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

TITLE: EXTENDED THROMBOPROPHYLAXIS WITH RIVAROXABAN IN PATIENTS WITH COVID-19 AT HIGH RISK OF THROMBOTIC EVENTS

DATE: 6 June 2022

Key findings

- This evidence brief summarises evidence about extended thromboprophylaxis using rivaroxaban in patients with COVID-19 at high risk of thrombotic events post-discharge from hospital
- The National Essential Medicines List Committee (NEMLC) identified a single open-label, randomized trial for inclusion (n=320)
- Overall, for all outcomes, the certainty of the evidence was rated as very low due to low event rates and small sample size, thus the trial was underpowered to answer the question. Overall, we are uncertain about the effect of rivaroxaban for this indication.
- We found that extended thromboprophylaxis with rivaroxaban in hospitalised COVID-19 patients at high risk of thrombotic events post-discharge resulted in little to no difference in clinically important outcomes of mortality [Risk Ratio (RR) 0.11 (95% CI 0.01 to 2.05)], number of thromboembolic events [RR 0.45 (95% CI 0.16 to 1.28)] and bleeding events [there were no major bleeding events in either arm], very low certainty.
- Implication for practice: Providing rivaroxaban at discharge to patients with COVID-19 at high risk for thrombotic events did not improve clinically important outcomes. There is currently insufficient evidence to support its inclusion in COVID-19 treatment guidelines in South Africa.

NEMLC 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: The Committee suggests that rivaroxaban should not be used for extended thromboprophylaxis in patients with COVID-19 at high risk of thrombotic events post-discharge from hospital, except in the context of a clinical trial. *Rationale:* The available evidence is from a single trial which indicates that rivaroxaban may be no more effective than standard care in preventing thrombotic events in patients with COVID-19 at high risk of thrombotic events post-discharge from hospital. Data is limited at present. **Level of Evidence: Very low certainty evidence**					

(Refer to appendix 2 for the evidence to decision framework)

NEML 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. Secretariat: Trudy Leong (NDoH), Milli Reddy (BHPSA).

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

PROSPERO registration: CRD42021286710

BACKGROUND

Rivaroxaban is a direct oral anticoagulant (DOAC) that exerts a factor Xa inhibitory effect. It has United States Food and Drug Administration (FDA) regulatory approval for reducing the risk of thromboembolic events in atrial fibrillation and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). It is also approved in the US to reduce the risk of major cardiovascular events in patients with coronary artery disease and peripheral arterial disease (1, 2).

Risk of thrombotic events was increased in patients with COVID-19 prompting the use of prophylactic parenteral anticoagulation during hospitalization (3). There is no consensus on the use of extended thromboprophylaxis in the post-hospitalisation COVID-19 population. A large prospective registry cohort study, comprising 4,906 post-discharge patients with COVID-19, showed that the incidence of the primary endpoint of venous thromboembolism (VTE), arterial thromboembolism, or all-cause death was 7.13%, and was 46% lower in patients who received post-discharge prophylactic anticoagulation (4). The MARINER trial (A Study of Rivaroxaban on the Venous Thromboembolic Risk in Post-Hospital Discharge Patients), a study performed some years prior to the SARS-CoV-2 pandemic, randomised 12,024 patients at hospital discharge to either once-daily rivaroxaban at a dose of 10 mg (with the dose adjusted for renal insufficiency) or placebo for 45 days. The primary efficacy outcome was a composite of symptomatic VTE or death due to VTE and the principal safety outcome was major bleeding. Of the 12,024 participants who underwent randomisation, 12,019 were included in the intention-to-treat analysis. The trial did not demonstrate superiority for the primary efficacy outcome which occurred in 50 of 6,007 participants (0.83%) who received rivaroxaban and in 66 of 6,012 participants (1.10%) who received the placebo (hazard ratio, 0.76; 95% confidence interval [CI], 0.52 to 1.09; P = 0.14). However, in the pre-specified secondary outcome of symptomatic non-fatal VTE there was a 56% reduction in the relative risk (hazard ratio, 0.44; 95% CI, 0.22 to 0.89) (5). A subsequent exploratory analysis of the same trial excluding those patients with moderate renal insufficiency given a lower dose of rivaroxaban 7,5 mg daily, found a 28% reduction (hazard ratio: 0.72; 95% confidence interval: 0.52 to 1.00; p= 0.049) in fatal and major thromboembolic events without a significant increase in major bleeding (6).

