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Antithrombotic Prophylaxis with Rivaroxaban in Patients with Prehospital COVID-19: A Meta-analysis of Two Placebo-Controlled Trials

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Abstract

Background We conducted a prespecified meta-analysis of two randomized, placebo-controlled trials of rivaroxaban 10 mg daily in prehospital patients with acute coronavirus disease 2019 (COVID-19). Individually, the trials had limited power to detect a treatment effect due to recruitment stopping ahead of plan.

Material and Methods The statistical analysis plan for the meta-analysis was finalized before unblinding of PREVENT-HD, the larger of the two trials. Pooled risk ratios and pooled risk differences along with the two-sided 95% confidence intervals were calculated using random-effect models.

Results Rivaroxaban did not reduce the occurrence of either the primary prespecified endpoint, a composite of symptomatic arterial and venous thromboembolism, myocardial infarction, ischemic stroke, acute limb ischemia, all-cause hospitalization, and all-cause mortality (risk difference: 0.0044; 95% confidence interval: −0.0263, 0.0175; $p = 0.69$ for pooled risk difference) or the secondary endpoint of all-cause hospitalization ($p = 0.76$). Although thrombotic events were infrequent, pooled analysis did reveal that rivaroxaban reduced arterial and venous thrombotic events (placebo 6 events, rivaroxaban 0 events; pooled risk difference: −0.0068; 95% confidence interval: −0.0132, −0.0006; $p = 0.03$). In the pooled studies, only one major bleeding event was observed in a rivaroxaban-allocated patient with no critical site or fatal bleeding events.

Conclusion Although this meta-analysis does not support antithrombotic prophylaxis with rivaroxaban in a broad prehospital population with acute COVID-19, the prevention of arterial and venous thrombotic events among rivaroxaban-allocated patients is consistent with the known thromboprophylactic effect of the drug in medically ill patients.

Keywords
- COVID-19
- clinical trial
- direct thrombin agent
- meta-analysis

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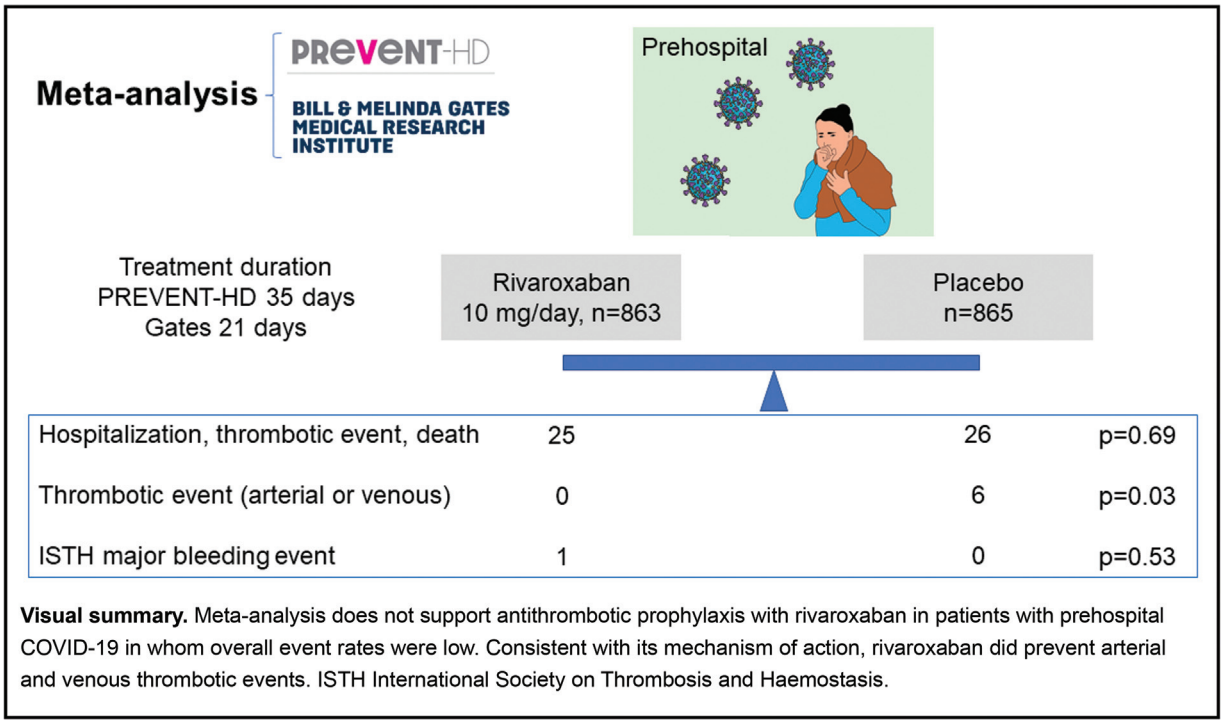

