Rivaroxaban to prevent major clinical outcomes in non-hospitalised patients with COVID-19: the CARE – COALITION VIII randomised clinical trial

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Summary

Background COVID-19 progression is associated with an increased risk of arterial and venous thrombosis. Randomised trials have demonstrated that anticoagulants reduce the risk of thromboembolism in hospitalised patients with COVID-19, but a benefit of routine anticoagulation has not been demonstrated in the outpatient setting.

Methods We conducted a randomised, open-label, controlled, multicentre study, evaluating the use of rivaroxaban in mild or moderate COVID-19 patients. Adults ≥18 years old, with probable or confirmed SARS-CoV-2 infection, presenting within ≤7 days from symptom onset with no clear indication for hospitalization, plus at least 2 risk factors for complication, were randomised 1:1 either to rivaroxaban 10 mg OD for 14 days or to routine care. The primary efficacy endpoint was the composite of venous thromboembolic events, need of mechanical ventilation, acute myocardial infarction, stroke, acute limb ischemia, or death due to COVID-19 during the first 30 days. ClinicalTrials.gov: NCT04757857.

eClinicalMedicine 2023;60: 102004
Published Online xxx https://doi.org/10.1016/j.eclinm.2023.102004

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Findings Enrollment was prematurely stopped due to sustained reduction in new COVID-19 cases. From September 29th, 2020, through May 23rd, 2022, 660 patients were randomised (median age 61 [Q1-Q3 47–69], 55.7% women). There was no significant difference between rivaroxaban and control in the primary efficacy endpoint (4.3% [14/327] vs 5.8% [19/330], RR 0.74; 95% CI: 0.38–1.46). There was no major bleeding in the control group and 1 in the rivaroxaban group.

Interpretation On light of these findings no decision can be made about the utility of rivaroxaban to improve outcomes in outpatients with COVID-19. Metanalyses data provide no evidence of a benefit of anticoagulant prophylaxis in outpatients with COVID-19. These findings were the result of an underpowered study, therefore should be interpreted with caution.

Funding COALITION COVID-19 Brazil and Bayer S.A.

Keywords: Anticoagulation; COVID-19; Outpatients; Randomised clinical trial

Research in context

Evidence before this study

Rivaroxaban and other anticoagulants have been evaluated either as therapeutic or prophylactic agents in hospitalised patients with COVID-19. The evidence for anticoagulants in different COVID-19 scenarios is conflicting and very uncertain. Nevertheless, higher-dose anticoagulants result in little to no difference in all-cause mortality, increasing minor bleeding in patients hospitalised with COVID-19, when compared to a lower-dose regimen. Furthermore, higher-dose anticoagulants may reduce pulmonary embolism with no additional benefits in any other major cardiovascular events. The role of routine anticoagulant prophylaxis in outpatients is unknown. There are ongoing trials in outpatients with COVID-19 which may possibly provide clearer evidence, but they are either completed with no posted results (NCT04508023), or in recruiting status (NCT04715295, NCT04351724), or have been terminated due to difficulties in patient recruitment (NCT04416048). Randomized trials have demonstrated that anticoagulants reduce the risk of thromboembolism in patients hospitalised with COVID-19, but a benefit of routine anticoagulation has not been demonstrated in outpatients with COVID-19.

Added value of this study

The CARE trial testing rivaroxaban versus control in 660 outpatients with COVID-19 found lower than expected event rates and no evidence that rivaroxaban prevented major thrombotic outcomes, hospitalisations requiring mechanical ventilation, and death within 30 days from randomisation.

Implications of all the available evidence

The results of the CARE trial suggest that there is no evidence to support the use of rivaroxaban to prevent micro or macro thrombosis-related disease progression or death in outpatients with COVID-19. The use of anticoagulant prophylaxis should not be routinely recommended in this clinical setting, and in light of these findings no decision can be made about the utility to improve patient outcomes.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections are characterised by a high prevalence of thrombotic complications.[1–3] Disease progression is accompanied by elevated blood levels of inflammatory and coagulation activation markers but these measures cannot reliably identify those at highest risk of thromboembolism and related complications.[4,5] In patients hospitalised with COVID-19, intensified compared with prophylactic anticoagulation reduces the risk of thromboembolism but increases the risk of bleeding, and has an uncertain net benefit.[6–11]

Anticoagulation is less well studied in outpatients with COVID-19. Small randomized trials completed to date have been inconclusive[12] and whether prophylaxis with rivaroxaban started in the early phase of COVID-19 might prevent adverse outcomes in this population is unknown.

We designed the CARE (COVID Antithrombotic Rivaroxaban Evaluation) randomised controlled trial (RCT) to assess whether early treatment with rivaroxaban 10 mg once daily (OD) for 14 days in outpatients with mild or moderate COVID-19 decreases the risk of major thrombotic outcomes, hospitalisation requiring mechanical ventilation, and death within 30 days from randomisation.

Methods

Study design and participants

The trial methods have been published previously.[13] Briefly, CARE was a randomised, open-label, controlled, multicenter study, evaluating the use of

rivaroxaban in outpatients with mild or moderate COVID-19. The trial was conducted in 33 sites in Brazil and was approved by national and institutional review boards. Written informed consent was obtained from all patients. Additional details of eligibility criteria, trial operations, participating centers, and number of patients randomized per site are available in the supplementary appendix (eTables 1 and 2). Trial was reported according to Consolidated Standards of Reporting Trials (CONSORT) 2010 updated statement[14] (Supplementary material).