This review aimed to assess the role of extended thromboprophylaxis using rivaroxaban in patients with COVID-19 at high risk of thrombotic events post discharge from hospital.

RESEARCH QUESTION: Should patients with COVID-19 who are at high risk of thrombotic events receive *rivaroxaban* thromboprophylaxis after discharge from hospital?

METHODS

The National Essential Medicines List Committee (NEMLC) identified a single trial by Ramacciotti *et al* (7) for inclusion. The COVID-nma.com Living review database was also searched on 16 May 2021. Data extraction was done by one reviewer (SE) and checked by a second reviewer. The main characteristics of the included study and study outcomes are shown in Table 1.

Review Manager (Revman) 5 software to perform the analyses and Risk of Bias was assessed using Cochrane risk of bias tool within Revman. We reported risk ratios (RR) for dichotomous data with 95% confidence intervals (CI). GRADE was used to assess the overall confidence of the evidence considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness (Guyatt *et al*) (8). Table 2 is a GRADE evidence profile for the comparison rivaroxaban compared to usual care.

Eligibility criteria for review

Population: Outpatient care post-discharge of patients who were randomised with COVID-19 and are at increased risk for thrombotic events (increased risk for venous thromboembolism defined as (International Medical Prevention Registry on Venous Thromboembolism [IMPROVE] venous thromboembolism score of ≥4 or 2–3 with a D-dimer >500 ng/mL)). These patients received standard heparin-based prophylaxis during hospitalization.

Intervention: Rivaroxaban (Direct-Acting Oral Anticoagulant [DOAC]) at prophylactic doses

Comparators: No anticoagulation, standard of care (regular follow-up)

Outcomes: Mortality; number of thromboembolic events; bleeding events; adverse reactions and adverse events

Study design/s: Randomised controlled trials and, systematic reviews of randomised controlled trials

RESULTS

Results of search

A single trial was identified for inclusion by the NEMLC (Ramacciotti *et al*); the COVID-nma.com Living review database search did not yield results relevant to the study PICO.

Description of studies

The Ramacciotti *et al* 2022 trial (MICHELLE) (7) investigated the role of extended thromboprophylaxis (post-discharge from hospital) using rivaroxaban in patients hospitalised with COVID-19 and at increased risk for venous thromboembolism (VTE) compared to standard of care i.e. regular follow-up and no anticoagulation in a 1:1 ratio. Increased risk for VTE was defined as (International Medical Prevention Registry on Venous Thromboembolism [IMPROVE] VTE score of ≥4 or 2–3 with a D-dimer >500 ng/mL). The authors hypothesised that "in patients hospitalised with COVID-19, prophylaxis with rivaroxaban 10 mg/day for 35 days after discharge would improve clinical outcomes, including major and fatal thromboembolic events".

The MICHELLE trial was a pragmatic, open-label (with blinded adjudication), multicentre, randomised, controlled trial in patients discharged after hospitalisation for COVID-19. The trial enrolled 320 participants from 14 hospitals in Brazil. Patients at discharge who were hospitalised with COVID-19 (confirmed by reverse-transcriptase–polymerase-chain-reaction [RT-PCR], antigen, or IgM tests) for a minimum of 3 days (with or without an intensive care unit (ICU) stay, were included. All patients received some form of heparin-based thromboprophylaxis (enoxaparin, unfractionated heparin or fondaparinux) during hospitalisation. Patients were also required to have an increased risk of VTE as defined previously. The exclusion criteria comprised participants under 18 years, suspicion or confirmation of a thromboembolic event, a recent history of any bleeding or major surgery, participant presenting allergy, hyper-or known intolerance to rivaroxaban or any of its excipients and others as listed in Table 1. 160 participants were assigned to receive rivaroxaban 10 mg/day orally for 35 days and 160 participants received regular follow-up on Day 7 and Day 35 post-discharge with no anticoagulation (control arm). Table 1 summarises the characteristics and results reported of the included trial. An intention-to-treat (ITT) analysis was conducted of patients randomised to rivaroxaban and usual standard of care but no anticoagulation.