Visual summary. Meta-analysis does not support antithrombotic prophylaxis with rivaroxaban in patients with prehospital COVID-19 in whom overall event rates were low. Consistent with its mechanism of action, rivaroxaban did prevent arterial and venous thrombotic events. ISTH International Society on Thrombosis and Haemostasis.

Introduction

Among patients with acute coronavirus disease 2019 (COVID-19), the vast majority have not required hospitalization.[1,2] Several randomized trials have been conducted to assess the role of antithrombotic prophylaxis to reduce the risk of hospitalization, death, and thrombotic events such as venous thromboembolism (VTE), myocardial infarction (MI), and ischemic stroke in those who did not require hospitalization at the time of COVID-19 diagnosis, termed "prehospital" patients.[3–10] All the trials were stopped ahead of plan due to recruitment challenges, lower than expected clinical event rates or futility, leading to inconclusive results.

Three of these randomized trials evaluated rivaroxaban 10 mg daily in patients with prehospital COVID-19.[7–9] Two trials were placebo-controlled, focused on extended thromboprophylaxis of 21 days or longer and enrolled nonhospitalized, ambulatory patients with COVID-19 in the United States.[8,9] Leveraging an increased number of events by merging the two studies of similar design and utilizing the same antithrombotic intervention to potentially improve power, we conducted a prespecified meta-analysis to address the clinically important question of whether prehospital patients benefit from this prophylactic anticoagulant regimen.

Methods

The designs of the Gates MRI (NCT04504032) and PREVENT-HD (NCT04508023) have been previously reported (►**Fig. 1**).[8,11] Gates MRI was conducted from August 2020 to February 2021; PREVENT-HD from August 2020 to April 2022. The planned sample sizes for Gates MRI and PREVENT-HD were 600 and 4,000 patients, respectively. Both studies had independent data monitoring committees. Gates MRI was stopped when the futility boundary was crossed at a planned interim analysis. PREVENT-HD was stopped early due to enrollment challenges and a lower-than-expected blinded pooled event rate.

Study Population

For both studies, eligible patients were required to have acute symptomatic COVID-19 infection, at least 1 high-risk characteristic and an initial treatment plan that did not include hospitalization. For Gates MRI high-risk characteristics included age >65 years, self-reported obesity and chronic conditions requiring daily treatment. For PREVENT-HD high-risk characteristics included age >60 years, body mass index > 35 kg/m^2, elevated D-dimer, history of VTE or thrombophilia or other chronic conditions (coronary, peripheral artery, or cerebrovascular disease, cancer, diabetes, or heart failure). Those requiring routine anticoagulation for high-risk clotting conditions or at high bleeding risk were excluded from both studies. The population for the meta-analysis included PREVENT-HD and Gates MRI specifically to focus on a U.S. COVID-19 population and extended thromboprophylaxis of at least 21 days.

