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 medicines 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, medicines (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 thromboembolism (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)
Medicines, e.g. anti-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 the 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:

- Direct acting oral anticoagulant (DOAC), e.g.: *LoE:Ib*[xxvii]
- Rivaroxaban, oral, 10 mg daily with food while hospitalised.

For patients hospitalised due to medical illnesses and in whom rivaroxaban is contraindicated:

- 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.

High risk of VTE: *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:

- Direct acting oral anticoagulant (DOAC), e.g.
- Rivaroxaban, oral, 10 mg daily with food.
  - Initated 6–10 hours post-surgery for duration of admission or a maximum of 10 days.

Following rivaroxaban, prescribe aspirin:

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

For elective total knee arthroplasty:

Total duration of prophylactic therapy: 14 days.

- Direct acting oral anticoagulant (DOAC), e.g.
- Rivaroxaban, oral, 10 mg daily with food.
  - Initiate anticoagulation 6–10 hours post-surgery for the duration of hospital admission for a minimum of 2 days and a maximum of 7 days.

Following rivaroxaban, prescribe aspirin:

- Aspirin, oral, 150 mg daily.
  - Treat with aspirin for remainder of VTE prophylaxis period, i.e. 14 days in total including days on rivaroxaban. *LoE:Ib*[xxxi]

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

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

OR *LoE:IVb*[xxxii]

- Unfractionated heparin, SC, 5 000 units 12 hourly. *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 daily.	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 (e.g. severe liver disease, peptic ulcer disease, neoplasm at high risk of bleeding, pulmonary cavitation with recent haemoptysis).
» 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 < 15 mL/min; enoxaparin requires renal dose adjustment.
» Coagulopathy.
» Uncontrolled hypertension.
» Concomitant anticoagulant or antiplatelet therapy.

Contraindications to rivaroxaban when used for VTE prophylaxis:

» Do not administer to patients with known rivaroxaban hypersensitivity.

Drug-drug interactions

Some common drug interactions with rivaroxaban are listed below. Evidence on potential drug-drug interactions is still evolving, so consult the latest literature if uncertain of potential drug interactions. The risk of some drug interactions may be altered in patients with renal impairment and careful anticoagulation risk assessment is required.

Medicine groups	Interaction information	Recommendation
Strong inhibitors of both CYP3A4 & P-glycoprotein. ▪ Ketoconazole ▪ Protease Inhibitors, e.g. ritonavir	Increased rivaroxaban concentrations with risk of bleeding.	Contraindicated. Use warfarin with INR monitoring instead.
Moderate inhibitors of CYP3A4. ▪ Fluconazole	Interaction not significant.	May be co-administered with rivaroxaban.
Strong inducers of CYP3A4. Medicines intended for long-term use. ▪ Phenytoin ▪ Carbamazepine	Decreased rivaroxaban concentrations with risk of clotting.	Refer to doctor for switching to safer alternative anti-seizure medicines, e.g. lamotrigine, *(See PHC Section 15.7.2: Epilepsy in Adolescents and Adults).* *Consider warfarin with INR monitoring if a switch to alternative anti-seizure medicine is not possible.*
Strong inducers of CYP3A4. Medicines intended for limited duration. ▪ Rifampicin	Decreased rivaroxaban concentrations with risk of clotting.	Use warfarin with INR monitoring for the duration of anti-TB treatment instead.

Table 2.5: Potential drug-drug interactions with rivaroxaban

2.8.2 VENOUS THROMBO-EMBOLISM – ACUTE TREATMENT

MEDICINE TREATMENT

For proximal deep venous thrombosis and/or pulmonary embolism:

- Direct acting oral anticoagulant (DOAC), e.g.:
- Rivaroxaban, oral, 15 mg twice daily with food for 3 weeks, followed by a maintenance dose of 20 mg once daily for 3 months.
  - For patients with moderate to severe renal impairment (i.e. creatinine clearance 15–50 mL/min) reduce the maintenance dose from 20 mg to 15 mg once daily, if there are risks of bleeding. *LoE:Ib*[xxxiv]

For patients assessed as high risk requiring longer-term anticoagulation, e.g. recurrent VTE, or lifelong anticoagulation treatment:

- Direct acting oral anticoagulant (DOAC), e.g.:

- Rivaroxaban, oral, 15 mg twice daily with food for 3 weeks, followed by a maintenance dose of 20 mg once daily for 6 months or longer, based on individual risk assessment.
    - After 6 months of treatment, consider reducing the rivaroxaban dose to 10 mg once daily, unless the patient remains at high risk of recurrent DVT or PE.
    - For patients with moderate to severe renal impairment (i.e. creatinine clearance 15–50 mL/min) reduce the six-month maintenance dose from 20 mg to 15 mg once daily if the risk of bleeding outweighs the risk for recurrent DVT or PE. No further dose adjustment is required if the patient is maintained on rivaroxaban, 10 mg once daily.

Switching from warfarin to rivaroxaban in patients requiring long-term or lifelong anticoagulation:
Stop warfarin treatment and monitor INR until INR is ≤ 2.5 mmol/L, then initiate treatment with:

- Direct acting oral anticoagulant (DOAC), e.g.:
- Rivaroxaban, oral, 20 mg once daily with food.
    - INR values may be falsely elevated following the initiation of rivaroxaban.

Contraindications to rivaroxaban when used for treatment of VTE
Rivaroxaban should not be administered to patients with: *LoE:IIIb*[xxxv]

» Known rivaroxaban hypersensitivity.
» Rheumatic heart disease-associated atrial fibrillation and mechanical heart valves.
» Triple-positive antiphospholipid syndrome.
Note: Warfarin is the preferred anticoagulant in all forms of antiphospholipid syndrome.

<u>If rivaroxaban is contraindicated:</u>

» Start unfractionated or low molecular weight heparin simultaneously with warfarin.
» After 5 days, heparin may be stopped if an INR within therapeutic range (INR between 2 and 3) has been reached and maintained for at least 24 hours.
» Note: Heparin and warfarin therapy should overlap for at least 5 days.

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 1.5 mg/kg daily, *LoE:I*[xxxvi]
OR
- Enoxaparin, SC, 1 mg/kg 12 hourly. *LoE:I*[xxxvii]

CAUTION – Enoxaparin
In morbid obesity, dosing of LMWH should be individualised in discussion

with a specialist. LoE:III[xxxviii]

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

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 a 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). LoE:IVb[xl]
  - Continue warfarin for 3 months with regular INR monitoring, provided that the precipitating cause 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[xli]
  - 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 thrombocytopenia.

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 thrombo-embolism:

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*[xiii]
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).

†Postpartum 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 postpartum prophylaxis, start 6–12 hours after delivery.

LoE:IIb[xliii]

LoE:IIIb[xliv]

Note:

- Although LMWH related skin reactions are generally rare, they are more common in pregnant women. Monitor injection sites 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).

Acute treatment of VTE or pulmonary embolism:

LoE:IIIb[xlv]

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 1 mg/kg every 12 hours.

LoE:IIIb[xlvi]

- Discontinue treatment at least 24 hours prior to delivery, if the delivery time is predictable.
- Continue treatment for 6 weeks postpartum, and for at least 3 months in total.

- Direct acting oral anticoagulants (DOAC), e.g.:
- Rivaroxaban, in the puerperium:
  - Rivaroxaban may be considered in the puerperium where cost and adherence challenges with injectable LMWH are significant.
  - Counselling on rivaroxaban should highlight the limited data available, while noting that current evidence indicates infant exposure through breast milk is minimal and unlikely to cause harm:
    - LMWH remains the agent of choice due to limited pharmacokinetic and pharmacodynamic data on rivaroxaban use in the puerperium.
    - Less than 2% of the maternal dose of rivaroxaban is excreted into breast milk – a negligible amount, unlikely to confer clinical significance.
    - Continued breastfeeding should be encouraged while monitoring the infant clinically for signs of bleeding (bruising on the skin, blood in urine, vomit, or stools).

- Direct acting oral anticoagulant (DOAC), e.g.: *LoE:IVb*[xlvii]
- Rivaroxaban, oral, 20 mg once daily to complete the treatment duration of 3 months.
  - Transition on day 5 after delivery, when maternal physiology begins to normalize and the risk of secondary postpartum bleeding is reduced.
  - Start at the time that LMWH was scheduled, and omit the LMWH dose.
  - INR monitoring is not needed for rivaroxaban.

LoE:IVb[xlviii]

- Warfarin use in the puerperium
  - Warfarin is safe when breastfeeding.
  - Warfarin use in the puerperium has a high risk of complications (most importantly severe secondary PPH, that may require the administration of blood products) and can take on average 9 additional inpatient days (but can take up to 30 days) to achieve a therapeutic INR in postpartum women.
  - Initiation of warfarin will require continued anticoagulation with LMWH at treatment doses (see above) until the INR is within the therapeutic range: *LoE:IIIb*[xlix]
    - 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).
  - 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.
- Women who were on lifelong anticoagulation with warfarin before pregnancy can also be converted from LMWH to warfarin postpartum when the risk of haemorrhage is reduced, usually 5–7 days after delivery. Unless contraindicated, a DOAC, e.g. rivaroxaban can be used. See Section 2.8.2: Venous Thrombo-Embolism – Acute Treatment.
- All women of reproductive age using warfarin or DOAC should be on appropriate contraception (see 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.

REFERRAL/CONSULTATION DURING PREGNANCY

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

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[xlviii] VTE Rivaroxaban, Oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Benefits and harms of oral rivaroxaban initiated post-delivery in women diagnosed with venous thromboembolism (VTE) during pregnancy and treated during pregnancy with subcutaneous enoxaparin, June 2026. https://www.health.gov.za/nhi-edp-stgs-eml/

[xlix] 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

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN NATIONAL DEPARTMENT OF HEALTH
NEMLC SUMMARY REPORT ON UPDATES MADE TO THE
THE STANDARD TREATMENT GUIDELINES AND ESSENTIAL MEDICINE LIST GUIDANCE PRODUCTS
AHC Chapter 2 Blood And Blood Forming Organs

Document Version Control

Report Version	Date	Detail
V1.0	*30/07/2025*	• *Inclusion of rivaroxaban oral anticoagulant in the puerperium/ postpartum period for Venous Thrombo-Embolism (VTE)* • *Update to Section 2.8 Venous thrombo-embolism*

Summary Tables

Medicine Amendments

Medicine amendment recommendations, with supporting evidence and rationale are listed below. If appropriate can include non-medicine amendments (for example if item has a large impact on how medicine is accessed). Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG). Include updates post initial publication first or mark/highlight appropriately.

STG/SECTION	GUIDANCE PRODUCTS (Tick relevant)				MEDICINE / MANAGEMENT	ADDED / DELETED / AMENDED	TI* CONSIDERATIONS (if applicable)
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML			
Report v1.0: *Inclusion of rivaroxaban oral anticoagulant in the puerperium/ postpartum period for Venous Thrombo-Embolism (VTE)*							
2.8.2 VTE – acute treatment		√			Rivaroxaban, oral for patients assessed as high risk requiring longer term anticoagulation	Added	Yes, refer to table below
2.8.3 VTE during pregnancy and the puerperium		√			Rivaroxaban, oral	Added	Dabigatran, oral (refer to table below)

*Therapeutic Interchange

Report V1.0

AH Blood And Blood Forming Organs Chapter 2

Section 2.8.1 VTE - prophylaxis

STG update: Editorial amendments

Editorial updates to the STG have been made in accordance with the professional information (PI) leaflet for rivaroxaban[1] as well as the updated NEMLC recommendation for use during pregnancy and lactation (see section 2.8.3 below VTE during pregnancy and the puerperium) as follows:

- Administration guidance updated to include administration with food.
- Contraindications now limited to patients with known rivaroxaban hypersensitivity.