Appraisal of the trial

The risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions (9). Domains evaluated include selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data) and reporting bias (selective reporting). Overall, the trial was judged to have a risk of bias with some concerns due to *selection (allocation concealment) and performance bias*. Random sequence generation was judged to be low risk as "randomisation was done in permuted blocks of variable size, using a central, concealed, web-based, automated randomisation system". The trial was an open-label study, with no masking of investigators or patients to group allocation; hence high risk of bias performance bias domains. An independent clinical events adjudication committee, whose members were unaware of the study treatment assignment, evaluated all events/outcomes. An independent core laboratory performed image analysis. Where imaging results were not available, but there was a high clinical suspicion of DVT or PE, the case was classified as such. Thus, detection bias was judged to be low risk. There was a low risk of bias for missing outcomes as data available to analyse was of >99% of the enrolled participants; two patients (one from each group) withdrew informed consent and were excluded from the primary analysis. Thus, 159 participants per group were included in the intention-to-treat analysis. The risk of bias was low in the selection of reported results since the outcomes and analyses plan were pre- specified in a published protocol (Figure 1).

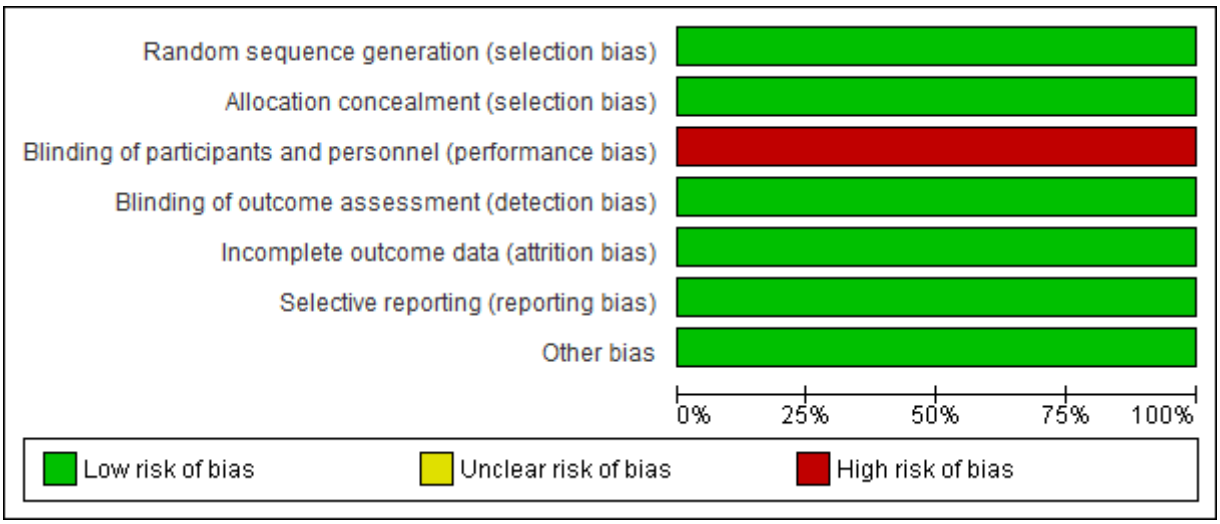

Figure 1. Risk of bias of the included studies

EFFECTS OF INTERVENTION

The GRADE Evidence Profile Table 2 and Summary of findings in Table 3 summarises the effects of the intervention for each of the following outcomes. The study outcomes are described in detail in Table 1.

Primary outcomes

For all outcomes, the certainty was rated as very low due to low event rates and small sample size, underpowered to answer the question. Therefore, overall, we are uncertain about the effect of rivaroxaban for this indication.

1. **Mortality (fatal PE and cardiovascular related)***
   There were three deaths (1.89%) due to PE and one death (0.63%) due to cardiovascular related causes in the control group (n = 159) and none in the rivaroxaban group. Rivaroxaban compared to no anticoagulation may result in little or no difference in mortality (day 35), Risk Ratio (RR) 0.11 (95% CI 0.01 to 2.05), n = 318, very low certainty evidence due to small sample size, very low event rates and confidence intervals that range from 99% reduction to 2 fold increase).

2. **Number of thromboembolic events** (A composite of symptomatic VTE, asymptomatic VTE detected by bilateral lower limb venous Doppler ultrasound and CT pulmonary angiogram, symptomatic arterial thromboembolism [myocardial infarction, non-haemorrhagic stroke, and major adverse limb event])
   Rivaroxaban (3.14%, [5/159]) compared to no anticoagulation (6.92%, [11/159]) may result in little to no difference in thromboembolic events (day 35), RR 0.45 (95% CI 0.16 to 1.28), n = 318, very low certainty evidence.

