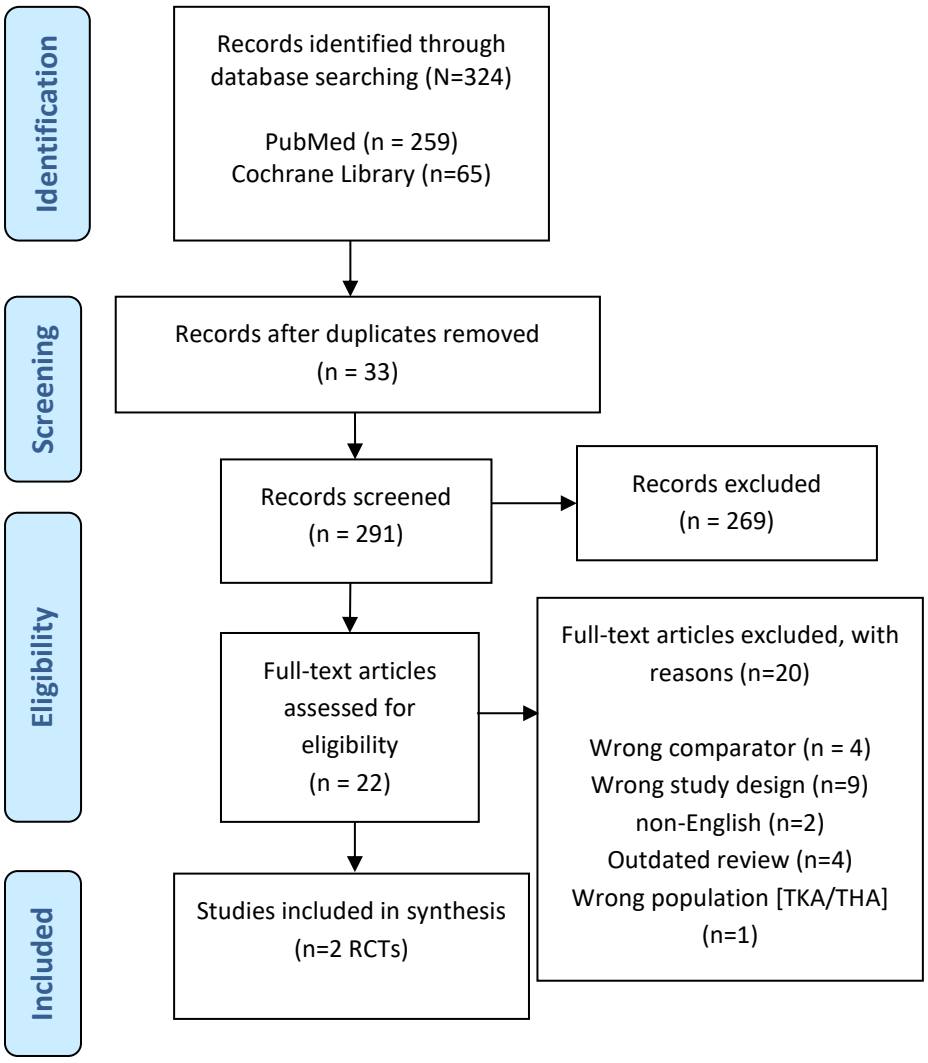


Figure 1: PRISMA flow diagram of included records

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).