Guidance on the management of specific drug-drug interactions has been added as tabulated below:

Drug-drug interactions

Some common drug interactions with rivaroxaban are listed below. Evidence on potential drug-drug interactions is still evolving, so consult the latest literature if uncertain of potential drug interactions. The risk of some drug interactions may be altered in patients with renal impairment and require careful anticoagulation risk assessment.

Medicine groups	Interaction information	Recommendation
Strong inhibitors of both CYP3A4 & P-glycoprotein ▪ Ketoconazole, ▪ Protease Inhibitors e.g. ritonavir	Increased rivaroxaban concentrations with risk of bleeding	Contraindicated Use warfarin with INR monitoring instead.
Moderate inhibitors of CYP3A4 ▪ Fluconazole	Interaction not significant	May be co-administered with rivaroxaban.
Strong inducers of CYP3A4 Medicines intended for long term use ▪ Phenytoin, ▪ Carbamazepine:	Decreased rivaroxaban concentrations with risk of clotting	Refer to doctor for switching to safer alternative anti-seizure medicines e.g. lamotrigine, *(See PHC Section 15.7.2 Epilepsy in Adolescents and Adults).* *Consider warfarin with INR monitoring if a switch to alternative anti-seizure medicine is not possible.*
Strong inducers of CYP3A4 Medicines intended for limited duration ▪ Rifampicin	Decreased rivaroxaban concentrations with risk of clotting	Use warfarin with INR monitoring for the duration of anti-TB treatment instead.

[1] South African Health Products Regulatory Authority. Professional information (PI) leaflet. Rivaroxaban (Xarelto®). Bayer (Pty) Ltd. Text last revised 12 May 2022

Section 2.8.2 VTE – Acute Treatment

Patients assessed as high risk of VTE requiring longer-term anticoagulation, e.g. recurrent VTE or lifelong treatment:

Rivaroxaban, oral: Added

Following the price reduction of rivaroxaban as included in the most recent HP09 contract circular[2], NEMLC has extended the STG indications for rivaroxaban in the management of venous thromboembolism (VTE) to include patients requiring long-term anticoagulation, including patients at risk of recurrent VTE or those requiring lifelong anticoagulation. This is an update to the previous NEMLC recommendation (2020-4 review cycle)[3], where a treatment duration exceeding 6 months was not supported, based on the cost of rivaroxaban at the time.

Updates to the STG are as tabulated below:

For patients assessed as high risk requiring longer term anticoagulation, e.g. recurrent VTE, or lifelong anticoagulation treatment:

- Direct acting oral anticoagulant (DOAC), e.g.:
- Rivaroxaban, oral, 15 mg twice daily with food for 3 weeks, followed by a maintenance dose of 20 mg once daily for 6 months or longer, based on individual risk assessment.
  - After 6 months of treatment, consider reducing the rivaroxaban dose to 10mg once daily, unless patient remains at high risk of recurrent DVT or PE.
  - For patients with moderate to severe renal impairment (i.e. creatinine clearance 15-50- ml/min) reduce the six month maintenance dose from 20 mg to 15 mg once daily, if the risk of bleeding outweighs the risk for recurrent DVT or PE. No further dose adjustment is required if the patient is maintained on rivaroxaban, 10 mg once daily.

Switching from warfarin to rivaroxaban in patients requiring long-term or lifelong anticoagulation:

Stop warfarin treatment and monitor INR until INR is ≤ 2.5mmol/L then initiate treatment with:

- Direct acting oral anticoagulant (DOAC), e.g.:
- Rivaroxaban, oral, 20 mg once daily
  - INR values may be falsely elevated following the initiation of rivaroxaban.

Updates to the list of contraindications for rivaroxaban when used as treatment of VTE are as tabulated below, in line with the professional information leaflet[4]:

Contraindications to rivaroxaban when used for treatment of VTE

Rivaroxaban should not be administered to patients with:

» Known rivaroxaban hypersensitivity.
» Rheumatic heart disease-associated atrial fibrillation and mechanical heart valves.
» Triple positive antiphospholipid syndrome.
Note: Warfarin is the preferred anticoagulant in all forms of antiphospholipid syndrome.

The therapeutic interchange recommendations: Retained

The therapeutic interchange recommendations for the treatment of VTE[5] are retained as tabulated below.

[2] HP09-2026SD: supply and delivery of solid dosage forms to the Department of Health for the period 01 May 2026 to 30 April 2029. (Ref: HP09-2026SD)

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

[4] South African Health Products Regulatory Authority. Professional information (PI) leaflet. Rivaroxaban (Xarelto®). Bayer (Pty) Ltd. Text last revised 12 May 2022

[5] AHCh2_BBFO_NEMLC report_2020-4 review_v1.0_23 September 2024

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)	Dabigatran	150	mg	oral

Section 2.8.3 VTE during pregnancy and the puerperium

Inclusion of rivaroxaban oral anticoagulant in the puerperium/ postpartum period for Venous Thrombo-Embolism (VTE)
Acute treatment of VTE or pulmonary embolism:
Rivaroxaban, oral: Added

NEMLC ratified the review[6] on benefits and harms of oral rivaroxaban initiated post-delivery in women diagnosed with venous thromboembolism (VTE) during pregnancy and who had been treated during pregnancy with subcutaneous enoxaparin and suggested essential medicine list inclusion of rivaroxaban oral anticoagulant in the puerperium/ postpartum period for Venous Thrombo-Embolism (VTE).

Certainty of evidence: Low; Strength of recommendation: Weak

In summary:

- Low Molecular Weight Heparin (LMWH) remains the agent of choice due to limited pharmacokinetic and pharmacodynamic data on rivaroxaban use in the puerperium.
- Rivaroxaban may be considered where cost and adherence challenges with injectable LMWH are significant.
    - Continued breastfeeding should be encouraged with monitoring of the infant clinically for signs of bleeding (bruising on the skin, blood in urine, vomit, or stools).
    - <2% of the maternal dose is excreted into breast milk - a negligible amount unlikely to confer clinical significance[7]

[6] VTE Rivaroxaban, Oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Benefits and harms of oral rivaroxaban initiated post-delivery in women diagnosed with venous thromboembolism (VTE) during pregnancy and treated during pregnancy with subcutaneous enoxaparin, June 2026. https://www.health.gov.za/nhi-edp-stgs-e

[7] Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Rivaroxaban. [Updated 2026 May 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500742/

- Counselling points have been added to the STGs:
    - Explanation to the mother that rivaroxaban does pass into breast milk, but available evidence suggests infant exposure is very low and not expected to cause harm.
    - Advise mother to continue breastfeeding while on rivaroxaban, but to monitor the baby's wellbeing and report any unusual symptoms promptly, while noting that safer alternatives exist if concerns arise.
    - Overall, counselling on rivaroxaban should highlight the limited data available, while noting that current evidence indicates infant exposure through breast milk is minimal and unlikely to cause harm
- Women that were on life-long anticoagulation with warfarin before pregnancy can also be converted from LMWH to warfarin postpartum when the risk of haemorrhage is reduced, usually 5–7 days after delivery. Unless contraindicated a DOAC e.g. rivaroxaban can be used.

Therapeutic interchange recommendations: Added
Therapeutic interchange recommendations for VTE during pregnancy and the puerperium were added in line with the professional information leaflet[8] as tabulated below.

Updates to the Therapeutic Interchange database

Section (Description)	Indication	Therapeutic class	INN	Strength (mg)	Formulation
VTE During Pregnancy And The Puerperium	Acute treatment of VTE or pulmonary embolism	Direct Oral Anticoagulants (DOACs)	Rivaroxaban	20mg	oral
VTE During Pregnancy And The Puerperium	Acute treatment of VTE or pulmonary embolism	Direct Oral Anticoagulants (DOACs)	Dabigatran	300mg (150mg taken twice a day)	oral

The STG was updated as follows:

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 postpartum, and for at least 3 months in total.

- Direct acting oral anticoagulants (DOAC), e.g.:
- Rivaroxaban, in the puerperium:
    - Rivaroxaban may be considered in the puerperium where cost and adherence challenges with injectable LMWH are significant.
    - Counselling on rivaroxaban should highlight the limited data available, while noting that current evidence indicates infant exposure through breast milk is minimal and unlikely to cause harm:
        - LMWH remains the agent of choice due to limited pharmacokinetic and pharmacodynamic data on rivaroxaban use in the puerperium.
        - Less than 2% of the maternal dose of rivaroxaban is excreted into breast milk – a negligible amount, unlikely to confer clinical significance.
        - Continued breastfeeding should be encouraged while monitoring the infant clinically for signs of bleeding (bruising on the skin, blood in urine, vomit, or stools).

- Direct acting oral anticoagulant (DOAC), e.g.:
- Rivaroxaban, oral, 20 mg once daily to complete the treatment duration of 3 months.
    - Transition on day 5 after delivery, when maternal physiology begins to normalize and the risk of secondary postpartum bleeding is reduced.

[8] South African Health Products Regulatory Authority. Professional information (PI) leaflet. Dabigatran etexilate base (as mesylate salt) (Pradaxa®). Boehringer Ingelheim. Approval Date 28 February 2025

- Start at the time that LMWH was scheduled, and omit the LMWH dose.
- INR monitoring is not needed for rivaroxaban.

- Warfarin use in the puerperium
  - Warfarin is safe when breastfeeding.
  - Warfarin use in the puerperium has a high risk of complications (most importantly severe secondary PPH, that may require the administration of blood products) and can take on average 9 additional inpatient days (but can take up to 30 days) to achieve a therapeutic INR in postpartum women.
  - Initiation of warfarin will require continued anticoagulation with LMWH at treatment 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).
    - 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.
  - Women who were on lifelong anticoagulation with warfarin before pregnancy can also be converted from LMWH to warfarin postpartum when the risk of haemorrhage is reduced, usually 5–7 days after delivery. Unless contraindicated, a DOAC, e.g. rivaroxaban can be used. See Section 2.8.2: Venous Thrombo-Embolism – Acute Treatment.
  - All women of reproductive age using warfarin or DOAC should be on appropriate contraception (see 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.

A correction was made to the STG for historical text regarding the use of warfarin in the puerperium:

The following sentence in the STG was revised from *"Initiation of warfarin will require continued anticoagulation with LMWH at prophylactic doses*" to "*Initiation of warfarin will require continued anticoagulation with LMWH at treatment doses"* i.e. the word prophylactic was corrected to treatment.

