South African National Department of Health
Evidence summary
Component: COVID-19

EVIDENCE SUMMARY

Date: 8 October 2021

Research question: Should rivaroxaban be used in the management of ambulant COVID-19 patients?

Key findings

- This summary describes the evidence base for the use of rivaroxaban in the management of COVID-19 in ambulant patients.
- One phase 2b randomised controlled trial (RCT) in ambulant patients (n=497) was identified.
- The study was stopped as the prespecified futility endpoint had been reached.
- The RCT found that rivaroxaban did not improve on progression from mild to moderate or severe COVID-19 in high-risk adults.
- The currently available evidence does not support the routine use of rivaroxaban in ambulant COVID-19 patients.

NEML MAC ON COVID-19 THERAPEUTICS RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			
Recommendation: We suggest that rivaroxaban not be used routinely in patients treated for COVID-19 in ambulatory care settings. *Rationale:* The evidence of efficacy and safety is very uncertain at this point. A single phase 2b RCT was stopped as the prespecified futility endpoint had been reached. **Level of Evidence:** Low certainty evidence **Review indicator:** Evidence of sufficient efficacy and safety					

NEMLC MAC on COVID-19 Therapeutics: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated when more relevant evidence becomes available.

Background:

Rivaroxaban is an oral anticoagulant that exerts a direct factor Xa inhibitory effect. It has regulatory approval for reducing the risk of thromboembolic phenomena in atrial fibrillation and for the treatment of deep vein thrombosis and pulmonary embolism. Additionally, it is approved to reduce the risk of major cardiovascular events in patients with coronary artery disease and peripheral arterial disease.[1,2] The local South African Health Products regulatory approval is for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.[3]

COVID-19 is associated with coagulation abnormalities, evidenced by increased D-dimer, increased fibrin and fibrin degradation product, longer prothrombin time and longer activated partial thromboplastin time.[4,5,6,7] There is interest in the role anticoagulants could play in preventing progression of COVID-19 disease.

Use of rivaroxaban in the management of hospitalised patients with severe COVID-19 is included in the updated rapid review of anticoagulants.[8] That rapid review summarised an RCT by Lopes *et al*., a multicentre open label trial conducted in Brazil, which included 615 participants (intervention = 311, control = 304). Clinically stable patients received oral rivaroxaban, 20 mg once daily (15 mg once daily if reduced creatinine clearance). Clinically unstable patients received subcutaneous enoxaparin 1 mg/kg twice per day, or IV unfractionated heparin at a dose to achieve anti-Xa concentration or partial thromboplastin time targets. Treatment continued to day 30. There was no difference regarding thromboprophylaxis between therapeutic or prophylactic anticoagulation noted in the study.[8,9]

A recent (15 September 2021) RCT published by Ananworanich *et al*., on the use of rivaroxaban in non-hospitalised COVID-19 patients triggered this review. [10]

EVIDENCE REVIEW:

An evidence summary rather than a complete rapid review was conducted, as only one phase 2 b randomised controlled trial (RCT) was identified.

Randomised-controlled trial:

A RCT of rivaroxaban vs. placebo in high-risk adults with mild COVID-19 was conducted at 13 outpatient clinics in 7 US states, and one virtual site (Decentralized Clinical Trial Operating System™) that enrolled participants from 40 states. The Decentralized Clinical Trial Operating System is a telemedicine platform. Participants were recruited through social media. See Table 1 for further details of the study.

Participants were randomized 1:1 to daily oral rivaroxaban 10 mg or placebo (multivitamin tablet) for 21 days and followed to day 35 with a total of 12 telemedicine visits (days 1, 4, 6, 8, 10, 12, 14, 18, 21, 24, 28 and 35). Randomization was stratified by site and symptom duration (<6 days vs ≥ 6 days). Participants were provided study drug, a thermometer, pulse oximeter, nasal swab test kit and labels, and personal protective equipment at their homes.