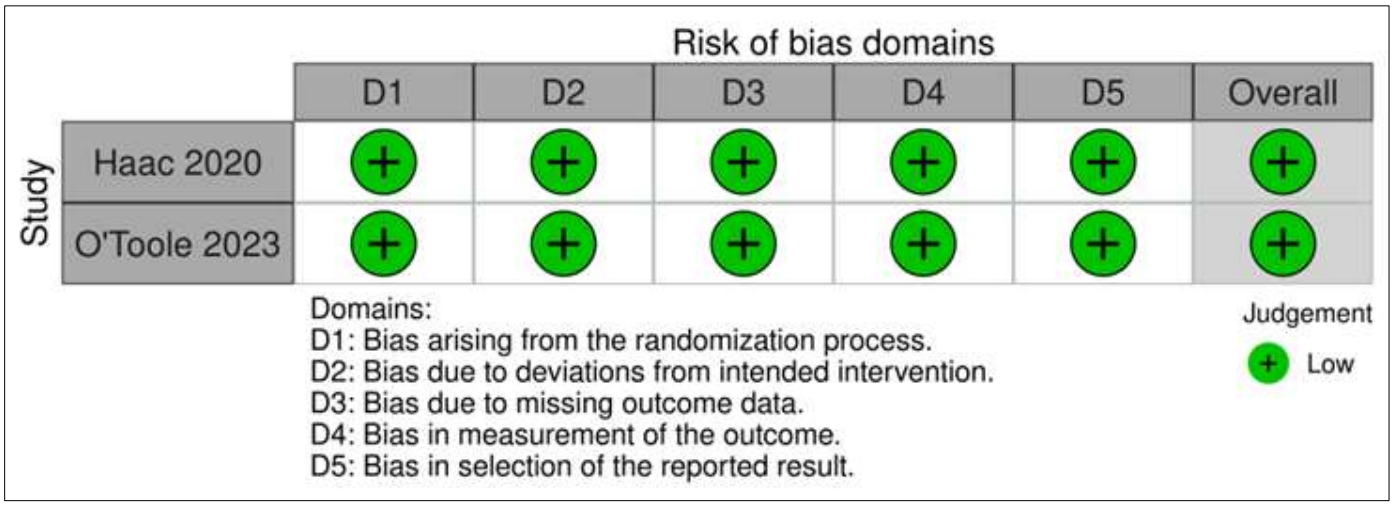


Figure 2: Risk of bias 2.0 of included trials

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).

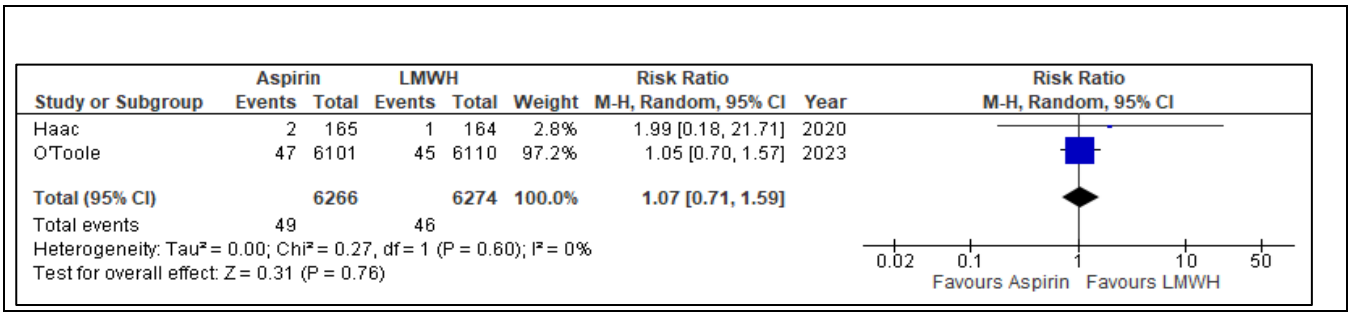


Figure5: Forest plot of Aspirin vs LMWH, outcome: Mortality

- **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).

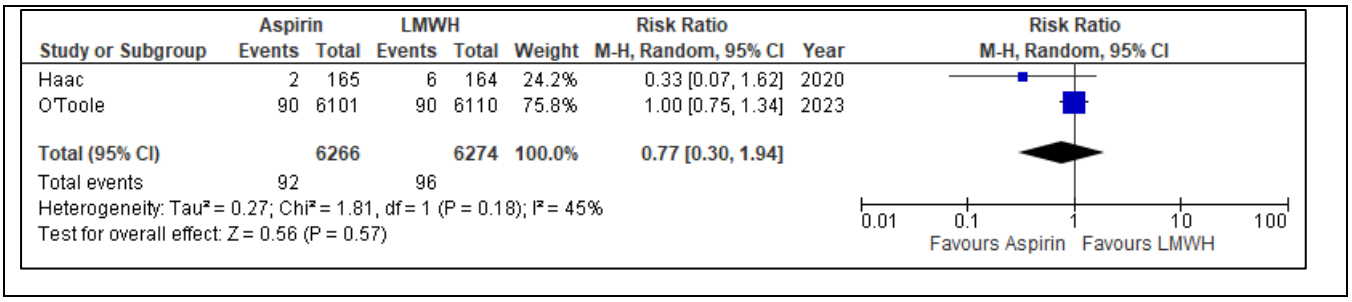


Figure6: Forest plot of Aspirin vs. LMWH, outcome: Pulmonary embolism

- **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).