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South African National Department of Health, National Essential Medicines List Committee

Benefits and harms of oral rivaroxaban initiated post-delivery in women diagnosed with venous thromboembolism (VTE) during pregnancy and treated during pregnancy with subcutaneous enoxaparin[1]

DATE: 14 May 2026

Medicine Class	Direct Oral Anticoagulants (DOACs)	*If applicable* *Please consider therapeutic interchange policy*
Medicine/s name **-INN:** **- South African name (if differs from INN)**	Rivaroxaban	*http://www.whocc.no/atc_ddd_index/*
Medicine/s (ATC5):	B01AF01	*http://www.whocc.no/atc_ddd_index/*
Indication (ICD-10 code):	**O88** Obstetric embolism	*https://www.health.gov.za/icd-10-master-industry-table/*
SAHPRA Approved	Yes	SAHPRA registered health products database *https://medapps.sahpra.org.za:6006/*
Dosage form/s	Tablet	
Route of administration/s	Oral	
Patient population	Women diagnosed with venous thromboembolism (VTE) during pregnancy and treated during pregnancy with subcutaneous enoxaparin	

[1] The review template is a tool utilised to systematically synthesise evidence and aid decision-making by the National Essential Medicines Committee (NEMLC) on amendments to the Standard Treatment Guidelines and Essential Medicines List. The template was revised through collaboration between the South African Medical Research Council, University of Stellenbosch, NEMLC, the Essential Drugs Programme (EDP) and SA GRADE Network and approved for piloting by the NEMLC in February 2025. The template is to be reviewed annually, utilised along with the relevant NEMLC approved policies, guidelines, methodology and processes and naming of review documents must adhere to the naming conventions set by the EDP. Current version updated post tabling at NEMLC meeting held 16th October 2025.

Prevalence and/or incidence of condition	Deep vein thrombosis (DVT) and pulmonary embolism (PE), the main clinical presentations of VTE, occur in 1.0 to 1.1 per 1000 person-years during pregnancy, a rate 10 times higher than in age-matched nonpregnant women.	*Reported in Laouenan et al. Epidemiology of venous thromboembolism during pregnancy and postpartum: results from the French prospective multicenter HEMOrrhage and venous THromboEmbolism in PostPartum study. J Thromb Haemost. 2026 Jan 29:S1538-7836(26)00048-6. doi: 10.1016/j.jtha.2025.12.028. Epub ahead of print. PMID: 41617038.*
Level of Care	Adult Hospital Level	
Prescriber level	Doctor prescribed	

EXECUTIVE SUMMARY

- Deep vein thrombosis (DVT) and pulmonary embolism (PE), the main clinical presentations of venous thromboembolism (VTE), are life-threatening complications of pregnancy.
- Management requires three months of anticoagulant treatment. Patients can be treated with enoxaparin up to six weeks post-partum.
- Given the concerns (with warfarin) and cost (of enoxaparin) of anticoagulant use during the postpartum period, the benefits and harms of oral rivaroxaban initiated post-delivery compared to oral warfarin initiated post-delivery or continued subcutaneous (sc) enoxaparin in women diagnosed with venous thromboembolism (VTE) during pregnancy and treated during pregnancy with subcutaneous enoxaparin was assessed.
- Given the paucity of data, a limited review was conducted on the topic.
- Three guidelines were identified through a search of PubMed and specific prespecified guideline websites relevant to the review question:
  - European Stroke Organization (2017)
  - European Society of Cardiology (Updated in 2025)
  - National Health Service (Updated 6 December 2024)
- A duplicate AGREE assessment was conducted on the three guidelines.
- Summary of quality assessment of guidelines and guideline recommendation.
  - **European Stroke Organization (2017):** AGREE II Score of 56% overall
    - Suggest therapy with subcutaneous LMWH in pregnant and puerperal patients with acute Cerebral Venous Thrombosis (CVT). Certainty of evidence: Low; Strength of recommendation: Weak
  - **European Society of Cardiology (Updated in 2025):** AGREE II Score of 72% overall
    - During lactation, alternative drugs should be preferred to DOACs due to the paucity of data
    - Rivaroxaban may be taken cautiously during lactation.
  - **National Health Service (Updated 6 December 2024) -** AGREE II Score of 26% overall
    - Rivaroxaban can be used breastfeeding woman with monitoring, but this guideline was low quality, according to the AGREE II score and would not be recommended for Adolopment.
- All three guidelines acknowledge the paucity of evidence regarding the use of rivaroxaban in the postpartum period and during breastfeeding. The evidence within the guidelines includes low quality nonrandomised studies, case reports and pharmacokinetic studies with very few participants.

➡ In view of the limited pharmacokinetic and pharmacodynamic data on rivaroxaban use during the puerperium, low-molecular-weight heparin (LMWH) remains the recommended agent in the first 6 weeks postpartum. Nevertheless, given important contextual factors, including the high cost and adherence challenges associated with injectable LMWH, rivaroxaban may be considered in non-breastfeeding women. In breastfeeding women, rivaroxaban could also be considered after appropriate counselling, noting that less than 2% of the maternal dose is excreted into breast milk - a negligible amount unlikely to confer clinical significance. In all cases, switch from LMWH to oral anticoagulants on day 5 after delivery, when the maternal physiology begins to normalize and the risk for secondary post-partum bleeding is smaller.

KEY RECOMMENDATIONS

Type of ERC 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 the option **(conditional)**	We recommend the option **(strong)**
	☐	☐	X	
High level summary of conclusions from Evidence to Decision Framework – See link	In view of the limited pharmacokinetic and pharmacodynamic data on rivaroxaban use during the puerperium, low-molecular-weight heparin (LMWH) remains the recommended agent in the first six weeks postpartum. However, given the high cost and adherence challenges associated with injectable LMWH, rivaroxaban may be considered for use in non-breastfeeding women in the first six weeks postpartum. In breastfeeding women, rivaroxaban can also be considered for use, after appropriate counselling, noting that less than 2% of the maternal dose is excreted into breast milk - a negligible amount unlikely to confer clinical significance. In this case, the mother should be advised to monitor the baby clinically for signs of bleeding (bruising on the skin, blood in urine, vomit, or stools). In all women starting rivaroxaban, switch from LMWH to rivaroxaban on Day 5 after delivery, when the maternal physiology begins to normalize and the risk for secondary post-partum bleeding is smaller.			
NEMLC Ratification	**Date**	**Comments**		
	4 June 2026	• Low-molecular-weight heparin (LMWH) remains the recommended agent in the first six weeks postpartum. • Rivaroxaban may be considered for use in non-breastfeeding women in the first six weeks postpartum. • In breastfeeding women, rivaroxaban can also be considered for use, after appropriate counselling. In this case, the mother should be advised to monitor the baby clinically for signs of bleeding (bruising on the skin, blood in urine, vomit, or stools). • In all women starting rivaroxaban, switch from LMWH to rivaroxaban on Day 5 after delivery, when the maternal physiology begins to normalize and the risk for secondary post-partum bleeding is smaller.		

EML Status	EML[2]	Non-EML – contingent on stated reference price threshold in Rand Value classified as **NEML-PT (Non EML Price Threshold)**			Non-EML	
	X	☐			☐	
Therapeutic Interchange Considerations (if applicable)	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval	If NO, tick box
		Dabigatran	Yes	Oral		X
Trigger for review	Alternative therapeutic agent at a lower price. Update based on new trial results.					

REVIEW TEAM

Review contributors as detailed below:

Name & Affiliation	Declaration of Interests	Defining the PICO	Protocol development	Literature search	Study selection	Data extraction & characteristics of included studies	Quality appraisal	Data analysis	GRADE assessment	Write up and referencing	Clinical Expertise & interpretation	Quality assurance
Dr Natasha Gloeck[1,2]	None to declare	X	X	X	X	X	X	X		X	X	X
Dr Millidhashni Reddy[3]	None to declare	X	X	X	X	X	X	X		X	X	X
Prof Stefan Gebhardt[4]	None to declare	X	X	X	X						X	X

1. Health Systems Research Unit, South African Medical Research Council,
2. South African GRADE Network
3. Pharmaceutical Consultant: Health Technology Assessment and Policy, National Department of Health
4. Stellenbosch University and Tygerberg Hospital

ACKNOWLEDGEMENTS

Broad reproductive working group of the Expert Review Committee: Dr Mantwa Chisale, Dr N Madikizela, Ms M Rapetsoa, Dr T Ruder

University of Cape Town, Medicines Information Centre for pharmacodynamic and pharmacokinetic inputs

[2] An item designated as 'EML' indicates that item is not subject to price threshold set by NEMLC however may be subject to benchmark reference pricing during the contracting process as per the Framework for the Inclusion of Items in National Pharmaceutical Contracts: Therapeutic Classes, Reference Pricing, and Series-Based Specification

The members of the Expert Review Committee (ERC), and National Essential Medicines List Committee. This research was supported by the E2D Collaboration, which brings together the NDoH, the Health Systems Research Unit (HSRU) and Cochrane South Africa at the South African Medical Research Council (SAMRC), and the Centre for Evidence-based Health Care (CEBHC) at Stellenbosch University.

EVIDENCE TO DECISION FRAMEWORK

Question	
What are the benefits and harms of oral rivaroxaban initiated post-delivery compared to oral warfarin initiated post-delivery or continued subcutaneous (sc) enoxaparin in women diagnosed with venous thromboembolism (VTE) during pregnancy and treated during pregnancy with sc enoxaparin?	
Population:	Women diagnosed with venous thromboembolism (VTE) during pregnancy and treated with enoxaparin. Sub-groups: — Provoked* VTE (Three months treatment in total, continued until 6 weeks post-delivery) — Unprovoked^ or clinically complicated VTE (Six months treatment in total, including the first 6 weeks after delivery) *Provoked VTE in pregnancy = VTE that develops due to transient risk factors e.g., physiological changes associated with pregnancy ^Unprovoked VTE in pregnancy = VTE occurring where there are no identified risk factors (transient or persistent)
Intervention:	Oral rivaroxaban
Comparison:	Standard of care or placebo Oral warfarin Sc enoxaparin *(Continued for duration of care)*
Outcomes	**MATERNAL OUTCOMES** — Recurrent venous thromboembolism (VTE) during remaining treatment period — Major bleeding# — Secondary Postpartum haemorrhage** — Clinically relevant nonmajor bleeding (CRNMB)^^ — Maternal mortality## — Maternal ICU admission — Serious adverse events (SAEs) and adverse events (AEs)

	INFANT OUTCOMES — Breastfeeding safety (drug concentration in breastmilk; infant plasma drug concentration) — Major bleeding[#] — Clinically relevant nonmajor bleeding (CRNMB) [^^] — Serious adverse events and adverse events **COST OUTCOMES** [#]Major bleeding = Bleeding that results in death and/or symptomatic bleeding in a critical area (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intrarticular, pericardial or intramuscular with associated compartment syndrome), and/or bleeding that results in a drop in haemoglobin level of 20 g/L (1.24 mmol/L) or more leading to the transfusion of two or more units of whole blood of red cells. [**]Secondary Postpartum haemorrhage = "abnormal or excessive bleeding from the birth canal between 24 hours and 12 weeks postnatally" [^^]CRNMB = a) Vaginal bleeding prompting a face-to-face evaluation, leading to hospitalisation, leading to antithrombotic therapy and/or related to early pregnancy loss b) Any sign or symptoms of haemorrhage including bleeding found by imaging along that prompts a face-to-face evaluation, and/or leads to hospitalisation or increased level of care, and/or requires medical intervention by a healthcare professional [##] Maternal mortality = "the death of a woman whilst pregnant or within 42 days of delivery or termination of pregnancy."
Setting:	**PUBLIC SECTOR SOUTH AFRICA**
Perspective:	**PUBLIC HEALTH/ POPULATION**