The primary endpoints were safety and progression to moderate or severe disease, measured by the Gates Medical Research Institute (MRI) scale and the WHO Ordinal Scale for Assessment of Clinical Status of COVID-19 Patients. The Gates MRI Scale for COVID-19 is an ordinal scale clinical endpoint with standard definitions ranging from 1 (asymptomatic/symptoms similar to pre-COVID status) to 7 (death). Gates MRI scale 3 included symptoms of shortness of breath, tachypnoea (respiratory rate ≥ 20 breathes per minute), or hypoxaemia. Gates MRI scale 4 to 7 includes critically ill status to death.

The primary safety endpoint was the frequency of adverse events (AEs) including Grades 3 and 4, resulting in discontinuation, serious AEs and hypersensitivity and major bleeding events through day 35. The primary efficacy endpoint was the proportion of participants who progressed to moderate or severe disease (Gates MRI scale ≥ 3) by day 28.

At each visit, adverse events, bleeding events and signs and symptoms were recorded. Temperature and oxygen saturation was self-reported. Participants also performed nasal swabs on Days 1, 4, 8, 14, 21, and 28, which were picked up by a courier and sent to the laboratory for PCR testing. Testing was performed sequentially, starting with the day 1 sample, until the last sample was tested, or until viral clearance (two consecutive negative PCR results).

The target sample size was 600 participants, but the Independent Data Monitoring Committee recommended early termination of the study because the prespecified futility endpoint had been reached. Most of 497 participants were < 65 years of age (85%, 379/444), female (60%, 267/444), with ≥2 comorbidities (69%, 305/444). Mean study drug exposure was 18.6 days and 82% had ≥75% compliance.

Outcomes

Primary endpoints:
Disease progression: In the intention to treat analysis, progression to moderate or severe disease (Gates MRI scale ≥ 3) occurred in 46/222 (20.7%) receiving rivaroxaban vs. 44/222 (19.8%) in the placebo group, with a risk difference of -1.0 (95% CI, 6.4 to 8.4).

Adverse events: Serious AEs occurred in 2/219 (0.9%) rivaroxaban recipients and in 7/230 (3.0%) placebo recipients. Adverse events resulting in discontinuation of the intervention occurred in 4/219 (1.8%) rivaroxaban and 5/230 (2.2%) placebo participants. No participant experienced hypersensitivity or major bleeding in either group. Clinically relevant non-major bleeding was rare (and included 3 participants with haematuria, and 2 with haemorrhoidal bleeding in the rivaroxaban group (2.3%, 5/219), and 1 participant with rectal bleeding and 1 with blood in the stool in the placebo group (0.9%, 2/230).

Secondary endpoints:
Asymptomatic participants at day 28: Participants reaching Gates MRI scale 1 was classified as asymptomatic. At day 28 the proportion of asymptomatic participants was higher in the rivaroxaban arm (123/192; 64.1%; 95% CI 57.1 to 70.6) than in the placebo arm (105/199; 52.8%; 95% CI 45.8 to 59.6).

Other endpoints:
Progression to hospital admission (ambulant patients): In the intention to treat analysis, proportion with hospitalisation occurred in 3/222 (1.4%) receiving rivaroxaban vs. 7/222 (3.2%) in the placebo group, with a risk difference of 0.43 (95% CI, 0.11 to 1.65).
Mortality: There were no deaths reported during the study period.

Guidelines:
The following guidelines were retrieved:

1. *National Institutes of Health (USA) COVID-19 Treatment Guidelines*[11]*: "*For non-hospitalized/ patients with COVID-19 who are managed as outpatients anticoagulants and antiplatelet therapy should not be initiated for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial"
2. *Australian guidelines for the clinical care of people with COVID-19*[12] recommend against offering routine use of therapeutic anticoagulant dosing in adults with moderate, severe or critical COVID-19; indicating that there is no additional indication for therapeutic dosing for anticoagulants in adults with severe or critical COVID-19 beyond current standard best practice.

