Canada's Drug and
Health Technology Agency

CADTH Reimbursement Review

Rivaroxaban

Nonsponsored

Therapeutic area: Venous thromboembolic events

Clinical Review

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Abbreviations

AE	adverse event
CI	confidence interval
CIAC	central independent adjudication committee
CVC	central venous catheter
CVT	cerebral venous thrombosis
CYP3A4	cytochrome P450 isoenzyme 3A4
DOAC	direct oral anticoagulants
HR	hazard ratio
HRQoL	health-related quality of life
INR	international normalized ratio
IQR	interquartile range
LMWH	low molecular weight heparin
OR	odds ratio
PE	pulmonary embolism
P-gp	P-glycoprotein
PTS	post-thrombotic syndrome
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thromboembolic event

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Rivaroxaban granules for oral suspension (1mg/mL when reconstituted) at a body weight adjusted dose
Indication	For the treatment of VTE and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents < 18 years old, after at least 5 days of initial parenteral anticoagulation treatment.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	January 12, 2021
Manufacturer	Bayer Inc.

NOC = Notice of Compliance; VTE = venous thromboembolic events.

Introduction

In recent years, venous thromboembolism (VTE), including venous thrombosis and/or pulmonary embolism (PE), are increasingly diagnosed in the pediatric population due increased exposure to various risk factors such as indwelling central venous catheter (CVC), malignant diseases, obesity, infections, cardiopathy, nephrotic syndrome, surgery, trauma, immobilization, and use of estrogen-containing oral contraceptives.[1-3] The majority of VTE cases are a result of identifiable (inherited or acquired) underlying conditions and risk factors, also known as "provoked" VTE.[1,3] The estimated incidence of VTE in childhood is approximately 0.07 per 10,000 individuals, which is a substantially lower incidence than in the adult population.[4-9] In the absence of timely diagnosis and treatment, VTE can have high mortality rates, as well as acute or chronic complications such as post-thrombotic syndrome (PTS).[1,10]

VTE is diagnosed using clinical examination and diagnostic imaging such as Doppler ultrasonography.[10] Depending on the affected blood vessel, the degree of vessel occlusion, and the affected organ, the main clinical manifestations include acute onset of swelling and pain in the affected limb, growth impairment of the involved limb, or loss of organ function.[10] Treatment goals include resolution of existing thrombus as well as prevention of local extension and embolization of the thrombus, VTE recurrence, and long-term complications.[1] The most commonly used drugs for inpatient and outpatient VTE management in children are LMWHs. Other drugs include UFHs and VKAs. Other anticoagulation agents marketed in Canada, such as fondaparinux and direct thrombin inhibitors, including argatroban and bivalirudin, are reported to be used less frequently in the pediatric population.[1,11-13] These agents require therapeutic drug monitoring with multiple blood draws and dose adjustments, parenteral administration, and may have multiple food and drug interactions.[1,14,15] In contrast, direct oral anticoagulants (DOACs) are available for oral administration, with rivaroxaban also available in a liquid formulation, and do not require regular therapeutic drug monitoring.

Rivaroxaban is a highly selective, direct factor Xa inhibitor with high oral bioavailability.[16] In Canada, rivaroxaban is indicated for the treatment of VTE and prevention of VTE recurrence, after at least 5 days of initial parenteral anticoagulation treatment, in the pediatric population, including term neonates (who at birth had at least 37 weeks of gestation, weigh at least 2.6 kg, and have had at least 10 days of oral feeding), infants, toddlers, children, and adolescents aged younger than 18 years.[16] The drug is available in tablet and suspension (granules for oral suspension) forms. The dose and frequency of administration is determined by body weight. The oral suspension is provided with a 1 mL, 5 mL, or a 10 mL blue syringe (oral dosing syringe) with its adaptor; and the reconstituted suspension is stable for 14 days.[16] Depending on risk factors and whether the VTE is provoked or idiopathic, guidelines suggest a treatment duration of between 6 weeks and an indefinite period with any anticoagulants.[14-16] The product monograph for rivaroxaban recommends a duration of treatment of at least 3 months in all children, except those aged younger than 2 years with catheter-related thrombosis, with an extension up to 12 months when clinically necessary. The recommended duration of treatment for those aged younger than 2 years with catheter-related thrombosis is 1 month, with an extension up to 3 months when clinically necessary. The benefit-risk of extended therapy (for all children) should be individually based and consider the risk for recurrent thrombosis versus the potential risk of bleeding.[16]

The objective of the current report is to perform a systematic review of the beneficial and harmful effects of rivaroxaban granules for oral suspension (1mg/mL when reconstituted) for the treatment of VTE and prevention of VTE recurrence in term neonates, infants, toddlers, children, and adolescents aged younger than 18 years after at least 5 days of initial parenteral anticoagulation treatment.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from the clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

CADTH did not receive any input from patient groups for this review.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Per the clinical experts consulted by CADTH, LMWHs and VKAs are the current therapies used for VTE in pediatric patients. The experts identified that the most important goal in an ideal treatment is to reduce the complications of thrombotic events (i.e., recurrent events, death related to thrombosis, post-thrombotic sequelae, reduction of mobility, impaired quality of life). The experts indicated that treatments with better tolerance, increased adherence, and convenience are needed (i.e., oral therapy may offer an advantage over once or twice-daily subcutaneous injections).

Per the clinical experts consulted by CADTH, rivaroxaban would cause a shift in the current treatment paradigm if funded as it would be used in place of LMWHs or other available anticoagulant therapies, where appropriate. Per the experts, rivaroxaban would also offer an alternative treatment option for patients who

fail other treatments (i.e., have thrombosis progression or recurrence) and for patients for whom bloodwork monitoring tests are difficult to complete.

The clinical experts consulted by CADTH indicated that pediatric patients with longer-term duration of anticoagulation (> 3 months) treatment are more likely to be offered the treatment under review. Patients with skin conditions or for whom subcutaneous injections can be more problematic would also benefit from availability of the product. The patients most likely to exhibit a response to rivaroxaban would be those who can have the medication administered orally and absorbed reliably. Per the experts, additional investigation (e.g., with serum creatinine levels and calculation of glomerular filtration rate) would be required to identify patients who would not be suitable to receive rivaroxaban.

Per the clinical experts consulted by CADTH, diagnosis of VTE requires confirmation via diagnostic imaging (compression ultrasound, CT pulmonary angiogram, ventilation-perfusion scan), which is widely available. Per the experts, pediatric patients with significant renal impairment, mechanical heart valves, triple positive antiphospholipid antibody syndrome, and predisposition to gastrointestinal bleeding or malabsorption syndromes would be least suitable for the treatment under review. Furthermore, clinical experts advised caution in taking rivaroxaban when managing menorrhagia. While this is not an absolute contraindication, it should be cautioned due to the potential increased risk of abnormal uterine bleeding.

Per the clinical experts consulted by CADTH, the assessment of response to treatment is typically aligned with the outcomes used in clinical trials. A clinically meaningful response to treatment includes an acceptably low event rate of recurrence and a low risk of progression or death from VTE. In addition, improving symptoms and quality of life, and reducing the incidence of PTS, chronic thromboembolic pulmonary hypertension, and treatment-related bleeding complications are important. The experts indicated that treatment response should initially be assessed weekly, to confirm symptoms are resolving, as well as at the end of the set duration of therapy (ranging from 6 weeks to 6 months), and treatment would be discontinued in the event of major bleeding, clinically relevant bleeding (i.e., gastrointestinal, urogenital, skin, nose and/or mouth), recurrent VTE, failure of therapy or progression of VTE, and when other treatment becomes necessary (i.e., deterioration of renal function, development of malabsorption, inability to take oral medication).

Per the clinical experts consulted by CADTH, the community setting, hospital outpatient clinics, and specialty clinics are appropriate settings for treatment with rivaroxaban.

Clinician Group Input

CADTH did not receive any input from clinician groups for this review.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for rivaroxaban granules for oral suspension:

- considerations for initiation of therapy

- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability
- care provision issues
- system economic issues.

Industry Input

Input was provided by Bayer Inc., a manufacturer of rivaroxaban at the time of completing this review. The manufacturer agreed with the proposed project scope and highlighted that dabigatran should not be a considered a comparator, citing that dabigatran does not currently have an approved pediatric indication from Health Canada for the treatment of VTE and prevention of VTE recurrence, and that clinical guidelines do not currently recommend its use, so it is not a commonly used medication in this context.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One pivotal trial (EINSTEIN-Jr) met the inclusion criteria for this review. EINSTEIN-Jr (N = 500) was a randomized 2:1, open-label phase III, multicentre, parallel group trial that aimed to evaluate the efficacy and safety of an age- and body weight–adjusted rivaroxaban regimen compared to standard of care (i.e., LMWH, fondaparinux, UFH, and/or VKA) in children with acute VTE.[17] The primary end point was symptomatic recurrent VTE. The mean age of patients was 11 years (standard deviation [SD] = 5.8) in the rivaroxaban group and 11.2 years (SD = 5.8) in the standard of care anticoagulation group. The majority of the patients were white (rivaroxaban = 81.2%; standard of care anticoagulation = 74.7%) and ranged from 12 to 18 years old (rivaroxaban = 54.7%; standard of care anticoagulation = 54.9%).

There were 3 study phases: a main study treatment period of 3 months, an optional extension phase of up to 9 months, and a 30 day follow-up. For children aged younger than 2 years who had catheter-related VTE, the study treatment period was 1 month, the extension phase was up to 2 months, and the follow-up was 30 days.[17,18]

In the EINSTEIN-Jr trial, 1.2% of patients (4 of 335) in the rivaroxaban group and 3% of patients (5 of 165) in the standard of care anticoagulation group had a recurrent VTE (hazard ratio [HR] = 0.40; 95% confidence interval [CI], 0.11 to 1.41). The trial was not powered to demonstrate a difference between the treatment groups.

The incidence of recurrent VTE in the extension phase was supportive of the main study findings. During the extended treatment period, 1 of 38 patients (2.6%) in the rivaroxaban group (during extension period 2) and 2 patients in the standard of care anticoagulation group (1 of 46 patients [2.2%] during extension period 1 and 1 of 19 [5.3%] patients during extension period 2) had a recurrent VTE.

Results of the secondary outcomes were as follows: Complete resolution of thrombus on repeat imaging without recurrent VTE occurred in 128 out of 335 patients (38.2%; 95% CI, 33.0% to 43.5%) in the rivaroxaban group and 43 out of 165 patients (26.1%; 95% CI, 19.8% to 33.0%) in the standard of care anticoagulation group (odds ratio [OR], adjusted for index event = 1.70; 95% CI, 1.11 to 2.58). A composite of recurrent VTE and asymptomatic deterioration occurred in 5 of 335 patients (1.5%; 95% CI, 0.6 to 3.4%) in the rivaroxaban group and in 6 of 165 patients (3.6%; 95% CI, 1.6% to 7.6%) in the standard of care anticoagulation group (HR = 0.41; 95% CI, 0.12 to 1.36). A composite outcome of symptomatic recurrent VTE or major bleeding events (net clinical benefit) occurred in 4 out of 335 patients (1.2%; 95% CI, 0.4% to 3.0%) in the rivaroxaban group and 7 out of 165 patients (risk difference = 4.2%; 95% CI, 2.0% to 8.4%) in the standard of care anticoagulation group (HR = 0.30; 95% CI, 0.08 to 0.93).

Nonfatal PE occurred in 1 patient (0.3%) in the rivaroxaban group and 1 patient (0.6%) in the comparator group. No fatal VTE events occurred during the study period.

Table 2: Summary of Key Results of the Included Study

Outcome	Rivaroxaban (N = 335)	Standard of care anticoagulation (N = 165)
VTE recurrence (symptomatic or asymptomatic)		
Recurrent VTE		
Events, n (%; 95% CI)	4 (1.2; 0.4 to 3.0)	5 (3.0; 1.2 to 6.6)
HR (95% CI)	0.40 (0.11 to 1.41)	
Absolute risk difference, % (95% CI)	−1.8 (−6.0 to 0.6)	
Complete resolution of thrombus on repeat imaging without recurrent VTE		
Events, n (%; 95% CI)	128 (38.2; 33.0 to 43.5)	43 (26.1; 19.8 to 33.0)
Odds ratio, % (95% CI)	1.70[a] (1.11 to 2.58)	
Composite of recurrent VTE and asymptomatic deterioration		
Events, n (%; 95% CI)	5 (1.5; 0.6 to 3.4)	6 (3.6; 1.6 to 7.6)
HR (95% CI)	0.41 (0.12 to 1.36)	
Net clinical benefit[b]		
Events, n (%; 95% CI)	4 (1.2; 0.4 to 3.0)	7 (4.2; 2.0 to 8.4)
HR (95% CI)	0.30 (0.08 to 0.93)	
Absolute risk difference, % (95% CI)	−3.0 (−7.5 to 0.3)	
Nonfatal pulmonary embolism		
Events, n (%)	1 (0.3%)	1 (0.6%)

CI = confidence interval; HR = hazard ratio; VTE = venous thromboembolism.

[a]adjusted for index event.

[b]Composite of symptomatic recurrent VTE or major bleeding events.

Source: Male et al. (2020).[17]

Harms Results

In the EINSTEIN-Jr trial, there were no notable differences between the rivaroxaban and the standard of care anticoagulation groups in the frequency of adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation. There were 2 deaths in the EINSTEIN-Jr trial, both in patients who were in the rivaroxaban group. Ten patients (3%) in the rivaroxaban group and 3 patients (2%) in the standard of care anticoagulation group had a major or clinically relevant nonmajor bleeding event (HR = 1.58; 95% CI, 0.51 to 6.27). The AEs, SAEs, deaths, and notable harms in the extension phase were supportive of the findings from the main study.

Table 3: Summary of Harms From Pivotal and Protocol Selected Studies (Safety Set) (N = 491)

Outcome	EINSTEIN-Jr Rivaroxaban (N = 329)	EINSTEIN-Jr Standard of care anticoagulation (N = 162)
Patients with at least 1 AE, n (%)	274 (83.3)	122 (75.3)
Patients with at least 1 SAE, n (%)	71 (21.6)	32 (19.8)
WDAE (from study treatment), n (%)	5 (1.5)	3 (1.9)
Deaths, n (%)	2 (0.6)	0
Notable harms		
Any confirmed bleeding, n (%)	119 (36.2)	45 (27.8)
Major bleeding, n (%)	0	2 (1.2)
Clinically relevant nonmajor bleeding, n (%)	10 (3.0)	1 (0.6)
Major or clinically relevant nonmajor bleeding		
Events, n (%)	10 (3.0)	3 (1.9)
HR (95% CI)	1.58 (0.51 to 6.27)	

AE = adverse event; CI = confidence interval; HR = hazard ratio; SAEs = severe adverse event; WDAE = withdrawal due to adverse events.

Source: FDA Clinical Review Report.[18]

Critical Appraisal

In the EINSTEIN-Jr trial, risk of bias arising from the randomization process is low. Risk of bias due to deviations from the intended interventions is also likely low, and the 9 deviations were considered to not have impacted the integrity of the study and occurred at a similar rate in both arms.[18] Treatment adherence seemed high in both groups but adherence data were not available for all patients. The risk of bias resulting from missing outcome data is low. The efficacy analysis was conducted in all randomized children (n = 500), and safety analyses included only those who have received at least 1 dose of the study medication (n = 491). The trial was assessed to have some risk of bias in measurement of the outcome. In this open-label study, an independent adjudication committee evaluated the initial diagnosis, all suspected outcomes, and repeat thrombosis imaging tests. However, objective testing was only undertaken for children with suspected outcome events. Due to low incidence of VTE among children, the study was not powered to demonstrate

noninferiority, and the effect estimates for most outcomes are affected by serious imprecision. The study deduced noninferiority by comparing the results from this study with results from clinical trials conducted in the adult population. While extrapolation from clinical trials in the adult population to the pediatric population is common, CADTH is unable to draw definitive conclusions.

Per the clinical expert consulted by CADTH, the study population, intervention, comparators, and concomitant medications were overall reflective of Canadian clinical practice. However, the clinical experts noted that the trial excluded preterm neonates and only had a small percentage of patients with idiopathic (unprovoked) VTE, patients aged younger than 2 years old, and patients with cerebral venous thrombosis (CVT) and cancer, limiting the generalizability of the study findings for these specific populations. Similarly, the clinical experts noted limited information on PE. While they noted that rivaroxaban, and in particular the liquid formulation, has the potential to improve a patient's quality of life due to ease of administration, the EINSTEIN-Jr trial did not assess the health-related quality of life (HRQoL).

Cost Information

As CADTH does not have access to an economic model to address the specified research question, the economic review will include a comparison between the treatment costs of rivaroxaban granules and those of the comparators deemed to be appropriate based on feedback from clinical experts and drug plans.