ASSESSMENT

Problem Priority (optional) **Why is this medicine being evaluated?**
Deep vein thrombosis (DVT) and pulmonary embolism (PE), the main clinical presentations of venous thromboembolism (VTE), occur in 1.0 to 1.1 per 1000 person-years during pregnancy, a rate 10 times higher than in age-matched nonpregnant women[1]. Management requires at least three months of anticoagulant treatment, but must be continued until 6 weeks post-delivery. Patients can be treated with enoxaparin up to 6 weeks post-partum. Given the concerns with warfarin and enoxaparin use during this important postpartum period, the option of oral rivaroxaban to complete the total three to six months management postpartum was recommended for review

Desirable Effects **How substantial are the desirable anticipated effects (i.e., benefits)?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies (if so, why?) ○ Don't know	We were not able to identify robust data regarding the desirable effects in this specific group. Based on a previous NEMLC review which assessed whether DOACs be used for the treatment of DVT or PE in hospitalized adult patients there is equivalent efficacy; and probably no difference in mortality between DOACS and LMWH in the treatment of venous thromboembolism; (Moderate certainty evidence). DOACS are safer with a lower risk of major bleeding. Rivaroxaban was also cheaper at 3 months of therapy.[2]	There is limited or no high quality data available regarding the desirable effects of rivaroxaban in postpartum woman. Given that this is a vulnerable population new RCT evidence is not anticipated. The decision for a conditional recommendation for use of rivaroxaban is based more on the feasibility, acceptability and equity related to the intervention (see below).
Undesirable Effects **How substantial are the undesirable anticipated effects (i.e., harms and toxicity)?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies (if so, why?) ○ Don't know	We were not able to identify robust data regarding the undesirable effects in this specific group. Based on a previous NEMLC review which assessed whether DOACs be used for the treatment of DVT or PE in hospitalized adult patients on the benefits and harms of DOACs in adults, there is equivalent efficacy; and probably no difference in mortality between DOACS and LMWH in the treatment of venous thromboembolism; (Moderate certainty evidence). DOACS are safer with a lower risk of major bleeding. Rivaroxaban was also cheaper at 3 months of therapy.[2]	There is limited or no high quality data available regarding the undesirable effects of rivaroxaban in postpartum woman. Given that this is a vulnerable population new RCT evidence is not anticipated. The decision for a conditional recommendation for use of rivaroxaban is based more on the feasibility, acceptability and equity related to the intervention (see below).

Certainty of evidence[3] What is the overall certainty of the evidence of effects (across all critical outcomes)?		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence emanates from low quality observational studies. International guidelines have utilised this evidence in their recommendations Summary of quality assessment of identified guidelines and summary of guideline recommendation. • **European Stroke Organization (2017):** AGREE II Score of 56% overall • **European Society of Cardiology (Updated in 2025):** AGREE II Score of 72% overall • **National Health Service (Updated 6 December 2024) -** AGREE II Score of 26% overall Weak recommendation, low certainty evidence	The decision for a conditional recommendation for use of rivaroxaban is based more on the feasibility, acceptability and equity related to the intervention (see below).
Values **Is there important uncertainty in how people with conditions, caregivers, healthcare providers or decision-makers value the main outcomes?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Important uncertainty ○ Possibly important uncertainty ○ Probably no important uncertainty ○ No important uncertainty	The options for treatment include oral treatments (warfarin and rivaroxaban) or an injectable formulation (enoxaparin). International normalized ratio (INR) (required for warfarin therapy) and Factor X monitoring are not required with oral rivaroxaban. Additionally, complex oral dosage adjustments are not required with rivaroxaban, and therefore patients can be initiated on the 20mg rivaroxaban dose immediately. If enoxaparin is continued post-discharge, the inconvenience	The decision for a conditional recommendation for use of rivaroxaban is based more on the feasibility, acceptability and equity related to the intervention (see below).

[3] **CERTAINTY OF EVIDENCE**
High certainty: confident in the evidence / We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: mostly confident, but further research may change the effect / 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: some confidence, further research likely to change the effect / Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: findings indicate uncertain effect / We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect

	of an injection is noted and adherence to injectable anticoagulation is a concern after hospital discharge.	

Balance of effects
Does the balance of effects favour the medicine being considered an essential medicine? Do the desirable effects outweigh the undesirable effects?

Judgement	Research evidence	Additional considerations (by committee)
○ Yes (*Favours the intervention*) ○ Probably Yes (*Probably favours the intervention*) ○ Probably No (*Probably favours the comparison*) ○ No (*Favours the comparison*) ○ *Varies (if so, why?)* ○ Don't know	In view of the limited pharmacokinetic and pharmacodynamic data on rivaroxaban use during the puerperium, low-molecular-weight heparin (LMWH) remains the recommended agent in the first 6 weeks postpartum. Given the high cost and adherence challenges associated with injectable LMWH, rivaroxaban may be considered in non-breastfeeding women. In breastfeeding women, rivaroxaban could also be considered after appropriate counselling, noting that less than 2% of the maternal dose is excreted into breast milk- a negligible amount unlikely to confer clinical significance[5]. When switching from LMWH to rivaroxaban, do this at 5 days after delivery, when the maternal physiology begins to normalize and the risk for secondary post-partum bleeding is smaller.	The committee considered the use of rivaroxaban in a subgroup of patients (non-breast-feeding woman in the puerperium period), as the paucity of good quality data is in breast feeding woman only. The decision for a conditional recommendation for use of rivaroxaban is based more on the feasibility, acceptability and equity related to the intervention (see below).

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations (by committee)
○ Large costs ○ Moderate costs ○ Negligible costs or savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Rivaroxaban is EML at AHL for • Acute Treatment - proximal deep vein thrombosis and/or pulmonary embolism • Venous Thrombo-embolism - Prophylaxis, elective total knee arthroplasty • Venous Thrombo-embolism - Prophylaxis, hospitalised, high risk of VTE	

Pricing as Per MHPL: May 2026

Description As Per Contract HP09-2026SD	Price 15% Vat
Rivaroxaban; 10mg; Tablet; 30 Tablets	R31.09
Rivaroxaban; 15mg; Tablet; 42 Tablets	R39.52
Rivaroxaban; 20mg; Tablet; 30 Tablets	R30.42

Description As Per Contract HP09-2026SD	Price 15% Vat
Warfarin; 5mg; Tablet; 100 Tablets	R30.99

Description As Per Contract HP06-2024SVP	Price 15% Vat
Enoxaparin; 20mg/0.2ml; Syringe, Prefilled; 0.2 ml	R43.99
Enoxaparin; 40mg/0.4ml; Syringe, Prefilled; 0.4 ml	R42.49

Comparison of monthly cost (30 days) and three-monthly

Medicine and assumed daily dose	Price for 30 days	Cost for 3 Months
Warfarin: 5 to 10 mg daily	R9.30 to R18.60	R27.90 to R55.80
Rivaroxaban: 20 mg daily	R30.42	R91.26
Enoxaparin; 40mg/0.4ml every 12 hours	R42.59 x 2 x 30 days = R 2555.40	2555.40 x 3 = R 7666.20

Assumptions:

- Cost for a patient with assumed body weight <100 kg
- 30 days = 1 month (Rivaroxaban pack size = 30 tablets)
- Warfarin dosing would range between 5mg to 10mg per day based on INR
- Price of warfarin tablet = R30.99/100 = 0.31 cents

Equity*
What would be the impact on health equity?

Judgement	Research evidence	Additional considerations (by committee)
○ Reduced ○ Probably reduced	Rivaroxaban does not require specialist initiation and could be prescribed as	

○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	outlined in the Standard Treatment Guidelines for a subgroup. By making this option available in a subgroup of patients we probably increase equitable access for woman in the puerperium period.	
Acceptability* Is the option acceptable to recommend as an essential medicine to key stakeholders?		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies (if so, why?) ○ Don't know	Rivaroxaban is an oral dosage form which does not require special monitoring. Warfarin requires special dosage adjustment based on INR monitoring. Enoxaparin is an injectable agent which might not be preferred and might impact adherence on discharge.	
Feasibility* Is the option feasible to implement?		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies (if so, why?) ○ Don't know	Rivaroxaban is an oral dosage form which does not require special monitoring compared to warfarin which would require INR monitoring and dosage adjustments in relation to the INR levels and enoxaparin which is an injection.	

SUMMARY OF JUDGEMENTS

Indicate the relevant judgements below per domain in **bold**

	Judgement						
Desirable effects	Trivial	Small	Moderate	Large		Varies	**Don't know**
Undesirable effects	Large	Moderate	Small	Trivial		Varies	**Don't know**
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison		Probably favors the intervention	Favors the intervention	Varies	**Don't know**
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION[4]

Monitoring and evaluation

N/A

Research priorities

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	X	

CONCLUSIONS

- In view of the limited pharmacokinetic and pharmacodynamic data on rivaroxaban use during the puerperium, low-molecular-weight heparin (LMWH) remains the recommended agent in the first six weeks postpartum.
- However, given the high cost and adherence challenges associated with injectable LMWH, rivaroxaban may be considered for use in non-breastfeeding women in the first six weeks postpartum.
- In breastfeeding women, rivaroxaban can also be considered for use, after appropriate counselling, noting that less than 2% of the maternal dose is excreted into breast milk - a negligible amount unlikely to confer clinical significance. In this case, the mother should be advised to monitor the baby clinically for signs of bleeding (bruising on the skin, blood in urine, vomit, or stools).
- In all women starting rivaroxaban, switch from LMWH to rivaroxaban on Day 5 after delivery, when the maternal physiology begins to normalize and the risk for secondary post-partum bleeding is smaller.

Recommendation

In view of the limited pharmacokinetic and pharmacodynamic data on rivaroxaban use during the puerperium, low-molecular-weight heparin (LMWH) remains the recommended agent in the first six weeks postpartum.

However, given the high cost and adherence challenges associated with injectable LMWH, rivaroxaban may be considered for use in non-breastfeeding women in the first six weeks postpartum.

In breastfeeding women, rivaroxaban can also be considered for use, after appropriate counselling, noting that less than 2% of the maternal dose is excreted into breast milk - a negligible amount unlikely to confer clinical significance. In this case, the mother should be advised to monitor the baby clinically for signs of bleeding (bruising on the skin, blood in urine, vomit, or stools).

- Review results when new trials are published

[4] **STRENGTH OF THE RECOMMENDATION:**
Strong recommendation
Strong recommendations are those recommendations for which the guideline development group is confident that the desirable consequences of implementing the recommendation outweigh the undesirable consequences. Strong recommendations can be adopted as practice (most patients should receive the recommended medicine) or policy (adapted as policy) in most situations. For patients, most people would want the recommended medicine and only a small proportion would not.
Conditional recommendation
The guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are very small. Therefore, discussion (or substantial debate) may be required before a conditional recommendation can be adopted as practice or policy. For patients, the majority if people would want the recommended medicine, but many would not.

In all women starting rivaroxaban, switch from LMWH to rivaroxaban on Day 5 after delivery, when the maternal physiology begins to normalize and the risk for secondary post-partum bleeding is smaller.

Justification

Cost of LMWH and choice of dosage form to encourage adherence.

Restrictions

All patients to be counselled on the risks and benefits of treatment options.

Implementation considerations

Patient counselling in mothers, where rivaroxaban is indicated, in the puerperium period.

Table of contents

REPORT

BACKGROUND

Deep vein thrombosis (DVT) and pulmonary embolism (PE), the main clinical presentations of VTE, occur in 1.0 to 1.1 per 1000 person-years during pregnancy [1], a rate 10 times higher than in age-matched nonpregnant women[3]. Management requires 3 months of anticoagulant treatment. Patients can be treated with enoxaparin up to 6 weeks post-partum.