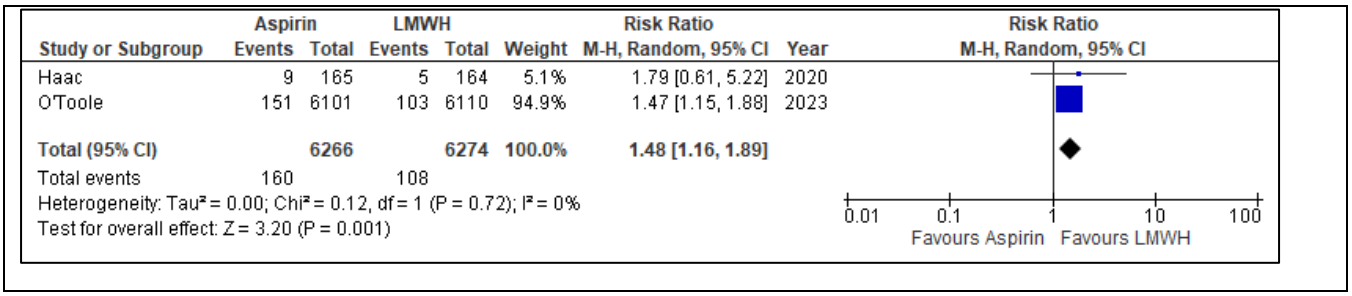


Figure7: Forest plot of Aspirin vs LMWH, outcome: Deep vein thrombosis

- **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).

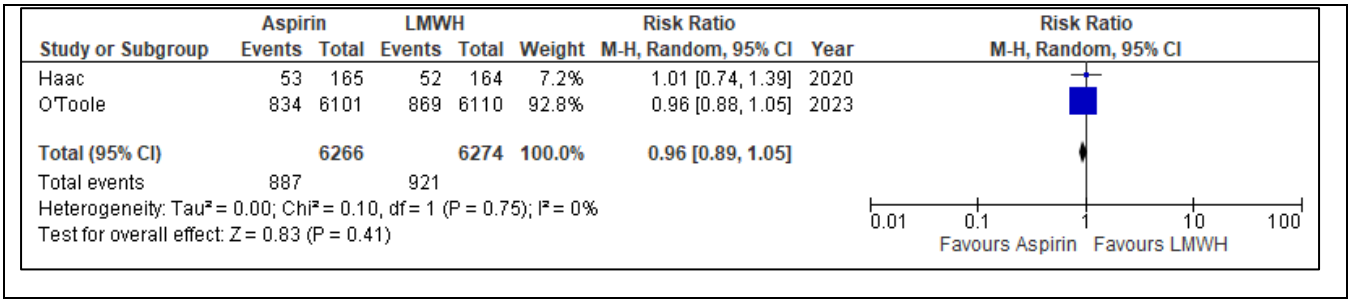


Figure8: Forest plot of Aspirin vs LMWH, outcome: Major bleeding

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.

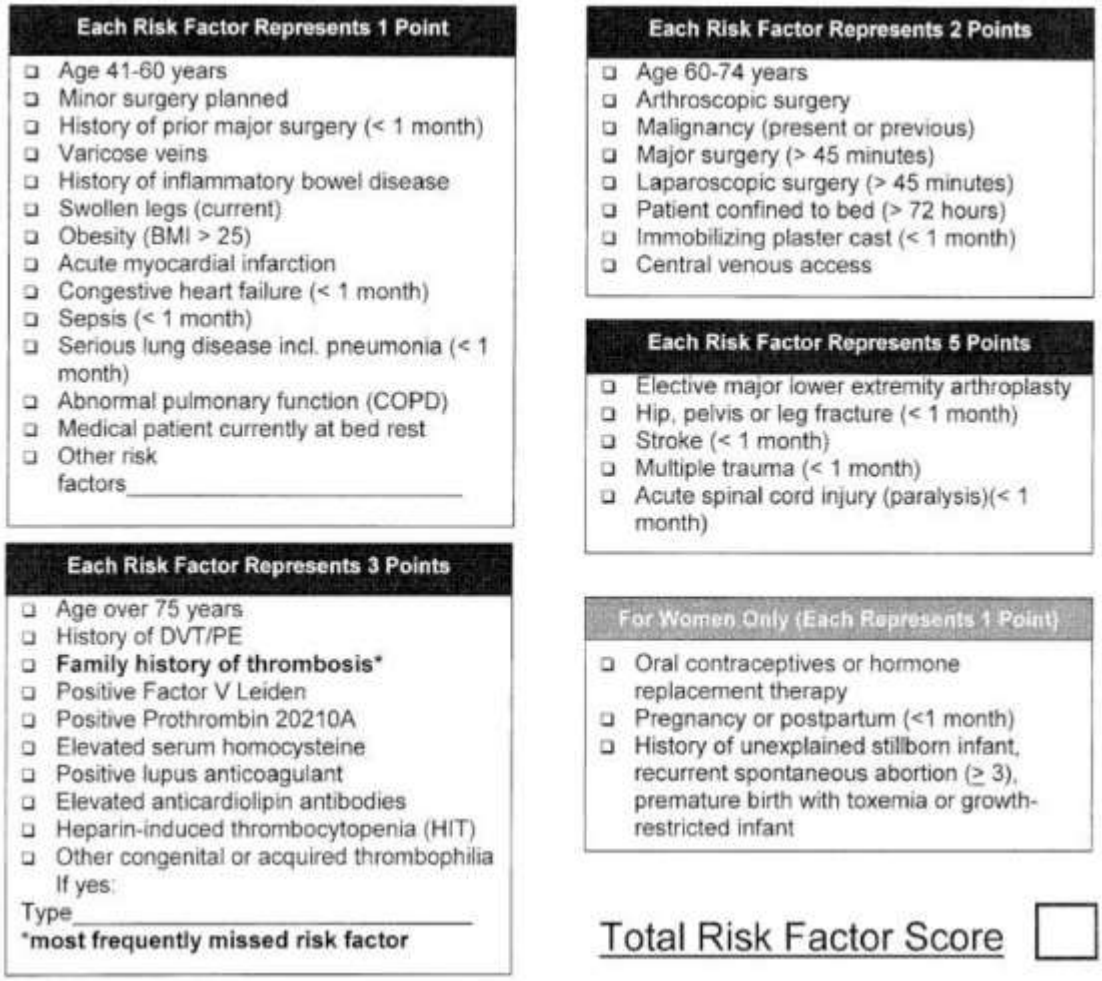
Appendix 4 : Supplementary Tab;e from O'Toole et al (19) (PREVENT CLOT) showing baseline characteristics including risk factors