3. **Major bleeding** (according to the International Society on Thrombosis and Haemostasis (ISTH) criteria is defined as evident haemorrhage associated with decrease in haemoglobin levels of 2 g/dl or higher or leading to transfusion of two or more units of red blood concentrate or whole blood, or haemorrhage occurring in a critical site: e.g., intracranial, intra-spinal, intraocular, pericardial, intra-articular, intramuscular with compartmental, retroperitoneal syndrome, or a fatal outcome)
   Rivaroxaban may result in little to no difference in major bleeding; there were no major bleeding events in either arm, n = 318, very low certainty evidence.

   *Deaths were counted from Table 2: Efficacy and safety outcomes (ITT analysis) in the Ramacciotti paper (7), Components of primary outcome

Secondary outcomes

1. **Bleeding events (Combination of clinically relevant non-major [CRNM] and other bleeding:** CRNM is defined as an evident haemorrhage not meeting the criteria of major bleeding but associated with medical intervention, unscheduled contact [visit or phone call] with a doctor, interruption [temporary] of study treatment, or associated with discomfort to the participant such as pain or impairment of daily activities. Other bleeding was

defined as any other evident haemorrhage that does not meet the ISTH criteria for major or non-major clinically relevant haemorrhage.
CRNM bleeding occurred in two patients treated with rivaroxaban (one nose and one urinary bleed) and two in the control group. The combination of CRNM, and other bleeding occurred in four (2.52%) of 159 patients receiving rivaroxaban and three (1.89%) of 159 patients allocated to no anticoagulation. Rivaroxaban compared to no anticoagulation may result in little to no difference in bleeding events, RR 1.33 (95% CI 0.30 to 5.86), n = 318, very low certainty evidence.

2. **Adverse reactions – Allergic reactions**
Rivaroxaban may result in little to no difference in adverse reactions; allergic reactions occurred in two (1.3%) of patients assigned to the rivaroxaban group (n=159).

CONCLUSION

We appraised and reported on the trial Ramacciotti 2022 (6) which was an open-label (with blinded adjudication), multi-centre, randomised, controlled trial, which reported on the use of rivaroxaban compared with no anticoagulation in patients discharged after being hospitalised with COVID-19. Between October 2020 and June 2021, the trial recruited 320 participants. Overall, extended thromboprophylaxis with rivaroxaban in hospitalised COVID-19 patients at high risk of thrombotic events post-discharge compared to no anticoagulation little or no difference in mortality, the number of thromboembolic events, non-major and other bleeding events, however, the overall evidence certainty is low and further studies may affect the effect sizes substantially.
Adding rivaroxaban to the standard of care for hospitalized patients with COVID-19 at high risk of VTE post-discharge may have little or no effect on clinically important outcomes, and the balance of benefit and harms of its use do not support inclusion in current guidelines.

REVIEWERS: Marc Blockman, Andy Parrish, Tamara Kredo, Sumayyah Ebrahim

DECLARATION OF INTERESTS: MB (Department of Pharmacology, University of Cape Town); AP (Walter Sisulu University); TK (Cochrane South Africa, South African Medical Research Council (SAMRC) and Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network; and SE (Cochrane South Africa, SAMRC and School of Clinical Medicine at University of KwaZulu-Natal), have no interests pertaining to rivaroxaban.

TK and SE are partly supported by the Research, Evidence and Development Initiative (READ-It) project and the Collaboration for Evidence Based Health Care and Public Health in Africa COVID-19 project funding (CEBHA+). READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies).

REFERENCES

1. US Food and Drug Administration. Xarelto (rivaroxaban) tablets, for oral use. 2011 [Cited 19 May 2022]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022406s015lbl.pdf
2. Bayer. Xarelto Prescribing Information. [Updated 02/22; cited 19 May 2022] Available from: https://www.xarelto.com/
3. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, Levi M, Samama CM, Giannis D. Scientific and standardization committee communication: Clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020.
4. Giannis D, Allen SL, Davidson A, et al. Thromboembolic outcomes of hospitalized COVID-19 patients in the 90-day post-discharge period: early data from the Northwell CORE-19 Registry. Blood 2020; 136: 33–34.
5. Spyropoulos AC, Ageno W, Albers GW, Elliott CG, Halperin JL, Hiatt WR, Maynard GA, Steg PG, Weitz JI, Suh E, Spiro TE. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. New England Journal of Medicine. 2018 Sep 20; 379(12):1118-27.
6. Spyropoulos AC, Ageno W, Albers GW, et al. Post-discharge prophylaxis with rivaroxaban reduces fatal and major thromboembolic events in medically ill patients. J Am Coll Cardiol 2020; 75: 3140–47.Ramacciotti E, Agati LB, Calderaro D, Aguiar VC, Spyropoulos AC, de Oliveira CC, Dos Santos JL, Volpiani GG, Sobreira ML, Joviliano EE, Júnior MS.
7. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. The Lancet. 2022 Jan 1; 399 (10319):50-9.
8. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011; 64 (4):383-94.