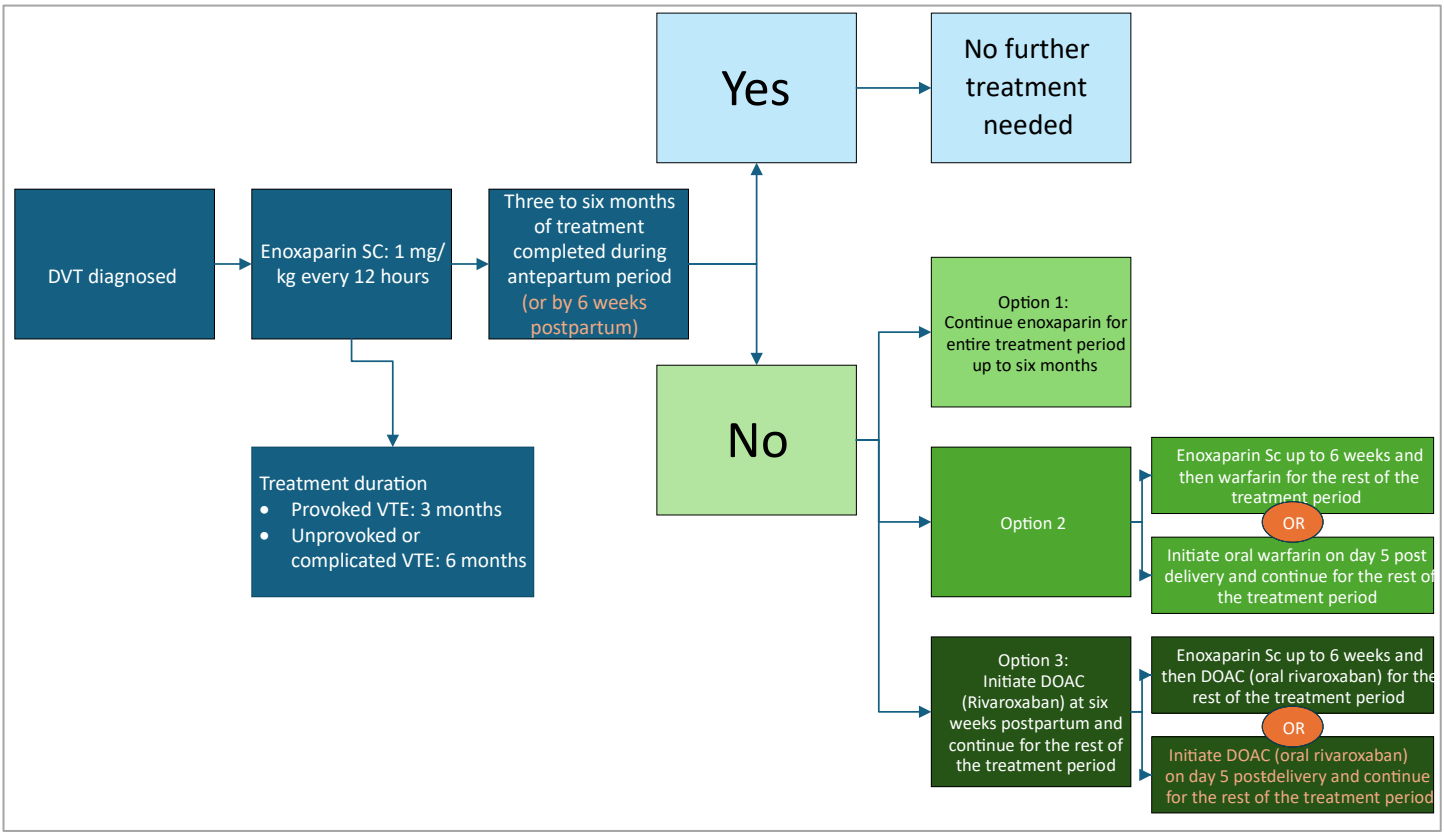

Figure 1 Clinical pathway for the treatment of acute VTE during pregnancy and into the puerperium

Current Adult Hospital Level (AHL)[4] recommendations for **VTE during pregnancy and the puerperium** include

<u>Prophylactic treatment</u>

- 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.

<u>Acute treatment of VTE or pulmonary embolism:</u>

- 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.

However, some women will not have completed the required three to six months of treatment at six weeks post-partum. The options for continued treatment post-delivery are either to continue the patient on enoxaparin (this may not be cost effective) or to prescribe oral warfarin, which presents challenges including longer hospital stays, and regular monitoring needs as outpatients, including blood tests and medication adjustments.

Oral rivaroxaban has been reported to have less maternal side effects, but there are concerns regarding its safety for use during the puerperium and in breastfeeding. Some evidence indicates that less than 2% (negligible amount) of the drug is passed into the breast milk[5]. Oral rivaroxaban is also used for anticoagulation in babies and younger children. International normalized ratio (INR) required for warfarin therapy and Factor X monitoring for enoxaparin are not required with oral rivaroxaban. Additionally, complex dosage adjustments are not required, and therefore patients can be started on the 20mg rivaroxaban dose immediately.

Adherence to injectable anticoagulation is a concern after hospital discharge. Adherence to an oral anticoagulant is more likely to be successful.

Given the concerns with warfarin and enoxaparin use during this important postpartum period, the option of oral rivaroxaban to complete the total three to six months management postpartum was recommended for review.

Table 1: PURPOSE/OBJECTIVE i.e., PICO question:

Population Subgroups	Women diagnosed with venous thromboembolism (VTE) during pregnancy and treated with enoxaparin. Sub-groups: — Provoked* VTE (Three months treatment in total, continued until 6 weeks post delivery) — Unprovoked^ or clinically complicated VTE (Six months treatment in total, including the first 6 weeks after delivery) *Provoked VTE in pregnancy = VTE that develops due to transient risk factors e.g., physiological changes associated with pregnancy ^Unprovoked VTE in pregnancy VTE occurring where there are no identified risk factors (transient or persistent)
Intervention(s)	Oral rivaroxaban
Comparator(s)	Standard of care or placebo Oral warfarin - *Initiated at day 5 post delivery during the puerperium period*

	Sc enoxaparin *Continued for duration of care*
Outcome(s)	**MATERNAL OUTCOMES** — Recurrent venous thromboembolism (VTE) during remaining treatment period — Major bleeding[#] — Secondary Postpartum haemorrhage[**] — Clinically relevant nonmajor bleeding (CRNMB)[^^] — Maternal mortality[##] — Maternal ICU admission — Serious adverse events (SAEs) and adverse events (AEs) **INFANT OUTCOMES** — Breastfeeding safety (drug concentration in breastmilk; infant plasma drug concentration) — Major bleeding[#] — Clinically relevant nonmajor bleeding (CRNMB) [^^] — Serious adverse events and adverse events **COST OUTCOMES** [#]Major bleeding = Bleeding that results in death and/or symptomatic bleeding in a critical area (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intrarticular, pericardial or intramuscular with associated compartment syndrome), and/or bleeding that results in a drop in haemoglobin level of 20 g/L (1.24 mmol/L) or more leading to the transfusion of two or more units of whole blood of red cells. [**]Secondary Postpartum haemorrhage = "abnormal or excessive bleeding from the birth canal between 24 hours and 12 weeks postnatally" [^^]CRNMB = c) Vaginal bleeding prompting a face-to-face evaluation, leading to hospitalisation, leading to antithrombotic therapy and/or related to early pregnancy loss d) Any sign or symptoms of haemorrhage including bleeding found by imaging along that prompts a face-to-face evaluation, and/or leads to hospitalisation or increased level of care, and/or requires medical intervention by a healthcare professional • [##] Maternal mortality = "the death of a woman whilst pregnant or within 42 days of delivery or termination of pregnancy."
Study types	Clinical practice guidelines (CPGs), Systematic Reviews of Randomised Controlled Trials (RCTs) or other, RCTs

METHODS

1. Data Sources

We searched for relevant clinical practice guidelines (CPGs) through PubMed, the American Cardiology Society and the UK

2. Search Strategy

We did a scoping search of PubMed to get an idea of the existing knowledge base and evidence available to answer this question. for existing evidence synthesis, or primary studies as appropriate. We also search for ongoing studies in trial registries.

3. Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis

Relevant clinical practice guidelines were identified by one reviewer and checked by a second reviewer. Guidelines were screened using a tool that matched the guideline PICO with our PICO and guidelines included or excluded accordingly. Relevant recommendations were

extracted from the included guidelines by one reviewer (NG) and checked by a second reviewer (MR). Any disagreements were resolved through discussion.

4. **Assessment of methodological quality**
We used the AGREE II tool[6] to assess clinical practice guidelines in duplicate.

5. **Assessment of methodological quality**
We used the AGREE II tool[7] to assess clinical practice guidelines.

RESULTS

In March 2026, the Expert Review Committee of the National Essential Medicines List Committee advised the broad reproductive working group review team to conduct a scoping of the literature to determine if a full review of the available data was required or a limited evidence review would suffice.

An initial scoping review on the topic in PubMed resulted in:

- 0 Systematic reviews,
- 3 relevant guidelines,
- 1 randomised control trial,
- 11 non-randomised studies (including 2 prospective cohort studies,
- 1 retrospective cohort study,
- 1 non-randomised open label trial and
- 7 cases studies and a pharmacokinetic analysis.

Refer to Appendix 1: Summary of literature identified through the scoping review for a summary of results.

We identified three guidelines during the initial PubMed search that were relevant to the review question from the European Stroke Organization[8], European Society of Cardiology[9] and National Health Service[10] through searching guideline databases/. Figure 2 summarises the literature search and the number and type of studies identified.

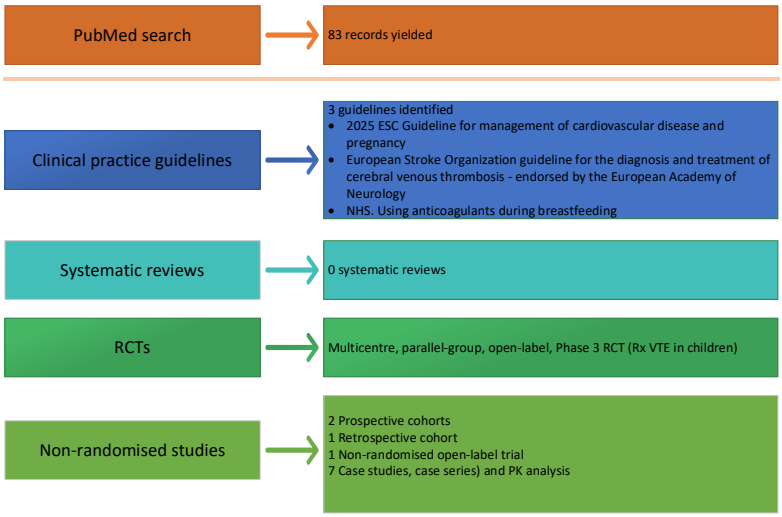

*Figure 2: Summary of literature search**

***Databases, type and number of studies**

The nonrandomised control trials were assessed as low quality and therefore the ERC took a decision to provide a summary of the three available guidelines.

Description of included studies (clinical practice guidelines, systematic reviews and RCTs) and critical appraisal

Table 1 reports a summary of the guideline recommendations; Appendix 2 provides the full AGREE II scoring for the guidelines.