Intervention

Eligible participants were randomized (1:1) to rivaroxaban 10 mg daily or placebo equivalent (multivitamin) for 21 days

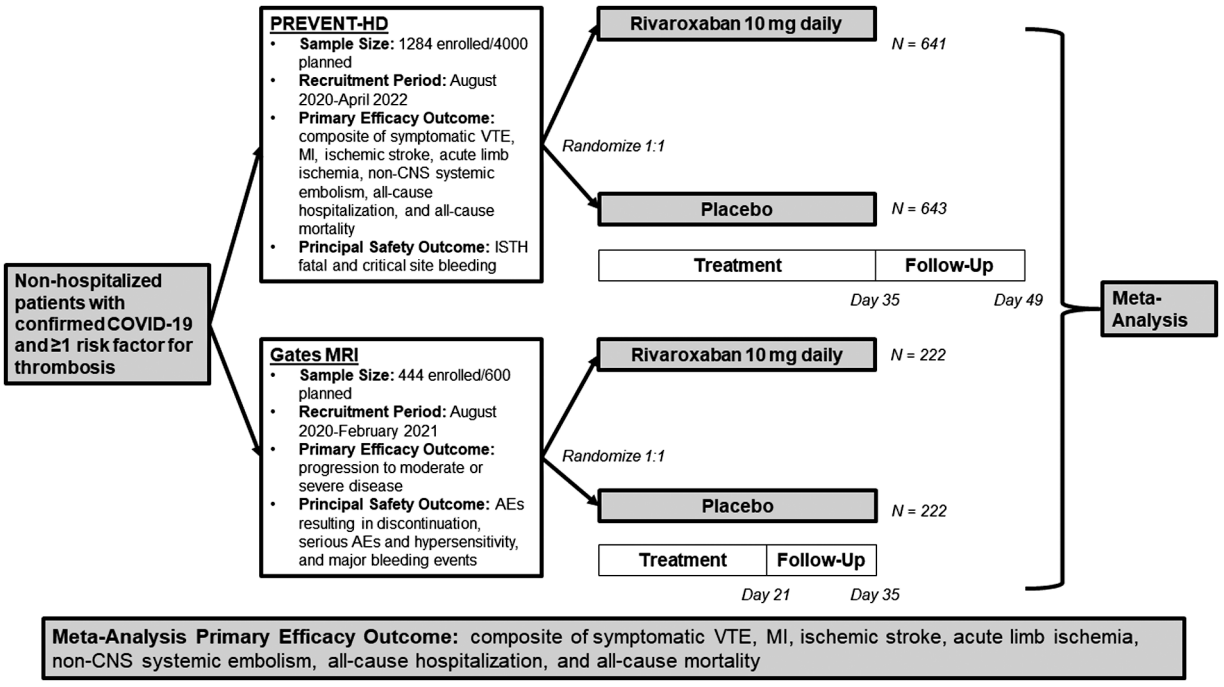

Fig. 1 Study designs and meta-analysis plan. AE, adverse event; CNS, central nervous system; COVID-19, coronavirus disease 2019; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; VTE, venous thromboembolism.

in Gates MRI or to rivaroxaban 10 mg daily or identical-appearing placebo for 35 days in PREVENT-HD. The rivaroxaban dose was selected to balance prevention of venous and arterial thrombosis with bleeding risk based on prior data in medically ill patients.[12] For both studies, study medication was delivered to the patient's home via a centralized pharmacy service.

Study Procedures

Both studies enrolled patients in the United States and were entirely remotely conducted. Gates MRI recruited at 13 outpatient clinics in 7 states and 1 virtual site, which enrolled patients from 40 states. PREVENT-HD recruited through 14 integrated health care delivery networks. Health care encounters, thrombotic, bleeding, and other adverse events were collected during remote follow-up contacts (telehealth or virtual visit). Follow-up duration was 35 days for Gates MRI and 49 days for PREVENT-HD.