CONCLUSION:
In adults presenting with mild COVID-19 with risk factors for progression to severe COVID-19, rivaroxaban did not reduce progression to moderate or severe disease. The currently available evidence does not support the routine use of rivaroxaban in non-hospitalised patients with COVID-19.

Reviewer(s): M Reddy, A Gray.

Declaration of interests: MR (Better Health Programme, South Africa), AG (Division of Pharmacology, University of KwaZulu Natal) declared no interests in respect of rivaroxaban for COVID-19.

Table 1: Characteristics of the RCT

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments

Ananworanich et al, 2021 [10]
 	
Protocol Number: Gates MRI-COD-01-T01-01
	RCT
	
	Multiple outpatient clinics & a virtual site (Decentralized Clinical Trial Operating System™) – representing 47 US states
	
	Follow-up duration (days): 35
	
	Funding: Bill & Melinda Gates Medical Research Institute (Gates MRI)
		n=497
		
		Inclusion criteria:
		≥18 years of age, with documented positive SARs-CoV-2 polymerase chain reaction (PCR) test within 10 days of screening, ≥1 COVID-19 sign/ symptom within 7 days of randomization. Mild COVID-19 at screening; high risk for severe COVID-19 (either ≥65 years of age, diagnosed with a chronic disease requiring daily treatment (such as diabetes, lung disease, heart disease, hypertension or cancer), or self-reported obesity).
		
		Exclusion criteria:
		Any condition associated with bleeding risk
			• Rivaroxaban (10 mg tablet)
			vs
			• Placebo (1 multivitamin tablet)
			
			Total duration of therapy: 21 days
				Primary outcomes:
				• **Primary safety endpoint:** frequency of adverse events (AEs), discontinuation, serious AEs , hypersensitivity & major bleeding events through Day 35.
				
				• **Primary efficacy endpoint:** Progression to moderate/severe disease category through Day 28.
				
				Endpoints measured using the Gates MRI scale for assessment of Clinical Status of COVID-19 Patients:
				
				-1: Asymptomatic or symptoms similar to pre-COVID status
				-2: Mild
				-3: Moderate or severe
				-4: Critically ill
				-5: Critically ill with invasive mechanical ventilation or extrapulmonary complication
				-6: Critically ill with Extra-Corporeal Membrane Oxygenation (ECMO)
				-7: Death
					246 - rivaroxaban & 251- placebo
					
					At interim analysis (03/02/21), the Independent Data Monitoring Committee recommended that the study be stopped because this futility boundary was crossed
					
					Rivaroxaban vs Placebo, respectively
					
					Primary safety endpoint:
					• Frequency of Any AEs: n=35/219 (16.0%) vs 36/230 (15.7%)
					• Serious AEs: 2/219 (0.9%) vs 7/230 (3.0%)
					• AEs resulting in discontinuation of study intervention: 4/219 (1.8%) vs 5/230 (2.2%)
					• Hypersensitivity: 0 (0%) - both groups
					• Major bleeding events: 0 (0%) - both groups
					• Clinically relevant non-major bleeding: 5/219 (2.3%) vs 2/230 (0.9%)
					• Discontinuation: All discontinued study due to clinically relevant bleeding
					
					Primary efficacy endpoint: Proportion with disease progression
					• ITT: 46/222 (20.7%) [15.8-26.4] vs 44/222 (19.8%) [15.0-25.5], Risk difference = 1.0 (p=0.78) [-6.4,8.4]
					• mITT (ITT who received ≥1 dose of study drug and had mild disease at Day 1): 18/192 (9.4.%) [5.8-14.1] vs 23/199 (11.6%) [7.7-16.6] Risk difference = -2.2 (p=0.47) [-8.4, 4.0]
						• Phase 2b study
						• Published article & protocol with statistical methods were available for data extraction
						• Sample size small to detect an effect size <35% for disease
						• Analyses:
						  ○ ITT analysis (all randomized)
						  ○ mITT (ITT who received ≥ 1 dose of study drug with mild disease at Day 1
						  ○ Per protocol (PP) population (mITT who did not deviate greatly from protocol).
						  ○ Safety analysis included participants who had at least 1 dose of study drug.
						