Based on publicly available list prices, rivaroxaban granules are expected to have a 3-month cost of between $113 and $308 per patient depending on the weight of the patient. A 3-month treatment duration of rivaroxaban granules is more costly than VKAs (incremental cost ranging from $107 to $293 per patient), and may be more or less costly than DOACs (incremental savings of $116 to an incremental cost of $228 per patient) and fondaparinux (incremental cost savings of $92 to an incremental cost of $181 per patient). A 3-month treatment duration of rivaroxaban granules is less costly than LMWHs (incremental cost savings ranging from $49 to $6,554 per patient) and UFHs (incremental cost savings ranging from $171 to $1,342 per patient). As the current standards of care for the treatment of VTE and prevention of VTE recurrence in term neonates, infants, toddlers, children, and adolescents aged younger than 18 years after at least 5 days of initial parenteral anticoagulation treatment are predominantly LMWHs and VKAs, rivaroxaban granules may be more costly or less costly depending on which standard of care is currently being used by patients. These incremental costs or savings are based on publicly available list prices and may not reflect the actual prices paid by public drug plans in Canada.

Rivaroxaban granules may result in fewer drug-related treatment administration and monitoring costs when compared with LMWHs, UFHs, and VKAs, though the magnitude of drug-related cost savings is unknown as it is dependent on the frequency and costs associated with treatment administration and monitoring.

Conclusions

The EINSTEIN-Jr trial was not powered to demonstrate noninferiority between treatment groups. An adequately powered trial is not likely possible due to the low incidence of the condition and challenges in enrolling the pediatric population in clinical trials. However, the results suggest a favourable clinical benefit

(i.e., composite of recurrent VTE and bleeding events) and that the occurrence of recurrent VTE may be similarly rare with rivaroxaban treatment as with standard of care anticoagulation.

The safety profile of rivaroxaban seems similar to standard anticoagulants with no additional serious safety concerns. The exclusion of preterm neonates, the small number of patients with unprovoked VTE, and the small sample of patients aged younger than 2 years old limits the generalization of these findings to these specific patient populations. There is some lack of clarity about the generalization of the findings to children with cancer and those with CVT due to their limited representation in the trial and very low event rate. The availability of oral suspension for an anticoagulant is intended to address the challenges associated with administration and monitoring of standard anticoagulants; however, the trial did not measure improvements in ease of use nor HRQoL.

As a cost-effectiveness analysis was not submitted, the cost-effectiveness of rivaroxaban granules in comparison with the appropriate comparators for the treatment of VTE and prevention of VTE recurrence in children and adolescents aged younger than 18 years could not be determined. As the standards of care most predominantly used currently are LMWHs and VKAs, the reimbursement of rivaroxaban granules may result in increased drug costs ($107 to $293 when compared with VKAs) or decreased drug costs ($49 to $6,554 compared with LMWHs), depending on the comparator treatment and patient characteristics (given that some treatment doses are based on a patient's weight or international normalized ratio [INR] ranges). CADTH consulted clinical experts as part of this review, and their feedback indicated there may be differences in the frequency of treatment-related resource use between rivaroxaban granules and relevant comparators. CADTH noted that rivaroxaban granules may be associated with lower treatment monitoring and administration costs than current standards of care. To adequately consider the treatment-related costs alongside the health care resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of rivaroxaban granules compared with all currently reimbursed treatments would be required.

Introduction

Disease Background

In recent years, more VTE events, including venous thrombosis and/or PE are being diagnosed in the pediatric population.[1-3] This is attributed to medical advances in improving the survival of children with life-threatening or chronic medical conditions, improved diagnostic techniques, as well as greater exposure to risk factors.[2,3] Spontaneous (idiopathic) VTE is not common in children, and the majority of VTE cases are a result of identifiable (inherited or acquired) underlying conditions and risk factors, also known as "provoked" VTE.[1,3] Risk factors such as an indwelling CVC account for more than 90% of neonatal VTE and more than 50% of pediatric VTE.[3] Malignant diseases, obesity, infections, cardiopathy, nephrotic syndrome, surgery, trauma, immobilization, and use of estrogen-containing oral contraceptive pills are other risk factors for pediatric VTE. In particular, obesity and oral contraceptive use have resulted in increased incidence of VTE in adolescents over the past 2 decades.[1,10]

The incidence of VTE in pediatrics remains substantially lower compared to the adult population.[4-9] In Canada, the estimated incidence of VTE in childhood is approximately 0.07 per 10,000 individuals.[4,7] Another study reported the highest occurrence in newborns, ranging from 0.24 (in neonatal intensive care) to 0.51 (neonates outside intensive care) per 10,000 individuals.[3] Timely diagnosis, treatment, and prophylactic strategies are important in pediatric VTE as it is associated with high mortality rates and acute or chronic complications such as PTS.[1,10] The risk of recurrence of VTE has been reported to range between 10% and 15% and the incidence of PTS between 10% and 60% depending on the assessment tools used.[19-22]

Both clinical examination and diagnostic imaging are used to diagnose VTE.[10] Depending on the affected blood vessel(s), the degree of vessel occlusion, and the affected organ, the main clinical manifestations include acute onset of swelling and pain in the affected limb, growth impairment of the involved limb, or impairment or loss of organ function.[10] Depending on the site of thrombosis, VTE can clinically manifest as pain and edema (limb); headache, neck pain, edema of the neck and head (superior vena cava); tenderness and edema in the lower limbs; abdominal pain (inferior vena cava); abdominal pain in the left upper quadrant leading to splenomegaly (splenic vein); abdominal pain leading to splenomegaly (portal vein); flank pain and hematuria (renal vein); pain in the right upper quadrant and hepatomegaly (hepatic vein); abdominal pain (mesenteric vein); chest pain, cough, respiratory failure, and dyspnea (PE); and headache, vomiting, focal neurologic signs, lethargy, and asthenia (cerebral sinuses).[10] Confirmatory diagnostic tests include Doppler and ultrasonography, echocardiography, CT, and MRI; compression Doppler ultrasonography is reported to be the preferred method in children.[10]

Standards of Therapy

The goals of treating VTE are to "prevent local extension and embolization of the thrombus, aid in resolving the existing thrombus, prevent VTE recurrence and minimize long-term complications (for example, post-thrombotic syndrome [PTS])" (p.2).[1] Heparins, including UFHs or LMWHs, and VKAs are the mainstays of treatment of pediatric VTE and prevention of VTE recurrence.[1] Other anticoagulation agents marketed in Canada, such as fondaparinux and direct thrombin inhibitors, including argatroban and bivalirudin, are reported to be used less frequently in the pediatric population.[1,11-13] UFHs, LMWHs, and VKAs require therapeutic drug monitoring with multiple blood draws and dose adjustments, which could be challenging in children and can increase the length of hospital stays.[1,14,15] Other than VKAs, the drugs are administered parenterally, intravenously (UFHs, bivalirudin and argatroban), or subcutaneously (LMWHs and fondaparinux), which are often not preferred by children. While VKAs are an oral medication, they are not available in a liquid oral formulation, which limits their ease of administration and dose titration in young children. Furthermore, VKA such as warfarin have a slow onset of action due to their long half-life as well as multiple food and drug interactions that can result in variations in metabolism.[14] Among the conventional anticoagulants, LMWHs are the most used for inpatient and outpatient VTE management, and preferred over UFHs due to their more predictable response, reduced requirement for laboratory monitoring and dose adjustment, and subcutaneous administration (preferred for infants and young children with poor venous access).[1,10] The limitation associated with the use of conventional anticoagulants in pediatric population could be addressed by DOACs such as rivaroxaban, which is now approved for use in treatment of VTE and prevention of VTE

recurrence in pediatrics.[14,16] Rivaroxaban, a DOAC, is available for oral route of administration, including a liquid formulation, and does not require dose adjustments to achieve a therapeutic level.[14-16]

Initial administration of a parenteral anticoagulant for 5 days to 10 days is suggested for the acute treatment of patients who have been newly diagnosed.[1,10] Following the initial treatment, the 2012 American College of Chest Physicians guidelines and 2018 American Society of Hematology guidelines for the treatment of pediatric VTE suggest the following duration of treatment with any anticoagulant: at least 3 months for secondary (provoked) VTE, and 6 months to 12 months for a first idiopathic (unprovoked) VTE[10,23,24] The 2012 American College of Chest Physicians guidelines also suggest an indefinite period of anticoagulant treatment for recurrent idiopathic (unprovoked) VTE.[10,23] However, based on a clinical study,[25] some experts suggest 6 weeks of anticoagulant therapy, instead of the conventional 3 months, for patients considered low risk. Patients considered low risk include those who have "no prior history of VTE; VTE is not severe or life threatening (example, not causing hemodynamic compromise, not requiring thrombolytic therapy); provoking risk factor is transient (CVC, recent surgery, trauma)and has resolved within six weeks (example, CVC has been removed);) and thrombus resolved or is nonocclusive within six weeks" (p. 3).[1] The available guidelines do not provide information on the use of rivaroxaban in children because they predate its approval in this population.

Drug

Rivaroxaban is a highly selective, direct factor Xa inhibitor with high oral bioavailability.[16] Activation of factor Xa has a key role in the cascade of blood coagulation by converting prothrombin to thrombin.[16] Therefore, inhibition of this pathway prevents thrombin generation and thrombus development.

In Canada, rivaroxaban granules for oral suspension are indicated for the treatment of VTE and prevention of VTE recurrence, after at least 5 days of initial parenteral anticoagulation treatment, in the pediatric population, including term neonates (who at birth had at least 37 weeks of gestation, weigh at least 2.6 kg, and have had at least 10 days of oral feeding), infants, toddlers, children, and adolescents aged younger than 18 years.

The drug is available as tablet and suspension (granules for oral suspension) form, and dose and frequency of administration is determined by body weight. The granules for oral suspension (1mg/mL) are indicated in term neonates, infants, toddlers, children, and adolescents aged younger than 18 years weighing at least 2.6 kg to less than 30 kg. The 15 mg film-coated tablet is indicated in children and adolescents aged younger than 18 years and weighing from 30 kg to 50 kg, and the 20 mg film-coated tablet is indicated in children and adolescents aged younger than 18 years and weighing 50 kg or more.[16] The tablet formulation is outside the scope of this report. The oral suspension is provided with a 1 mL, 5 mL, or 10 mL blue syringe (oral dosing syringe) with its adaptor; and the reconstituted suspension is stable for 14 days.[16]

For most children, the recommended duration of treatment is at least 3 months, with an extension of up to 12 months when clinically necessary.[16] The recommended duration of treatment for those aged younger than 2 years with catheter-related thrombosis is 1 month, with an extension of up to 3 months when clinically necessary.[16] The balance of benefits and risks of extended therapy (for all children) should be evaluated

for each individual patient (i.e., considering the risk for recurrent thrombosis versus the potential risk of bleeding).[16]

Rivaroxaban (granules for oral suspension) have not been previously reviewed by CADTH.

Table 4: Key Characteristics of Rivaroxaban and Relevant Comparators

Comparators	Mechanism of action	Indication[a]	Route of administration	Recommended dose[b]	Serious adverse effects or safety issues
Rivaroxaban	Direct factor Xa inhibitor	Pediatrics: Treatment of VTE and prevention of VTE recurrence (after at least 5 days of initial parenteral anticoagulation treatment) in • term neonates, infants, toddlers, children, and adolescents aged < 18 years (oral suspension) • children and adolescents aged < 18 years and weighing from 30 kg to 50 kg (15 mg oral tablet) • children and adolescents < 18 years and weighing > 50 kg (20 mg oral tablet)	Granules for oral suspension (1mg/mL)	Based on body weight (refer to Table 3)	Contraindications: Clinically significant active bleeding, lesions, or conditions at increased risk of clinically significant bleeding, hepatic disease, concomitant systemic treatment with both strong CYP3A4 inhibitors and P-glycoprotein inhibitors, or concomitant treatment with other anticoagulants Major safety concern is bleeding
Low molecular weight heparin (e.g., enoxaparin)	Inhibits (preferentially) coagulation factors Xa and IIa	Prophylaxis of thromboembolic disorders in patients undergoing orthopedic, colorectal, and high-risk abdominal, gynecological, or urological surgeries are bedridden due to specific CV or respiratory conditions, and prevention of thrombus formation in the extracorporeal circulation during hemodialysis	Subcutaneous injection	Pediatric dose based on clinical experience Treatment of thrombosis: • Preterm neonates: 2 mg/kg SC dose every 12 hours • Term neonates: 1.5 to 1.7 mg/kg SC dose SC every 12 hours • Infants ≥ 2 months, children, and adolescents: 1 mg/kg SC dose every 12 hours[c]	Contraindications: active bleeding or conditions at increased risk of bleeding, history of HIT Major safety concern is bleeding

Comparators	Mechanism of action	Indication[a]	Route of administration	Recommended dose[b]	Serious adverse effects or safety issues
		Pediatric use not authorized by Health Canada. For the treatment of deep vein thrombosis, with or without pulmonary embolism.		Prevention of thrombosis: • Infants < 2 months: 0.75 mg/kg SC dose every 12 hours • Infants ≥ 2 months, children, and adolescents: 0.5 mg/kg SC dose every 12 hours	
Unfractionated heparin	Inactivates (in combination with antithrombin III) activated factor X and inhibits conversion of prothrombin to thrombin; inactivates thrombin and prevents conversion of fibrinogen to fibrin; inhibits activation of fibrin-stabilizing factor	Anticoagulation therapy, prophylaxis and/or treatment of VTE and PE, peripheral arterial embolism, clotting in arterial and heart surgery, and diagnosis and treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation) No adequate and well-controlled studies in pediatric patients	IV injection or infusion; subcutaneous injection	Pediatric dose based on clinical experience Initial dose: 75 to 100 units/kg (IV bolus over 10 minutes) Maintenance dose: Infants: 25 to 30 units/kg per hour Monitoring: Adjust heparin to maintain aPTT of 60 to 85 seconds, assuming this reflects an antifactor Xa level of 0.35 to 0.70 Children > 1 year: 18 to 20 units/kg per hour	Contraindicated in neonates, and infants who were premature or had low birth weight (due to preservative benzyl alcohol), HIT and HITTS Risk of medication error leading to fatal hemorrhages in pediatrics Contraindications: Active bleeding or conditions at increased risk of bleeding Major safety concern is bleeding
Vitamin K antagonists (warfarin)	Inhibits synthesis of vitamin K–dependent clotting factors (factors II, VII, IX and X, and the anticoagulant proteins C and S)	Prophylaxis and/or treatment of VTE and PE No adequate and well-controlled studies in pediatric patients	Oral	Based on INR	Contraindications: Active bleeding or conditions at increased risk of bleeding, history of HIT or HITTS, and pregnancy Major safety concern is bleeding
Other direct oral anticoagulants (dabigatran)	Direct thrombin inhibitor; inhibits free thrombin, fibrin-bound thrombin, and thrombin-induced platelet aggregation	Prevention of VTE in patients who have undergone elective THR or TKR Treatment of VTE (DVT and PE) and prevention of	Oral	Adult dose: 110 mg or 150 mg capsules 1 to 2 times daily depending on initial or maintenance dose and indication	Contraindications: Active bleeding or conditions at increased risk of bleeding, severe renal impairments, concomitant systemic treatment

Comparators	Mechanism of action	Indication[a]	Route of administration	Recommended dose[b]	Serious adverse effects or safety issues
		recurrent DVT and PE Pediatric use not authorized by Health Canada			with P-glycoprotein inhibitors, or other anticoagulants, patients with prosthetic heart valve(s) requiring anticoagulation due to valvular status itself and those who are nursing Major safety concern is bleeding
Fondaparinux	Potentiates ATIII, which selectively inhibits factor Xa	Treatment of acute DVT and PE Prophylaxis of VTE in patients undergoing orthopedic or high-risk abdominal surgery Pediatric use not authorized by Health Canada	Subcutaneous injection	Adult dose prophylaxis following orthopedic or abdominal surgery: 2.5 mg once daily Treatment of DVT and PE: 5 mg (body weight < 50 kg), 7.5 mg (body weight of 50 kg to 100 kg), or 10 mg (body weight > 100 kg), once daily	Contraindications: Active bleeding or conditions at increased risk of bleeding, thrombocytopenia Major safety concern is bleeding

aPTT = activated partial thromboplastin clotting time; ATIII = antithrombin III; CV = cardiovascular; DVT = deep vein thrombosis; HIT = heparin-induced thrombocytopenia; HITTS = heparin-induced thrombocytopenia with thrombosis syndrome; INR = international normalized ratio; PE = pulmonary embolism; SC = subcutaneous; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolic events.

[a]Health Canada–approved indication, and specific to thrombosis only. These drugs are also indicated in other conditions such as atrial fibrillation (e.g., enoxaparin, rivaroxaban). When available, only pediatric indications are specified.

[b]When available, only pediatric dose is specified.

[c]Some clinicians use slightly higher doses of enoxaparin in infants and young children (e.g., for infants ages 3 to 12 months, 1.5 mg/kg SC dose every 12 hours; for children ages 1 to 5 years, 1.2 mg/kg SC dose every 12 hours).

