health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

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.

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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.

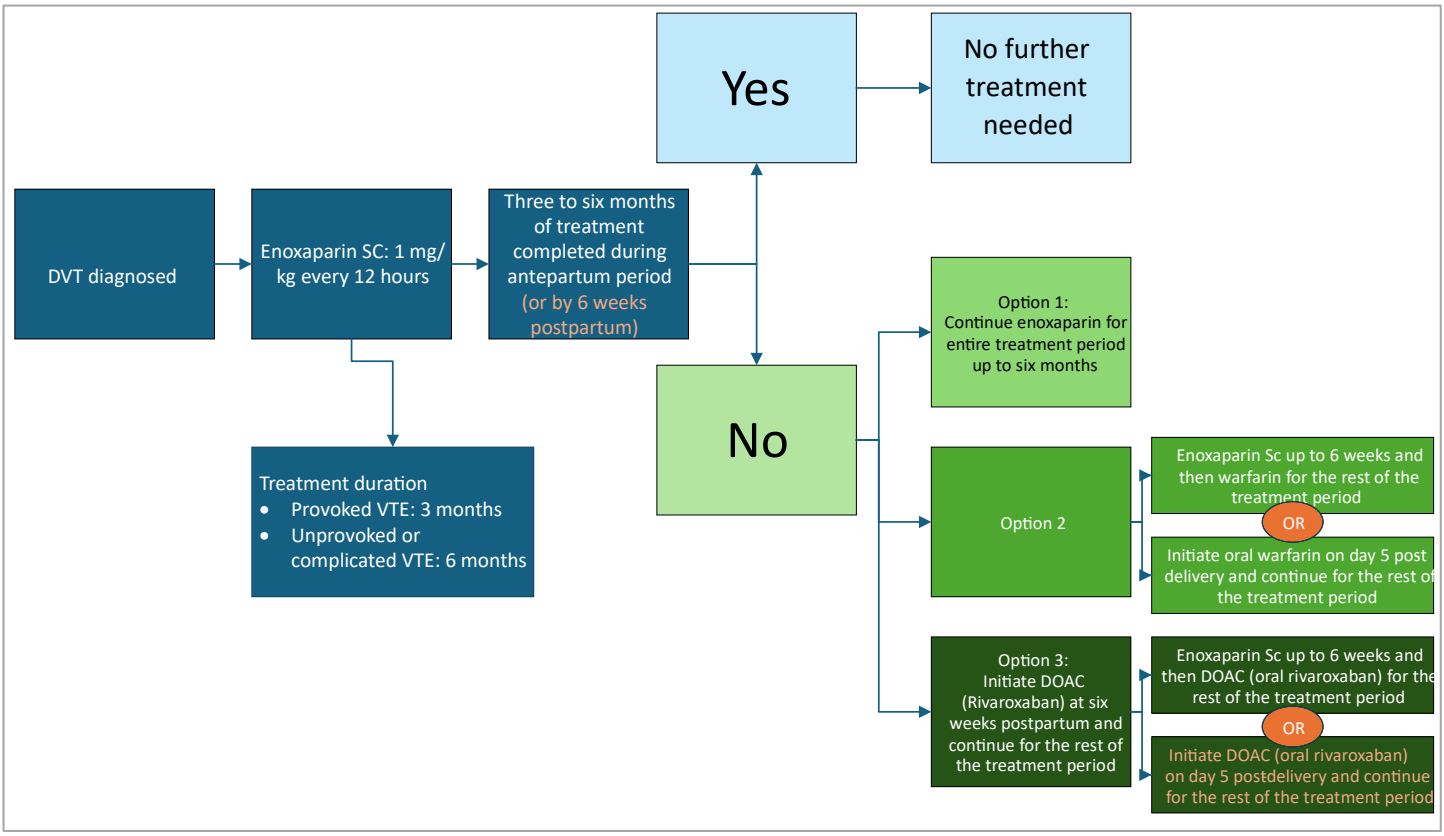

Figure 1 Clinical pathway for the treatment of acute VTE during pregnancy and into the puerperium

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.

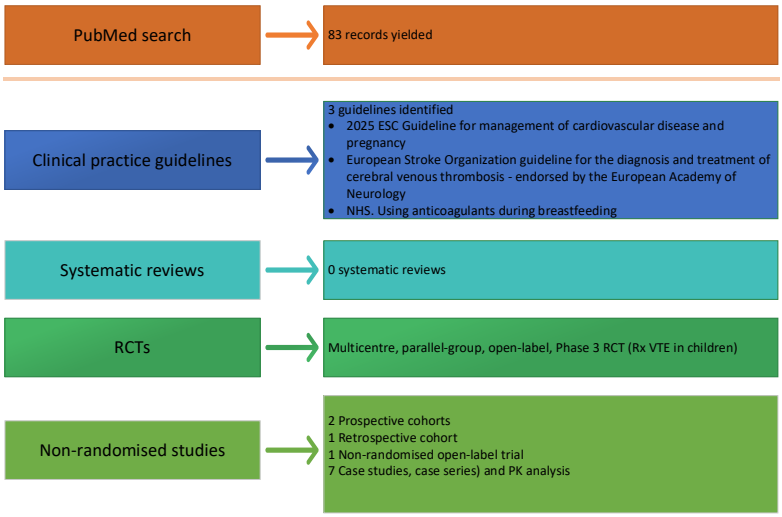

*Figure 2: Summary of literature search**

***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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