Higgins J, Deeks JJ, Altman DG. Special topics in statistics. In Higgins JP GS, editor(s). ed, *Cochrane handbook for systematic reviews of interventions Version 510*. Chapt 16. UK: The Cochrane Collaboration; 2011

TABLE 1. CHARACTERISTICS OF INCLUDED STUDIES

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
Ramacciotti E, Agati LB, Calderaro D, Aguiar VC, Spyropoulos AC, de Oliveira CC, Dos Santos JL, Volpiani GG, Sobreira ML, Joviliano EE, Júnior MS. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. The Lancet. 2022 Jan 1; 399 (10319):50-9.	Design Open-label, multi-centre, randomised trial conducted at 14 centres in Brazil Follow-up duration (days) 35 Funding Bayer: "The study funder had no role in the planning and design of the study, data collection, analysis, and interpretation, nor writing of the manuscript". Declarations "ER reports grants and consulting fees from Bayer and Pfizer; grants from the Brazilian Ministry of Science and Technology; and personal fees from Aspen Pharma, Biomm Pharma, and Daiichi Sankyo, outside of the submitted work. LBA reports grants from Bayer, Pfizer, and the Brazilian Ministry of Science and Technology. DC reports personal fees from Bayer, Janssen, Daiichi Sankyo, and Pfizer; and grants from Stago. ACS reports consulting fees from Janssen Research & Development, Bayer, Portola, Boehringer Ingelheim, Bristol Myers Squibb, and ATLAS group; and grants from Janssen and Boehringer Ingelheim. MLS reports personal fees from Bayer, Pfizer, and Sanofi. EEJ reports consulting and personal fees form Bayer. CD reports consulting and personal fees from Bayer, Novartis, and Daiichi Sankyo. SMVS reports	Sample size N=320 participants were randomly assigned (160 patients assigned to rivaroxaban 10mg/day and 160 to regular follow-up with no anticoagulation) for 35 days. Inclusion criteria 1. Male and non-pregnant female patients 18 years of age or older 2. Positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for SARS-CoV-2 in a respiratory tract sample 3. Pneumonia confirmed by chest imaging 4. ≥ 3 days of hospitalization 5. Both groups should have received prophylactic doses of enoxaparin (40 mg SC once daily), fondaparinux (2.5 mg once daily) or unfractionated heparin (UFH, 5.000 IU twice or three times a day), during the hospital stay 6. Additional risk factors for VTE, as indicated by a total modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk score of 4 or higher (scores range from 0 to 10, with higher scores indicating a higher risk of venous thromboembolism) or a risk score of 2 or 3 plus a plasma d-dimer level of more than twice the upper limit of the normal range at the time of discharge 7. Agreement to participate by providing the informed consent form	Intervention rivaroxaban 10mg/day Control Regular follow-up with no anticoagulation	Primary Outcomes • Efficacy: A composite of symptomatic or fatal venous thromboembolism, asymptomatic venous thromboembolism detected by bilateral lower limb venous Doppler ultrasound and CT pulmonary angiogram, symptomatic arterial thromboembolism (myocardial infarction, non-haemorrhagic stroke, and major adverse limb event), and cardiovascular death at day 35 analyzed in the ITT population • Safety: The primary safety outcome was major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria. "During the study, we added an amendment including arterial events for the primary outcome. We included myocardial infarction, non-haemorrhagic stroke, and major adverse limb events". Secondary Outcomes (Secondary endpoints are to compare rivaroxaban with standard post-hospital discharge treatment in clinically ill patients at high risk for VTE) • Efficacy: efficacy outcomes were a combination of symptomatic or fatal venous thromboembolism; a composite of symptomatic venous thromboembolism or all-cause mortality; and a composite of symptomatic venous thromboembolism, myocardial infarction, non-haemorrhagic stroke, or cardiovascular death (death from known cardiovascular disease or death in which cardiovascular disease cause cannot be excluded). • Safety: safety outcomes were a combination of major, clinically relevant non-major, and other bleeding, according to ISTH criteria *Results* • Two patients (one from each group) withdrew informed consent and were excluded from the primary analysis. Thus, 159 patients per group were included in the ITT analysis