Patients were eligible if they were aged ≥18 years with suspected or confirmed COVID-19 of mild or moderate severity, presenting within ≤7 days from symptom onset. In addition, at least two of the following risk factors for clinical deterioration were required for eligibility: age >65 years, hypertension diabetes mellitus, asthma, chronic obstructive pulmonary disease (COPD) or other chronic lung disease, current smoking, immunosuppression, obesity (defined as body mass index [BMI] ≥ 30 kg/m^2), history of non-active cancer, bedridden patient or with reduced mobility (cannot walk ≥50% of the awake time), previous history of VTE, or use of oral hormonal contraception. Risk factors were defined by a panel of trialists, cardiologists, infectious disease specialists, methodologists, and internal medicine experts, supported by the best available evidence. Risk factors chosen considered those mainly related with clinical respiratory and cardiovascular deterioration. Other factors which could be considered, as D-dimer, were not fully available in Brazil at the time trial was designed, therefore, were not considered. Detailed definitions of suspected or confirmed cases have been provided elsewhere[11] (See COVID-19 screening and trial procedures). Exclusion criteria were clinical indication for hospitalisation, positive test for influenza at the first medical care, known hypersensitivity to rivaroxaban, any known liver disease associated with coagulopathy (INR>1.5), pregnancy, lactation, persons of childbearing age not using a reliable contraceptive method, increased risk of bleeding, stroke in the last 30 days or any history of hemorrhagic or lacunar stroke, or any intracranial bleeding, or any intracranial neoplasm, brain metastasis, arteriovenous malformation or brain aneurysm, heart failure with left ventricular ejection fraction <30% or New York Heart Association (NYHA) class III or IV symptoms, estimated glomerular filtration rate (eGFR) < 30 mL/min, clinical indication for dual antiplatelet therapy or anticoagulation therapy (VTE, atrial fibrillation/flutter, mechanical valve prosthesis), severe thrombocytopenia (platelet count <50,000/mm^3), known non-cardiovascular disease associated with poor prognosis, systemic treatment with strong CYP 3A4 and p-glycoprotein inhibitors, patients currently under treatment with an investigational drug, concurrent participation in another experimental study for COVID-19, and chloroquine or hydroxychloroquine use associated with azithromycin.

Randomisation and allocation concealment

Patients were assigned through a 24-h, centralised, automated, internet-based randomisation system in a 1:1 ratio to receive open-label rivaroxaban 10 mg OD for 14 days or control (routine care). Randomisation was performed in permuted blocks of eight.

COVID-19 screening and trial procedures

All patients with acute flu-like signs and symptoms suspected of COVID-19 underwent nasopharyngeal/oropharyngeal swabs to test for SARS-CoV-2 infection as per local practice and availability of tests. Patients who were within 4–7 days from symptom onset underwent real-time reverse transcription–polymerase chain reaction assay (RT-PCR) or rapid immunochromatographic antigen test, whereas those who were >7 days from symptom onset underwent serum enzyme-linked immunoassays (ELISA) for IgM/IgG detection. Patients with negative test results released after study recruitment were instructed to stop rivaroxaban, but all randomized patients completed the planned 30-day follow-up.

Data were collected through an electronic case report form (e-CRF) system using REDCap software.[15] Each research center user received a unique access and was trained on how to use the system. Each center collected the data directly from the participant and/or its medical records and safely stored them in the e-CRF. The following demographic and clinical data were collected: age, sex, and relevant sociodemographic characteristics; results from molecular or serology tests for COVID-19 (according to the most appropriate time window for diagnosis); co-interventions; and duration of symptoms. Two follow-up visits were scheduled after randomisation: at 15 days, to assess study drug adherence and safety, and at 30 days, to assess efficacy and safety endpoints. This trial was registered at ClinicalTrials.gov, NCT04757857.

Primary and secondary outcomes

The primary efficacy endpoint was the composite of venous thromboembolic events (VTE), need of mechanical ventilation, MACE (defined as acute myocardial infarction, stroke, or acute limb ischemia), and death not attributed to major injury within 30 days from randomisation. Indication for hospitalisation followed the local practice and clinical judgement at each participating site. Secondary endpoints included: time from randomisation to hospitalisation; admission to intensive care unit; need for orotracheal intubation; composite vascular endpoint I: non-fatal myocardial infarction, non-fatal ischemic stroke, cardiovascular death, or VTE; composite vascular endpoint II: cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, acute limb ischemia, or VTE; major bleeding; and mortality. Hospitalisations due to COVID-19 were documented by the local study team and

essential data was collected and uploaded into the electronic data capture system at the coordinating center. We restricted VTE outcomes to symptomatic events and did not perform routine screening.

Safety was assessed during the 30-day follow-up. The main safety outcome was the International Society on Thrombosis and Hemostasis (ISTH) criteria for major bleeding, which include: fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.[16–18]

All outcomes were adjudicated by blinded members of the clinical events committee, which included two research physicians with experience in pharmacovigilance and clinical events classification in national and international studies.