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.
https://www.ncbi.nlm.nih.gov/pubmed/23547704

References

1. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Archives of internal medicine. 2003;163(14):1711-7.
2. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Archives of internal medicine. 2002;162(11):1245-8.
3. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thrombosis and haemostasis. 2003;90(3):446-55.
4. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. Archives of internal medicine. 1998;158(14):1525-31.
5. Lobastov K, Urbanek T, Stepanov E, Lal B, Caprini J. The thresholds of Caprini score associated with increased risk of venous thromboembolism across different Specialties: a systematic review. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2023 Mar 1;11(2):453.
6. Montinari MR, Minelli S, De Caterina R. The first 3500 years of aspirin history from its roots - A concise summary. Vascular pharmacology. 2019;113:1-8.
7. Gómez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct-acting oral anticoagulants: pharmacology, indications, management, and future perspectives. Eur J Haematol. 2015;95(5):389-404.
8. Agnelli G. Prevention of venous thromboembolism in surgical patients. Circulation. 2004 Dec 14;110(24_suppl_1):IV-4.
9. Wall V, Fleming KI, Tonna JE, Nunez J, Lonardo N, Shipley RW, Nirula R, Pannucci CJ. Anti-factor Xa measurements in acute care surgery patients to examine enoxaparin dose. The American Journal of Surgery. 2018 Aug 1;216(2):222-9.
10. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clinical research ed). 2017;358:j4008.
11. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 205-28.
12. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Completing 'Summary of findings' tables and grading the certainty of the evidence. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 375-402.
13. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Advances. 2019;3(23):3898-944.
14. Jiang Y, Du H, Liu J, Zhou Y. Aspirin combined with mechanical measures to prevent venous thromboembolism after total knee arthroplasty: a randomized controlled trial. Chinese medical journal. 2014;127(12):2201-5.
15. Kulshrestha V, Kumar S. DVT prophylaxis after TKA: routine anticoagulation vs risk screening approach - a randomized study. The Journal of arthroplasty. 2013;28(10):1868-73.
16. Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. The Journal of arthroplasty. 2006;21(6 Suppl 2):139-43.
17. Zou Y, Tian S, Wang Y, Sun K. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2014;25(7):660-4.

18. Haac BE, O'Hara NN, Manson TT, Slobogean GP, Castillo RC, O'Toole RV, et al. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: A patient-centered randomized controlled trial. PloS one. 2020;15(8):e0235628.
19. O'Toole RV, Stein DM, O'Hara NN, Frey KP, Taylor TJ, Scharfstein DO, et al. Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture. The New England journal of medicine. 2023;388(3):203-13.
20. Sidhu VS, Kelly TL, Pratt N, Graves SE, Buchbinder R, Adie S, et al. Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty: The CRISTAL Randomized Trial. Jama. 2022;328(8):719-27.
21. Farey JE, An VVG, Sidhu V, Karunaratne S, Harris IA. Aspirin versus enoxaparin for the initial prevention of venous thromboembolism following elective arthroplasty of the hip or knee: A systematic review and meta-analysis. Orthopaedics & traumatology, surgery & research : OTSR. 2021;107(1):102606.
22. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, Lake E. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021 Dec 1;160(6):e545-608.
23. (Haac BE, O'Hara NN, Mullins CD, et al. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment [published correction appears in BMJ Open. 2017 Dec 22;7(12):e016676corr1]. *BMJ Open*. 2017;7(8):e016676 10.1136/bmjopen-2017-016676)

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):
Gayle Tatz, Ntombifuthi Blose, Mashudu Mthethwa, Zahiera Adam, Sumayyah Ebrahim, Tamara Kredo, Marc Blockman

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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).