Sources: Apo-Warfarin product monograph,[26] Arixtra product monograph,[27] Inclunox product monograph,[28] Heparin Sodium Injection product monograph,[29] Pradaxa product monograph,[30] Xarelto product monograph,[16] and UpToDate publication.[31]

Stakeholder Perspectives

The information in this section is a summary of input provided by the clinical experts and public drug plans consulted by CADTH for the purpose of this review, and by the manufacturer of rivaroxaban on the project protocol.

Patient Group Input

No patient groups responded to CADTH's call for input.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 3 clinical specialists with expertise in the diagnosis and management of VTE in adult and pediatric patients.

Unmet Needs

Per the clinical experts consulted by CADTH, LMWHs and VKAs are the current therapies used in for VTE in pediatric patients. Current treatments prevent progression and recurrence of thrombotic events, which provides an opportunity for thrombosis resolution and symptom improvement. Thrombosis resolution also reduces the likelihood of some long-term complications of thrombosis (e.g., PTS).

The experts identified that the most important goal in an ideal treatment is to reduce the complications of thrombotic events (i.e., recurrent events, death related to thrombosis, post-thrombotic sequelae, reduction of mobility, impaired quality of life). Additional goals of ideal therapies are to have an acceptable side effect profile (i.e., no clinically relevant increase in bleeding) and to be easy to administer (i.e., daily oral administration is preferable to subcutaneous injections). As identified by the clinical experts, there are several unmet needs with current treatments, and treatments with better tolerance, increased adherence, and convenience are needed (i.e., oral therapy offers an advantage over once or twice-daily subcutaneous injections).

Place in Therapy

Per the clinical experts consulted by CADTH, rivaroxaban would cause a shift in the current treatment paradigm if funded. Rivaroxaban would be used in place of LMWHs or other available anticoagulant therapies. Per the experts, rivaroxaban would offer an alternative treatment option for patients who fail on other treatments (i.e., have thrombosis progression or recurrence) and for patients for whom bloodwork monitoring tests are difficult to complete.

The clinical experts indicated that it would be inappropriate to recommend that patients try other treatments before initiating treatment with rivaroxaban. Most VTE events in children are provoked and do not require long-term anticoagulation. The subset of pediatric patients for whom longer-term anticoagulation is necessary (e.g., patients with cardiac defects or conditions with predisposition to thrombosis or recurrent thrombosis), would benefit from having an option that does not require regular bloodwork monitoring or daily injections.

Patient Population

Per the clinical experts, pediatric patients with longer-term duration of anticoagulation treatment (> 3 months) would be more likely to be offered the treatment under review. Patients with skin conditions or for whom subcutaneous injections can be more problematic would also benefit from the availability of

the product. Patients most likely to exhibit a response to rivaroxaban would be those who can have the medication administered and absorbed reliably. Per the experts, testing (e.g., with serum creatinine levels and calculation of glomerular filtration rate) would be required to identify patients who would not be suitable to receive rivaroxaban.

Per the experts, diagnosis of VTE requires confirmation through diagnostic imaging (compression ultrasound, CT pulmonary angiogram, ventilation-perfusion scan), which is widely available. Misdiagnosis is unlikely in clinical practice given that it would largely be due to failure to recognize symptoms and perform diagnostic imaging, as once diagnostic confirmation test is performed, the diagnosis of VTE is rarely missed. Relative to adults, diagnosis may be missed more commonly in children when thrombosis is not considered as a diagnostic possibility. Patients who are asymptomatic, in whom VTE is incidentally identified (i.e., imaging done for another indication) are generally treated the same as patients with symptoms.

Per the experts, pediatric patients with significant renal impairment, mechanical heart valves, triple positive antiphospholipid antibody syndrome, and predisposition to gastrointestinal bleeding or malabsorption syndromes would be least suitable for the treatment under review. Furthermore, the clinical experts advised caution in managing menorrhagia when taking rivaroxaban due to increased risk of abnormal uterine bleeding.

Assessing Response to Treatment

Per the clinical experts consulted by CADTH, the assessment of response to treatment is typically aligned with outcomes used in clinical trials. Clinical experts also noted that, if clinical symptoms are worsening rather than improving, then repeat diagnostic imaging and comparison of clot burden is used. Per the experts, these clinical parameters used in practice include improvement of pain, improvement of respiratory symptoms, normalization of heart rate, normalization of oxygen saturation, decrease in leg swelling, and erythema.

Per the experts, a clinically meaningful response to treatment includes an acceptably low event rate of recurrence and a low risk of progression or death from VTE. In addition, improving symptoms and quality of life, and reducing the incidence of PTS, chronic thromboembolic pulmonary hypertension, and treatment-related bleeding complications are important.

Per the experts, treatment response should initially be assessed weekly to confirm symptoms are resolving, as well as at the end of the set duration of therapy (ranging from 6 weeks to 6 months).

Discontinuing Treatment

Per the clinical experts consulted by CADTH, treatment would be discontinued in the event of major bleeding, clinically relevant bleeding (e.g., gastrointestinal, urogenital, skin, nose, and/or mouth), recurrent VTE, failure of therapy or progression of VTE, and when other treatment becomes necessary (i.e., deterioration of renal function, development of malabsorption, inability to take oral medication).

Prescribing Conditions

Per the clinical experts consulted by CADTH, the community setting, hospital outpatient clinics, and specialty clinics are appropriate settings for treatment with rivaroxaban.

Clinician Group Input

No clinician groups responded to CADTH's call for input.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 5.

Table 5: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Policy considerations	
Can FMEC comment on rivaroxaban use without prior use of parenteral anticoagulation?	For FMEC consideration
Is it possible that patients may require re-treatment after successfully completing a treatment course?	Per the clinical experts consulted by CADTH for this review, patients may require re-treatment after successfully completing a treatment course. Any patients with presence or recurrence of a risk factor may qualify for re-treatment (e.g., cancer, inflammatory bowel disease flares, rheumatology disorders that flare, nephrotic syndrome).
Is there a clear duration of therapy required by these patients? Would re-treatment, or long-term treatment, ever be necessary in these indications? If yes, in what condition would there be a need for long-term treatment in the pediatric population?	The clinical experts indicated that the duration of therapy would be a standard of 3 months; however, patients may be treated for a shorter (i.e., 6 weeks) or longer duration (> 3 months). Patients with no prior VTE, nonsevere VTE, provoked risk factor resolved, or thrombosis resolved, and with very low risk of provoked DVT may be suited to a shorter treatment duration.
How is treatment response monitored? How is clot resolution assessed? Is there a need for imaging in clinical practice to determine the need for ongoing treatment? If so, would that need exist for all anticoagulants used in this patient population?	The clinical experts stated that the main clinical outcome of interest is to prevent extension, embolization, and recurrence of VTE events in the follow-up. Radiographic resolution is not typically considered as the main clinical outcome, as persistent vein occlusion is frequent, and it does not affect duration of treatment (taken from adult experience).
Who would be the appropriate prescribers of this medication? Pediatricians, pediatric hematologists, other? Will treatment always start in hospital? Will it ever originate while patients are in the community? What is the breakdown of hospital starts compared to community starts?	The clinical experts indicated that anticoagulants may not necessarily be initiated by a pediatric hematologist. Almost all patients who are infants and young children start in hospitals (except for a small number of children who start as outpatients), where they could be initiated in the emergency department at community hospitals, for example. Up to a third (20% to 30%) of older children would be starting in the hospital, while some may be started in community settings (e.g., DVT caused by use of oral contraceptives).
Is there potential for rivaroxaban to be used In conditions beyond VTE treatment or prevention of VTE recurrence?	The clinical experts provided 1 example of off-label use of rivaroxaban — cardiologists can possibly use it to facilitate the Fontan procedure (mixed opinion).

Drug program implementation questions	Clinical expert response
Is there an opportunity for drug wastage considering the different size syringes and 14-day stability of reconstituted suspension?	The clinical experts outlined that the younger the patients are, the smaller the dose they would require, therefore wastage would be expected.
Are reversal agents studied and/or indicated in children? How are bleeding events reversed in pediatrics?	The experts indicated that, at the time, no reversal agents were available for use in Canada, although they were available in the US. However, since then, andexanet alfa has been approved in Canada and is pending funding review at CADTH. The experts clarified that the drug would be removed by dialysis and supportive products.
System and economic issues	
How many patients would be anticipated to require rivaroxaban? Are most patients in this population group going to be candidates for rivaroxaban? Which treatment alternatives' (products) market share is likely to be replaced due to use of rivaroxaban for this population?	The experts noted that approximately 50% of patients would be anticipated to require rivaroxaban as rivaroxaban would be seen as an alternative for LMWH and not every patient would be a candidate (e.g., significant renal impairment).
Is posttreatment imaging a routine associated cost in this treatment population? Does it apply regardless of which anticoagulation product is used?	The clinical experts noted that posttreatment imaging is independent of the anticoagulation product.
Would the availability of rivaroxaban granules for suspension help to facilitate discharge from hospital or other care centres sooner?	The clinical experts noted that the availability of rivaroxaban granules for suspension has the potential help to facilitate discharge from hospital to other care centres sooner, but by only by a short amount of time.

DVT = deep vein thrombosis; FMEC = CADTH Formulary Management Expert Committee; LMWH = low molecular weight heparin; VTE = venous thromboembolic events.

Industry Input

Industry input was submitted by Bayer Inc., the manufacturer of rivaroxaban granules for oral suspension in Canada at the time of this review.

The manufacturer agreed that the project scope, proposed population, and outcomes posted on the CADTH website accurately reflect the treatment landscape for VTE and prevention of VTE recurrence in term neonates, infants, toddlers, children, and adolescents aged younger than 18 years after at least 5 days of initial parenteral anticoagulation treatment. The manufacturer also noted that rivaroxaban is the first anticoagulant to be approved by Health Canada for use in the pediatric population with VTE. The approval is based on findings from the EINSTEIN-Jr phase III study,[17] which, according to the manufacturer, is the first completed trial of a NOAC in children, and at publication, the largest trial of anticoagulant treatment performed in children.

With regards to comparators, the manufacturer noted that LMWHs (dalteparin, enoxaparin, tinzaparin), UFHs, and warfarin were appropriate. However, the manufacturer noted that dabigatran does not have a Health Canada–approved indication for children, is not recommended by clinical practice guidelines, or commonly used in the Canadian treatment landscape for the treatment of VTE and prevention of VTE recurrence in the pediatric population.[23,30]

Clinical Evidence

The clinical evidence included in the review of rivaroxaban is presented in 3 sections. The first section, the Systematic Review, includes studies that were selected according to an a priori protocol (Table 6). The second section includes indirect evidence selected from the literature that met the selection criteria specified in Table 6 (aside from study design). The third section includes long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence but did not meet the selection criteria of the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

The objective of this review was to perform a systematic review of the beneficial and harmful effects of rivaroxaban granules for oral suspension (1mg/mL when reconstituted) for the treatment of VTE and prevention of VTE recurrence in term neonates, infants, toddlers, children, and adolescents aged younger than 18 years after at least 5 days of initial parenteral anticoagulation treatment.

Methods

Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 6. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 6: Inclusion Criteria for the Systematic Review

Criteria	Description
Population	Patients aged < 18 years (i.e., term neonates, infants, toddlers, children, and adolescents) with VTE or who require prevention of VTE recurrence following ≥ 5 days of initial parenteral anticoagulation treatment Subgroups: • Presence of a CVAD (yes vs. no) • Cerebral vein thrombosis (yes vs. no) • Symptom status (symptomatic vs. asymptomatic) • Underlying risk factor (e.g., cancer, renal disease, hematologic malignancies, congenital heart disease) • Age (≤ 2 years vs. > 2 years) • Provoked clot (i.e., due to trauma, hospitalization, central lines) vs. unprovoked clot (e.g., VTE in an adolescent with a family history and no other provoking factors)
Intervention	Rivaroxaban granules for oral suspension (1mg/mL when reconstituted) at a body weight–adjusted dose
Comparators	• Low molecular weight heparin (enoxaparin, dalteparin, tinzaparin, nadroparin) • Unfractionated heparin • Vitamin K antagonists (warfarin) • Direct oral anticoagulants (dabigatran)[a] • Fondaparinux

Criteria	Description
Outcomes	**Efficacy outcomes:** • VTE recurrence (symptomatic and/or asymptomatic) • VTE-related mortality • HRQoL • Thrombotic burden **Harms outcomes:** AEs, SAEs, WDAEs, mortality, notable harms (i.e., clinically relevant minor bleeding, major bleeding)
Study designs	Published and unpublished phase III and IV RCTs

AE = adverse event; CVAD = central venous access device; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; VTE = venous thromboembolism; WDAE = withdrawal due to adverse event; vs. = versus.

[a]Dabigatran is not yet approved for use in pediatric population in Canada; the drug is approved by the FDA and the European Medicines Agency for use in VTE prevention and treatment in pediatric population.[32,33]

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist.[34]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in Endnote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were rivaroxaban and venous thromboembolism. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on October 24, 2022, and was last updated on June 9, 2023. Regular alerts updated the search until the meeting of the CADTH Formulary Management Expert Committee (FMEC) on August 24, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature reference.[35] Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with clinical experts.

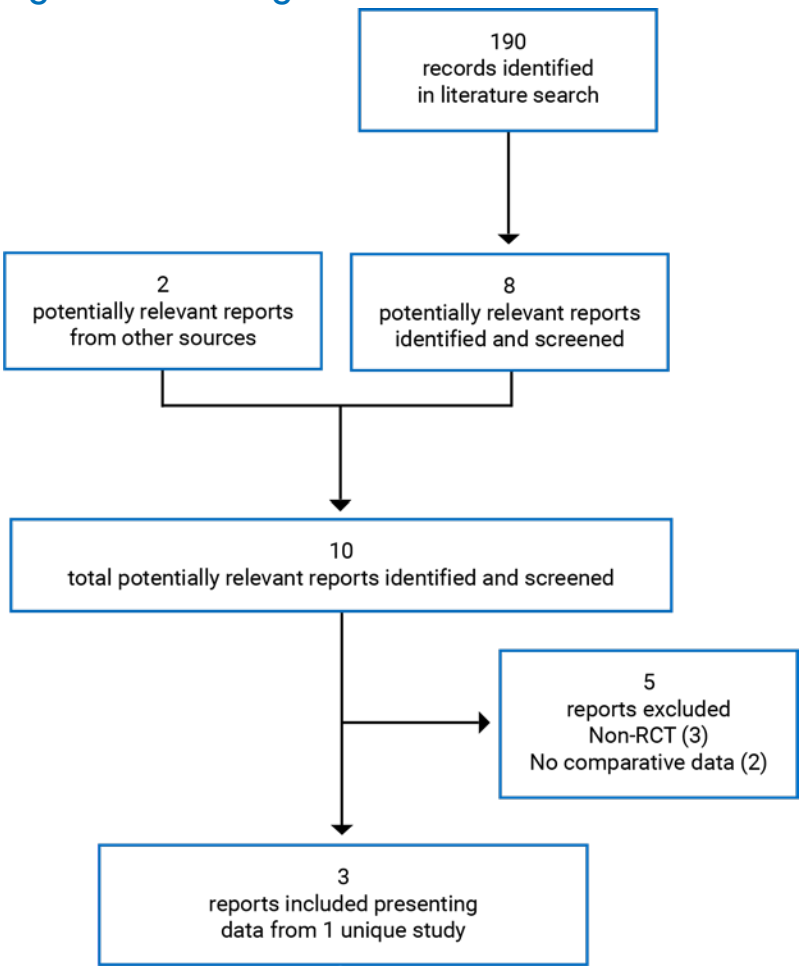
Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially

relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

Three reports of 1 study were identified from the literature for inclusion in the systematic review. The study is summarized in Table 7. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



RCT = randomized controlled trial.