Statistical analysis

Assuming 1:1 allocation, a 25% event rate in the control group for the primary outcome, and a 2-sided p value of 0.05, 932 (466 per allocation group) patients would provide 80% power to detect a 30% relative risk reduction. Further allowing for up to 5% loss to follow up, the target sample size was 1000 (500 per group) individuals. The sample size calculation was carried out using SAS 9.4 (PROC POWER procedure).[19] We acknowledge in retrospect that our projected event rate in the control group were unrealistically high. Several factors may have contributed: i) Lack of reliable information on true event rates; ii) Effect of increasing herd immunity which may have lowered event rates; and iii) Later effects of less virulent viral variants.

Descriptive analyses were presented as frequency and percentage, and as median and interquartile range. Pearson's chi-square test and Fisher's exact test were applied to evaluate the significance of differences in categorical variables, and the Mann–Whitney test was used for continuous variables.

Treatment effect size was assessed as Relative Risk (RR) with corresponding 95% confidence intervals (95% CI), calculated by the Wald's method.[20] In addition, the effect of the intervention on the primary outcome was expressed as hazard ratio (HR) and 95% CI derived from Cox regression. We examined the consistency of the effects of treatment in subgroups defined by sex, age, diabetes, hypertension and obesity, and hypertension and age. The results of subgroup analyses are presented with p-values for interaction.[21]

Based on patient recruitment, epidemiological data continuously gathered by the Ministry of Health, and regional reports regarding the number of new COVID-19 cases and related major adverse outcome rates, the Steering Committee (blinded to emerging treatment data) prespecified one additional endpoint, comprised of components of the primary outcome plus hospitalisation due to COVID-19, and to apply two additional statistical methods to the overall clinical efficacy assessment: a) Win-loss ratio analysis for the primary efficacy endpoint; and b) Win-loss ratio analysis for the primary efficacy endpoint plus hospitalisations due to COVID-19. By applying a nonparametric method, the win-loss ratio approach compared each participant from the treatment group with each participant from the control group using a hierarchical analysis that considered all binary events during the first 30 days after randomization: death, requirement of mechanical ventilation, thromboembolic event, and including COVID-19 hospitalisation. The win-loss ratio indicator represents the total number of wins divided by the total number of losses between the two arms of the study. A value greater than 1 indicates a result in favor of the rivaroxaban group. The win-loss ratio was reported with 95% CI.[22,23]

A sensitivity analysis only considering those patients with positive COVID-19 testing was performed. All statistical analyses were performed on the R statistic environment version 4.0.2. All analyses codes were electronically stored, and data might be shared according to principles, assumptions, and formal requests.

Analyses followed the intention-to-treat principle. Moreover, two interim analyses for safety and efficacy assessments were conducted according to the Haybittle–Peto approach, when the sample size reached 25% (250 individuals) and 50% (500 individuals). Because of the extreme boundaries employed at interim analyses, the final p-values were not adjusted.

After review and discussion with the Coalition COVID-19 Brazil Executive Committee, the Data and Safety Monitoring Board (DSMB), and with notification to Local and National Ethics Committees and participating sites, enrollment was prematurely stopped due to sustained reduction in new COVID-19 cases in Brazil and event rates lower than observed in the first year of the pandemic. The current COVID-19 vaccination rate in Brazil (80.56% with two doses and 50.52% with one booster dose) leads to fewer people at risk of developing clinical aggravation and requiring healthcare services, consequently affecting recruitment rates in clinical studies. The Executive Committee's decision to stop the study was made blinded to the study results.

We conducted a pairwise metanalysis to evaluate the whole evidence for hospitalisation, bleeding, thrombotic events, and death in the COVID-19 outpatient setting. We adopted both fixed and random effects metanalysis according to Mantel Haenszel method. Sensitivity analysis comprised leave-one out method and adjustment for similar sample size and event rate by means of Sidik-Jonkman estimator for Tau[2] and Hartung-Knapp adjustment for random effects model (KHSJ). Results are depicted for subgroups (LMWH, DOAC and Sulodexide) with the respective confidence and predictive intervals.

Furthermore, a Trial Sequential Analysis (TSA) was run for the primary outcome hospitalisation to assess whether the optimal informal size is achieved. Considering the metanalysis for hospitalisation estimates, we adopted a relative risk reduction of 13% (RR 0.87 in the random effects model), an event rate of 8.11% in the control arm and 80% of power. This model considered a type one error of 5.0% with and alfa-spending function of O'Brien-Fleming. Heterogeneity correction was model variance based.

Role of the funding source

Bayer Pharmaceutical provided the study drug (rivaroxaban) and had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. The authors had full access to all study data and final responsibility for the decision to submit for publication.

Changes from the planned protocol

Due to both the low event rate and health deterioration, outcomes as mechanical ventilation free-survival, out-of-hospital death not attributed to major injury, hospitalization in Intensive Care Unit, clinical requirement of mechanical ventilation and its duration were not reported since we had low event rate or because they did not occur.

Win-Ratio analyses and the endpoint hospitalization due to COVID-19 were not prespecified and were added as exploratory analyses.