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
	personal fees from Bayer. RCC reports personal fees from Boehringer Ingelheim and AstraZeneca. ATaf reports personal fees from Janssen and Recovery Force and grants from Bio Tap, Idorsia, Bristol Myers Squibb, Novo Nordisk, Janssen, and Doasense. RDL reports grants and personal fees from Bristol Myers Squibb, Pfizer, GlaxoSmithKline, Medtronic PLC, and Sanofi; and personal fees from Amgen, Bayer, and Boehringer Ingelheim, outside of the submitted work. All other authors declare no competing interests". <u>Informed Consent</u> All participants provided written or electronically signed informed consent.	<u>Exclusion criteria</u> 1. Age <18 years 2. Physician decision that involvement in the trial was not in the patient's best interest 3. Any hemorrhage (defined as hemorrhage requiring hospitalization, transfusion, surgical intervention, invasive procedures, occurring in an anatomically critical site, or causing disability) within three months before randomization or occurring during the initial hospitalization period 4. Major surgery, parenchymal organ biopsy, ophthalmic surgery (excluding cataract surgery) or serious trauma (including head trauma) within four weeks prior to randomization. The investigator's criterion should be applied, but the following guidelines can be considered for the purpose of this study: Major surgeries often involve opening one or more major body cavities: the abdomen, chest, or skull, and can stress vital organs. Major surgeries are usually performed using general anesthesia in a hospital operating room by a surgeon (or surgeons) and usually require admission for at least one night in the hospital after surgery. On the other hand, with minor surgeries, the main body cavities are not opened. Minor surgeries may involve the use of local, regional, or general anesthesia and can be performed in the emergency room, in an outpatient operating room, or in a clinical office. Vital organs are usually not stressed, and surgery can be performed by a single		• Baseline characteristics were balanced between groups. The mean age was 57.1 years; Standard Deviation (SD) 15.2 years), 127 (40%) were women, 191 (60%) were men • For the primary efficacy outcome at day 35, five (3.14%) of 159 patients allocated to the rivaroxaban group and 15 (9.43%) of 159 patients allocated to the control group had a primary efficacy outcome event (Relative risk [RR] 0.33, 95% Confidence Interval [CI] 0.13–0.90; p=0.0293) yielding a relative risk reduction of 67% • For the primary safety outcome: there were no ISTH-defined major bleeding events in either group • For the pre-specified secondary efficacy outcomes, symptomatic and fatal venous thromboembolism occurred in one (0.63%) of 159 patients in the rivaroxaban group compared with eight (5.03%) of 159 patients in the control group (RR 0·13, 95% CI 0.02–0.99; p=0.0487); symptomatic venous thromboembolism and all-cause mortality occurred in four (2.52%) of 159 patients in the rivaroxaban group and nine (5.66%) of 159 patients in the control group (RR 0.44, 95% CI 0.14–1.41; p=0.1696); and the composite of symptomatic venous thromboembolism, myocardial infarction, stroke, or cardiovascular death occurred in one (0.63%) of 159 patients in the rivaroxaban group and nine (5.66%) of 159 patients patients in the control group (RR 0.11, 95% CI 0.01–0.87; p=0.0360) • For the secondary safety analysis, clinically relevant non-major bleeding occurred in two patients treated with rivaroxaban (one nose and one urinary bleed) and two in the control group (RR 1.00, 95% CI 0.14–7.01; p=1.0000). The prespecified combination of major, clinically relevant non-major, and other bleeding occurred in four (2.52%) of 159 patients receiving rivaroxaban and three (1.89%) of 159 patients allocated to no anticoagulation (RR 1.33, 95% CI 0.30–5.86; p=0.7034) • Allergic reactions occurred in two (1.3%) of patients assigned to the rivaroxaban group