Table 7: Details of the Included Study

Detail	EINSTEIN-Jr
Design and population	
Study design	Phase III, randomized, parallel group, open-label, active-controlled trial
Locations	107 pediatric hospitals in 28 countries in Asia, Australia, Europe, North America, and South America (including 6 centres in Canada)
Patient enrolment dates	November 13, 2014, to September 28, 2018
Randomized (N)	500
Inclusion criteria	• Children aged between birth and < 18 years with confirmed VTE who received initial treatment with therapeutic dosages of UFH, LMWH, or fondaparinux and required anticoagulant therapy for at least 90 days • Pediatric patients with catheter-related VTE aged < 2 years were required to have anticoagulant therapy for at least 30 days • For pediatric patients younger than 6 months: ◦ gestational age at birth of at least 37 weeks ◦ oral feeding, nasogastric feeding, or gastric feeding for at least 10 days ◦ body weight ≥ 2,600 g
Exclusion criteria	• Active bleeding or bleeding risk contraindicating anticoagulant therapy • An estimated glomerular filtration rate < 30 mL/min/1.73 m^2 (in children younger than 1 year, serum creatinine results above the 97.5th percentile excluded participation) • Hepatic disease that is associated with either coagulopathy leading to a clinically relevant bleeding risk, or ALT > 5 times the ULN, or total bilirubin > 2 times the ULN with direct bilirubin > 20% of the total • Platelet count < 50 × 10^9/L • Sustained uncontrolled hypertension defined as > 95th age percentile • Life expectancy < 3 months • Concomitant use of strong inhibitors of both CYP3A4 and P-gp, including but not limited to all HIV protease inhibitors and the following azole antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically • Concomitant use of strong inducers of CYP3A4, including but not limited to rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine • Child-bearing potential without proper contraceptive measures, pregnancy, or breast feeding
Drugs	
Intervention	Rivaroxaban (age and body weight–adjusted dosing equivalent to 20 mg rivaroxaban in adults), after 5 days to 9 days of anticoagulation with a parenteral anticoagulant (UFH, LMWH, or fondaparinux): • once daily (for body weight of ≥ 30 kg) or twice daily (for body weight of 12 kg to < 30 kg), as tablets, or • once daily (for body weight of ≥ 30 kg), twice daily (for body weight of 12 kg to < 30 kg) or 3 times daily (for body weight of < 12 kg) as oral suspension administered using a standard dosing device The main treatment period was 3 months, which could then be extended in blocks of 3 months to a maximum of 12 months. For children with catheter-related thrombosis aged younger than 2

Detail	EINSTEIN-Jr
	years, the main treatment period was 1 month, and this could be extended in blocks of 1 month to a maximum of 3 months.
Comparator(s)	Standard anticoagulation with UFH, LMWH, or fondaparinux or VKA therapy at the discretion of the treating physician, at standard of care dose and duration, after 5 days to 9 days of anticoagulation with a parenteral anticoagulant (UFH, LMWH, or fondaparinux)
Duration	
Phase	
Screening	NR
Initial parenteral anticoagulation treatment	5 days to 9 days
Main open-label treatment period	3 months (1 month for children aged younger than 2 years with catheter-related thrombosis)
Extended open-label treatment period	3 to 9 months (1 to 2 months for children aged younger than 2 years with catheter-related thrombosis)
Follow-up	30 days after the last treatment visit
Outcomes	
Primary end point	Symptomatic recurrent VTE (assessed by the central independent adjudication committee)
Secondary end points	• Composite of symptomatic recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging • Composite of recurrent venous thromboembolism and major bleeding[a] Safety end points: • AEs, SAEs, WDAEs, deaths • Composite of overt major and clinically relevant nonmajor bleeding[b]
Notes	
Publications	Male et al. (2020)[17] Thom et al. (2020)[36] Connor et al. (2020)[37]

ALT = alanine transaminase; CYP3A4 = cytochrome P450 isoenzyme 3A4; LMWH = low molecular weight heparin; NR = not reported; P-gp = P-glycoprotein; UFH = unfractionated heparin; ULN = upper level of normal; VKA = vitamin K antagonist; VTE = venous thromboembolic events.

Note: The FDA clinical review report for rivaroxaban granules for oral suspension[18] was consulted for additional information.

[a]Defined as overt bleeding and associated with a fall in hemoglobin of 2 g/dL or more, or leading to a transfusion of the equivalent of 2 or more units of packed red blood cells or whole blood in adults, or occurring in a critical site (e.g., intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or contributing to death).

[b]Overt bleeding not meeting the criteria for major bleeding, but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, discomfort for the child such as pain, or impairment of activities of daily life (such as loss of school days or hospitalization).

Sources: Male et al. (2020),[17] FDA Clinical Review Report.[18]

Description of the Study

One published phase III, multicentre, open-label, active-controlled, randomized controlled trial sponsored by Bayer AG and Janssen Research and Development, LLC,[38] was included in the systematic review that evaluated the efficacy and safety of an age- and body weight–adjusted rivaroxaban regimen compared to standard of care anticoagulation treatment in children with acute VTE (EINSTEIN-Jr trial; n = 500). In the

EINSTEIN-Jr trial, patients were randomized in a 2:1 ratio to receive either rivaroxaban (oral suspension or tablets) or standard anticoagulation therapy. Randomization was stratified by age groups (birth to 23 months, 2 years to 5 years, 6 years to 11 years, and 12 years to 17 years) and the site of VTE (cerebral vein or sinus thrombosis; catheter related-venous thrombosis; and noncatheter-related venous thrombosis). In the rivaroxaban group, a body weight–adjusted dose of rivaroxaban was given in a once, twice, or thrice-daily regimen, following completion of 5 days to 9 days of parenteral anticoagulation. Those randomized to the comparator group received standard of care anticoagulation (a LMWH, fondaparinux, a UFH, and/or a VKA).[17] There were 3 study phases: a main study treatment period of 3 months, an optional extension phase of up to 9 months, and a 30-day follow-up. For children younger than 2 years who had catheter-related VTE, the study treatment period was 1 month, the extension phase was up to 2 months, and the follow-up was 30 days.[17,18] Children aged 0 to 17 years old were recruited from 107 pediatric hospitals in 28 countries, including 6 centres in Canada.[17] Due to safety reasons, a stepped-down approach to enrolling pediatric patients was adopted. Initially, patients 12years to 17 years were enrolled, followed by children aged 6 years to 11 years, 2 years to 5 years, and younger than 2 years.[17,18] Patients were enrolled between November 14, 2014, and September 28, 2018.

Populations

Inclusion and Exclusion Criteria

The key inclusion and exclusion criteria of the EINSTEIN-Jr trial are summarized in Table 7. The study enrolled children aged between newborn and younger than 18 years with confirmed VTE who received initial treatment with therapeutic dosages of a UFH, an LMWH, or fondaparinux and required anticoagulant therapy for at least 90 days (30 days for patients with catheter-related VTE aged < 2 years). Patients younger than 6 months had to have at least 37 weeks gestational age at birth, weigh at least 2,600 g, and be on oral, nasogastric, or gastric feeding for at least 10 days.

Baseline Characteristics

Baseline characteristics are presented in Table 8 for the safety set and were generally balanced between treatment groups. Patients enrolled in the trial had a median age of 11 years (in the rivaroxaban group) and 11.2 years (in the comparator standard anticoagulants group). In total, 11% of the patient population in both treatment groups were under the age of 2 years, with over 50% in both groups aged between 12 years and younger than 18 years. The majority of the patients in both treatment groups were white (81.2% in the rivaroxaban group and 74.7% in the standard of care anticoagulation group).[18]

Additional baseline characteristics from the efficacy set are presented in Table 9. The majority of the patients in both groups had noncatheter–related VTE (> 50%), symptomatic VTE (> 80%), and first episode VTE (> 90%). Cerebral vein or sinus thrombosis was present in 22% of the rivaroxaban group and 26% of the standard anticoagulant group; catheter-related VTE was present in 27% of the rivaroxaban group and 22% of the standard anticoagulant group.[17]

Table 9 presents the VTE risk factors at baseline for the full analysis set. The majority (87.6%) of the patients had provoked VTE, including those provoked by transient risk factors (47.2%), persistent risk factors (17.4%), or both (23%).[17] The most common persistent risk factors were major organ disease (16.6%), especially

cardiac (9.8%), and active cancer (11.2%), mostly hematologic malignancy (7.2%) and solid tumour (4%). The most common transient risk factors were major infectious disease (28.4%) and the use of CVC (25.2%).[17]

Table 8: Summary of Baseline Demographic Characteristics in EINSTEIN-Jr (Safety Set, N = 491)

Characteristic	Rivaroxaban (N = 329)	Standard of care anticoagulants (N = 162)
Sex, n (%)		
Female	159 (48.3)	82 (50.6)
Male	170 (51.7)	80 (49.4)
Age, years		
Mean (SD)	11 (5.8)	11.2 (5.8)
Age group, years, n (%)		
< 0.5 years	15 (4.6)	8 (4.9)
0.5 years to < 2 years	21 (6.4)	9 (5.6)
2 years to < 6 years	46 (14.0)	22 (13.6)
6 years to < 12 years	67 (20.4)	34 (21.0)
12 years to < 18 years	180 (54.7)	89 (54.9)
Ethnicity, n (%)		
Hispanic or Latino	17 (5.2)	11 (6.8)
Not Hispanic or Latino	286 (86.9)	136 (84.0)
Not reported	26 (7.9)	15 (9.3)
Race, n (%)		
American Indian or Alaska Native	0 (0)	2 (1.2)
Asian	20 (6.1)	8 (4.9)
Black or African American	12 (3.6)	12 (7.4)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0)
White	267 (81.2)	121 (74.7)
Multiple	3 (0.9)	1 (0.6)
Not reported	26 (7.9)	18 (11.1)

SD = standard deviation.

Source: FDA Clinical Review Report.[18]

Table 9: Summary of Baseline VTE Characteristics in EINSTEIN-Jr (FAS, N = 500)

Characteristic	Rivaroxaban (N = 335)	Standard of care anticoagulants (N = 165)
Cause of index thromboembolism, n (%)		
Unprovoked	31 (9.3)	25 (15.2)
Provoked	303 (90.4)	135 (81.8)
Transient risk factor only	151 (45.1)	85 (51.5)
Persistent risk factor only	62 (18.5)	25 (15.2)
Persistent and transient risk factor	90 (26.9)	25 (15.2)
Unknown	1 (0.3)	5 (3.0)
Provoked VTE, number of risk factors n (%)		
1	158 (47)	82 (50)
2	109 (33)	37 (22)
> 2	34 (10)	15 (9)
Provoked VTE, risk factor present in ≥ 10% in either group, n (%)		
Active cancer[a]	40 (12)	16 (10)
Major organ disease	63 (19)	20 (12)
Cardiac	35 (10)	14 (8)
Major surgery or trauma	78 (23)	42 (25)
Major infectious disease	96 (29)	46 (28)
Venous catheter	90 (27)	36 (22)
Use of estrogen or progestins[d]	53 (16)	24 (15)
Index venous thrombosis location, n (%)		
Cerebral vein or sinus thrombosis	74 (22)	43 (26)
Catheter-related VTE	90 (27)	37 (22)
Non–catheter-related VTE	171 (51)	85 (52)
Symptomatic VTE, n (%)	271 (81)	136 (82)
First episode of VTE, n (%)	326 (97)	152 (92)
Initial heparinization[e]	335 (100)	165 (100)
Plus thrombolysis or thrombectomy, or both, n (%)	20 (6)	6 (4)

FAS = full analyses set; VTE = venous thromboembolism.

[a]Active cancer is defined as presence of metastases or recently (< 6 months) diagnosed or treated.

[b]Antiphospholipid syndrome (that is, lupus anticoagulant, anticardiolipin or anti–beta-2-glycoprotein 1 antibodies, or both).

[c]First degree (that is, parent or sibling).

[d]In girls aged 12 years to 17 years.

[e]Included unfractionated heparin, low molecular weight heparin, and fondaparinux.

Source: Male et al. (2020).[17] Reprinted from The Lancet Hematology, 7(1), Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomized, controlled, phase 3 trial, e18-e27., Copyright 2020, with permission from Elsevier.

Interventions

Patients in the rivaroxaban group received either the tablet or oral suspension based on age and body weight–adjusted dosing, equivalent to 20 mg of rivaroxaban in adults. The tablet formulation was given once daily (for body weights of ≥ 30 kg) or twice daily (for body weights of 12 kg to < 30 kg). The oral suspension was given once daily (for body weights of ≥ 30 kg), twice daily (for body weights of 12 kg to 30 kg) or 3 times daily (for body weights of < 12 kg), using a standard dosing device.[18]

Per the inclusion criteria, patients had received initial treatment (5 days to 9 days) with therapeutic dosages of a UFH, an LMWH, or fondaparinux and required anticoagulation for at least 90 days. For patients switching from a UFH, the first dose was planned 4 hours after stopping the infusion. For patients switching from an LMWH, the first dose was planned either 12 hours after the last injection (for the twice-daily regimen) or 24 hours after the last injection (for the once-daily regimen). For patients switching from fondaparinux, the first rivaroxaban dose was planned 24 hours after the last injection.[18]

Treatment with UFHs, LMWHs, or fondaparinux was discontinued after initiating rivaroxaban. Patients randomized to the comparator group continued with a UFH, an LMWH, or fondaparinux or switched to VKA therapy, at the discretion of the treating physician and at standard of care dose and duration. VKA dosages were adjusted to maintain the INR within the therapeutic range (target = 2.5; range = 2.0 to 3.0). Once the INR was above 2.0 on 2 separate occasions, 24 hours apart, the UFH, LMWH, or fondaparinux could be discontinued.[18]

The main study treatment period was 3 months, with an extension phase of up to 3 blocks of 3 months each at the discretion of the treating physician. For children younger than 2 years who had catheter-related VTE, the main study treatment period was 1 month, with an extension phase of up to 2 blocks of 1 month each.[17,18]

Concomitant Medications

According to the EINSTEIN-Jr study protocol, concomitant use of strong inhibitors of both CYP3A4 and P-gp, and strong inducers of CYP3A4 were forbidden. Nonsteroidal anti-inflammatory drugs and antiplatelet agents were discouraged, and when indicated, it was recommended that the lowest possible dose be used to reduce the risk of bleeding. Concomitant fluconazole was allowed.[39]

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 10. These end points are further summarized in the following.

Table 10: Summary of Efficacy Outcomes of Interest Identified in the CADTH Review Protocol

Outcome identified in the CADTH protocol	Outcome assessed in EINSTEIN-Jr	Outcome ranking in EINSTEIN-Jr
VTE recurrence (symptomatic and/or asymptomatic)	Symptomatic recurrent VTE	Primary
	Composite of symptomatic recurrent VTE and other clinically significant thrombosis	Exploratory
	Fatal or nonfatal pulmonary embolism	Exploratory
VTE-related mortality	Assessed within the symptomatic recurrent VTE outcome	Not reported
	Fatal pulmonary embolism	Exploratory
HRQoL	Not assessed	Not applicable
Thrombotic burden	Normalization of thrombotic burden assessment on repeat imaging at the end of the main treatment period without confirmed symptomatic recurrent VTE	Exploratory
VTE recurrence plus thrombotic burden (composite outcomes identified in the CADTH protocol)	Composite of symptomatic recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging	Secondary
	Composite of symptomatic recurrent VTE and asymptomatic deterioration and no change in thrombotic burden assessment on repeat imaging at the end of the main treatment period	Exploratory
	Composite of symptomatic recurrent VTE and thrombotic burden assessment on repeated imaging at the end of the main treatment period (symptomatic recurrent VTE, asymptomatic deterioration, no relevant change, uncertain, improved, normalized)	Exploratory

HRQoL = health-related quality of life; VTE = venous thromboembolism.
Source: Clinicaltrials.gov (statistical analysis plan).[39]

The primary efficacy outcome in the trial was symptomatic recurrent VTE as classified by the central independent adjudication committee (CIAC). Other outcomes assessed as secondary end points were the composite of symptomatic recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging, and the composite of symptomatic recurrent VTE and major bleeding (referred to as "net clinical benefit"[17]). Repeat thrombosis imaging was done at the end of the main treatment period and compared by the CIAC with baseline to classify the results into 1 of the following 3 categories: normalized (no residual thrombosis observed), improved (thrombosis still present but partly recanalized or involving less venous segments), or deteriorated (new venous segment involved). A structured questionnaire at monthly follow-up visits was used to assess signs and symptoms of study outcomes.[17] Objective testing was undertaken for those with suspected outcome events.

The principal safety outcome was a composite of overt major and clinically relevant nonmajor bleeding. Major bleeding was defined as "overt bleeding and associated with a fall in hemoglobin of 2 g/dL or more, or leading to a transfusion of the equivalent of 2 or more units of packed red blood cells or whole blood in adults, or occurring in a critical site, e.g. intracranial, intraspinal, intraocular, pericardial, intra-articular,

intramuscular with compartment syndrome, retroperitoneal, or contributing to death," and clinically relevant nonmajor bleeding was defined as "overt bleeding not meeting the criteria for major bleeding, but associated with: medical intervention, or unscheduled contact (visit or telephone call) with a physician, or (temporary) cessation of study treatment, or discomfort for the child such as pain, or impairment of activities of daily life (such as loss of school days or hospitalization" (supplementary appendix, p.10).[17] Bleeding events were classified by the CIAC. Other safety outcomes include all deaths and other vascular events (i.e., myocardial infarction, cerebrovascular accident, and non-CNS systemic embolism).[39] Safety was assessed through the outcome of AEs.[39]

Statistical Analysis

Sample Size Determination

The study aimed to include at least 170 children based on feasibility assessment rather than a power calculation.[39] The sponsor determined that it was not possible to power the study for noninferiority assessment because formal power calculations indicated that a large sample size would be needed (e.g., 953 to 1,860 patients) and would not be feasible for the pediatric population.[39] Efficacy analysis included all randomized children (full analysis set) and efficacy outcomes were analyzed for the main treatment period. Safety analysis included patients who have received at least 1 dose of the study medication (safety analysis set), and safety outcomes for the main treatment period during the time of administration of first dose to 2 days after the administration of last dose were presented.[17] Analyses of the extended treatment period were presented separately.