Clinical Endpoints

The primary endpoint prespecified in the meta-analysis statistical analysis plan was the PREVENT-HD primary endpoint, a composite of symptomatic VTE, MI, ischemic stroke, acute limb ischemia, noncentral nervous system systemic embolism, all-cause hospitalization, and all-cause mortality. For the Gates MRI study, the primary efficacy endpoint was progression to moderate or severe disease (Gates MRI scale 3 or higher). Those with Gates MRI scale 3 had at least one of the following: shortness of breath, tachypnea (respiratory rate $\geq$ 20 breath/min) or hypoxemia. Scales 4 to 7 progressed from critically ill status to death. The secondary endpoint for the meta-analysis was all-cause hospitalization, which was a secondary endpoint for each of the individual studies. Occurrence of thrombotic events was evaluated as a component of the primary composite endpoint in PREVENT-HD and as an adverse event in Gates MRI. Safety was assessed using the International Society on Thrombosis and Haemostasis (ISTH) bleeding classification.[13] Clinical events in PREVENT-HD were classified by a blinded, centrally trained clinical endpoint committee with at least one member in each health system, enabling review of the full electronic medical record.[11] In the Gates MRI study, clinical events were classified by site investigators using standardized definitions.

Statistical Methods

The statistical analysis plan for the meta-analysis was finalized before PREVENT-HD was unblinded and prespecified the inclusion of data from the PREVENT-HD and Gates MRI trials. Data were extracted from published summary data outputs from both studies for reported follow-up durations. The primary efficacy endpoint was defined in the PREVENT-HD as the occurrence of all major venous and arterial thrombotic events (symptomatic VTE, MI, ischemic stroke, acute limb ischemia, and noncentral nervous system systemic embolization), all-cause hospitalization, and all-cause mortality. The most similar primary efficacy endpoint was extracted from the Gates MRI summary tables, by using the reported hospitalization data combined with reported adverse events related to venous and arterial thrombotic events. The secondary efficacy endpoint as defined in the PREVENT-HD was the occurrence of all-cause hospitalization. The results of the secondary endpoint of all-cause hospitalization were extracted from summary data from the Gates MRI trial data to directly map to the all-cause hospitalization endpoint of the PREVENT-HD study. Finally, an exploratory endpoint was defined as occurrence of all

major venous and arterial thrombotic events, extracted from the summary efficacy tables from PREVENT-HD study and summary adverse events tables from the Gates MRI study.

Under the random-effects model, the true effect sizes are allowed to differ, due to possible differences in the participant characteristics, follow-up duration, time period, or general design differences between studies (heterogeneity). The meta-analysis was implemented using aggregate summary data with a random-effects model to account for between-study heterogeneity using inverse variance weighting.[14] The pooled point estimates and two-sided 95% confidence intervals (CIs) are therefore presented, with I^2 as a measure of the degree of between-study heterogeneity. We calculated the risk ratio (RR) and 95% CI for incidence of composite outcomes. Pooled risk differences (RD) and corresponding 95% CI were calculated for component outcomes if there were zero events in either trial arm. Analyses were conducted on the intention-to-treat population defined as all randomized subjects.

Results

In aggregate, Gates MRI and PREVENT-HD randomly allocated 1,728 patients with acute COVID-19 to rivaroxaban 10 mg daily or placebo. Baseline characteristics are summarized (►**Table 1**). PREVENT-HD recruited an older cohort with more non-White participants (Black, Asian, American Indian, or Alaskan native). The trials enrolled a similar proportion of Hispanic or Latino participants, who could be White or non-White. Both cohorts enrolled patients with elevated body mass index, a similar proportion with diabetes mellitus and more women than men.

For the primary composite endpoint of symptomatic VTE, MI, ischemic stroke, acute limb ischemia, noncentral nervous system systemic embolism, all-cause hospitalization, and all-cause mortality, rivaroxaban had an overall neutral effect in pooled RD analysis (RD: 0.0044; 95% CI: −0.0263, 0.0175; $p = 0.69$; ►**Fig. 2A**). Similarly, rivaroxaban was not observed to reduce all-cause hospitalization compared with placebo (RD: −0.0036; 95% CI: −0.0271, 0.0198; $p = 0.76$; ►**Fig. 2B**). Pooled RR for the composite and all-cause hospitalization endpoints are shown in the ►**Supplementary Material** (available in the online version). No significant heterogeneity was observed for any of these analyses.