Results

From September 29th, 2020, through May 23rd, 2022, 657 patients were randomised (Fig. 1). The baseline characteristics of the participants were well balanced between the groups (Table 1). The median age was 61 (47–69) years, 365 (56%) were women, and most prevalent risk factors were hypertension (521, 79%), obesity (392, 60%), diabetes, (235, 36%), current smoking (78, 12%), asthma (72, 11%), other lung diseases (27, 4%), and cancer (36, 5%). The most frequent signs and symptoms at presentation were cough (522, 79%), headache (435, 66%), fatigue (422, 64%), myalgia (365, 56%), sore throat (303, 46%), and fever (258, 39%). SARS-CoV-2 testing was positive in 552 (84%) patients. Median time from symptom onset to randomisation was 5 (3–6) days.

In the rivaroxaban group, 250 (76.5%) patients completed ≥12 days on study drug. The most common reasons to stop taking rivaroxaban were attending physician recommendation, patient decision not related to serious adverse events or side effects, and negative SARS-CoV-2 testing.

In the control group, 16 patients did receive non-study anticoagulation (16/330 = 4.85%). The use of non-study anticoagulant was an attending physician's decision. The main reasons for stopping study medication from physicians can be summarized as following: negative COVID-19 test result, minor bleeding, study endpoint hospitalization.

There was no significant difference in the primary efficacy endpoint rates between rivaroxaban (4% [14/327]) and control (6% [19/330]), with a RR 0.74 [95% CI 0.38–1.46]. When hospitalisation due to COVID-19 was added, event rates were 11% versus 11% (RR 0.98 [95%CI 0.64–1.51]). In addition, there was no treatment effect in any secondary efficacy outcome measure of the composite vascular endpoints I and II.

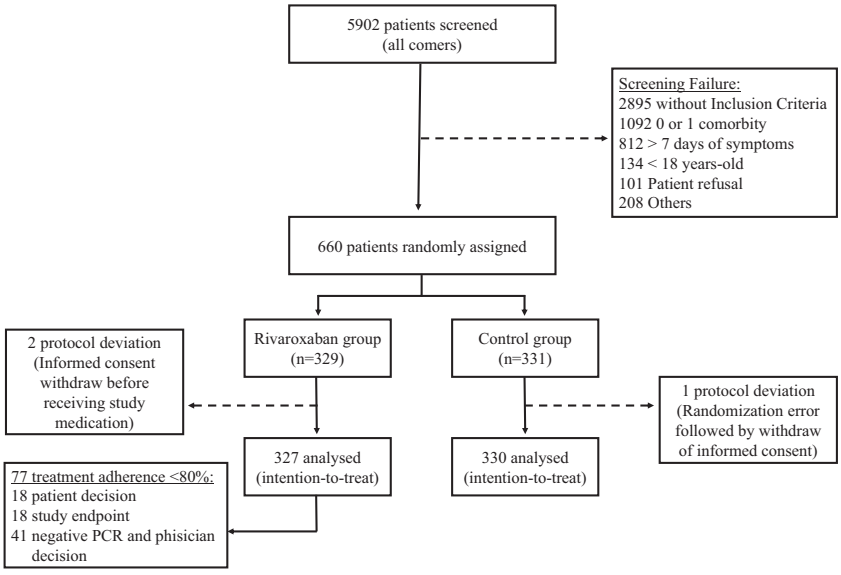

Fig. 1: CONSORT flow diagram for the CARE study.

	Rivaroxaban (n = 327)	Control (n = 330)	Total
Female, n (%)	187 (57)	178 (54)	365 (56)
Age, median (Q1, Q3)	61 (49, 69)	60 (46, 69)	61 (47, 69)
Race, n (%)			
White	250 (77)	248 (76)	498 (76)
Black	13 (4)	20 (6)	33 (5)
Mixed	60 (18)	58 (18)	118 (18)
Asian	3 (1)	1 (<1)	4 (1)
Educational level, n (%)			
Elementary	83 (27)	72 (23)	155 (25)
High school	134 (43)	145 (45)	279 (44)
University	95 (30)	101 (32)	196 (31)
Clinical history, n (%)			
Hypertension	259 (79)	262 (79)	521 (79)
Obesity	203 (62)	189 (57)	392 (60)
Diabetes mellitus	113 (35)	122 (37)	235 (36)
Asthma	33 (10)	39 (12)	72 (11)
Cancer	20 (6)	16 (5)	36 (5)
Lung disease	15 (5)	12 (4)	27 (4)
Myocardial infarction	7 (2)	11 (3)	18 (3)
Stable angina	8 (2)	6 (2)	14 (2)
Unstable angina	2 (1)	1 (<1)	3 (<1)
PCI	12 (4)	8 (2)	20 (3)
CABG surgery	5 (2)	4 (1)	9 (1)
Aortic aneurysm	0 (–)	4 (1)	4 (1)
VTE	11 (3)	6 (2)	17 (3)
Heart Failure	5 (2)	6 (2)	11 (2)
Rheumatological disease	6 (2)	8 (2)	14 (2)
Stroke	9 (3)	1 (<1)	10 (2)
Chronic renal disease	2 (1)	1 (<1)	3 (<1)
HIV/Aids	1 (<1)	2 (1)	3 (<1)
Current smoking	41 (12)	37 (11)	78 (12)
Clinical presentation, n (%)			
Cough	261 (80)	261 (79)	522 (79)
Headache	216 (66)	219 (66)	435 (66)
Fatigue	200 (61)	222 (67)	422 (64)
Myalgia	186 (57)	179 (54)	365 (56)
Sore throat	146 (45)	157 (48)	303 (46)
Fever	130 (40)	128 (40)	258 (39)
Diarrhea	86 (26)	81 (25)	167 (25)
Vomiting	65 (20)	73 (22)	138 (21)
Dyspnea	70 (21)	56 (17)	126 (19)
Chest pain	48 (15)	54 (16)	102 (16)
Abdominal pain	58 (18)	41 (12)	99 (15)
Wheezing	20 (6)	15 (5)	35 (5)
Vital signs and anthropometrics, median (Q1, Q3)			
Respiratory rate, bpm	18.0 (16.0, 19.0)	18.0 (16.0, 18.2)	18.0 (16.0, 19.0)
Heart rate, bpm	80.0 (72.0, 90.0)	81.0 (72.0, 91.0)	80.5 (72.0, 91.0)
SBP, mm/Hg	133.0 (122.0, 147.0)	133.0 (120.0, 146.0)	133.0 (120.0, 147.0)
DBP, mm/Hg	82.0 (79.0, 90.0)	80.0 (77.0, 91.0)	81.0 (78.0, 91.0)
Body mass index, kg/m^2	31.2 (27.3, 34.3)	30.8 (27.5, 34.9)	31.1 (27.4, 34.6)
Oxygen saturation, %	97.0 (96.0, 98.0)	97.0 (96.0, 98.0)	97.0 (96.0, 98.0)