Analysis of Outcome Data

Cox proportional hazards models were used to analyze both safety (bleeding events) and efficacy outcomes, and stratified by index event (cerebral venous sinus thrombosis, CVC-VTE, and non–CVC-VTE). This analysis included the time to event primary efficacy outcome (symptomatic recurrent VTE), the composite of all symptomatic recurrent VTE and major bleeding, and the treatment-emergent principal safety outcome up to the end of the main treatment period.[17,18,38,40] Firth's penalized maximum likelihood estimation was used to reduce bias in the parameter estimates related to a low number of events. Kaplan-Meier curves presented the distribution of events over time. Absolute differences in risk were presented, accompanied by 2-sided 95% CIs for the frequency of efficacy and principal safety outcomes, which were calculated by applying the exact Blyth-Still-Casella method.[18] The following outcomes did not undergo formal statistical analysis: composite of recurrent VTE, asymptomatic deterioration and no change on repeat imaging, and fatal or nonfatal PE.[18]

The nonparametric van Elteren test (an extension of Wilcoxon's rank sum test) was used to compare the ordered categories of change in thrombus burden (normalized, improved, uncertain, no relevant change, asymptomatic deterioration, or symptomatic recurrent VTE) at the end of the main treatment period between treatment groups for the stratified ordinal response data. Results were presented descriptively, and for each age category (0 months to 23 months, 2 years to 5 years, 6 years to 11 years, and 12 years to 17 years) without formal statistical comparisons.[17,18,38]

AEs were summarized descriptively by treatment group using counts and frequencies.

All planned analyses were undertaken without control for multiple comparisons.

Missing Data Handling

For efficacy and safety outcomes, incomplete or missing event dates were imputed as per prespecified imputation rules (e.g., if day is missing, impute the maximum of date of randomization, first date of study medication; 01 month year). Similar imputation rules were also specified for partial or completely missing dates for start and stop date of study medication from the exposure dataset for patients who took the study medication, stop date of initial treatment, and stop date of any anticoagulant therapy, including those started within 7 days after the actual stop of the main study treatment period. However, if the stop date of initial treatment was missing due to patient withdrawal, the stop date was considered indeterminate and was not imputed. Imputation rules were also established for thrombus burden assessment if repeated imaging was not performed or done outside of the time window. Time window limits were specified for time to event variables, including symptomatic recurrent VTE, composite of overt major and clinically relevant nonmajor bleeding, composite of symptomatic recurrent VTE and major bleeding, and composite of symptomatic recurrent VTE and other clinically significant thrombosis. Patients were censored at a minimum of the last visit date of the patient or as per outlined in the protocol of the study.[40]

Sensitivity Analyses

Sensitivity analyses were planned to evaluate the potential influence of dropouts on the incidence of the primary efficacy outcome for the main treatment period. Patients with premature termination were assumed to have a hazard of recurrence of VTE 1.5 times and twice as high as the hazard calculated for all patients within each treatment group, assuming informative censoring.[18,40]

Subgroup Analyses

Several subgroups were prespecified, including based on age (birth to < 2 years [birth to < 0.5 years and 0.5 years to < 2 years]; 2 years to < 6 years; 6 years to < 12 years; and 12 years to < 18 years); body weight; sex; presentation of index event (cerebral venous sinus thrombosis, CVC-VTE, non–CVC-VTE), if the index event was a recurrent episode of venous thrombosis (yes or no); risk factors (provoked thrombosis by persistent risk factor, provoked thrombosis by persistent and transient risk factors, provoked thrombosis by transient risk factor, unprovoked, unconfirmed/unknown); dosing formulation assignment (rivaroxaban tablets, rivaroxaban oral suspension, comparator) for the safety analysis set and per-protocol set; and presence of catheter (only at baseline, at baseline and end of main treatment, no). These subgroup analyses were described at the end of the main treatment period.[40]

Results

Patient Disposition

Of the 520 patients screened, a total of 500 patients were randomized to the rivaroxaban (n = 335) and standard of care anticoagulation (n = 165) groups. Discontinuation rates were similar (10% or less) for both treatment groups. The most frequent reasons for discontinuation in the rivaroxaban group were AEs, followed by patient or physician decision (Table 11).

Table 11: Patient Disposition in EINSTEIN-Jr (N = 500)

Patient disposition	Rivaroxaban	Standard of care anticoagulants
Screened, N	520	
Eligible, N	500	
Randomized, N	335	165
Patients not treated, N (%)[a]	6 (1.8)	3 (1.8)
Discontinued from study, N (%)[a]	32 (9.7)	15 (9.3)
Reason for discontinuation, N (%)[a]		
Adverse event	11 (3.3)	2 (1.2)
Death	1 (0.3)	0 (0)
Efficacy outcome reached	2 (0.6)	2 (1.2)
Lost to follow-up	1 (0.3)	1 (0.6)
Noncompliance with study drug	1 (0.3)	2 (1.2)
Other	3 (0.9)	2 (1.2)
Patient convenience	2 (0.6)	1 (0.6)
Physician decision	5 (1.5)	1 (0.6)
Protocol violation	1 (0.3)	0 (0)
Recovery	1 (0.3)	0 (0)
Withdrawal by patient	4 (1.2)	4 (2.5)
FAS, N	335	165
Safety, N	329	162

FAS = Full analyses set.

[a]Percentage of randomized population.

Source: Male et al. (2020)[17] and Clinicaltrials.gov.[39] Reprinted from The Lancet Hematology, 7(1), Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomized, controlled, phase 3 trial, e18-e27., Copyright 2020, with permission from Elsevier.

Exposure to Study Treatments

Duration of Exposure

Exposure to study treatments is summarized in Table 12. In the rivaroxaban group, the median duration of treatment was 13.4 (interquartile range [IQR] = 12.4 to 25.6) weeks. In the standard of care anticoagulation group the median duration of treatment was 13.6 (IQR = 12.5 to 25.5) weeks.[18] Details of the concomitant treatments are not available.

In the rivaroxaban arm, 60% of patients received the oral suspension and 37% received the tablet formulation.[17]

Table 12: Duration of Exposure in EINSTEIN-Jr (Safety set, N = 491)

Outcome measure	Rivaroxaban (N = 329)	Standard of care anticoagulants (N = 162)
Duration of exposure		
Mean (SD) weeks	20.1 (13.1)	19.9 (13.6)
Median (Q1, Q3) weeks	13.4 (12.4 to 25.6)	13.6 (12.5 to 25.5)
Range weeks	0.1 to 55	0.1 to 53.9
Total exposure in person-years	127	62
Patients treated, by duration, n (%)		
< 12 weeks	54 (16.4)	27 (16.7)
≥ 12 weeks to < 26 weeks	199 (60.5)	99 (61.1)
≥ 26 weeks to < 50 weeks	48 (14.6)	19 (11.7)
≥ 50 weeks to < 100 weeks	28 (8.5)	17 (10.5)
≥ 100 weeks	0	0

Q1 = first quartile; Q3 = third quartile; SD = standard deviation; VTE = venous thromboembolism.

Source: FDA Clinical Review Report.[18]

Table 13: Exposure to Treatments in EINSTEIN-Jr (FAS, N = 500)

Characteristic	Rivaroxaban (N = 335)	Standard of care anticoagulants (N = 165)
Rivaroxaban formulation n (%)		
Tablet	125 (37)	NA
Suspension	204 (60)	NA
No study medication given	6 (2)	NA
Standard anticoagulation group, n (%)		
Heparins[a] only	NA	106 (64)
Heparins and VKA	NA	56 (34)
No study medication given	NA	3 (2)
Study Treatment duration, days, median (IQR)		
3-month intended study period	91 (88 to 95)	91 (87 to 94)
1-month intended study period (for birth to 23 months, only)	31 (29 to 35)	29 (28 to 31)

FAS = full analyses set; IQR = interquartile range; NA = not applicable; VKA = vitamin K antagonist.

[a]Included unfractionated heparin, low molecular weight heparin, and fondaparinux.

Source: Male et al. (2020).[17] Reprinted from The Lancet Hematology, 7(1), Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomized, controlled, phase 3 trial, e18-e27., Copyright 2020, with permission from Elsevier.

Concomitant Medications

According to the FDA's appraisal of rivaroxaban, in the EINSTEIN-Jr trial, most patients (95.1%) received at least 1 concomitant medication.[18] This information was not reported in the trial publication, and CADTH was therefore unable to confirm its accuracy.

Adherence

Adherence data were collected through dispensed medications that were returned. For patients in the rivaroxaban group (n = 329), adherence data were available for 304 patients (92.4%). Of the 304 patients, 98.0% had treatment adherence above 80% and 2% of patients had adherence between 50% and 80%.

For patients in the standard of care anticoagulation group (n = 165), adherence data were available from select sites for 91 patients (55.2%). Of the 91 patients, 94.5% had treatment adherence above 80% and 4.4% of patients had adherence between 50% and 80%. In total, 1.1% of patients had treatment adherence below 50%.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported in the following. Refer to Appendix 3 for detailed efficacy data. The length of follow-up was a median of 95 days (IQR = 87 to 95) in those with a 3-month treatment period (n = 463) and 31 days (IQR = 29 to 35) in those with a 1-month treatment period (n = 37).

VTE Recurrence (Symptomatic and/or Asymptomatic)

In the EINSTEIN-Jr trial, 4 of 335 patients (1.2%) in the rivaroxaban group had a recurrent VTE, whereas in the standard anticoagulation group, 5 of 165 patients (3%) had a recurrent VTE (HR = 0.40; 95% CI, 0.11 to 1.41).[17]

Fatal or Nonfatal PE

Nonfatal PE occurred in 1 patient (0.3%) in the rivaroxaban group and 1 patient (0.6%) in the comparator group.

Subgroup Analysis of VTE Recurrence

VTE Recurrence by Age Subgroup

No patients aged from birth to 23 months (n = 54) experienced symptomatic VTE recurrence. Among patients aged 2 years to 5 years (n = 99) and 6 years to 11 years (n = 101), no patients in the rivaroxaban group and 1 patient in each age group in the standard of care group experienced symptomatic VTE recurrence.[17] Among patients aged 12 years to 17 years (n = 276), 4 (2.2%) in the rivaroxaban group and 3 (3.4%) in the standard of care group experienced a symptomatic recurrent VTE.[17]

Catheter-Related VTE Subgroup

In the EINSTEIN-Jr trial, 126 patients with symptomatic (n = 76; 60%) and asymptomatic (n = 50; 40%) CVC-VTE received either rivaroxaban (n = 90) or standard anticoagulation (n = 36). The median follow-up during the study period was 31 days (IQR = 29 days to 35 days) in children aged younger than 2 years (n = 36), and

91 days (IQR = 86 days to 95 days) in children aged 2 years or older (n = 90). Recurrent VTE did not occur in any of the 126 patients (0%; 95% CI, 0.0% to 2.8%).[36]

CVT Subgroup

In the EINSTEIN-Jr trial, 114 children with confirmed CVT received either rivaroxaban (n = 73; 64%) or standard anticoagulation (n = 41; 36%). The median study treatment duration was 92 days with an IQR of 87 days to 95 days for the rivaroxaban group and 90 days to 95 days for the standard anticoagulation group. Recurrent VTE did not occur in any children in the rivaroxaban group and occurred in 1 child (2.4%) in the standard anticoagulant group after 3 months of treatment (absolute difference = 2.4%; 95% CI, – 2.6% to 13.5%).[37]

VTE-Related Mortality

No fatal VTE events occurred during the study period.

Health-Related Quality of Life

The outcome of HRQoL was not assessed in the EINSTEIN-Jr trial.

Thrombotic Burden

In the EINSTEIN-Jr trial, an exploratory efficacy outcome was complete resolution of thrombus on repeat imaging without recurrent VTE. This outcome occurred in 128 out of 335 patients (38.2%; 95% CI, 33.0% to 43.5%) in the rivaroxaban group and 43 out of 165 patients (26.1%; 95% CI, 19.8% to 33.0%) in the standard of care anticoagulation group, the OR, adjusted for index event was 1.70 (95% CI, 1.11 to 2.58) (Table 14).

Table 14: Thrombotic Burden Assessment at the End of the Main Treatment Period in EINSTEIN-Jr (FAS, N = 500)

Outcome	Rivaroxaban (N = 335)	Standard of care anticoagulants (N = 165)
Change in thrombotic burden, n (%)		
Normalized	128 (38.2)	43 (26.1)
Improved	129 (38.5)	75 (45.5)
Uncertain	57 (17)	28 (17)
No relevant change	16 (4.8)	13 (7.9)
Deterioration	1 (0.3)	1 (0.6)

FAS = full analysis set.

Source: Male et al. (2020).[17]

Composite of Recurrent VTE or Asymptomatic Deterioration

In the EINSTEIN-Jr trial, the secondary efficacy outcome was a composite of recurrent VTE or asymptomatic deterioration. This outcome occurred in 5 of 335 patients (1.5%; 95% CI, 0.6% to 3.4%) in the rivaroxaban group and in 6 of 165 patients (3.6%; 95% CI, 1.6% to 7.6%) in the standard of care anticoagulation group (HR = 0.41; 95% CI, 0.12 to 1.36).

Composite of Symptomatic Recurrent VTE or Major Bleeding Events (Net Clinical Benefit)

In the EINSTEIN-Jr trial, a secondary efficacy outcome was a composite outcome of symptomatic recurrent VTE or major bleeding events. This outcome occurred in 4 out of 335 patients (1.2%; 95% CI, 0.4% to 3.0%) in the rivaroxaban group and 7 out of 165 patients (risk difference = 4.2%; 95% CI, 2.0% to 8.4%) in the standard of care anticoagulation group (HR = 0.30; 95% CI, 0.08 to 0.93).

Composite of Recurrent VTE, Asymptomatic Deterioration, and No Change on Repeat Imaging

In the EINSTEIN-Jr trial, an exploratory efficacy outcome was the composite outcome of recurrent VTE, asymptomatic deterioration, and no change on repeat imaging. This outcome occurred in 21 out of 335 patients (6.3%) in the rivaroxaban group and 19 out of 165 patients (11.5%) in the comparator group.

Harms

Only those harms identified in the review protocol are reported herein.

Adverse Events

The frequency of patients experiencing at least 1 AE was high across both groups (rivaroxaban = 83.3%; standard of care anticoagulation = 75.3%).[18]

The most frequently occurring treatment-emergent adverse events (TEAEs) (> 10% of patients in either group) were headache (rivaroxaban = 17.0% versus standard of care anticoagulation = 14.8%), epistaxis (rivaroxaban = 11.2% versus standard of care anticoagulation = 11.1%), vomiting (rivaroxaban = 10.6% versus standard of care anticoagulation = 8.0%), and pyrexia (rivaroxaban = 10.3% versus standard of care anticoagulation = 8.0%) (Table 15).

Serious Adverse Events

In the main treatment period, 21.6% of patients in the rivaroxaban group and 19.8% of patients in the standard of care anticoagulation group reported at least 1 SAE. There were no notable differences in the frequency of SAEs between both treatment groups.

Table 15: Common AEs in EINSTEIN-Jr in 5% or More in Either Treatment Group (Safety Set, N = 491)

AEs	Rivaroxaban (N = 329)	Standard of care anticoagulants (N = 162)
Any AE, n (%)	274 (83.3)	122 (75.3)
Common AEs (> 5% in either treatment group), n (%)		
Menorrhagia	23 (7.0)	5 (3.1)
Nasopharyngitis	25 (7.6)	8 (4.9)
Pain in extremity	23 (7.0)	7 (4.3)
Vomiting	35 (10.6)	13 (8.0)
Fatigue	20 (6.1)	6 (3.7)
Pyrexia	34 (10.3)	13 (8.0)

AEs	Rivaroxaban (N = 329)	Standard of care anticoagulants (N = 162)
Headache	56 (17.0)	24 (14.8)
Nausea	21 (6.4)	7 (4.3)
Diarrhea	23 (7.0)	9 (5.6)
Subcutaneous hematoma	12 (3.6)	4 (2.5)
Epistaxis	37 (11.2)	18 (11.1)
Abdominal pain	18 (5.5)	9 (5.6)
Contusion	14 (4.3)	9 (5.6)
Cough	16 (4.9)	10 (6.2)

AE = adverse event; VTE = venous thromboembolism.

Source: Male et al. (2020).[17] Reprinted from The Lancet Hematology, 7(1), Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomized, controlled, phase 3 trial, e18-e27., Copyright 2020, with permission from Elsevier.

Table 16: SAEs in EINSTEIN-Jr in 1% or More of Rivaroxaban Safety Set

SAE	Rivaroxaban (N = 329), n (%)	Standard of care anticoagulants (N = 162), n (%)
Blood and lymphatic system disorders (SOC), n (%)	10 (3.0)	3 (1.9)
Febrile neutropenia	7 (2.1)	1 (0.6)
Gastrointestinal disorders (SOC), n (%)	10 (3.0)	3 (1.9)
Vomiting	6 (1.8)	0
General disorders and administration site conditions (SOC), n (%)	6 (1.8)	3 (1.9)
Pyrexia	4 (1.2)	2 (1.2)
Nervous system disorder (SOC), n (%)		
Headache	3 (0.9)	3 (1.9)
Seizure	1 (0.3)	2 (1.2)

SAE = serious adverse event; SOC = system organ class.