Arterial and venous thrombotic events were infrequent overall and observed less frequently with rivaroxaban compared with placebo (pooled RD: −0.0068; 95% CI: −0.0132, −0.0006; $p = 0.03$). In the Gates MRI study, one patient in the placebo group had VTE and in PREVENT-HD, three patients in the placebo group had at least one VTE and two patients had an ischemic stroke. In aggregate, no arterial or venous thrombotic events were identified among rivaroxaban-allocated patients (►**Fig. 2C**).

Major bleeding was rare with only one major bleed identified in a rivaroxaban-allocated patient in PREVENT-HD and none in the Gates MRI study ($p = 0.53$ vs. placebo, ►**Fig. 3**). No critical site or fatal bleeding events were observed. Based on the pooled RD between treatment groups, rivaroxaban would be estimated to result in 13 major bleeding events per 10,000 patients treated. Assessing the potential benefit against the potential risk in these two trials, prehospital rivaroxaban treatment of 10,000 patients with acute COVID-19 could prevent 69 arterial and venous thrombotic events while resulting in 13 major bleeds (►**Fig. 4**).

Discussion

In the individual trials, both of which were terminated prior to completing planned enrollment, and the meta-analysis, rivaroxaban 10 mg daily was not observed to reduce a composite endpoint of thrombotic events, all-cause hospitalization, and death among prehospital patients with COVID-19, nor all-cause hospitalization. Consistent with its mechanism of action and established efficacy and safety in thromboprophylaxis for medically ill patients, rivaroxaban reduced arterial or venous thrombotic events with a very low risk of major bleeding.

In addition to clinical outcomes data, the trials also provide useful lessons for clinical trial conduct during future pandemics. Both PREVENT-HD and Gates MRI demonstrated the feasibility of conducting entirely remote randomized, controlled trials including delivery of study medication to participants' homes in a population with acute, symptomatic infectious disease. Despite the absence of in-person contact or established relationships with investigators or site personnel, nearly all participants completed study participation. PREVENT-HD was conducted in large health systems, which

Table 1 Baseline characteristics

	Gates MRI		PREVENT-HD	
	Rivaroxaban	Control	Rivaroxaban	Placebo
n	222	222	641	643
Age, y	49	49	56	56
Female, %	57	64	63	60
Non-White, %	11	11	28	28
Hispanic/Latino, %	22	18	15	15
Body mass index, kg/m^2	35	33	34	34
Diabetes mellitus, %	26	30	22	21