(Table 1 continues on next page)

	Rivaroxaban (n = 327)	Control (n = 330)	Total
(Continued from previous page)			
Diagnostic testing, n (%)			
COVID-19 positive rt-PCR test	272 (83)	280 (85)	552 (84)
Symptoms onset to randomization, days	5.0 (4.0–6.0)	5.0 (3.0–6.0)	5.0 (3.8–6.0)

Missing data: race (n = 4), educational level (n = 27), respiratory rate (n = 13), heart rate (n = 13), SBP (n = 11), DBP (n = 30), oxygen saturation (n = 14), COVID-19 test not performed (n = 10), symptoms onset to randomization (n = 5). PCI = Percutaneous coronary intervention, CABG = Coronary artery bypass graft, VTE = Venous Thromboembolism, SBP = Systolic blood pressure, DBP = Diastolic blood pressure.

Table 1: **Patient baseline characteristics.**

There was one severe gastrointestinal bleeding in the rivaroxaban group and no major bleeding among patients in the control group (Table 2). Consistent results were observed in the sensitivity analysis including patients with positive testing for SARS-CoV-2 (supplementary appendix, eTable 3). Furthermore a post hoc per protocol analysis excluding patients who did not receive the intervention from rivaroxaban group and excluding those patients who received non-study anticoagulant drugs from control arm showed similar results (Supplementary appendix, eTable 4).

Time-to-first primary endpoint occurrence was not different between the two groups, with a HR 0.74 (95% CI 0.37–1.48), log-rank p = 0.39 (Fig. 2), and similar results were seen in the sensitivity analysis considering only patients with positive testing for SARS-CoV-2 (supplementary appendix, eFig. 1).

Subgroup analysis by age, sex, and cluster of comorbidities did not reveal any significant treatment interaction for the primary outcome measure, as shown in Fig. 3. Furthermore, the win-loss ratio analyses (intention-to-treat sample) for the primary endpoint either with or without adding hospitalisation due to COVID-19 (supplementary appendix, eTable 5), and for the sensitivity analysis only considering those patients with positive testing for SARS-CoV-2 showed similar and consistent results (supplementary appendix, eTable 6).

Metanalysis for hospitalisation showed no significant difference between anticoagulants and controls. The results are consistent within and between subgroups with low heterogeneity. Fixed and random effects estimates are similar, which indicates low between-study heterogeneity. Predictive intervals suggests that future studies might comprise the null effect. Leave-one-out test showed that final pooled result did not change when each one of the studies is omitted at random. Furthermore, KHSJ adjustment did not change the results (Fig. 4A).

Death and thrombotic events were not differently distributed between anticoagulant and control groups. There was no difference across subgroups and no relevant heterogeneity. The results remained similar when adjusting for Knapp-Hartung-Sidik-Jonkman factor (supplementary appendix, eFigs. 2 and 3).

However, anticoagulants seem to elevate bleeding rate when compared to control. This was the case for DOAC but not for LMWH. Pooled results for both DOAC and LMWH showed an increased bleeding risk when using anticoagulants in non-hospitalised COVID-19 patients. Results are quite the same with fixed and