Source: FDA Clinical Review Report.[18]

Withdrawals Due to Adverse Events

According to the FDA's appraisal of rivaroxaban, AEs leading to discontinuation were minimal across both treatment groups (rivaroxaban = 3.3% [11 out of 329]; standard of care anticoagulants = 1.9% [3 out of 162]). There were no notable differences between the rivaroxaban and the comparator group in the frequency of AEs leading to discontinuation, with bleeding (rivaroxaban = 1.5% [5 out of 329]; standard of care anticoagulants = 1.9% [3 out of 162]) and vomiting (rivaroxaban = 0.6% [2 out of 329]; standard of care anticoagulants = none) as the most frequent TEAEs associated with drug discontinuation for the rivaroxaban group.[18]

Mortality

There were 2 deaths in the EINSTEIN-Jr trial; both patients were in the rivaroxaban group.

Notable Harms

In total, 119 patients (36.2%) in the rivaroxaban group had at least 1 TEAE of bleeding, compared to 45 patients (27.8%) in the standard of care anticoagulation group. No patient in the rivaroxaban group had a major bleeding event. In total, 2 patients (1.2%) in the standard of care anticoagulation group had a major bleeding event. Ten patients (3%) in the rivaroxaban group and 3 patients (2%) in the standard of care anticoagulation group had a major or clinically relevant nonmajor bleeding event (HR = 1.58; 95% CI, 0.51 to 6.27).

Table 17: Bleeding Events in EINSTEIN-Jr (Safety Set, N = 329)

Bleeding event category	Rivaroxaban (N = 329)	Standard of care anticoagulants (N = 162)
Any confirmed bleeding, n (%)	119 (36.2)	45 (27.8)
Major or clinically relevant nonmajor bleeding, n (%)	10 (3)	3 (2)
Major bleeding, n (%)	0	2 (1.2)
Pulmonary	0	1 (0.6)
Intracranial	0	1 (0.6)
Clinically relevant nonmajor bleeding, n (%)	10 (3)	1 (0.6)
Gastrointestinal	4 (1.2)	0
Urogenital	2 (0.6)	0
Skin	1 (0.3)	0
Nasal or mouth	3 (1)	1 (0.6)
Trivial bleeding, n (%)	113 (34.3)	44 (27.2)

Sources: FDA Clinical Review Report[18] and Male et al. (2020).[17]

Extended Treatment

Treatment Extension of the EINSTEIN-Jr Trial

Patients requiring longer anticoagulation for their specific medical condition were allowed up to 3 treatment extensions with blocks of 3 months, except for patients with CVC-VTE who were aged younger than 2 years; these patients were allowed up to 2 treatment extensions with blocks of 1 month each. Of the 500 randomized children, 218 (43.6% of total randomized) entered and 179 (35.8% of total randomized) completed the first block of extended treatment, 91 (18.2% of total randomized) entered and 84 (16.8% of total randomized) completed the second block of extended treatment, and 48 (9.6% of total randomized) entered and all 48 (9.6% of total randomized) completed the third block of extended treatment.

During the extended treatment period, 1 out of 38 patients (2.6%) in the rivaroxaban group (during extension period 2) and 2 patients in the standard of care anticoagulation group had a recurrent VTE (1 out of 46 patients [2.2%] during extension period 1 and 1 out of 19 patients [5.3%] during extension period 2). This occurred only in children aged 12 to younger than 18 years with non–CVC-VTE as an index event.

Note that this information is reported in the FDA's appraisal of rivaroxaban;[18] as such, this information was not available in the trial publication, and CADTH was therefore unable to confirm its accuracy.

Table 18: Patient Disposition With Respect to the Extended Treatment Phase

Disposition outcome	Rivaroxaban (N = 335), n (%)	Standard of care anticoagulants, (N = 165), n (%)	Total (N = 500), n (%)
Randomized	335 (100)	165 (100)	500 (100)
Treated	329 (98.2)	162 (98.2)	491 (98.2)
Premature treatment discontinuation (withdrawal)	1 (0.3)	3 (1.8)	4 (0.8)
Completed main treatment period	328 (97.9)	159 (96.4)	487 (97.4)
No extension	179 (53.4)	90 (54.5)	269 (53.8)
Started extension 1	149 (44.5)	69 (41.8)	218 (43.6)
Did not complete extension 1	26 (7.8)	13 (7.8)	39 (7.8)
Adverse event	4 (1.2)	0	4 (0.8)
Noncompliance	2 (0.6)	0	2 (0.4)
Other	2 (0.6)	3 (1.8)	5 (1)
Physician decision	16 (4.8)	8 (4.8)	24 (4.8)
Protocol deviation	1 (0.3)	0	1 (0.2)
Recovery	1 (0.3)	0	1 (0.2)
Withdrawal	0 (0.3)	2 (1.2)	2 (0.4)
Completed extension 1	123 (36.7)	56 (33.9)	179 (35.8)
No extension 2	61 (18.2)	27 (16.4)	88 (17.6)
Started extension 2	62 (18.5)	29 (17.6)	91 (18.2)
Did not complete extension 2	5 (1.5)	2 (1.2)	7 (1.4)
Adverse event	1 (0.3)	0	1 (0.2)
Lost to follow-up	1 (0.3)	1 (0.6)	2 (0.4)
Physician decision	3 (0.8)	1 (0.6)	4 (0.8)
Completed extension 2	57 (17)	27 (16.4)	84 (16.8)
No extension 3	26 (7.8)	10 (6.1)	36 (7.2)
Started extension 3	31 (9.3)	17 (10.3)	48 (9.6)
Did not complete extension 3	0	0	0

Disposition outcome	Rivaroxaban (N = 335), n (%)	Standard of care anticoagulants, (N = 165), n (%)	Total (N = 500), n (%)
Completed extension 3	31 (9.3)	17 (10.3)	48 (9.6)

Source: FDA Clinical Review Report.[18]

Critical Appraisal

Internal Validity

Risk of bias arising from the randomization process is low for all outcomes in the EINSTEIN-Jr study. The allocation was done centrally using an interactive web response system. The baseline characteristics of the groups were balanced at baseline, indicating that the randomization was successful.

Risk of bias due to deviations from the intended interventions is likely low. The study was open label, meaning both participants and the personnel delivering the intervention were aware of the treatment assignment. The FDA noted 9 treatment deviations (6 patients in the rivaroxaban group and 3 in the comparator group did not take the study drug), which were considered to not have impacted the integrity of the study.[18] Treatment adherence was high in the rivaroxaban and standard of care anticoagulation groups. However, adherence data were not available for all patients (up to 45% was missing). Most patients in the trial (95.1%) received at least 1 concomitant medication;[18] however, details of these treatments were unavailable and it is unclear whether this would have any impact on outcomes. The analysis was appropriate to assess the effect of assignment to the intervention (intent to treat).

The risk of bias resulting from missing outcome data is low. The efficacy analysis was conducted in all randomized children (n = 500), including those who did not receive any study medication (n = 9) and those who discontinued (n = 13). The safety analyses included those who had received at least 1 dose of the study medication (n = 491). Approximately 10% of the study population discontinued from the study (in both groups). Sensitivity analyses were performed to evaluate the potential influence of dropouts on the incidence of the primary efficacy outcome for the main treatment period; however, the results of the sensitivity analyses were not reported. It is therefore possible that the losses to follow-up could have biased the findings.

The trial was assessed to have some risk of bias in measurement of the outcome. While the study was open label, an independent adjudication committee evaluated the initial diagnosis, all suspected outcomes, and repeat thrombosis imaging tests. However, objective testing was only undertaken for children with suspected outcome events based on a structured questionnaire. This may have resulted in some events being missed. An algorithm was developed to classify the change in thrombotic burden on repeat imaging, and 17% of events in both groups were concluded to be uncertain.[18]

Due to low incidence of VTE among children and the lack of a known effect in the control group (standard of care), the study was not powered to demonstrate noninferiority of rivaroxaban in comparison with the standard of care. The effect estimates for most outcomes are affected by serious imprecision as a result of the small sample size and low event rates, which reduces the certainty of the conclusions. Though the

estimate of net clinical benefit achieved statistical significance, the statistical testing was unadjusted for multiple comparisons and the low event rate renders the effect estimate and its 95% CI potentially unstable. The subgroup analyses in CVC-VTE and CVT were predefined but were underpowered. A formal statistical comparison between rivaroxaban and standard of care was not considered to be feasible.

External Validity

Per the clinical expert consulted by CADTH, the study population, intervention, most comparators, and concomitant medications were overall reflective of Canadian clinical practice. However, the clinical experts noted that the trial excluded preterm neonates and only had a small percentage of patients with idiopathic (unprovoked) VTE; therefore, there is uncertainty about the generalizability of the study findings for this population. Furthermore, the proportion of patients aged younger than 2 years was very small (11% in the rivaroxaban group and 10.3% in the comparator group) compared to other age groups. Approximately two-thirds of the patient population in both groups were over the age of 6 years, with over 50% in both groups adolescents (12 years to < 18 years). Only 25% of the patients in the trial had CVC-VTE, which in low given that it is the most common reason for VTE in pediatrics. While this review aims to assess the oral suspension, only 60% of the patients in the rivaroxaban group received the oral suspension. Only 40% of the adolescent population, who represent over half of the patient population in the trial, received the oral suspension. The rest of the patients received oral tablets; however, the clinical experts consulted by CADTH did not have any concerns about this affecting the relevance of the findings to the oral suspension.

The clinical experts confirmed that the dosing schedule and switching strategy (to rivaroxaban), as well as dose exposure were consistent with routine clinical practice and the product monograph. However, the experts noted that some clinicians may choose to forgo the initial 5 days of parenteral anticoagulant but follow the adult initial loading dosing for adolescents. The clinical experts deemed the outcomes to be clinically relevant, and practical measures, including the timing of imaging (that is, at diagnosis and at end of treatment), except when recurrence is suspected or there is a high risk of bleeding.

Given the small number of patients with CVT and cancer in the trial, and the complications associated with CVT and cancer, the clinical experts noted that there are limitations in generalizing the findings (and of the subgroup analyses) to this population and advised caution when using rivaroxaban in this population.

A search was conducted to identify any other relevant evidence, including any indirect evidence comparing rivaroxaban with standard anticoagulants in pediatric population with VTE; none were identified.

Economic Evidence

As this review is part of the CADTH nonsponsored reimbursement review program, in which an application filed by a sponsor is absent, CADTH does not have access to an economic model for rivaroxaban granules in this clinical condition. As a result, the economic review will consist of only a cost comparison for rivaroxaban granules compared with appropriate comparators for the treatment of VTE and prevention of VTE recurrence in children and adolescents aged younger than 18 years.

CADTH Analyses

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on each product's respective product monographs and validated by clinical experts. If discrepancies in dosing between the product monograph and Canadian clinical practice were noted, the dose specified by the clinical experts was used. Clinical expert feedback indicated that the standard duration of treatment would be 3 months, which has been used for the base analysis. Based on public list prices from the Ontario Drug Benefit Formulary accessed in April 2023, the price of rivaroxaban granules for suspension ranges from $7.34 for 51.7 mg/100 mL to $14.67 for 103.4 mg/250 mL. Pricing for all other treatments was based on publicly available list prices. The 51.7 mg/100 mL strength is to be used for patients weighing less than 4 kg, while the 103.4 mg/250 mL strength is to be used for patients weighing 4 kg or more.[41]

Clinical expert feedback obtained by CADTH noted that for children and adolescents with VTE, the current treatment options available include LMWHs, UFHs, VKAs, DOACs, and fondaparinux, although UFHs and fondaparinux are not often used. The relevant comparators within each class are listed in Table 19. As part of the review, CADTH noted that enoxaparin and dalteparin (forms of LMWHs) are available as single-use and multiuse products. Although the product monographs indicate that the multiuse products are not to be used in pediatric patients due to the presence of benzyl alcohol, clinical expert feedback was obtained that the multiuse products are commonly used off-label for pediatric patients in clinical practice. Results of the cost-comparison analysis demonstrate that the cost of rivaroxaban granules over a 3-month period ranges from $113 to $308 depending on the patient's weight. At this cost, rivaroxaban granules are more costly than VKAs, may be more or less costly than DOACs and fondaparinux, and are less costly than LMWHs and UFHs. Note that results may differ by jurisdiction if there are differences in their list prices for the drugs under review compared to those presented in Table 19.

Clinical expert feedback obtained by CADTH noted that an adult dosing regimen of rivaroxaban may be used in adolescent patients. CADTH performed a sensitivity analysis to assess alternate dosing regimens (i.e., adult dosing for rivaroxaban, extended dosing of rivaroxaban [6 months], and using single-dose enoxaparin and dalteparin); the results of this sensitivity analysis demonstrated that using adult dosing of rivaroxaban would result in increased costs (i.e., 3-month costs = $322), while use of single-dose enoxaparin and dalteparin, typically in adolescent patients, is associated with lower costs than the base-case estimates (Table 23).

Table 19: CADTH Cost Comparison Table for the Treatment of Venous Thromboembolic Events in Pediatric Patients

Treatment	Strength or concentration	Form	Price	Recommended dosage	Daily cost	3-month cost[a]
Rivaroxaban (XARELTO)	**51.7 mg/100 mL 103.4 mg/250 mL**	**Granule for oral suspension (1 mg/mL)**	**$7.3400 $14.6750[b]**	**Dose and frequency is weight dependent (2.4 mg to 20 mg per day)**	**$1.13 (5 kg) $3.38 (50 kg)**	**$113 (5kg) $308 (50 kg)**
Direct oral anticoagulants						
Dabigatran etexilate (generics)	75 mg 110 mg 150 mg	Oral tablets	$1.4711[c] $1.2540 $1.2540	75 mg to 150 mg twice daily[d]	$2.51 to $2.94	$229 to $269
Edoxaban (Lixiana)	15 mg 30 mg 60 mg	Oral tablets	$2.9393 $2.9393 $2.9393	30 mg once daily[e]	$2.94	$268
Low molecular weight heparin						
Dalteparin sodium (Fragmin)	25,000 IU	Multiuse vial[f]	$175.4700	100 IU/kg to 150 IU/kg twice daily for patients under the age of 18	$12.53 (5 kg) $75.20 (50 kg)	$1,144 (5 kg) $6,862 (50 kg)
Enoxaparin (Lovenox)	300 mg/3 mL	Multiuse vial[g]	$66.1700	1.5 mg/kg once daily or 1 mg/kg twice daily	$2.36 (5 kg) $22.06 (50 kg)	$216 (5 kg) $2,013 (50 kg)
Enoxaparin (Redesca)	300 mg/3 mL	Multiuse vial[g]	$49.6200	1.5 mg/kg once daily or 1 mg/kg twice daily	$1.77 (5 kg) $17.72 (50 kg)	$162 (5 kg) $1,617 (50 kg)
Nadroparin calcium (Fraxiparine, 9,500 IU/mL)	0.3 mL 0.4 mL 0.6 mL 1.0 mL	Prefilled syringes for subcutaneous or IV injection	$5.4150 $6.8400 $9.0580 $9.0580	171 anti-Xa IU/kg once daily (0.4 mL)[h]	$5.15 (5 kg) $9.06 (50 kg)	$469 (5 kg) $827 (50 kg)
Tinzaparin sodium (Innohep)	2,500 IU/0.25 mL 3,500 IU/0.35 mL 4,500 IU/0.45 mL 8,000 IU/0.4 mL	Prefilled syringes for subcutaneous or IV injection	$6.4095 $8.9633 $11.5276 $19.9363	175 anti-Xa IU/kg once daily[i]	$6.41 (5 kg) $26.14 (50 kg)	$585 (5 kg) $2,386 (50 kg)

Treatment	Strength or concentration	Form	Price	Recommended dosage	Daily cost	3-month cost[a]
	10,000 IU/0.5 mL 12,000 IU/0.6 mL 14,000 IU/0.7 mL 16,000 IU/0.8 mL 18,000 IU/0.9 mL		$26.1426 $31.4003 $36.6333 $41.8675 $47.0952			
Unfractionated heparin						
Unfractionated heparin (Heparin Sodium Injection)	10 000 USP	IV or subcutaneous	$5.2500	50 units per kg, followed by 100 units per kg (or 3,333 units per m^2), 6 times per day[j]	$5.25 to $15.75	$479 to $1,437
Vitamin K antagonists						
Warfarin (Apo-Warfarin)	1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 10 mg	Oral tablets	$0.0796 $0.0841 $0.0674 $0.1043 $0.1043 $0.0675 $0.1211	Dosage adjusted individually so patients can maintain an INR in the range of 2.0 to 3.0 with a target INR of 2.5	$0.07 to $0.12	$6 to $11
Warfarin (Taro-Warfarin)	1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg	Oral tablets	$0.0796 $0.0841 $0.0674 $0.1043 $0.1043 $0.2085	Dosage adjusted individually so patients can maintain an INR in the range of 2.0 to 3.0 with a target INR of 2.5	$0.07 to $0.21	$6 to $19
Fondaparinux						
Fondaparinux	2.5 mg 7.5 mg	Subcutaneous injection	$11.1300 $18.1356	5 to 10mg by subcutaneous injection daily	$18.14 to $29.27	$127 to $205[k]

INR = international normalized ratio.