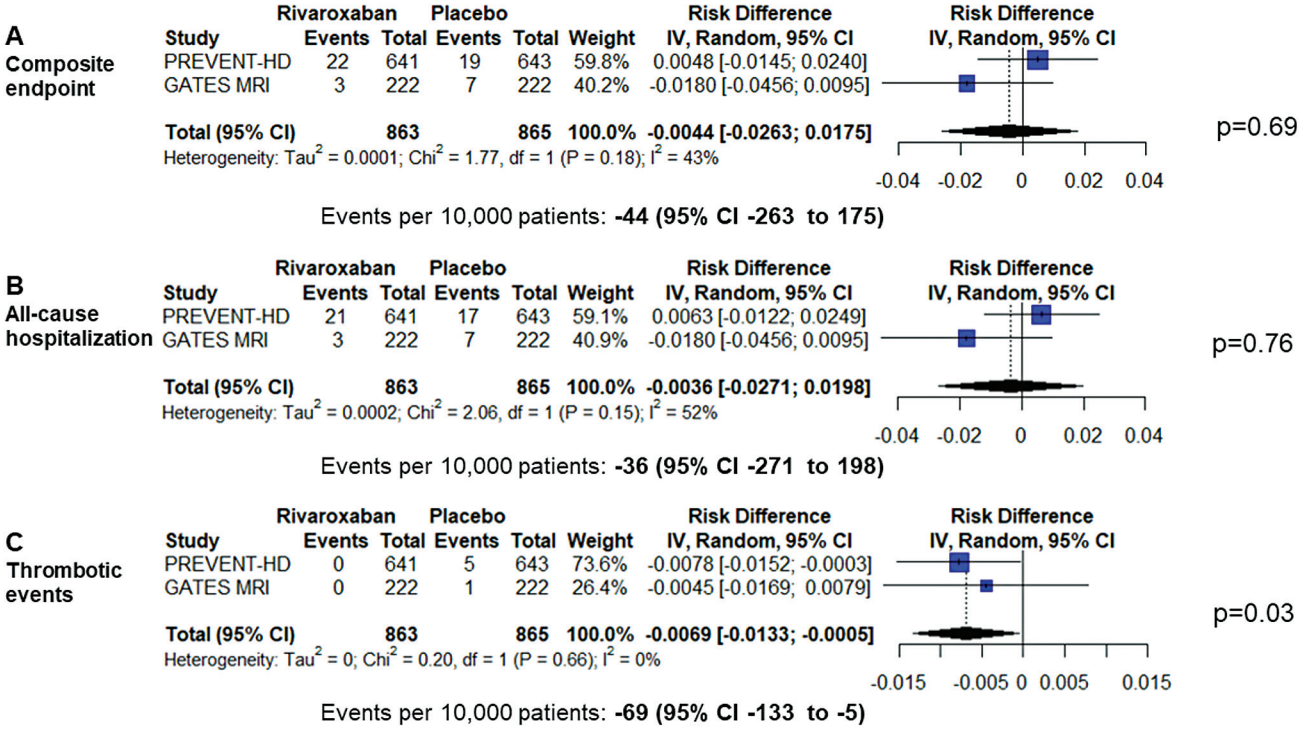

Fig. 2 Forest plots of the effect of rivaroxaban on clinical efficacy endpoints. (**A**) Pooled risk difference for the composite endpoint of symptomatic VTE, MI, ischemic stroke, acute limb ischemia, noncentral nervous system systemic embolism, all-cause hospitalization, and all-cause mortality. (**B**) Pooled risk difference for all-cause hospitalization. (**C**) Pooled risk difference for arterial and venous thrombotic events. See ►**Supplementary Material** (available in the online version) for pooled risk ratios for the composite endpoint and all-cause hospitalization. MI, myocardial infarction; VTE, venous thromboembolism.

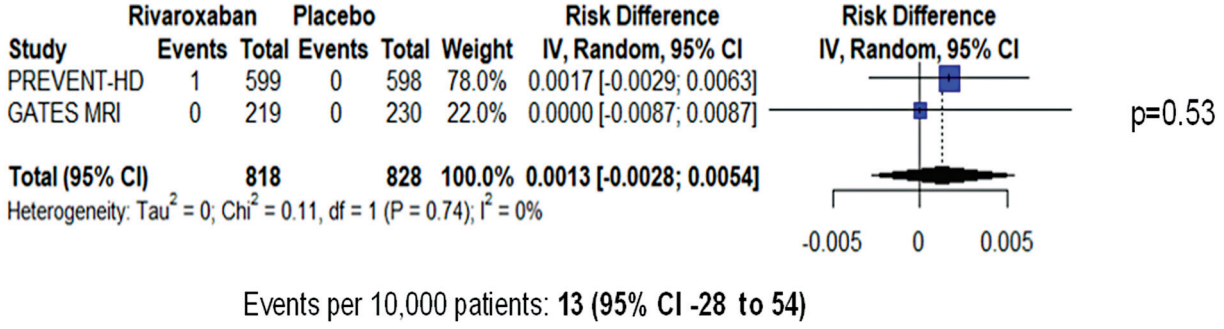

Fig. 3 Forest plot of the effect of rivaroxaban on ISTH bleeding. Pooled risk difference for ISTH major bleeding. ISTH, International Society on Thrombosis and Haemostasis.

may have facilitated retention (0/1284 lost to follow-up), whereas Gates MRI was conducted at outpatient clinics and a virtual site that enrolled patients in 40 states (15/497 [3%] lost to follow-up). No problems were encountered with identification and management of adverse events in either study.