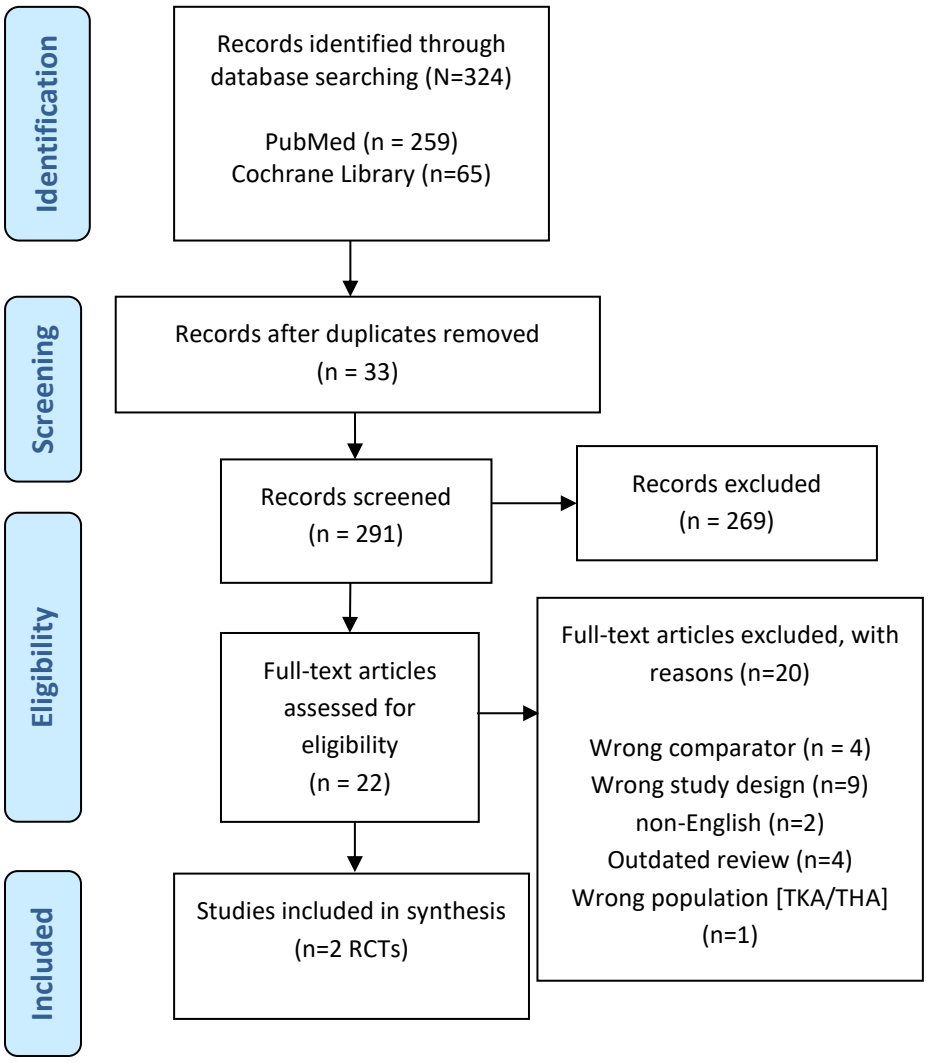


Figure 1: PRISMA flow diagram of included records

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).