Notes: All prices are from the Ontario Drug Benefit Formulary (accessed January 2023), unless otherwise indicated, and do not include dispensing fees. CADTH assumed weight ranges of 5 kg to 50 kg for patients, and considered drug wastage. Dosing was based on product monographs (PMs), unless previously noted.

[a]CADTH-consulted clinical experts recommended a 3-month cost analysis–based expected treatment duration for pediatric venous thromboembolism.

[b]Price obtained from IQVIA Delta PA Database (accessed April 2023). Dosing per the rivaroxaban PM. Rivaroxaban PM states that in patients weighing more than 4 kg, the 103.4 mg dose size should be used.[41] As a result, the analysis considers only the 103.4 mg dose size for patients weighing 5 kg to 50 kg.

[c]Off-formulary interchangeable price as noted on the Ontario Drug Benefit Formulary.

[d]Dabigatran Canadian PM does not specify pediatric dosing; however, US product information provides guidance for patients with a body weight between 11 kg and 41 kg.[42,43] This usage may not be commonly followed across Canada.

[e]Edoxaban Canadian PM does not specify pediatric dosing; however, it does provide dosing guidance for patients with body weights of < 60kg.[44] Patients treated for VTE may require 60 mg once daily following initial use of a parenteral anticoagulant for 5 to 10 days; in this case, the cost would increase by up to $30.

[f]Dalteparin PM denotes that the multidose vial must be used within 2 weeks.[45] Given the assumed weight ranges, the number of multidose vials ranges between 1 and 6 per patient per 28 days. Feedback noted that for patients weighing about 50 kg or older adolescents, single-use syringes may be more commonly used (Table 23).

[g]Enoxaparin PM denotes that the multidose vial must be used within 28 days.[46] Given the assumed weight ranges, the number of multidose vials ranges between 1 and 10 per patient per 28 days. Feedback noted that for patients weighing about 50 kg or older adolescents, single-use syringes may be more commonly used (Table 23).

[h]Nadroparin PM indicates that expected duration is 10 days.[47] If used over this shorter time frame, the cost of treatment may range from $51 to $91.

[i]Tinzaparin PM indicates that average duration is 7 days.[48] If used over this shorter time frame, the cost of treatment may range from $45 to $183.

[j]Heparin Sodium Injection PM denotes that the multidose vial must be used within 28 days. The pediatric dose is that noted in the PM.[49,50]

[k]Cost per 7-day treatment period as specified in the PM.[27]

Issues for Consideration

Rivaroxaban has previously been reviewed by the CADTH Canadian Drug Expert Committee (CDEC) for the treatment of venous thromboembolic events (DVT and PE) and prevention of recurrent DVT and PE. A recommendation of reimburse with clinical criteria and/or conditions was issued on March 26, 2014.[51] The submitted price for that review ($2.84 for a 15 mg or 20 mg tablet) is similar the current list prices of rivaroxaban tablets (Table 23).

There is limited dosing information for comparators in the pediatric setting, and clinical expert opinion regarding pediatric dosing of treatments differs within Canada. As a result, relative doses and costs have wide CIs, which should be taken into account when interpreting the results. Clinical expert feedback noted that adult dosing regimens may be used in older adolescent patients. CADTH explored the potential impact of adult dosing of rivaroxaban in scenario analyses.

Drug wastage was considered in the cost comparison table calculations; however, it should be noted that CADTH-consulted clinical experts indicated that drug wastage would be greater in young pediatric (i.e., infant) patients due to their lower body weight.

CADTH obtained feedback from the clinical experts that resource use will differ for rivaroxaban granules compared with currently available treatments. Product monographs and treatment guidelines were reviewed to obtain key resource use considerations, and further feedback from clinical experts was obtained to inform resource use differences. According to that feedback, patients receiving rivaroxaban granules require fewer platelet count monitoring tests than patients receiving LMWHs, and do not require any anti-FXa assays, while patients on LMWHs require up to 6 assays throughout the course of treatment. Furthermore, patients prescribed rivaroxaban granules are likely to have fewer physicians visits and platelet count monitoring tests throughout the course of their treatment than patients prescribed UFHs, and do not require any anti-FXa assays, while patients on UFHs require daily anti-FXa assays or activated partial thromboplastin clotting time assays over the course of treatment; this results in fewer resource costs for patients receiving rivaroxaban granules. Moreover, UFHs and LMWHs are injected or infused products, which lead to increased costs and may have to be given in hospital. Finally, patients receiving rivaroxaban do not require INR testing, while patients receiving VKAs require INR testing every 3 weeks to 5 weeks; which results in more resource use costs for VKAs.

Discussion

Summary of Available Evidence

One pivotal trial (EINSTEIN-Jr) was included in this review. EINSTEIN-Jr (N = 500) was a randomized, open-label phase III, multicentre, parallel group trial that aimed to evaluate the efficacy and safety of an age- and body weight–adjusted rivaroxaban regimen compared to standard of care (i.e., LMWHs, fondaparinux, UFHs, and/or VKAs) in children with acute VTE.[17] The primary end point was symptomatic recurrent VTE. The mean age of patients was 11 years (SD = 5.8) in the rivaroxaban group and 11.2 years (SD = 5.8) in the comparator

group. The majority of the patients were white (rivaroxaban = 81.2%; comparator = 74.7%) and ranged from 12 years to 18 years old (rivaroxaban = 54.7%; comparator = 54.9%). The key limitation of the study was that it was underpowered to demonstrate noninferiority of rivaroxaban in comparison with the standard of care. The availability of oral suspension for an anticoagulant is intended to address the challenges associated with administration and monitoring of standard anticoagulants. However, the trial did not measure improvements in ease of use nor HRQoL.

Cost

Based on publicly available list prices, rivaroxaban granules are expected to have a 3-month cost between $113 and $308 per patient depending on the weight of the patient. A 3-month treatment duration of rivaroxaban granules is more costly than VKAs (incremental cost ranging from $107 to $293 per patient), and may be more or less costly than DOACs (incremental savings of $116 to an incremental cost of $228 per patient) and fondaparinux (incremental cost savings of $92 to an incremental cost of $181 per patient). A 3-month treatment duration of rivaroxaban granules is less costly than LMWHs (incremental cost savings ranging from $49 to $6,554 per patient) and UFHs (incremental cost savings ranging from $171 to $1,342 per patient). As the current standards of care for the treatment of VTE and prevention of VTE recurrence in term neonates, infants, toddlers, children, and adolescents aged younger than 18 years after at least 5 days of initial parenteral anticoagulation treatment are predominantly LMWHs and VKAs, rivaroxaban granules may be more costly or less costly depending on which standard of care is currently being used by the patient. These incremental costs or savings are based on publicly available list prices and may not reflect actual prices paid by public drug plans in Canada.

Rivaroxaban granules may result in fewer drug-related treatment administration and monitoring costs when compared with LMWHs, UFHs, and VKAs. The magnitude of drug-related cost savings is unknown as it is dependent on the frequency and costs associated with treatment administration and monitoring.

Interpretation of Results

Efficacy

In the pivotal, phase III EINSTEIN-Jr trial, there seemed to be a lower incidence of recurrent VTE in the rivaroxaban group versus the comparator in the main treatment period as well as the extended treatment period. The analysis was not powered to assess the comparative efficacy, and the results should be interpreted in light of a low event rate, which contributes to imprecision and potential instability of the effect estimate. All the recurrent VTE in the rivaroxaban occurred in patients in the 12 years to 17 years age group, who represent more than half of the patient population in the trial. Nonfatal PE was rare and observed in only 1 patient in each group. No conclusions could be drawn for any subgroup of the population due to no or very few events occurring in each subgroup. Additionally, there seemed to be a similar or lower incidence in the rivaroxaban group versus the standard anticoagulation group for the following exploratory outcomes: composite of recurrent VTE and asymptomatic deterioration; composite of symptomatic recurrent VTE or major bleeding (net clinical benefit); and composite outcome of recurrent VTE, asymptomatic deterioration, and no change on repeat imaging. Though the estimate of net clinical benefit achieved statistical

significance, the statistical testing was unadjusted for multiple comparisons and the low event rate renders the effect estimate and its 95% CI potentially unstable. A higher incidence of complete resolution of thrombus on repeat imaging without recurrent VTE was observed in the rivaroxaban group versus the standard anticoagulation group. As per the clinical experts consulted by CADTH, the complete resolution of thrombus on repeat imaging would be considered a surrogate outcome that may not be predictive of VTE recurrence in children. However, a complete resolution of thrombus on repeat imaging would result in treatment being stopped. The small sample size and low event rate for most outcomes limits the ability to draw a conclusion regarding the efficacy of rivaroxaban compared to standard anticoagulants. The results suggest a favourable clinical benefit (i.e., composite of recurrent VTE and bleeding events) and that the occurrence of recurrent VTE may be similarly rare with rivaroxaban treatment as with standard of care anticoagulation.

The study deduced noninferiority by comparing the results from this study (in the pediatric population) with results from clinical trials conducted in adult populations. Primary and secondary outcomes (recurrent VTE, major bleeding, major or clinically relevant nonmajor bleeding, net clinical benefit, and mortality) from the EINSTEIN-Jr. trial were informally compared to those observed in the EINSTEIN-DVT and EINSTEIN-PE studies in adult populations. The interpretation of these findings should consider that the noninferiority margin was not developed for comparisons in children, and while the informal indirect comparison of effect estimates for recurrent VTE and net clinical benefit for adults and children showed that the effects were overlapping, both were affected by an important degree of imprecision. While the clinical experts noted that extrapolation from clinical trials in adult populations to pediatric populations is common, CADTH is unable to draw any definitive conclusions. The partial extrapolation of efficacy data from the adult population to support the findings of the phase III trial was appropriate given the low incidence and severity of the disease and the unmet need for new oral anticoagulants in neonates, infants, and young children.

While the clinical trial (population, intervention, comparators, concomitant medications, dosing schedule, switching strategy [to rivaroxaban], and dose exposure) was reflective of Canadian clinical practice and the product monograph, the clinical experts noted the exclusion or limited representation of certain populations. Hence, the generalizability of the study findings is uncertain for these specific populations. Preterm neonates and those who have not received the initial 5 days to 9 days of parenteral anticoagulation were excluded from the study, and there were only small numbers of patients with unprovoked VTE, patients aged younger than 2 years, and patients with cancer or CVT.[17] The availability of oral suspension for an anticoagulant is intended to address the challenges associated with administration and monitoring of standard anticoagulants. However, the trial did not measure improvements in ease of use nor HRQoL.

Harms

There were no notable differences between the rivaroxaban and the standard of care anticoagulation groups in the frequency of TEAEs, SAEs, and discontinuations due to AEs. Discontinuations due to AEs were minimal. While there were no major bleeding events in the rivaroxaban group, a higher incidence of clinically relevant nonmajor bleeding events were seen in the rivaroxaban group compared to the standard of care

anticoagulation group, with gastrointestinal bleeding being the most frequent. Two deaths were reported, both in the rivaroxaban group.

The clinical experts suggested that the AEs and their frequency were consistent with those observed in routine clinical practice and did not indicate any safety signals unique to rivaroxaban (compared to other anticoagulants) based on the reported AEs.

Other Considerations

The clinical experts noted that the availability of an oral suspension could improve ease of drug administration, particularly in younger children.

Conclusions

The EINSTEIN-Jr trial was not powered to demonstrate a difference between treatment groups. An adequately powered trial is unlikely possible due to the low incidence of the condition and challenges in enrolling the pediatric population in clinical trials. However, the results suggest a favourable clinical benefit (i.e., composite of recurrent VTE and bleeding events) and that the occurrence of recurrent VTE may be similarly rare with rivaroxaban treatment as with standard of care anticoagulation.

The safety profile of rivaroxaban seems similar to standard anticoagulants with no additional serious safety concerns. The exclusion of preterm neonates, the small number of patients with unprovoked VTE, and the small sample of patients aged younger than 2 years limits the generalization of these findings to these specific patient populations. There is some lack of clarity about the generalization of the findings to children with cancer and those with CVT due to their limited representation in the trial and very low event rate. The availability of oral suspension for an anticoagulant is intended to address the challenges associated with administration and monitoring of standard anticoagulants; however, the trial did not measure improvements in ease of use nor HRQoL.

As a cost-effectiveness analysis was not submitted, the cost-effectiveness of rivaroxaban granules in comparison with the appropriate comparators for the treatment of VTE and prevention of VTE recurrence in children and adolescents aged younger than 18 years could not be determined. As the standards of care most predominantly used currently are LMWHs and VKAs, the reimbursement of rivaroxaban granules may result in increased drug costs ($107 to $293 when compared with VKAs) or decreased drug costs ($49 to $6,554 compared with LMWHs), depending on the comparator treatment and patient characteristics (given that some treatment doses are based on a patient's weight or INR ranges). CADTH consulted clinical experts as part of this review, and their feedback indicated there may be differences in the frequency of treatment-related resource use between rivaroxaban granules and relevant comparators. CADTH noted that rivaroxaban granules may be associated with lower treatment monitoring and administration costs than current standards of care. To adequately consider the treatment-related costs alongside the health care resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of rivaroxaban granules compared with all currently reimbursed treatments would be required.

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27. Arixtra (fondaparinux sodium): 2.5 mg/0.5 mL, 5.0 mg/0.4 mL, 7.5 mg/0.6 mL, 10.0 mg/0.8 mL solution for injection [product monograph]. Oakville (ON): Aspen Pharmacare Canada Inc.; 2019.
28. INCLUNOX *(enoxaparin), 120 mg/0.8 mL, 150 mg/mLmg/mL, 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, Intravenous or Subcutaneous* [product monograph]. Boucherville (QC): Sandoz Canada Inc.; 2020.
29. HEPARIN SODIUM *(heparin), 10 000 USP units per mL, intravenous or subcutaneous use* [product monograph]. Kirkland (QC): Pfizer Canada ULC 2018.
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42. Pradaxa Dabigatran Etexilate: Dosing Administration. 2022; https://pro.boehringer-ingelheim.com/us/products/pradaxa/dosing-administration. Accessed Apr 2023.
43. Medscape. Dabigatran (Rx): Pediatric dosing and uses. 2021; https://reference.medscape.com/drug/pradaxa-dabigatran-342135. Accessed Apr 2023.
44. *Lixiana (edoxaban): 15 mg, 30 mg and 60 mg, Film-coated tablets* [product monograph]. Laval (QC): Servier Canada Inc; 2023.
45. Fragmin (dalteparin sodium): solution and prefilled syringe with safety needle device [product monograph]. Kirkland (QC): Pfizer Canada ULC; 2022.
46. Enoxaparin sodium (Lovenox): solution for injection [product monograph]. Laval (QC): sanofi-aventis Canada Inc.; 2021.
47. Fraxiparine (nadropain calcium): 9500 anti-Xa IU/mL pre-filled syringes [product monograph]. Oakville (ON): Aspen Pharmacare Canada Inc; 2022.
48. Tinzaparin sodium (innohep): multi-dose vial and pre-filled syringe with safety needle device [product monograph]. Thornhill (ON): Leo Pharma Inc; 2017.
49. Heparin Sodium Injection: *10000 USP units per mL* [product monograph]. Kirkland (QC): Pfizer Canada ULC; 2020.
50. Heparin Sodium Injection: *1000 USP Units / mL, 10000 USP Units / mL vials, 5000 USP Units / 0.5 mL Prefilled Syringe* [product monograph]. Toronto (ON): Fresenius Kabi Canada Ltd; 2021.
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Appendix 1: Literature Search Strategy

Note this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: October 24, 2022

Alerts: Biweekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits

- Conference abstracts: excluded

Table 20: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary

Syntax	Description
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
.jx	Journal title word (Embase)
freq = #	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

Multidatabase Strategy

1. rivaroxaban/
2. (rivaroxaban* or xarelto* or bay 59-7939 or bay59-7939 or bay597939 or bay 597939 or 9NDF7JZ4M3 or JNJ-39039039 or JNJ39039039).ti,ab,kf,ot,rn,nm.
3. or/1-2
4. "Venous Thromboembolism"/ or exp "Venous Thrombosis"/ or exp "Pulmonary Embolism"/
5. (Thrombophlebit* or DVT or VTE or Phlebothrombos* or Postphlebitic).ti,ab,kf.
6. ((clot* or thrombos* or thromboembo* or phlebothromb*) and (vein or venous or vena or deep)).ti,ab,kf.
7. ((pulmonary or lung) and (embol* or thrombos* or thromboembo* or microembol* or infarction*)).ti,ab,kf.
8. "Thromboembolism"/ and (vein or venous or vena).ti.
9. or/4-8
10. Pediatrics/ or Hospitals, Pediatric/ or Intensive Care Units, Pediatric/ or Adolescent/ or exp Child/ or exp Infant/ or Pediatric Nursing/ or Child, Hospitalized/ or Adolescent, Hospitalized/
11. (child* or infant* or baby or babies or newborn* or newborns or neonate or neonates or neonatal or preemie? or infancy or paediatric* or pediatric* or toddler* or girl? or boy? or kid? or teen or teens or teenage* or youngster? or youth* or preteen* or adolescent* or adolescence or preschooler* or pre-schooler* or nursery school* or daycare* or school age? or (months adj2 age) or (month? adj2 old) or preadolescen* or juvenile* or prepubescen* or prepubert* or pre-pubescen* or pre-pubert* or pre-adolescen*).ti,ab,kf.
12. (pediat* or paediat* or child* or adolescen* or juvenile*).jw.