1.1. Clinical Practice Guidelines

We included three clinical practice guidelines.

- The first guideline by the European Stroke Organization[11] was published in 2017 aimed to update the previous European Federation of Neurological Societies guidelines on cerebral venous thrombosis (CVT) diagnosis using a clearer evidence-based methodology providing recommendation for pregnant and puerperal patients with acute CVT.

- The second guideline included guidance from the European Society of Cardiology[12] (published in 2025) as an update to the 2018 ESC Guidelines on cardiovascular disease during pregnancy, postpartum and lactation.

- The third guidance were extracted from the NHS[13] recommendations (Published 2 November 2021 · Last updated 6 December 2024) during breastfeeding.

European Stroke Organization:

The European Stroke Organization reviewed for patients with cerebral venous thrombosis (CVT), does treatment with direct oral anticoagulants improve clinical outcome, reduce major haemorrhagic complications and reduce thrombotic recurrences compared with conventional anticoagulation.
(heparin and vitamin K antagonists). Evidence emanated from two case series on the use of direct oral anticoagulants (rivaroxaban and dabigatran) in patients with CVT. All patients treated received heparin in the acute phase. No major haemorrhagic complications or thrombotic recurrences were reported. The quality of evidence was judged as very low because all studies were observational with a high risk of bias, therefore direct oral anticoagulants (factor Xa or thrombin inhibitors) for
the treatment of CVT, especially during the acute phase was not recommended.

Certainty of evidence Very low.
Strength of recommendation Weak.

AGREE II Score of 56% overall

European Society of Cardiology:

After delivery, the ESC recommends LMWH or VKAs be given during lactation. due to the paucity of data In pregnant or post-partum women with a diagnosis of VTE without haemodynamic instability, therapeutic-dose LMWH based on early pregnancy body weight is advised (Class I evidence, Level C) In pregnant or post-partum women with a diagnosis of acute high-risk PE, A catheter-based reperfusion strategy or systemic thrombolysis should be considered (Class 11a evidence, Level C) In pregnant or post-partum women with a diagnosis of acute high-risk PE, a catheter-based approach or systemic thrombolysis is advised (Class 11b evidence, Level C).

In summary, during lactation, alternative drugs should be preferred to DOACs. The ESC does advise that rivaroxaban may be taken cautiously during lactation.

AGREE II Score of 72% overall

NHS

Warfarin is the preferred oral anticoagulant to use during breastfeeding due to wider experience and no reported infant side effects. There is less published evidence for direct oral anticoagulants (DOACs). Dabigatran or rivaroxaban can be used if clinically indicated based on passage into breast milk, the amount likely to be absorbed by the infant and the availability of published evidence.

The NHS reported that rivaroxaban has a high oral bioavailability, very low levels are expected in breastmilk due to its other pharmacokinetic properties, so infant exposure should still be minimal. Limited evidence from maternal doses between 15 and 30mg rivaroxaban daily have reported very small amounts in breast milk, (weight-adjusted maternal dose 1.3% to 5%). Blood samples from three new-born breastfed infants, whose mothers were taking rivaroxaban 15mg daily, showed undetectable levels of rivaroxaban. From the limited published evidence, no side effects have been observed in infants after exposure to rivaroxaban through breast milk.

The NHS guidance acknowledged the limited evidence of rivaroxaban breastfeeding. However, recommended rivaroxaban can be used during breastfeeding, although infant monitoring is required. It is recommended to monitor the infant for bruising on the skin, blood in urine, vomit, or stools to pick up any potential issues. It is reiterated that further investigation be conducted before the cause can be attributed to the medicine.

The reviewers confirmed via electronic mail, with the UK Drugs in Lactation Advisory Service (UKDILAS), that the NHS guideline is produced by the *Specialist Pharmacy Service Medicines Advice Service and UK Drugs in Lactation Advisory Service* based at the University Hospitals of Leicester NHS Trust.

AGREE II Score of 26% overall

The recommendations relevant to the current review are summarised below in Table 2, together with the AGREE II assessment per guideline.

Two reviewers (NG, MR) assessed the quality of the three guidelines using the AGREE II tool. See Appendix 2 for both reviewer assessments and scoring per domain. A secondary appraisal of the guidelines for overall timeousness and credibility was also conducted. The top-scoring guidance in this assessment was European Society of Cardiology[9] guidance with an AGREE II Score of 72% overall.

Table 1 Recommendations from included clinical practice guidelines.

Citation	Recommendation	AGREE II (combined)
Ferro JM, et al; European Stroke Organization. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. Eur J Neurol. 2017 Oct;24(10):1203-1213. doi: 10.1111/ene.13381. Epub 2017 Aug 20. PMID: 28833980.	Suggest therapy with subcutaneous LMWH in pregnant and puerperal patients with acute CVT. Certainty of evidence: Low Strength of recommendation: Weak	– Scope and purpose (D1) 75% – Stakeholder involvement (D2) 25% – Rigour of development (D3) 67% – Clarity of presentation (D4) 86% – Applicability (D5) 8% – Editorial independence (D6) 83% **Overall 57%**
De Backer et al; ESC Scientific Document Group. 2025 ESC Guidelines for the management of cardiovascular disease and pregnancy. Eur Heart J. 2025 Nov 14;46(43):4462-4568. doi: 10.1093/eurheartj/ehaf193. Erratum in: Eur Heart J. 2026 Feb 18;47(7):812. doi: 10.1093/eurheartj/ehaf1011. PMID: 40878294.	**During Lactation:** • *"During lactation, alternative drugs should be preferred to DOACs due to the paucity of data."* • *"In lactating women* treated with 15–20 mg/day rivaroxaban, the breastfed infant would receive a low dose, corresponding to 1.3%–5% of the maternal weight-adjusted dosage. Therefore, dabigatran and rivaroxaban may be taken cautiously during lactation. Signs of bleeding should be monitored in neonates of lactating mothers taking dabigatran." **During Pregnancy:** • "DOACs are not recommended during pregnancy." Class III recommendation, **Level C evidence** (5.2.1) **After Delivery:** • "After delivery, therapeutic-dose anticoagulation should be administered for a minimum of 6 weeks, up to an overall duration of 3 months, except for cases in which an indefinite duration of anticoagulation is indicated. LMWH or VKAs may be given during lactation." (11.4) **In pregnant or post-partum women with a diagnosis of VTE without haemodynamic instability:** • Anticoagulation is recommended by using therapeutic-dose LMWH based on early pregnancy body weight." **Class I evidence, Level C** **In pregnant or post-partum women with a diagnosis of acute high-risk PE:** • A catheter-based reperfusion strategy or systemic thrombolysis should be considered" **Class 11a evidence, Level C** **In pregnant or post-partum women with a diagnosis of acute high-risk PE:**	– Scope and purpose (D1) 67% – Stakeholder involvement (D2) 75% – Rigour of development (D3) 69% – Clarity of presentation (D4) 94% – Applicability (D5) 35% – Editorial independence (D6) 92% **Overall, 72%**

Citation	Recommendation	AGREE II (combined)
	A catheter-based approach or systemic thrombolysis." **Class 11b evidence, Level C**	
National Health Service. Using oral anticoagulants during breastfeeding. Published 2 November 2021 · Last updated 6 December 2024. https://www.sps.nhs.uk/articles/using-oral-anticoagulants-during-breastfeeding/	Warfarin is the preferred oral anticoagulant to use during breastfeeding due to wider experience and no reported infant side effects. **Rivaroxaban:** Rivaroxaban can be used during breastfeeding, although infant monitoring is required.	– Scope and purpose (D1) 36% – Stakeholder involvement (D2) 14% – Rigour of development (D3) 2% – Clarity of presentation (D4) 89% – Applicability (D5) 17% – Editorial independence (D6) 0 **Overall 26%**

DOACS = Direct oral anticoagulant
Class I = Evidence and or/general agreement that a given treatment or procedure is beneficial, useful, effective
Class 11a = Weight of evidence /opinion is in favour of usefulness /efficacy
Class 11b =
Level C = evidence comes from observational studies, non-systematic clinical reviews, randomized, controlled trials with serious flaws.

EFFECTIVENESS OF THE INTERVENTION

Table 2: Characteristics of the studies included guidelines reviewed:

3s; Ferro JM, et al; European Stroke Organization. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. Eur J Neurol. 2017 Oct;24(10):1203-1213. doi: 10.1111/ene.13381. Epub 2017 Aug 20. PMID: 28833980.

Study (Type)	Population	Intervention	Comparison	Outcomes and Results
Geisbusch C, Richter D, Herweh C, Ringleb PA, Nagel S. Novel factor xa inhibitor for the treatment of cerebral venous and sinus thrombosis: first experience in 7 patients. Stroke 2014; 45: 2469–2471.				
Mendonca MD, Barbosa R, Cruz-E-Silva V, Calado S, Viana-Baptista M. Oral direct thrombin inhibitor as an alternative in the management of cerebral venous thrombosis: a series of 15 patients. Int J Stroke 2015; 10: 1115–1118. * Retrospective study of clinical, imaging *Does not match review PICO*	Series of 15 cerebral vein thrombosis patients treated with dabigatran.	Dabigatran.	Not applicable	• N=18 were admitted for cerebral vein thrombosis. • Dabigatran started in n=11 • Warfarin started in n=7. • N=4 on warfarin were switched to dabigatran because of adverse effects at 0·5, 1, 3·5, and 4 months. • A total of n=15 were treated with dabigatran with median follow-up time of 19 months. • Excellent outcome was observed in 87% of patients and recanalization in 80%.

DISCUSSION

All three guidelines acknowledge the paucity of evidence regarding the use of rivaroxaban in the postpartum period and during breastfeeding. The evidence within the guidelines includes low quality nonrandomised studies, case reports and pharmacokinetic studies with very few participants. The guideline with the highest AGREE II score by the European Stroke Organisation suggest therapy with subcutaneous LMWH in pregnant and puerperal patients (weak recommendation, low certainty evidence). This was similar to the recommendation by the European society of Cardiology. One guideline by the NHS advised that rivaroxaban can be used breastfeeding woman with monitoring, but this guideline was low quality, according to the AGREE II score and would not be recommended for Adolopment.

CONCLUSION

In view of the limited pharmacokinetic and pharmacodynamic data on rivaroxaban use during the puerperium, low-molecular-weight heparin (LMWH) remains the recommended agent in the first six weeks postpartum.

However, given the high cost and adherence challenges associated with injectable LMWH, rivaroxaban may be considered for use in non-breastfeeding women in the first six weeks postpartum.

In breastfeeding women, rivaroxaban can also be considered for use, after appropriate counselling, noting that less than 2% of the maternal dose is excreted into breast milk - a negligible amount unlikely to confer clinical significance. In this case, the mother should be advised to monitor the baby clinically for signs of bleeding (bruising on the skin, blood in urine, vomit, or stools).

In all women starting rivaroxaban, switch from LMWH to rivaroxaban on Day 5 after delivery, when the maternal physiology begins to normalize and the risk for secondary post-partum bleeding is smaller.