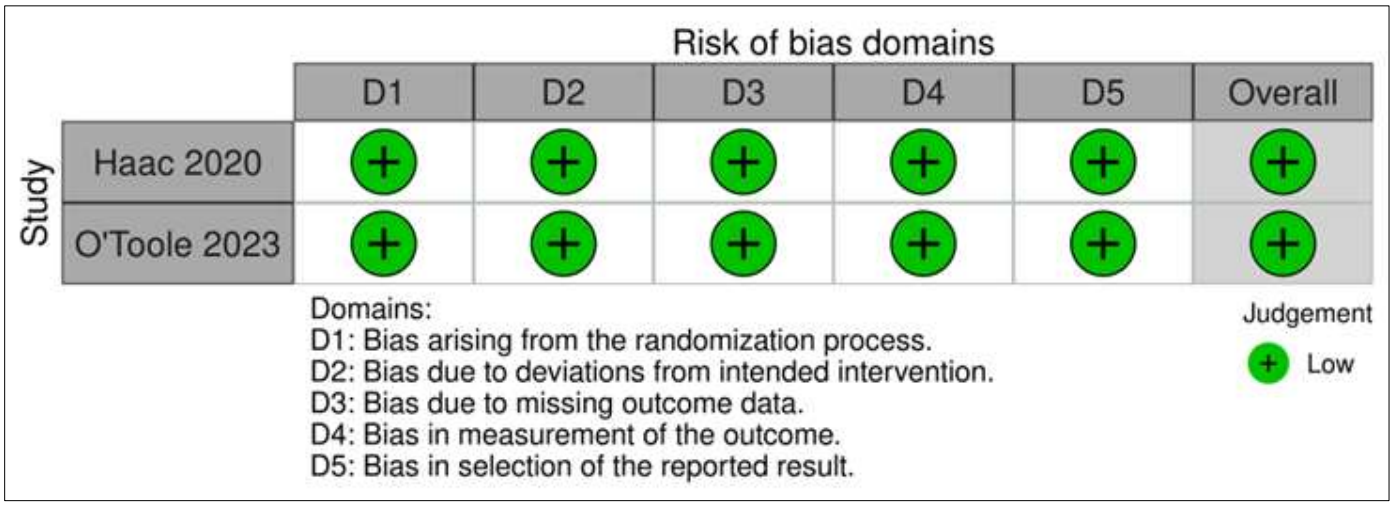


Figure 2: Risk of bias 2.0 of included trials

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).

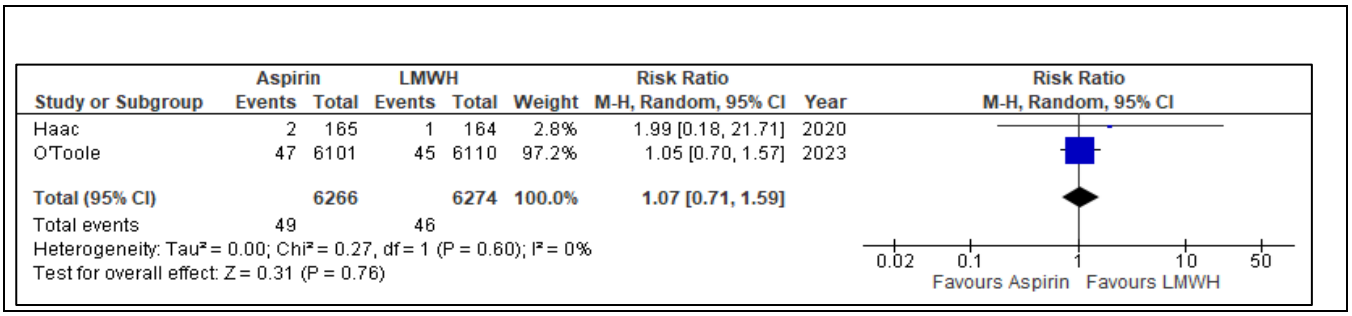


Figure5: Forest plot of Aspirin vs LMWH, outcome: Mortality

- **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).

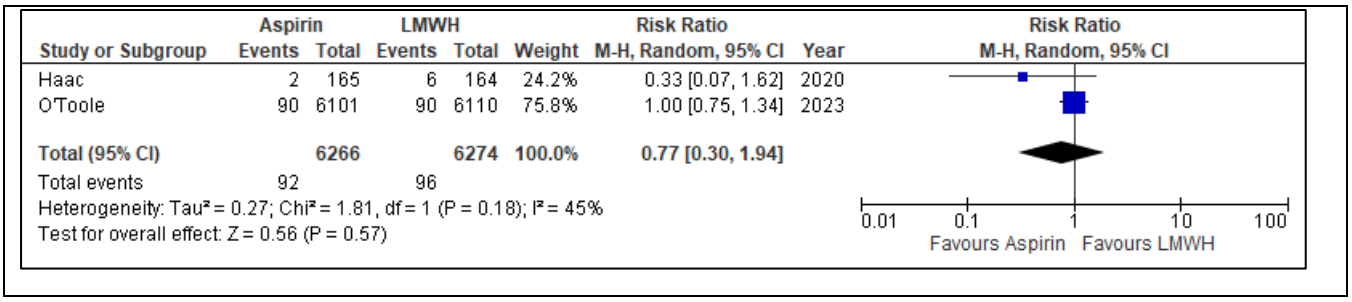


Figure6: Forest plot of Aspirin vs. LMWH, outcome: Pulmonary embolism

- **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).