	Rivaroxaban (n = 327)	Control (n = 330)	RR (95% CI)	p-value[a]
Primary composite endpoint	14 (4%)	19 (6%)	0.74 (0.38–1.46)	0.476
Vascular composite endpoint I	4 (1%)	6 (2%)	0.67 (0.19–2.36)	0.752
Vascular composite endpoint II	8 (2%)	14 (4%)	0.58 (0.24–1.36)	0.278
Primary composite endpoint plus COVID-19 hospitalisation	36 (11%)	37 (11%)	0.98 (0.64–1.51)	1.000
Requirement of invasive mechanical ventilation	12 (4%)	11 (3%)	1.10 (0.49–2.46)	0.835
COVID-19 Hospitalization	36 (11%)	32 (10%)	1.13 (0.72–1.78)	0.610
Death	6 (2%)	9 (3%)	0.67 (0.24–1.87)	0.603
Thromboembolic event	3 (1%)	5 (2%)	0.60 (0.14–2.52)	0.725
Stroke	1 (<1%)	1 (<1%)	1.01 (0.06–16.06)	1.000
Venous Thromboembolism	0 (–)	4 (1%)	–	–
Myocardial infarction	2 (1%)	0 (–)	–	–
Acute limb ischemia	0 (–)	0 (–)	–	–
Safety outcome - Major bleeding	1 (<1%)	0 (–)	–	–

RR = Relative risk. (–) once no outcome event was observed, thus treatment effect analysis was not performed. [a]Fisher's Exact Test for Count Data.

Table 2: **Primary composite endpoint and individual components.**

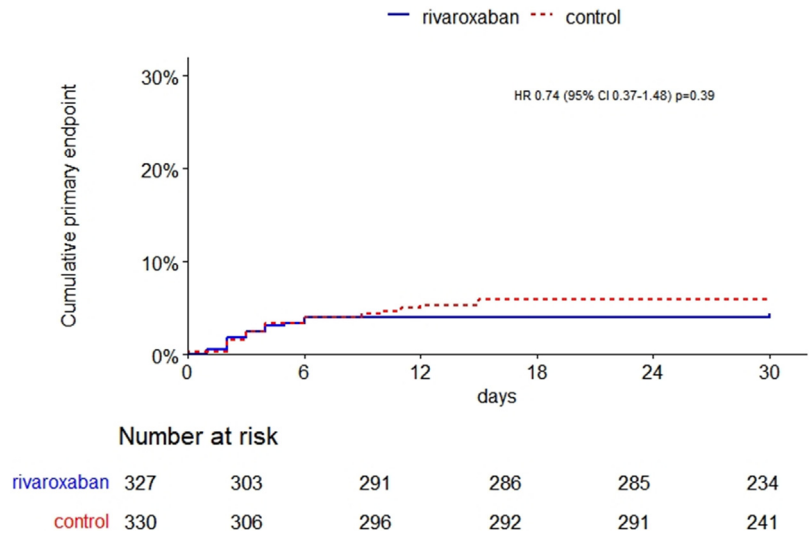

Fig. 2: Cumulative incidence of primary endpoint at 30 days (ITT population).

random effects, with no important heterogeneity detected. Leave-one-out test showed that final pooled result did not change when each one of the studies is omitted at random. However, the predictive interval for both DOAC and final sample comprise the null effect. Therefore, future big RCT might have a role to clarify the differences between anticoagulants and control concerning bleeding (supplementary appendix, eFig. 4).

Optimal information size boundary was set at 26,558 participants, which is far distant from the 2306 already considered in the metanalysis. Therefore, despite the results demonstrating the apparent non-difference between anticoagulants and control for the reduction of hospitalisations in non-hospitalised patients with COVID-19, we do not have enough precision to refute or confirm the presented results (Fig. 4B).

Discussion

In this open-label, multicenter, randomised trial, rivaroxaban 10 mg once daily for 14 days did not significantly reduce the risk of VTE, requirement for invasive mechanical ventilation, MACE (acute myocardial infarction, stroke, or acute limb ischemia), or out-of-hospital death, as compared with routine care in symptomatic non-hospitalised patients. The efficacy evidence of antithrombotic therapy in different COVID-19 scenarios has been conflicting, which might be due to different

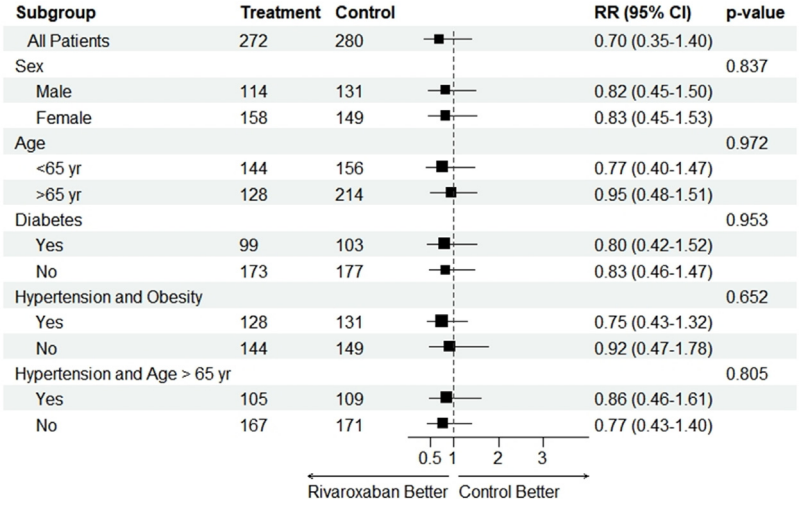

Fig. 3: Subgroup analysis for the primary outcome.