Appendix 1: Summary of literature identified through the scoping review

Citation	Study design	Participants	Interventions	Outcomes	Results
Beyer-Westendorf J, Tittl L, Bistervels I, Middeldorp S, Schaefer C, Paulus W, et al. Safety of direct oral anticoagulant exposure during pregnancy: a retrospective cohort study. Lancet Haematol 2020;7:e884–91. https://doi.org/10.1016/S2352-3026(20)30327-6 **(2025 ESC guideline)**	Retrospective cohort DOAC exposure during pregnancy	614 case reports	Rivaroxaban (n=505) Dabigantran (n=26) Apixaban (n=50) Edoxaban (n=23)	Embryotoxicity	"The available data do not suggest that DOAC exposure in pregnancy carries a high risk of embryopathy. "
Zhao Y, Arya R, Couchman L, Patel JP. Are apixaban and rivaroxaban distributed into human breast milk to clinically relevant concentrations? Blood 2020;136:1783–5. https://doi.org/10.1182/blood.2020006231 Trial "An Open Label, Non-Randomised, Phase IV Clinical Trial to Determine the Transfer of Apixaban and Rivaroxaban in Breast Milk Following Oral Administration" **(2025 ESC guideline)**	Letter to the editor Single-center, non-randomised, open-label trial (EudraCT 2018-003852-19) To investigate if oral apixaban and rivaroxaban transfer into breast milk	N = 4; one withdrawal "Breastfeeding mothers aged ≥18 and are at least 6 weeks postpartum with negative pregnancy test when enter the study and about to stop breastfeeding their infants during the trial period and are able to provide written informed consent; Mothers < 6 weeks postpartum will be eligible if they had already weaned or plan to wean their infants after the study."	Apixaban (1) Rivaroxaban (2)	• Rivaroxaban in plasma and breastmilk at various timepoints from 0 up to 24 hours after oral ingestion • Apixaban in plasma and breastmilk at various timepoints from 0 up to 24 hours after oral ingestion If apixaban/rivaroxaban are detectable in breast milk: PK parameters will include • AUC from zero to last quantifiable concentration; AUC from zero to 24 hours	"This clinical trial found a significant distribution of apixaban into human breastmilk, while rivaroxaban distribution was significantly less. The results suggest that rivaroxaban may hold promise for breastfeeding women and further research from women in the early period after delivery is needed, to confirm this."
Wiesen MH, Blaich C, Müller C, Streichert T, Pfister R, Michels G. The direct factor Xa inhibitor rivaroxaban passes into human breast milk. Chest 2016;150: e1–4.	Case study	N = 1 Peripartum cardiomyopathy	Rivaroxaban	Plasma and breast milk concentrations of rivaroxaban	"Rivaroxaban passes into human breast milk in the early period of lactation. Results must be interpreted with caution as the relative infant dose only estimates the infant's exposure to the drug in milk and does not take the

Citation	Study design	Participants	Interventions	Outcomes	Results
https://doi.org/10.1016/j.chest.2016.01.021 **(2025 ESC guideline)**					bioavailability of rivaroxaban in the infant into consideration." "Thus, based on a single case presented here, no conclusions can be drawn regarding the safety of rivaroxaban in nursing mothers and their breastfed infants."
Muysson M, Marshall K, Datta P, Rewers-Felkins K, Baker T, Hale TW. Rivaroxaban treatment in two breastfeeding mothers: a case series. Breastfeed Med 2020;15: 41–3. https://doi.org/10.1089/bfm.2019.0124 **(2025 ESC guideline)**	Case series	N= 2 Two lactating mothers	Rivaroxaban	Rivaroxaban concentration in milk samples Relative infant dose	"In these two cases, we found the levels of rivaroxaban in milk to be quite low, and the RID to be 5% of the maternal dose. Although the levels detected were low, rivaroxaban does transfer into breast milk. Caution should be exercised until further studies are conducted and report the safety profile of rivaroxaban in breastfeeding infants."
de Moreuil C, Robin S, Tromeur C, Morcel K, Anouilh F, Laouenan E, Couturaud F, Pan-Petesch B, Le Moigne E. Direct oral anticoagulants in the postpartum period: a report of real-life experience in the Hemorrhages and Thromboembolic Venous Disease of the Postpartum cohort study. J Thromb Haemost. 2026 Mar 13:S1538-7836(26)00187-X. doi: 10.1016/j.jtha.2026.03.002. Epub ahead of print. PMID: 41833695.	HEMOTHEPP cohort study (NCT02443610) Multicentre prospective cohort study conducted in six maternity wards in the Brittany Region of France between 1 June 2015 and 31 January 2019. The study aimed to describe the prevalence and risk factors for VTE during pregnancy and postpartum and for postpartum hemorrhage, with a 3-month postpartum follow-up"	Women aged ≥16 years admitted for delivery after 15 weeks gestation and treated with DOAC, VKA or LMWH between delivery and 12 weeks postpartum HEMOTEPP cohort (n=20 238) • Received oral anti-coagulants postpartum (n=45) • Breastfeeding (DOAC initiation n=0; LMWH n=3 at 12 weeks postpartum) • Reasons for DOAC prescription: diagnosed VTE n=18; resumption of long-term anticoagulation n=2; VTE prophylaxis n=3.	• Direct oral anticoagulants (DOAC) (n=23: rivaroxaban n = 15 and apixaban n= 8) • Vitamin K agonists (VKA) (n=23) • Low molecular weight heparin (LMWH) (n=8: enoxaparin only n=1; tirnazepan only n=1; enoxaparin and tirnazepan n=3; enoxaparin and fondaparinux n=1) Both VKA and then DOAC (n=1)		• Delay between delivery and anticoagulant initiation: median (IQR) 14 (7 to 21 days) ○ DOAC: Apixaban 10 (6 to 18) days; mean (SD) 16 (15) days ○ DOAC: Rivaroxaban 31 (10 to 44) days; mean (SD) 30 (23) days ○ VKA: Warfarin 12 (5 to 32) days; mean (SD) 21 (23) days • Duration of anticoagulant treatment: median (IQR) 4 (3 to 7) months ○ DOAC: Apixaban 4 (3 to 7) months; mean (SD) 7 (5) months ○ DOAC: Rivaroxaban 4 (2 to 7) months; mean (SD) 9 (15) months ○ VKA: Warfarin 4 (2 to 7) months; mean (SD) 17 (32) months • Abnormal uterine bleeding (AUB) reported in 10% of women on DOACs at standard dose (in line with rates observed outside of postpartum) • Postpartum hemorrhage (PPH): n (%) 6 (13.3%) ○ DOAC 4 (17.4%) ○ VKA 3 (13.0%) ○ LMWH 0

Citation	Study design	Participants	Interventions	Outcomes	Results

					• Severe PPH: n (%) 4 (8.9%)
					  ○ DOAC 3 (13.0%)
					  ○ VKA 2 (8.7%)
					  ○ LMWH 0
					• Hemorrhagic event under anticoagulation: n (%) 3 (6.7%)
					  ○ DOAC 2 (8.7%) (apixaban 1 rivaroxaban 1)
					  ○ VKA 1 (4.3%) (warfarin 1)
					  ○ LMWH 0
					• VTE recurrence under anticoagulation: n (%) 1 (2.2%)
					  ○ DOAC 0
					  ○ VKA 1 (4.3%)
					  ○ LMWH 1 (12.5%)
					
					*Results for fluindione (VKA) not included

Butler AS, Cole S, Arya R, Patel JP. Considerations of safety for women prescribed apixaban or rivaroxaban who breastfeed-a physiologically based pharmacokinetic analysis. J Thromb Haemost. 2026 Feb;24(2):520-529. doi: 10.1016/j.jtha.2025.09.040. Epub 2025 Oct 27. PMID: 41161415.	PK analysis To utilize established PBPK models of apixaban and rivaroxaban to simulate infant exposure to maternal ingestion.				"Our PBPK work, coupled with published clinical data, suggests that rivaroxaban holds promise for breastfeeding women, if oral unmonitored anticoagulation is required, while apixaban has been shown to have higher infant exposure and may not be suitable in the lactation setting. Important questions around maternal rivaroxaban exposure and efficacy during the immediate postpartum period remain due to perinatal physiological changes and further work, formally testing rivaroxaban in breastfeeding mothers in a clinical trial is warranted to better understand this."
Jerjes-Sánchez C, Rodriguez D, Farjat AE, Kayani G, MacCallum P, Lopes RD, Turpie AGG, Weitz JI, Haas S, Ageno W, Goto S, Goldhaber SZ, Angchaisuksiri P, Nielsen JD, Schellong S, Bounameaux H, Mantovani LG, Prandoni P, Kakkar AK; GARFIELD-VTE investigators. Pregnancy-Associated Venous Thromboembolism: Insights from GARFIELD-VTE. TH Open. 2021 Jan 27;5(1):e24-e34. doi: 10.1055/s-0040-	GARFIELD–VTE (ClinicalTrials.gov identifier: NCT02155491) is an on-going prospective, observational study that enrolled 10,688 VTE patients from 415 sites in 28 countries.	Women with PA-VTE were defined by the investigators as those of 18 to 45 years of age, diagnosed with VTE during any stage of pregnancy or within 6-weeks postpartum. Versus		Al-cause mortality, recurrent VTE episode, bleeding, and arterial events (myocardial infarction/acute coronary syndromes, stroke/transient ischemic accident) over 12-months from VTE diagnosis.	

<table>
<tr><th>Citation</th><th>Study design</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Results</th></tr>
<tr><td>1722611. PMID: 33532693; PMCID: PMC7840428.</td><td></td><td>The control group of women, those with NPA-VTE, were defined as those with 18 to 45 years of age, diagnosed with a VTE who were neither currently pregnant nor in the 6-week puerperium stage post-pregnancy.</td><td></td><td></td><td></td></tr>
<tr><td>Male C, Lensing AWA, Palumbo JS, Kumar R, Nurmeev I, Hege K, et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. Lancet Haematol. 2020 Jan;7(1):e18-e27. doi: 10.1016/S2352-3026(19)30219-4. Epub 2019 Nov 5. PMID: 31699660.</td><td>Multicentre, parallel-group, open-label, Phase 3 RCT

To compare the efficacy and safety of bodyweight-adjusted paediatric rivaroxaban dose regimens with those of standard anticoagulants in children with acute venous thromboembolism who had completed at least 5 days of initial heparinisation.</td><td>Children aged from birth to 17 years with objectively confirmed VTE for which heparin treatment was initiated.

<table><tr><th>Age</th><th>Riva (n)</th><th>SoC (n)</th></tr><tr><td>0 to 23 mo</td><td>37</td><td>17</td></tr><tr><td>2 to 5 yrs</td><td>47</td><td>22</td></tr><tr><td>6 to 11 yrs</td><td>67</td><td>34</td></tr><tr><td>12 to 17 yrs</td><td>184</td><td>92</td></tr><tr><td>Total</td><td>335</td><td>165</td></tr></table>
90% of participants had VTE linked to an underlying disorder.</td><td>Rivaroxaban compared to standard anticoagulants (continued herparin treatment or switched to VKA)

Rivaroxaban: bodyweight-adjusted 20 mg equivalent dose, given once-daily (for bodyweights of ≥30 kg), twice-daily (for bodyweights of 12–<30kg), or thrice-daily (for bodyweights of <12kg)</td><td>Primary
- Symptomatic recurrent VTE
- Composite safety outcome: overt major and clinically relevant non-major bleeding
Secondary outcomes:
- Composite of recurrent VTE and deteriorate on repeat imaging
- Composite of recurrent VTE and major bleeding (net clinical benefit)</td><td>“Clinically relevant bleeding was observed in ten (3%) of the 329 rivaroxaban recipients (all were non-major) and in three (2%) of the 162 standard anticoagulation recipients (two major and one non-major [HR 1·58, 95% CI 0·51 to 6·27]; table 3), an absolute difference in risk of 1·2 percentage points (95% CI −2·8 to 4·0). The major bleeding events presented as an intracranial and pulmonary bleeding. The composite of recurrent venous thromboembolism or major bleeding occurred in four (1%) of 335 children in the rivaroxaban group and seven (4%) of 165 children in the standard anticoagulation group (HR 0·30 [0·08 to 0·93]). The death of a single child in the rivaroxaban group was due to cancer progression”

“In summary, in children with acute venous thromboembolism, treatment with rivaroxaban in bodyweight adjusted 20 mg-equivalent dose regimens resulted in a similar low risk of recurrent venous thromboembolism and improved clot resolution without increased bleeding, as compared with standard anticoagulation.”