During the early stages and certainly during subsequent surges, the vast majority of patients with COVID-19 did not require hospitalization. In August 2020, when both Gates MRI and PREVENT-HD were initiated, approximately 330,000 cases/week were identified in the United States of which 41,000 were hospitalized (12%).[1,2] As such, we, along with other investigators, evaluated therapies intended to reduce the need for hospitalization at a time when health resource needs exceeded capacity. Rapid initiation of PREVENT-HD and Gates MRI was possible due to accelerated procedures for COVID-19 trials implemented by health authorities and health care institutions, and the established dosing and safety profile for rivaroxaban in medically ill outpatients.[12] The proportion of patients with COVID-19 requiring hospitalization fell to approximately 8% by February 2021 when Gates MRI completed, and to 5% by April 2022 when PREVENT-HD completed. Overall, the magnitude of the problem under study diminished as both the proportion of patients with COVID-19 requiring hospitalization and the incidence of thrombotic events fell.

Although our prespecified meta-analysis included the PREVENT-HD and Gates MRI trials with rivaroxaban, three other studies in prehospital patients studied different factor

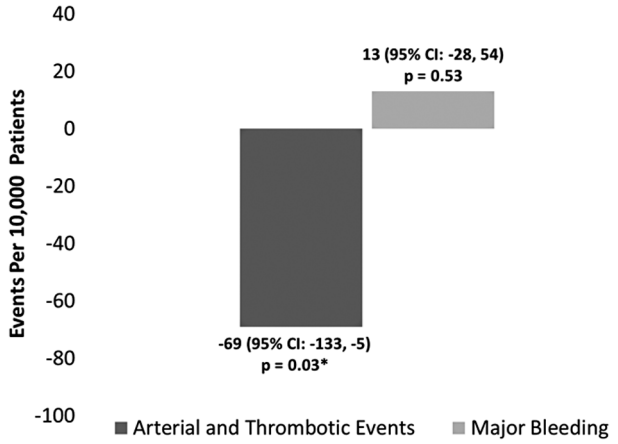

Fig. 4 Pooled benefit: risk Treating 10,000 prehospital patients with acute COVID-19 with rivaroxaban 10 mg daily could prevent an estimated 69 arterial and venous thrombotic events while causing 13 major bleeds.

Xa inhibitors or treatment duration.[5–7] All were stopped ahead of plan due to lower than expected clinical event rates and/or waning of the pandemic; antithrombotic therapy did not significantly reduce clinical events in any of the trials.

The randomized antithrombotic trials in patients with prehospital COVID-19 focused on detecting a reduction in hospitalization, reflecting the belief that thrombosis was a key driver of disease progression leading to hospitalization.[15] As our understanding of the pathophysiology has evolved in parallel with the dynamic landscape of viral variants, vaccines, and antiviral medications, it has become apparent that micro- and macrothrombosis are just two of the mechanisms contributing to the clinical syndrome and deterioration and hospitalization. Unlike established effects on reducing macrovascular thrombosis, whether anticoagulants reduce thrombotic microangiopathy and thromboinflammatory mechanisms that can lead to worsening disease severity in COVID-19 and other infectious disorders is still a matter of debate.[16]

This meta-analysis does demonstrate that rivaroxaban reduced thrombotic events in prehospital COVID-19, consistent with its established antithrombotic effect in other populations, including the medically ill.[12,17] The frequency of thrombotic events among patients with prehospital COVID-19 was considerably lower than that of hospitalized patients.[18] In the prehospital COVID-19 trials of antithrombotic therapies,[3–9] thrombotic events were identified in only 0.9% of control group-allocated patients, an incidence which would not support thromboprophylaxis with either a direct oral anticoagulant or low-molecular weight heparin.