						Overall judgement with regards to risk of bias: HIGH
						• *Randomisation*: Randomization was conducted & stratified by site & number of days since onset of symptoms. **LOW RISK**
						• *Selection:* Concerns over limited enrollment of participants with the highest risk for COVID-19 (elderly, minorities and subjects with comorbidities) due to recruitment via social media and virtual trial design platforms. **HIGH RISK**
						• *Performance:* Protocol indicated that efforts would be taken to blind patients & staff, although if investigated one could identify the active drug due to embossing on the tablet. **HIGH RISK**
						• *Missing outcome data:* n=64 discontinued the study and n=89 discontinued study drug (similar between groups). **MODERATE RISK**
						• *Measurement of the outcome:* Gates MRI scale was not validated. Initiation of study drug might have been delayed by 2 days due to shipping resulting in proportion of participants experiencing negative SARS CoV-2 PCR and/or COVID-19 progression at Day 1. **HIGH RISK**
						• *Selection of the reported results:* Trial analysed as pre-specified for the outcomes collected as outlined in the protocol. **LOW RISK**

REFERENCES

[1] Xarelto (rivaroxaban) label – Accessdata.fda.gov. [Accessed 7 October 2021]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022406s015lbl.pdf

[2] Xarelto. Prescribing Information. [Accessed 7 October 2021]. https://www.xarelto-us.com/

[3] SAHPRA Approved Package insert. [Accessed 7 October 2021]. http://www.sahpra.org.za/wp-content/uploads/2020/06/Xarelto_PI_Bayer_MCC-Format27-January-2010.pdf

[4] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020; https://doi.org/10.1111/ jth.14768

[5] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18: 1094–1099. https://doi.org/10.1111/jth.14817

[6] Paranjpe I, Fuster V, Lala A, Russak A, Glicksberg BS, Levin MA, Charney AW, Narula J, Fayad ZA, Bagiella E, Zhao S, Nadkarni GN, Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19, Journal of the American College of Cardiology (2020), https://doi.org/10.1016/j.jacc.2020.05.001

[7] Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020 Aug;18(8):1995-2002. https://pubmed.ncbi.nlm.nih.gov/32369666/

[8] South African National Department of Health. A Review of the Optimal Dose of Either Unfractionated Heparin or Low Molecular Weight Heparin in the Prevention of Venous Thromboembolism in Patients With Severe COVID-19: Evidence Review of the Clinical Benefit and Harm. [Accessed 7 October 2021]. https://www.health.gov.za/covid-19-rapid-reviews/

[9] Lopes RD, de Barros e Silva PGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open label, multicentre, randomised, controlled trial. The Lancet. 2021;397(10291):2253-63. https://pubmed.ncbi.nlm.nih.gov/34097856/

[10] Ananworanich J, Mogg R, Dunne MW, Bassyouni M, David CV, Gonzalez E, Rogalski-Salter T, Shih H, Silverman J, Medema J, Heaton P. Randomized study of rivaroxaban vs. placebo on disease progression and symptoms resolution in high-risk adults with mild COVID-19. Clin Infect Dis. 2021 Sep 15:ciab813. doi: 10.1093/cid/ciab813

[11] National Institute of Health. COVID-19 treatment guidelines. Antithrombotic Therapy in Patients With COVID-19. Last Updated 11 February 2021. [Accessed 7 October 2021]. https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/

[12] National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19. Version 43.1. Published 29 September 2021. [Accessed 7 October 2021] https://covid19evidence.net.au/