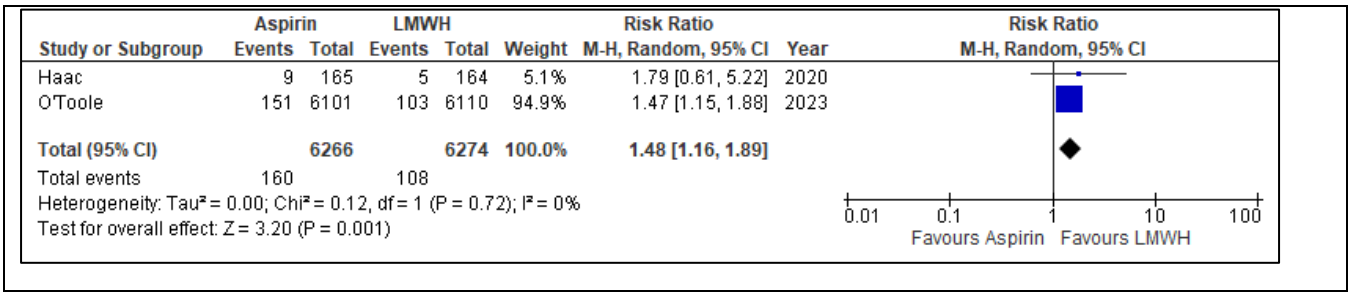


Figure7: Forest plot of Aspirin vs LMWH, outcome: Deep vein thrombosis

- **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).

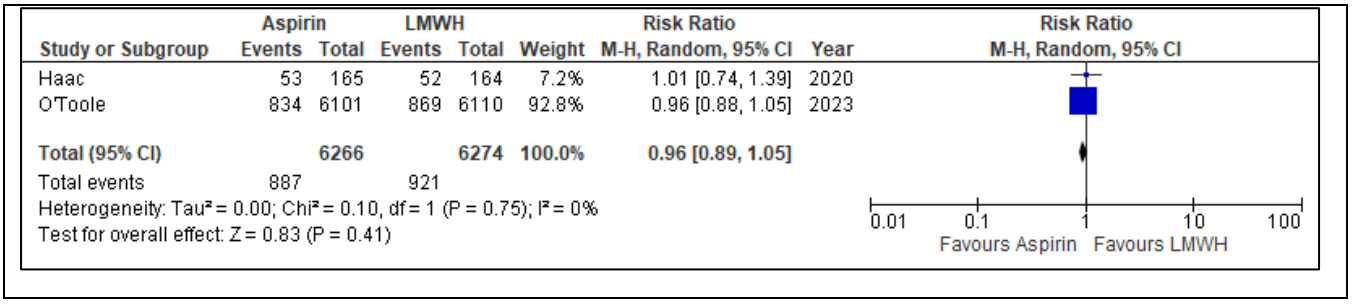


Figure8: Forest plot of Aspirin vs LMWH, outcome: Major bleeding

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.

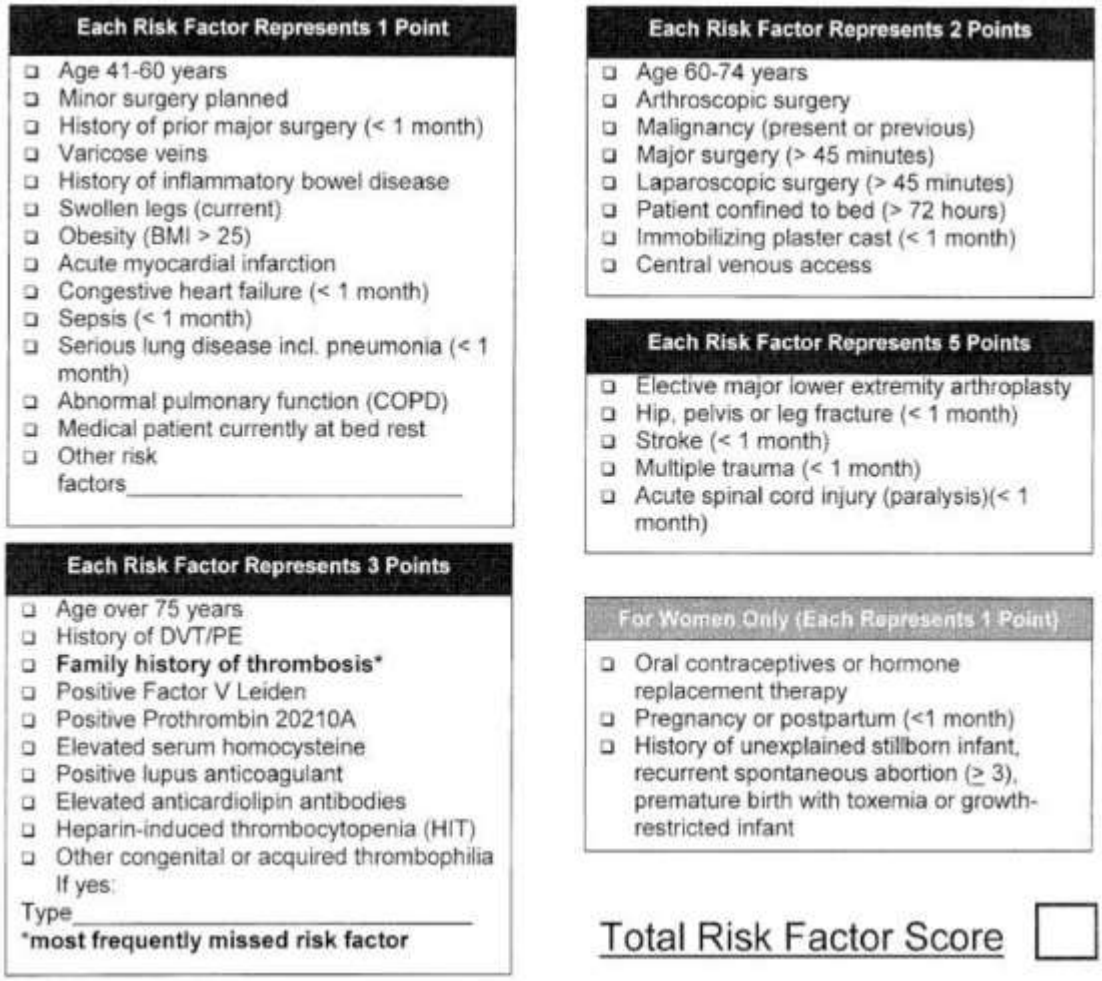
Appendix 4 : Supplementary Tab;e from O'Toole et al (19) (PREVENT CLOT) showing baseline characteristics including risk factors