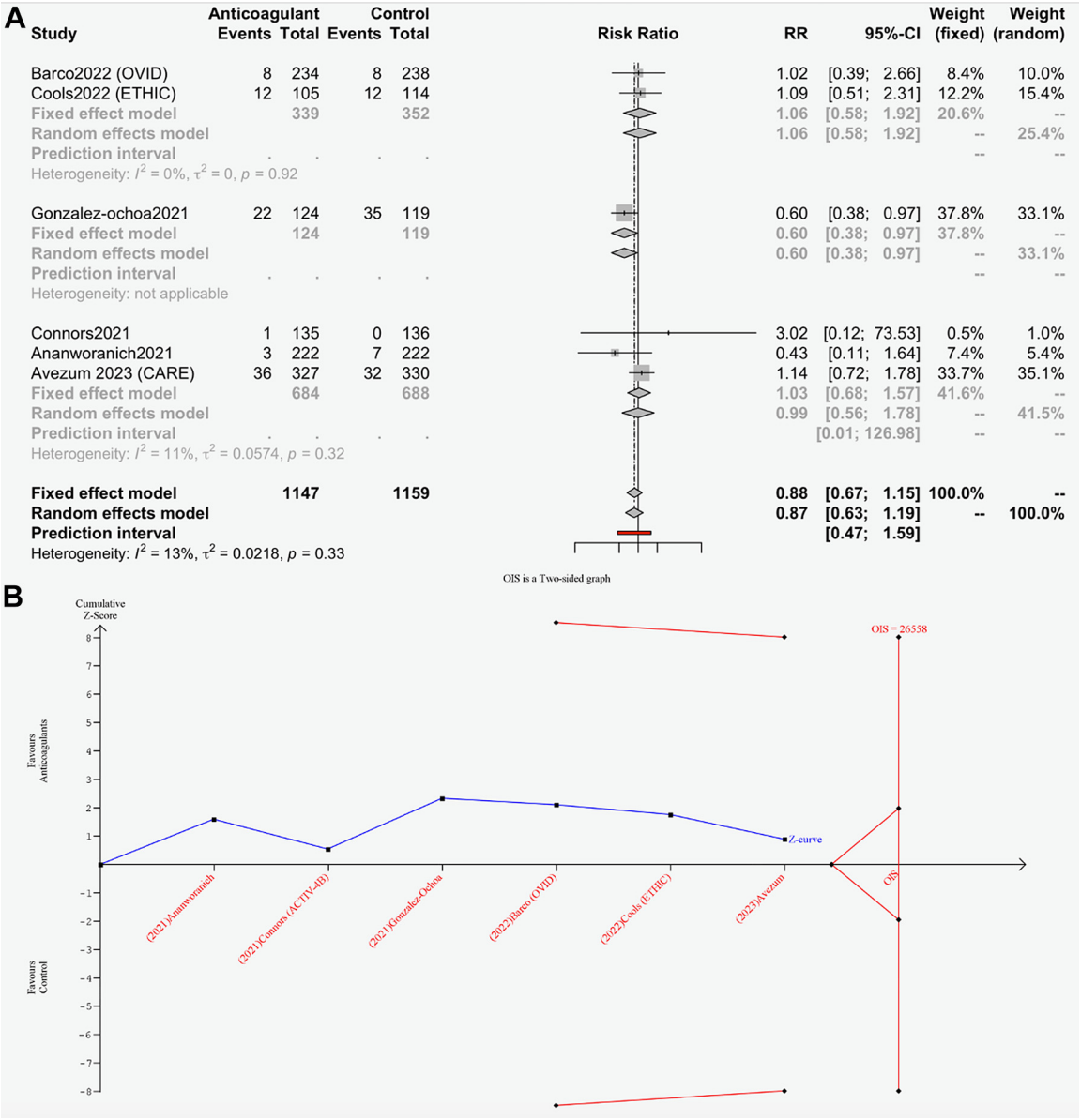

Fig. 4: A) pairwise metanalysis for hospitalization. Barco 2022 and Cools 2022 evaluated Low-Molecular Weight Heparin - Connors 2021, Ananworanich 2021, and Avezum 2023 evaluated direct anticoagulants and Gonzalez-Ochoa 2021 evaluated sulodexide; B) Trial sequential analysis showing the optimal information size considering the estimate from hospitalization metanalysis.

anticoagulants, dosing regimens, administration routes, severity of the disease, and time of initiation and duration of treatment.

Rivaroxaban has not been adequately evaluated in outpatients with COVID-19. One study has been completed but the results have not yet been released (NCT04508023) and others are currently recruiting (NCT04715295, NCT04351724) or have been terminated due to difficulties in patient recruitment (NCT04416048). Two trials were prematurely stopped due to low event rates,[12,24] and did not shown a benefit of either rivaroxaban[12] or apixaban.[24] Adherence rate in CARE is lower than in some other COVID-19 trials, particularly those conducted in the hospital setting. Several outpatient trials have reported similarly low adherence (e.g., Ananworanich et al., 2021[12] reported 72.4% adherence to rivaroxaban).