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
		doctor, who may or may not be a surgeon. In general, the person can return home on the same day that minor surgery is performed. The investigator's criteria should be applied, but fracture or concussion should be considered serious head trauma, although external trauma without fracture or concussion may be considered for inclusion 5. Any major planned surgery (see exclusion criterion #2) or important invasive diagnostic procedure provided for during the clinical study 6. Participants with any known coagulopathy or hemorrhagic diathesis or an international normalized ratio (INR) > 1.5 during initial hospitalization without a subsequent value (the last value before randomization) that is ≤ 1.5 7. A history of hemorrhagic stroke or any intracranial hemorrhage at any time in the past, evidence of primary intracranial hemorrhage on CT or MRI imaging of the brain, or clinical presentation consistent with intracranial hemorrhage. This also applies to participants hospitalized due to ischemic stroke at randomization. Participants with hemorrhagic transformation of an ischemic infarction prior to randomization are not excluded unless there is evidence of parenchyma hemorrhage (types HP-1 and HP-2): Hemorrhagic infarction type 1 (IH-1) is defined as a small petechiae along the margins of the infarction and type 2 IH (IH-2) is		

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
		defined as more confluent petechiae within the infarcted area, but without expansive effect. HP type 1 (HP-1) is defined as hematoma in ≤ 30% of the infarct area with some mild expansive effect; HP type 2 (HP-2) is defined as dense hematoma > 30% of the infarction area with substantial expansive effect or as any hemorrhagic lesion outside the infarction area (Berger, 20012). Participants with type 1 and IH-2 hemorrhagic infarction are NOT excluded from this study, but participants with HP-1 and HP2 are excluded from this study 8. The participant has a history or presence of intracranial neoplasia (benign or malignant), brain metastases, arteriovenous malformation (VA) or aneurysm 9. Active gastroduodenal ulcer, defined as diagnosed at three months, or current known or symptomatic arteriovenous malformations of the gastrointestinal tract 10. Platelet count in the screening < 50 x 109 cells/l 11. Active cancer (excluding non-melanoma skin cancer), defined as cancer that is not in remission or requires active chemotherapy or auxiliary therapies such as immunotherapy or radiotherapy. Chronic hormone therapy (e.g., tamoxifen, anastrozole, leuprolide acetate) is allowed for cancer in remission 12. Any clinical picture (e.g., atrial fibrillation) requiring the use of any		

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
		parenteral(s) or oral anticoagulant(s) (e.g., sodic warfarin or vitamin K antagonists, factor II inhibitors or Xa, fibrinolytics) concomitantly with the study drug 13. Bilateral and unilateral amputation of the lower extremities above the knee 14. Participant presenting allergy, hyper or known intolerance to rivaroxaban or any of its excipients 15. Severe renal failure (baseline CrCl < 30 ml/min calculated using the Cockcroft-Gault) 16. Known significant liver disease (e.g., acute hepatitis, active chronic hepatitis, cirrhosis) that is associated with coagulopathy or moderate or severe hepatic impairment 17. Known HIV infection		

TABLE 2: GRADE EVIDENCE PROFILE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rivaroxaban	No anticoagulation	Relative (95% CI)	Absolute (95% CI)	
Mortality											
1	RCT	not serious	not serious	not serious	Critically serious[a]	none	0/159 (0.0%)	4/159 (2.5%)	**RR 0.11** (0.01 to 2.05)	**22 fewer per 1,000** (from 25 fewer to 26 more)	⊕◯◯◯ Very low
Thromboembolic events											
1	RCT	not serious	not serious	not serious	Critically serious[b]	none	5/159 (3.1%)	11/159 (6.9%)	**RR 0.45** (0.16 to 1.28)	**38 fewer per 1,000** (from 58 fewer to 19 more)	⊕◯◯◯ Very low
Major bleeding											
1	RCT	not serious	not serious	not serious	Critically serious[c]	none	There no major bleeding events in either arm				⊕◯◯◯ Very low
Bleeding events											
1	RCT	not serious	not serious	not serious	Critically serious[d]	none	4/159 (2.5%)	3/159 (1.9%)	**RR 1.33** (0.30 to 5.86)	**6 more per 1,000** (from 13 fewer to 92 more)	⊕◯◯◯ Very low
Adverse reactions											
1	RCT	not serious	not serious	not serious	Critically serious[e]	none	Two patients (1.3%) in in the rivaroxaban group (n=159) experienced allergic reactions. No details about the severity of the allergic reaction was provided.				⊕◯◯◯ Very low

CI: confidence interval; **RR:** risk ratio

Explanations

a. Downgraded by two levels for imprecision: Small sample size, low number of events and wide confidence interval ranging from a 99% reduction in risk to a 2-fold increase in risk

b. Downgraded by two levels for imprecision: Small sample size, low number of events and wide confidence interval ranging from a 84% reduction in risk to a 28% increase in risk

c. Downgraded by two levels for imprecision: Small sample size and no events occurred

d. Downgraded by two levels for imprecision: Small sample size, low number of events and wide confidence interval ranging from a 70% reduction in risk to a 5.8 fold increase in risk

e. Downgraded by two levels for imprecision: Small sample size, low number of events