Rivaroxaban is used in children, even newborns, a small amount of the drug that crosses into the breastmilk not harmful</td></tr>
</table>

Citation	Study design	Participants	Interventions	Outcomes	Results
Yamashita Y, Hira D, Morita M, Katsube Y, Takakura M, Tomotaki H, et al. Potential treatment option of rivaroxaban for breastfeeding women: A case series. Thromb Res. 2024 May;237:141-144. doi: 10.1016/j.thromres.2024.04.003. Epub 2024 Apr 5. PMID: 38593524.	Case series (PK)	Breastfeeding women (n=2); infants (n=3 (twins))	Rivaroxaban for VTE	Drug concentration in • Maternal plasma • Breastmilk • Neonatal plasma	• Rivaroxaban was detectable in breastmilk samples after a 15 mg oral administration • All plasma rivaroxaban concentrations in the infants 2 h after breastfeeding were below the lower limit of quantification in all infants. • As the high-exposure case scenario, the infant exposure was fixed at a peak breastmilk concentration with the amount of breastfeeding at 150 mL/ kg/day. Even in that scenario, the infant plasma concentration level was below the lower limit of quantification (2.5 ng/mL)
Saito J, Kaneko K, Yakuwa N, Kawasaki H, Yamatani A, Murashima A. Rivaroxaban Concentration in Breast Milk During Breastfeeding: A Case Study. Breastfeed Med. 2019 Dec;14(10):748-751. doi: 10.1089/bfm.2019.0230. Epub 2019 Nov 20. PMID: 31746638. No access (information from abstract)	Case report	N=1 38-year-old female diagnosed with the antiphospholipid syndrome received rivaroxaban after delivery. The infant was partially breastfed until the age of 18 months.	Breast milk rivaroxaban concentrations measured 3 months after delivery by a validated liquid chromatography-tandem mass spectrometry method. Breast milk samples were collected sequentially after 15 mg of oral rivaroxaban	Mean minimum and maximum rivaroxaban concentrations in breast milk Mean daily infant and the mean relative infant dose (RID) via breast milk Health of the infant	The mean minimum and maximum rivaroxaban concentrations in breast milk were 9.73 ng/mL before each dose and 53.9 ng/mL at 6 hours after each dose, respectively. The mean daily infant dose was 0.0034 mg/kg and the mean relative infant dose (RID) via breast milk was 1.79%. The RIDs of rivaroxaban did not exceed 10% of the maternal dose, suggesting that exposure of rivaroxaban via breastfed is seldom clinically relevant for the infant. A paediatric assessment of the infant found no detectable drug-related adverse effects.
Rudd, K.M., Winans, A.R.M. and Panneerselvam, N. (2015), Possible Rivaroxaban Failure during the Postpartum Period. Pharmacotherapy, 35: e164-e168. https://doi.org/10.1002/phar.1662	Case Report	N=1 35-year-old postpartum woman who presented to the emergency department with a diagnosis of a new multiple segmental PE 5 days after starting rivaroxaban therapy for a diagnosis of DVT.	Patient, heparin infusion started for the management of PE, rivaroxaban discontinued. Transitioned to enoxaparin 1 mg/kg (90 mg) subcutaneously every 12 hours the next day, bridged to warfarin, discharged on		Probably first case report of potential failure associated with rivaroxaban therapy in the postpartum period. Possibly due to pharmacokinetic alterations seen in the postpartum period contributing to decreased drug exposure, yielding reduced anticoagulant efficacy.

Citation	Study design	Participants	Interventions	Outcomes	Results
			the overlapping regimen with follow-up by the pharmacist-managed outpatient Anticoagulation Management Service.		
Bond AM, Bartle B, Rudd KM, McFee Winans AR. Possible Rivaroxaban Failure during the Postpartum Period: An Alternative Viewpoint. Pharmacotherapy. 2016 Apr;36(4):e26-7. doi: 10.1002/phar.1736. Epub 2016 Apr 6. PMID: 26952042. Regarding 'failure' when used in the puerperium- there is also an alternative view on the 'treatment failure' Bond et al, were of the opinion that it is highly questionable that the case presented by Rudd et al., 2015 represents rivaroxaban failure.	Commentary on the Rudd et al (2015), case report	1. Anticoagulation decreases the risk of recurrent venous thromboembolism (VTE) in patients with DVT to 6.3/100 patient years. However, this is after the discontinuation of anticoagulant therapy. The risk of recurrent VTE is not static and decreases over time. Recurrent VTE has been shown to occur in 6% of VTE patients within the first 3 months of anticoagulant therapy, with 26% of these events occurring within the first 7 days. PE after starting therapy for DVT is an unlikely outcome but not an unexpected outcome. 2. Computed tomography angiography of the chest, although not indicated at the time of DVT diagnosis, may have shown a PE. It is likely the patient had PE at the time of DVT diagnosis but was asymptomatic. 3. The risk of VTE is increased during pregnancy and the postpartum period. Obesity also increases the risk of VTE. The EINSTEIN-DVT study excluded pregnant or breastfeeding patients, and only 0.3% and 14% of patients were in the postpartum period and > 100 kg, respectively. It is reasonable to assume that this patient was at higher risk of VTE than patients in the EINSTEIN- DVT study and that rivaroxaban may not have been the most appropriate option. 4. Levels of rivaroxaban and anti_factor Xa and international normalized ratio were not reported. Therefore, it is difficult to determine if there was a reduced anticoagulation effect secondary to decreased drug exposure			
Bofang Yi, et al. Mechanistic Prediction of Apixaban and Rivaroxaban Secretion into Human Milk and Infant Systemic Exposure Through an Integrated PBPK Framework. 2026. https://doi.org/10.1016/j.dmd.2026.100271	PK Study EXPERIMENTAL - pharmacokinetic (PBPK) lactation model	N is unclear	Experimentally derived parameters were incorporated into an adult physiologically based pharmacokinetic (PBPK) lactation model, which closely reproduced observed plasma and milk pharmacokinetics across dosing regimens, with simulated milk-to-plasma (M/P) ratios deviating less than 10% from clinical measurements. The		Using maternal milk concentration–time profiles to drive the infant PBPK model, predicted plasma exposures for both anticoagulants were substantially below therapeutic levels. Simulations showed low infant plasma concentrations for both drugs, with rivaroxaban producing relative infant daily dose (RIDD) values below the commonly accepted 10% safety threshold, whereas apixaban exceeded this threshold with high absolute systemic exposure in infants.

Citation	Study design	Participants	Interventions	Outcomes	Results
			simulated maternal breast milk concentration–time profiles were subsequently used to drive a pediatric PBPK model, enabling an estimation of infant exposure with 2-hour feeding intervals.		

Appendix 2: AGREE II Individual reviewer ratings

AGREE II assessment scores																								
European Stroke Organization. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology (2017)																								
Scoring the guidelines																								
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	4	5	4	5	1	1	6	6	5	6	6	5	1	1	6	6	6	2	1	1	1	7	4	4
Appraiser 2	6	7	7	6	1	1	7	7	7	6	7	7	2	1	7	6	6	1	2	2	2	7	6	6
Item Total	10	12	11	11	2	2	13	13	12	12	13	12	3	2	13	12	12	3	3	3	3	14	10	10
Domain Total	33			15			80								37			12				24		201
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**75%**			**25%**			**67%**								**86%**			**8%**				**83%**		**57%**
Overall assessment: The Guideline is recommened for use in this context																								

AGREE II assessment scores																								
European Society of Cardiology Guidelines for the management of cardiovascular disease and pregnancy (2026)																								
Scoring the guidelines																								
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	5	4	5	6	5	7	6	6	6	6	6	6	1	4	7	7	7	1	5	1	3	7	7	5
Appraiser 2	6	5	5	4	5	6	4	4	6	6	6	6	7	2	6	6	7	3	6	1	5	6	6	6
Item Total	11	9	10	10	10	13	10	10	12	12	12	12	8	6	13	13	14	4	11	2	8	13	13	11
Domain Total	30			33			82								40			25				26		236
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**67%**			**75%**			**69%**								**94%**			**35%**				**92%**		**72%**
Overall assessment: The Guideline is recommened for use in this context																								

AGREE II assessment scores																								
NHS - Using oral anticoagulants during breastfeeding (2024)																								
Scoring the guidelines																								
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	2	2	3	2	1	2	1	1	1	1	1	2	1	1	6	6	7	1	1	1	5	1	1	2
Appraiser 2	4	4	4	1	1	4	1	1	1	1	1	2	1	1	6	6	7	1	1	1	5	1	1	2
Item Total	6	6	7	3	2	6	2	2	2	2	2	4	2	2	12	12	14	2	2	2	10	2	2	4
Domain Total	19			11			18								38			16				4		106
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**36%**			**14%**			**2%**								**89%**			**17%**				**0%**		**26%**

Overall assessment: The Guideline is not recommened for use in current format

Using an approach used in Mc Allister *et al*. Advancing guideline quality through country-wide and regional appraisal of CPGs: a scoping review, 22 September 2022, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-1850020/v1]

Guideline	Scope and purpose Domain 1	Stakeholder involvement Domain 2	Rigour of development Domain 3	Clarity of presentation Domain 4	Applicability Domain 5	Editorial independence Domain 6	Overall Assessment Score
ESO	75%	25%	67%	86%	8%	83%	57%
ESC	67%	75%	69%	94%	35%	92%	72%
NHS	36%	14%	2%	89%	17%	0%	26%

Low: < 40%	Moderate: 40% - 59%	High: ≥ 60%

Assessment of Timeliness and Credibility of Guidelines			
Guideline	Timeliness	Credibility	Use of GRADE	Overall Assessment Score
ESO	3	3	2	8
ESC	3	3	2	8
NHS	3	3	1	7

Key to Scoring:

Timeliness (CPG level)

- Guideline is out-of-date and likely to miss important recent evidence 1
- Guideline is recent and unlikely to miss recent important evidence 3

Credibility (CPG level)

- Guideline is not credible (e.g., < 60% overall for Domain 1, 3 and 6) 1
- Guideline is credible but has significant limitations (e.g., > 60% in either D1, D3 or D6) 3
- Guideline is credible (e.g., high overall scores across domains) 5

Use of GRADE (CPG Level)

- Does not use/report GRADE or GRADE EtD 1
- Guidelines uses GRADE 2
- Guidelines reported GRADE EtD tables 3

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[2] DOACS (treatment of VTE): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review. Should DOACs be used for the treatment of DVT or PE in hospitalized adult patients DOACS: Treatment of DVT&PE_Adults_v6.0_30 November 2023_final..

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