We hypothesized that by reducing coagulation activation caused by endothelial damage in micro- and macrovascular beds, rivaroxaban would reduce the need for

hospitalisation due to thrombotic complications and related lung damage leading to respiratory failure. However, rates of clinically evident thromboembolism were much lower than expected, and we found no significant reduction in the need for hospitalisation due to COVID-19 progression. It remains unclear whether approaches that specifically target microvascular thrombosis might be more effective for preventing disease progression and related complications. The clinical profile of patients enrolled in the CARE study suggested that they would be at high risk of clinical deterioration as well as for thrombotic complications. In fact, a substantial number of patients had metabolic risk factors, including the clusters of hypertension and obesity (17.6%), hypertension and age ≥65 years (10.6%), and hypertension, obesity, and diabetes (7.9%). It is unclear whether the low rates of clinical deterioration that we observed may in part be explained by a reduction in the virulence of the SARS-CoV-2 variants over time. Our study included patients with either initially suspected or confirmed diagnosis of COVID-19. During the first months of the pandemic, we observed a rapid surge of confirmed cases and, due to an increased demand for diagnostic tests worldwide, there was lack of availability of reverse transcription polymerase chain reaction testing in Brazil. In addition, the release of testing results was delayed by 2–5 days due to the large number of tests that were being performed. Therefore, following Brazilian Ministry of Health and WHO, we considered as eligible both confirmed and suspected cases in the initial study protocol based on high level of clinical suspicion, which makes sense in terms of public health approach. We found 84% positivity for SARS-CoV-2, which correlates with the high level and appropriate clinical suspicion for COVID-19. However, sensitivity analyses restricted to patients who tested positive also found no benefit of rivaroxaban, which suggests that the inclusion of patients who did not test positive does not explain our results.

A strength of our study is that we applied an exploratory win-loss ratio method to assess the composite outcomes as an alternative to conventional Cox proportional hazards models. This approach allows the hierarchical assessment of individual outcomes as well as their timing by considering the most important component firstly. The consistency of results obtained with this approach further strengthens our conclusions regarding the lack of benefit of rivaroxaban in outpatients with COVID-19. In addition, we want to highlight that metanalyses regarding anticoagulants for COVID-19 outpatients showed no significant difference for hospitalisation, death, and thrombotic events, which corroborates our findings. Furthermore, our metanalysis suggests some uncertainty regarding significant bleeding in the group that received anticoagulants. In this metanalysis, we can see that CARE study has similar event rate as compared to other trials evaluating DOACs and LMWHs. However, as a reflex of sample size and event rate, the weights of each trial are outcome dependent and fluctuations can be seen.

Our study also has limitations, including lower than planned sample size and its impact on statistical power, open-label study design, lack of information regarding vaccination rate, and lower than expected event rates. Statistical evaluation of heterogeneity, in subgroup analysis, is of limited value in small studies. Nevertheless, we have elected to retain these analyses for a better interpretation of study results.

In non-hospitalised patients with mild or moderate forms of COVID-19, rivaroxaban 10 mg OD given in the early phase of the disease for 14 days did not reduce the risk of major cardiovascular and thrombotic events, hospitalisations due to hypoxemia requiring mechanical ventilation, or mortality within 30 days, and was not associated with major bleeding. The totality of published available evidence through a metanalyses, does not support the use of antithrombotics in non-hospitalised patients with COVID-19. In light of these findings, no decision can be made about the utility to improve patient outcomes. These results suggest that rivaroxaban 10 mg once daily should not be routinely recommended in this clinical setting.

Contributors

AA conceived the trial and wrote the initial proposal, contributed to the literature search, study design, selecting participating sites, data interpretation, obtaining funding and drafting of the manuscript. GBFO contributed to the literature search, study design, selecting participating sites, obtaining funding, data interpretation, and drafting of the manuscript. HAOJ contributed to the study design, literature search, data interpretation, metanalysis, obtaining funding and drafting of the manuscript. PDMMN contributed to the literature search, study design, selecting participating sites, obtaining funding, data interpretation, and drafting of the manuscript. LB estimated the sample size, drafted the statistical analysis plan and contributed to statistical analyses, including the final data analysis. ABC, VCV, RGR, LCPA, RDL, and OB contributed to study design, data interpretation, and critical review of the manuscript. SLZ, OMS, RCSD, APMK, EBS, ASS, RS, BSP, AR, ADMF, PLMB, PFNG, MEH, ALF, JMSE, APT contributed to data collection and critical review of the manuscript. JE and IB contributed to study design and critical review of the manuscript. All authors had access to the data, contributed to the manuscript, agreed to submit for publication, and vouch for the integrity, accuracy, and completeness of the data and for the fidelity of the trial to the protocol.

Data sharing statement

Anonymised participant data can be made available upon requests directed to the corresponding author. Proposals will be reviewed based on scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement.

Declaration of interests

OB reports grants from AstraZeneca, Pfizer, Bayer, Servier, and Amgen, and Novartis, unrelated to this submitted work. RDL reports grants and personal fees from Bristol Myers Squibb, Pfizer, GlaxoSmithKline, Medtronic PLC, and Sanofi; and personal fees from Amgen, Bayer, Daiichi Sankyo, Merck, Portola and Boehringer Ingelheim, outside of this submitted work. The other authors have no conflict to declare.

Acknowledgments

The authors are indebted to all collaborating sites and respective teams who worked hard to enroll participants with high data quality, and to all healthcare professionals who provided recommended care for all patients during the study conduction. This trial was funded by the

COALITION COVID-19 Brazil Research Institutions. Bayer S.A. provided partial funding and the study drugs, without any involvement in the study conduction, analysis, or decision to publish these results.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102004.

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