TABLE 3: SUMMARY OF FINDINGS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no anticoagulation	Risk with rivaroxaban			
Mortality	25 per 1,000	**3 per 1,000** (0 to 52)	**RR 0.11** (0.01 to 2.05)	318 (1 RCT)	⊕◯◯◯ Very low[a]
Thromboembolic events	69 per 1,000	**31 per 1,000** (11 to 89)	**RR 0.45** (0.16 to 1.28)	318 (1 RCT)	⊕◯◯◯ Very low[a]
Major bleeding	There no major bleeding events in either arm			318 (1 RCT)	⊕◯◯◯ Very low[a]
Bleeding events	19 per 1,000	**25 per 1,000** (6 to 111)	**RR 1.33** (0.30 to 5.86)	318 (1 RCT)	⊕◯◯◯ Very low[a]
Adverse reactions	Two patients (1.3%) in in the rivaroxaban group (n=159) experienced allergic reactions. No details about the severity of the allergic reaction was provided			318 (1 RCT)	⊕◯◯◯ Very low[a]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations
a: Downgraded by two levels for imprecision

APPENDIX 1: EVIDENCE TO DECISION FRAMEWORK

Desirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies **x Don't know**	**Desirable effects: Mortality and thromboembolic events**	Uncertainty of evidence

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no anticoagulation	Risk with rivaroxaban			
Mortality	25 per 1,000	**3 per 1,000** (0 to 52)	**RR 0.11** (0.01 to 2.05)	318 (1 RCT)	⊕◯◯◯ Very low[a]
Thromboembolic events	69 per 1,000	**31 per 1,000** (11 to 89)	**RR 0.45** (0.16 to 1.28)	318 (1 RCT)	⊕◯◯◯ Very low[a]
Major bleeding	There no major bleeding events in either arm			318 (1 RCT)	⊕◯◯◯ Very low[a]
Bleeding events	19 per 1,000	**25 per 1,000** (6 to 111)	**RR 1.33** (0.30 to 5.86)	318 (1 RCT)	⊕◯◯◯ Very low[a]
Adverse reactions	Two patients (1.3%) in in the rivaroxaban group (n=159) experienced allergic reactions. No details about the severity of the allergic reaction was provided			318 (1 RCT)	⊕◯◯◯ Very low[a]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Undesirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies **X Don't know**	Undesirable effects: Bleeding, adverse events See table above	The number of events was noted to be small. However, there is uncertainty of the bleeding risk associated with rivaroxaban in the COVID-19 patient. .

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **X Probably no important uncertainty or variability** ○ No important uncertainty or variability		

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Favors the comparison **X Probably favors the comparison** o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know	On balance, the Committee considered that the balance of evidence probably favors the standard of care.	
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Large costs **X Moderate costs** o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	**Acquisition costs:** **Rivaroxaban 10mg/day x 35 days:** 1) R16.30 per tablet =R 569.93 - *Contract circular HP09-2021SD* 2) R30.60 per tablet (Bayer generic) = R1071.0 - *SEP database, 2 December 2021*	
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies **X No included studies**	No cost-effectiveness study was commissioned or reviewed	
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o Reduced o Probably reduced **X Probably no impact** o Probably increased o Increased o Varies o Don't know		
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
o No o Probably no **X Probably yes** o Yes o Varies o Don't know	No studies were reviewed, however, there is no reason to consider that this intervention, if effective, would not be acceptable to key stakeholders affected by this recommendation.	

Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no **X Probably yes** ○ Yes ○ Varies ○ Don't know	The intervention is SAHPRA registered and available in South Africa.	Reversal agent for rivaroxaban is currently not SAHPRA registered and not accessible in South Africa.

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
1	3 June 2022	MB, AP, TK, SE	Rivaroxaban should not be used for extended thromboprophylaxis in patients with COVID-19 at high risk of thrombotic events post-discharge from hospital, except in the context of a clinical trial. Very low certainty evidence shows that rivaroxaban may be no more effective than standard care.

For internal NDoH use:
WHO INN: Rivaroxaban
ATC: B01AF01
ICD10: U07.1/U07.2