13. or/10-12
14. and/3,9,13
15. 14 use medall
16. *rivaroxaban/
17. (rivaroxaban* or xarelto* or bay 59-7939 or bay59-7939 or bay597939 or bay 597939 or 9NDF7JZ4M3 or JNJ-39039039 or JNJ39039039).ti,ab,kf,dq.
18. or/16-17
19. exp Venous thromboembolism/ or exp vein thrombosis/ or lung embolism/
20. (Thrombophlebit* or DVT or VTE or Phlebothrombos* or Postphlebitic).ti,ab,kf,dq.
21. ((clot* or thrombos* or thromboembo* or phlebothromb*) and (vein or venous or vena or deep)).ti,ab,kf,dq.
22. ((pulmonary or lung) and (embol* or thrombos* or thromboembo* or microembol* or infarction*)).ti,ab,kf,dq.
23. thromboembolism/ and (vein or venous or vena).ti.
24. or/19-23
25. exp pediatrics/ or pediatric hospital/ or pediatric intensive care unit/ or exp adolescent/ or exp child/ or exp pediatric nursing/
26. (child* or infant* or baby or babies or newborn* or newborns or neonate or neonates or neonatal or preemie? or infancy or paediatric* or pediatric* or toddler* or girl? or boy? or kid? or teen or teens or teenage* or youngster? or youth* or preteen* or adolescent* or adolescence or preschooler* or pre-schooler* or nursery school* or daycare* or school age? or (months adj2 age) or (month? adj2 old) or preadolescen* or juvenile* or prepubescen* or prepubert* or pre-pubescen* or pre-pubert* or pre-adolescen*).ti,ab,kf.
27. (pediat* or paediat* or child* or adolescen* or juvenile*).jx.
28. or/25-27
29. and/18,24,28
30. 29 use oemezd
31. conference abstract.pt.
32. 30 not 31
33. or/15,32
34. remove duplicates from 33

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | rivaroxaban, pediatrics]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- rivaroxaban, pediatrics]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- rivaroxaban, pediatrics]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- rivaroxaban, pediatrics]

Grey Literature

Search dates: October 13, 2022 – October 19, 2022

Keywords: Rivaroxaban, Xarelto, VTE

Limits: None

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

Appendix 2: Excluded Studies

Note that this appendix has not been copy-edited.

Table 21: Excluded Studies

Reference	Reason for exclusion
PALUMBO, J., et al. Blood Adv 2022 6 (22): 5821-5828.	Study design (non-comparative)
SANCHEZ VAN KAMMEN, M., et al. Pediatric Neurology 2022 128: 20 to 24	Study design (non-comparative)
YOUNG, G., et al. Journal of Thrombosis & Hemostasis 2020 18(7):1672 to 1685	Study design (not an RCT)
KRAUSE, M., et al. Thrombosis Research 2016 148:145-151	Study design (not an RCT)
SCIASCIA, S., et al. Blood Coagulation & Fibrinolysis 2015 26(4):476-7	Study design (not an RCT)

RCT = randomized controlled trials.

Appendix 3: Descriptive Comparisons to Studies in Adults

Note that this appendix has not been copy-edited.

Descriptive Comparisons to Data From Studies in Adults

The safety and efficacy outcomes are compared descriptively with the historical 3-month efficacy and safety data from studies that compared rivaroxaban with standard anticoagulants in 8,282 adult patients with acute VTE.[52-54] The extrapolation considered similarity in children and adults based on: drug exposure with pediatric dose regimen (20 mg-equivalent rivaroxaban) as observed in adults receiving therapeutic dose of 20 mg once-daily; clinical course of VTE (incidences of symptomatic recurrent VTE, major bleeding and mortality); and the response to rivaroxaban therapy as compared to standard anticoagulation. The analysis was done on the FAS, including assessment of incidences and the corresponding two-sided 95% confidence intervals by treatment group; and assessment of the relative treatment effects (hazard ratios and their 95, 90, 80, 50% confidence intervals) for the primary efficacy outcome, composite of primary efficacy outcome and major bleeding, composite of major and clinically relevant nonmajor bleeding. The upper margin of the 95% CI of the rivaroxaban versus standard of care anticoagulation hazard ratio was used for comparison with the non-inferiority margin as established for the Einstein DVT and PE program.[52-54] The accepted non-inferiority margin was 2.0 for individual Einstein DVT and PE studies, and 1.75 for the pooled Einstein DVT and PE data.[40]

Efficacy and Safety Outcomes Reported in EINSTEIN-Jr in Children Compared With Those Observed in EINSTEIN DVT and PE in Adults

The study authors interpreted their findings partially by extrapolation of data from trials in adult population (EINSTEIN DVT and PE).[52-54] The extrapolation assumed that adult and children have similar clinical course of VTE and relative treatment effects between children and adults are similar. The upper margin of the 95% CI of the HR for the main efficacy outcome of the comparison of rivaroxaban with standard anticoagulant was 1.41 (Table 22)[17]

Table 22: Recurrent VTE, Major Bleeding, and Mortality at 3 months in EINSTEIN-Jr (children) Compared to Pooled EINSTEIN-DVT and EINSTEIN-DVT and EINSTEIN-PE Results (Adults)

	Rivaroxaban		Standard of care anticoagulants		Absolute risk difference	Hazard ratio
Outcome	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)	(95% CI)
Recurrent VTE						
EINSTEIN-Jr	4/335	1.2 (0.4 to 3.0)	5/165	3.0 (1.2 to 6.6)	−1.8 (−6.0 to 0.6)	0.40 (0.11 to 1.41)
EINSTEIN DVT/PE	69/4,150	1.7 (1.3 to 2.1)	82/4131	2.0 (1.6 to 2.5)	−0.3 (−0.9 to 0.3)	0.82 (0.60 to 1.13)

Outcome	Rivaroxaban		Standard of care anticoagulants		Absolute risk difference	Hazard ratio
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)	(95% CI)
Major Bleeding						
EINSTEIN-Jr	0/328	0.0 (0.0 to 1.1)	2/164	1.2 (0.1 to 4.3)	−1.2 (−2.9 to 0.5)	—
EINSTEIN DVT/PE	28/4,130	0.7 (0.5 to 1.0)	49/4116	1.2 (0.9 to 1.6)	−0.5 (−0.9 to −0.1)	0.55 (0.35 to 0.88)
Major or CRNM bleeding						
EINSTEIN-Jr	10/329	3.0 (1.6 to 5.5)	3/162	1.9 (0.5 to 5.3)	1.2 (−2.8 to 4.0)	1.58 (0.51 to 6.27)
EINSTEIN DVT/PE	286/4,130	6.9 (6.2 to 7.7)	287/4116	7.0 (6.2 to 7.8)	0.0 (−1.1 to 1.0)	0.98 (0.83 to 1.16)
Net clinical benefit[a]						
EINSTEIN-Jr	4/335	1.2 (0.4 to 3.0)	7/165	4.2 (2.0 to 8.4)	−3.0 (−7.5 to 0.3)	0.30 (0.08 to 0.93)
EINSTEIN DVT/PE	100/4,150	2.4 (2.0 to 2.9)	131/4131	3.2 (2.7 to 3.8)	−0.8 (−1.5 to −0.1)	0.74 (0.57 to 0.96)
Mortality						
EINSTEIN-Jr	1/335[b]	0.3 (0.1 to 2.2)	0/165	0.0 (0.0 to 2.2)	0.3	—
EINSTEIN DVT/PE	53/4,150	1.3 (1.0 to 1.7)	61/4131	1.5 (1.1 to 1.9)	−0.2 (−0.7 to 0.3)	0.81 (0.56 to 1.17)

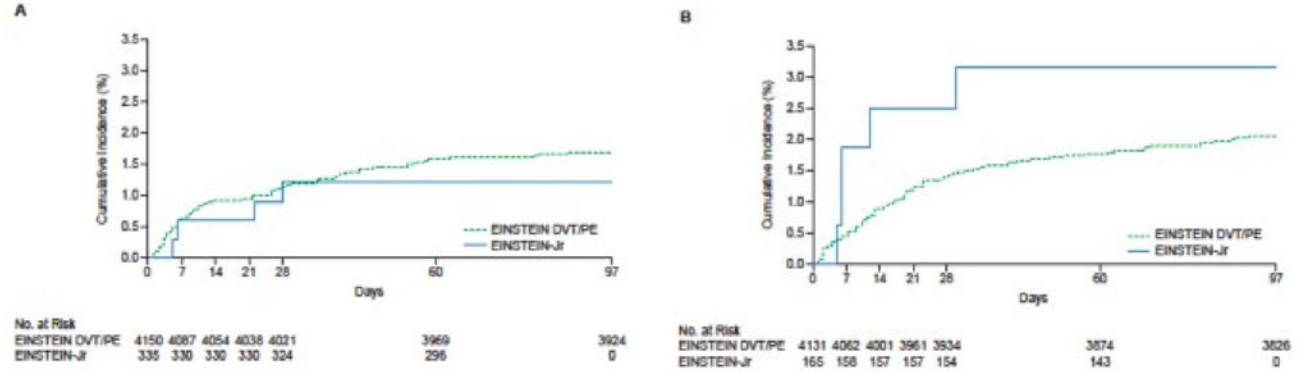
CRNM = clinically relevant nonmajor; DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism

[a]composite of recurrent VTE and major bleeding.

[b]Death related to progression of cancer

Source: Male et al. (2020) supplementary appendix[17] Reprinted from The Lancet Hematology, 7(1), Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomized, controlled, phase 3 trial, e18-e27., Copyright 2020, with permission from Elsevier.

Figure 2: Kaplan-Meier of Recurrent VTE With Rivaroxaban and Standard Anticoagulation in EINSTEIN-Jr in Children as Compared With Those Observed in the EINSTEIN DVT and PE Program in Adults

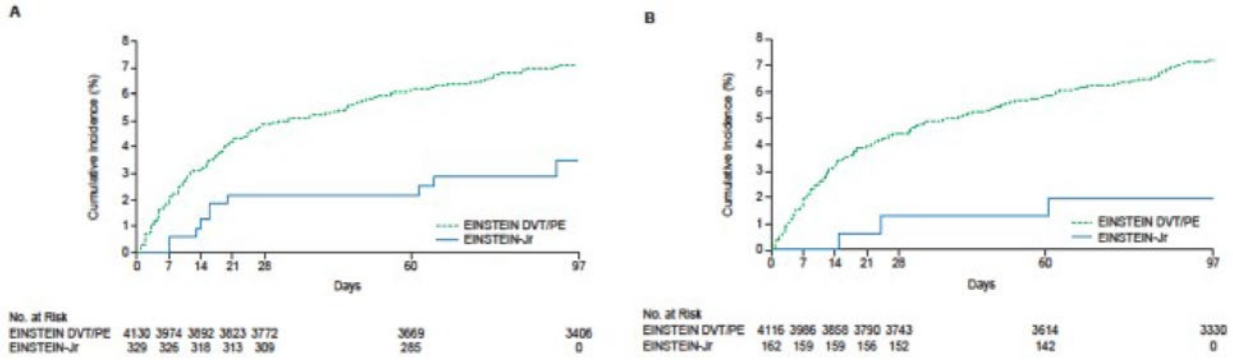


VTE = venous thromboembolism.

Note: Panel A presents results for rivaroxaban and Panel B represents results for standard anticoagulation.

Source: Male et al. (2020) supplementary appendix.[17] Reprinted from The Lancet Hematology, 7(1), Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomized, controlled, phase 3 trial, e18-e27., Copyright 2020, with permission from Elsevier.

Figure 3: Kaplan-Meier Rates of Major or Clinically Relevant Nonmajor Bleeding With Rivaroxaban and Standard Anticoagulation in EINSTEIN-Jr in Children as Compared With Those Observed in the EINSTEIN DVT and PE Program in Adults



VTE = venous thromboembolism.

Note: Panel A presents results for rivaroxaban and Panel B represents results for standard anticoagulation.

Source: Male et al. (2020) supplementary appendix.[17] Reprinted from The Lancet Hematology, 7(1), Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomized, controlled, phase 3 trial, e18-e27., Copyright 2020, with permission from Elsevier.

Appendix 4: Economic Evidence for Alternative Dosing Assumptions

Table 23: CADTH Cost Comparison Table for the Treatment of Venous Thromboembolic Events in Pediatric Patients (Alternate Dosing Regimens)

Treatment	Strength and concentration	Form	Price	Recommended dosage	Daily cost	3-month cost[a]
Rivaroxaban (XARELTO)	**2.5 mg 10 mg 15 mg 20 mg**	**Oral Tablet**	**$1.4200 $2.8700 $2.8700 $2.8700**	**15 mg twice daily for the first three weeks followed by 20mg once daily for the remaining duration of treatment[b] (adult dosing)**	First 3 weeks: $5.74 Subsequently: $2.87	Initial 3 months: $322 Subsequent 3 months: $262
Apixaban (generics)	2.5 mg 5 mg	Oral Tablets	$0.4084	10 mg taken twice daily for 7 days then; 5 mg taken orally twice daily. Dosing over a longer duration is 2.5 mg twice daily[c]	Induction: $1.63 Maintenance: $0.82	$80
Dalteparin Sodium (FRAGMIN)	2500 IU 3500 IU 5000 IU 7500 IU 10000 IU 12500 IU 15000 IU 16500 IU 18000 IU	Prefilled Syringes for Subcutaneous or IV Injection	$5.8500 $8.1890 $11.6990 $17.5500 $23.4000 $29.2500 $35.0900 $38.6000 $42.1100	100 IU/kg to 150 IU/kg twice daily for patients under the age of 18. Patients weighing 46kg to 56kg may receive up to 10000 IU per day, via single dose pre-filled syringe (single use vial)	$11.70 (5 kg) $23.40 (50 kg)	$1,068 (5 kg) $2,135 (50 kg)
Enoxaparin (Noromby, Inclunox, Redesca)	20 mg/0.2 mL 30 mg/0.3 mL 40 mg/0.4 mL 60 mg/0.6 mL	Prefilled Syringes for Subcutaneous or IV Injection	$3.5280 $4.9620 $6.6160 $9.9240	1.5 mg/kg once daily or 1 mg/kg twice daily (single use vial)	$3.52 (5 kg) $13.23 to $16.54 (50 kg)	$322 (5 kg) $1,207 to $1,509 (50 kg)

Treatment	Strength and concentration	Form	Price	Recommended dosage	Daily cost	3-month cost[a]
	80 mg/0.8 mL 100 mg/mL 120 mg/0.8 mL 150 mg/mL		$13.2320 $16.5400 $19.8480 $24.8100			
Enoxaparin (Lovenox)	30 mg/0.3 mL 40 mg/0.4 mL 60 mg/0.6 mL 80 mg/0.8 mL 100 mg/mL 120 mg/0.8 mL 150 mg/mL	Prefilled Syringes for Subcutaneous or IV Injection	$6.6170 $8.8220 $13.2330 $17.6450 $22.0560 $26.4670 $33.0850	1.5 mg/kg once daily or 1 mg/kg twice daily	$6.62 (5 kg) $17.65 to 26.47 (50 kg)	$604 (5 kg) $1,610 to $2,415 (50 kg)

Note: Prices are from the Ontario Drug Benefit Formulary (accessed April 2023) unless otherwise indicated, and do not include dispensing fees. CADTH assumed weight ranges of 5kg to 50kg for patients, and considered drug wastage. Dosing was based on product monograph, unless previously noted.

[a]CADTH consulted clinical experts recommended a 3-month cost analysis based expected treatment duration for pediatric venous thromboembolism

[b]Dose adjustments are noted in the PM. If these doses are included in practice, given the cost of the 2.5 mg tablet, the estimated cost of rivaroxaban is underestimated.

[c]Apixaban Canadian product monograph does not specify pediatric dosing; although pharmacokinetic / pharmacodynamic data are available from a single-dose pediatric study (28 days to 18 years).[55]

Note that this appendix has not been copy-edited.

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