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.
https://www.ncbi.nlm.nih.gov/pubmed/23547704

References

1. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Archives of internal medicine. 2003;163(14):1711-7.
2. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Archives of internal medicine. 2002;162(11):1245-8.
3. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thrombosis and haemostasis. 2003;90(3):446-55.
4. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. Archives of internal medicine. 1998;158(14):1525-31.
5. Lobastov K, Urbanek T, Stepanov E, Lal B, Caprini J. The thresholds of Caprini score associated with increased risk of venous thromboembolism across different Specialties: a systematic review. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2023 Mar 1;11(2):453.
6. Montinari MR, Minelli S, De Caterina R. The first 3500 years of aspirin history from its roots - A concise summary. Vascular pharmacology. 2019;113:1-8.
7. Gómez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct-acting oral anticoagulants: pharmacology, indications, management, and future perspectives. Eur J Haematol. 2015;95(5):389-404.
8. Agnelli G. Prevention of venous thromboembolism in surgical patients. Circulation. 2004 Dec 14;110(24_suppl_1):IV-4.
9. Wall V, Fleming KI, Tonna JE, Nunez J, Lonardo N, Shipley RW, Nirula R, Pannucci CJ. Anti-factor Xa measurements in acute care surgery patients to examine enoxaparin dose. The American Journal of Surgery. 2018 Aug 1;216(2):222-9.
10. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clinical research ed). 2017;358:j4008.
11. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 205-28.
12. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Completing 'Summary of findings' tables and grading the certainty of the evidence. Cochrane Handbook for Systematic Reviews of Interventions2019. p. 375-402.
13. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Advances. 2019;3(23):3898-944.
14. Jiang Y, Du H, Liu J, Zhou Y. Aspirin combined with mechanical measures to prevent venous thromboembolism after total knee arthroplasty: a randomized controlled trial. Chinese medical journal. 2014;127(12):2201-5.
15. Kulshrestha V, Kumar S. DVT prophylaxis after TKA: routine anticoagulation vs risk screening approach - a randomized study. The Journal of arthroplasty. 2013;28(10):1868-73.
16. Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. The Journal of arthroplasty. 2006;21(6 Suppl 2):139-43.
17. Zou Y, Tian S, Wang Y, Sun K. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2014;25(7):660-4.

18. Haac BE, O'Hara NN, Manson TT, Slobogean GP, Castillo RC, O'Toole RV, et al. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: A patient-centered randomized controlled trial. PloS one. 2020;15(8):e0235628.
19. O'Toole RV, Stein DM, O'Hara NN, Frey KP, Taylor TJ, Scharfstein DO, et al. Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture. The New England journal of medicine. 2023;388(3):203-13.
20. Sidhu VS, Kelly TL, Pratt N, Graves SE, Buchbinder R, Adie S, et al. Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty: The CRISTAL Randomized Trial. Jama. 2022;328(8):719-27.
21. Farey JE, An VVG, Sidhu V, Karunaratne S, Harris IA. Aspirin versus enoxaparin for the initial prevention of venous thromboembolism following elective arthroplasty of the hip or knee: A systematic review and meta-analysis. Orthopaedics & traumatology, surgery & research : OTSR. 2021;107(1):102606.
22. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, Lake E. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021 Dec 1;160(6):e545-608.
23. (Haac BE, O'Hara NN, Mullins CD, et al. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment [published correction appears in BMJ Open. 2017 Dec 22;7(12):e016676corr1]. *BMJ Open*. 2017;7(8):e016676 10.1136/bmjopen-2017-016676)