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:

<table>
<thead>
<tr>
<th>Type of recommendation</th>
<th>We recommend against the option and for the alternative (strong)</th>
<th>We suggest not to use the option or to use the alternative (conditional)</th>
<th>We suggest using either the option or the alternative (conditional)</th>
<th>We suggest using the option (conditional)</th>
<th>We recommend the option (strong)</th>
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</thead>
<tbody>
<tr>
<td>Recommendation:</td>
<td>X</td>
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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\(^{16}\)) 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 breaths 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*: “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* 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>
<thead>
<tr>
<th>Citation</th>
<th>Study design</th>
<th>Population (n)</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Effect sizes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ananworanich et al, 2021</td>
<td><strong>RCT</strong> Multiple outpatient clinics &amp; a virtual site (Decentralized Clinical Trial Operating System™) – representing 47 US states</td>
<td>n=497</td>
<td>• Rivaroxaban (10 mg tablet) vs Placebo (1 multivitamin tablet)</td>
<td><strong>Primary outcomes:</strong> Frequency of adverse events (AEs), discontinuation, serious AEs, hypersensitivity &amp; major bleeding events through Day 35.</td>
<td>246 - rivaroxaban &amp; 251 - placebo</td>
<td>• Phase 2b study</td>
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<tr>
<td>Protocol Number:</td>
<td>Gates MRI-COD-01-T01-01</td>
<td></td>
<td>Total duration of therapy: 21 days</td>
<td>• Primary safety endpoint: frequency of adverse events (AEs), discontinuation, serious AEs, hypersensitivity &amp; major bleeding events through Day 35.</td>
<td></td>
<td>• Published article &amp; protocol with statistical methods were available for data extraction</td>
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<tr>
<td>Funding: Bill &amp; Melinda Gates Medical Research Institute (Gates MRI)</td>
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<td></td>
<td><strong>Primary efficacy endpoint:</strong> Progression to moderate/severe disease category through Day 28.</td>
<td><strong>Primary safety endpoint:</strong> Frequency of Any AEs: n=35/219 (16.0%) vs 36/230 (15.7%)</td>
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<td>• Sample size small to detect an effect size &lt;35% for disease</td>
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<td><strong>Endpoints measured using the Gates MRI scale for assessment of Clinical Status of COVID-19 Patients:</strong></td>
<td><strong>Primary safety endpoint:</strong> Serious AEs: 2/219 (0.9%) vs 7/230 (3.0%)</td>
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<td>• Analyses:</td>
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<td></td>
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<td></td>
<td>• Asymptomatic or symptoms similar to pre-COVID status</td>
<td><strong>AEs resulting in discontinuation of study intervention:</strong> 4/219 (1.8%) vs 5/230 (2.2%)</td>
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<td>o ITT analysis (all randomized)</td>
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<td></td>
<td></td>
<td></td>
<td>• Mild</td>
<td><strong>Hypersensitivity:</strong> 0 (0%) - both groups</td>
<td><strong>Primary efficacy endpoint:</strong> Proportion with disease progression</td>
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<td></td>
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<td></td>
<td>• Moderate or severe</td>
<td><strong>Major bleeding events:</strong> 0 (0%) - both groups</td>
<td>• 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]</td>
<td><strong>Performance:</strong> Protocol indicated that efforts would be taken to blind patients &amp; staff, although if investigated one could identify the active drug due to embossing on the tablet.</td>
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<td></td>
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<td></td>
<td>• Critically ill</td>
<td><strong>Clinically relevant non-major bleeding:</strong> 5/219 (2.3%) vs 2/230 (0.9%)</td>
<td>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]</td>
<td><strong>Missing outcome data:</strong> n=64 discontinued the study and n=89 discontinued study drug (similar between groups).</td>
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<td>• Critically ill with invasive mechanical ventilation or extrapulmonary complication</td>
<td><strong>Discontinuation:</strong> All discontinued study due to clinically relevant bleeding</td>
<td></td>
<td>• 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.</td>
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<td></td>
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<td></td>
<td>• Critically ill with Extra-Corporeal Membrane Oxygenation (ECMO)</td>
<td><strong>Primary efficacy endpoint:</strong> Proportion with disease progression</td>
<td></td>
<td><strong>HIGH RISK</strong></td>
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<td>-7: Death</td>
<td><strong>Primary safety endpoint:</strong></td>
<td>• ITT analysis (all randomized)</td>
<td>• 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.</td>
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<td>-6: Critically ill with Extra-Corporeal Membrane Oxygenation (ECMO)</td>
<td><strong>Primary efficacy endpoint:</strong> Proportion with disease progression</td>
<td>• 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]</td>
<td><strong>Performance:</strong> Protocol indicated that efforts would be taken to blind patients &amp; staff, although if investigated one could identify the active drug due to embossing on the tablet.</td>
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<td>-5: Critically ill with invasive mechanical ventilation or extrapulmonary complication</td>
<td><strong>Primary efficacy endpoint:</strong> Proportion with disease progression</td>
<td>• 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]</td>
<td><strong>Measuring the outcome:</strong> 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.</td>
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<td>-4: Critically ill</td>
<td><strong>Primary efficacy endpoint:</strong> Proportion with disease progression</td>
<td>• 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]</td>
<td><strong>Selection of the reported results:</strong> Trial analysed as pre-specified for the outcomes collected as outlined in the protocol.</td>
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**Table 1:** Characteristics of the RCT

- **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
REFERENCES

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