Strengths of this meta-analysis are the similarities in the two trials' study designs and use of the same anticoagulant regimen. Pooled analysis mitigated, at least in part, the shortfall in statistical power due to early closure; in this meta-analysis, the previously observed lack of effect of rivaroxaban on the composite endpoint and all-cause hospitalization[9] is corroborated. Although the analysis of thrombotic events is consistent with rivaroxaban's known mechanism of action and antithrombotic effect in diverse patient populations, the limited number of events and post hoc nature of the analysis are limitations. Another potential limitation is the difference between the primary endpoint prespecified in the meta-analysis statistical analysis plan and the Gates MRI primary endpoint of disease progression. This is unlikely to have affected completeness of clinical event ascertainment since all-cause hospitalization was the secondary endpoint in Gates MRI and there were no deaths.

Results of this meta-analysis are in line with the National Institutes of Health antithrombotic guideline for COVID-19 updated October 10, 2023, which recommends against routine prehospital thromboprophylaxis.[19] Although thrombosis was quite infrequent, rivaroxaban did reduce the frequency of arterial and venous thrombotic events with a low rate of major bleeding. Based on recent estimates of disease emergence from zoonotic reservoirs associated with climate change, the probability of extreme epidemics has been projected to increase up to 3-fold in the near term.[20] Having established the safety and antithrombotic efficacy of this rivaroxaban regimen may prove useful when a population at particularly high thrombotic risk is identified in a future pandemic.

What is known about this topic?

- Several randomized trials have been conducted to assess the role of antithrombotic prophylaxis to reduce morbidity and mortality among patients not requiring hospitalization at the time of COVID-19 diagnosis.
- All were stopped ahead of plan due to recruitment challenges, lower than expected clinical event rates or futility, leading to inconclusive results.

What does this paper add?

- This meta-analysis of the two placebo-controlled trials of rivaroxaban was prespecified.
- By augmenting the number of clinical endpoint events in the two trials of similar design and using the same antithrombotic intervention, this analysis increased power to address the clinically important question of whether prehospital patients benefit from prophylactic anticoagulation.

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Conflict of Interest
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References

1 Centers for Disease Control and Prevention. COVID Data Tracker. Accessed April 19, 2023 at: covid.cdc.gov/COVID-data-tracker/#datatracker-home
2 COVID-19 Hospitalization Tracking Project. Accessed September 15, 2023 at: carlsonschool.umn.edu/mili-misrc-covid19-tracking-project
3 Cools F, Virdone S, Sawhney J, et al; ETHIC investigators. Thromboprophylactic low-molecular-weight heparin versus standard of care in unvaccinated, at-risk outpatients with COVID-19 (ETHIC): an open-label, multicentre, randomised, controlled, phase 3b trial. Lancet Haematol 2022;9(08):e594–e604
4 Barco S, Voci D, Held U, et al; OVID investigators. Enoxaparin for primary thromboprophylaxis in symptomatic outpatients with COVID-19 (OVID): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet Haematol 2022;9(08):e585–e593
5 Connors JM, Brooks MM, Sciurba FC, et al; ACTIV-4B Investigators. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. JAMA 2021;326(17):1703–1712
6 Lopes RD, de Barros e Silva MPG, Macedo AVS, et al; Apixaban for prophylaxis of thromboembolic outcomes in COVID-19. The primary results of the APOLLO randomized trial Presented at: European Society of Cardiology Scientific Sessions, Barcelona, 2022
7 Avezum Á, Oliveira Junior HA, Neves PDMM, et al; Coalition VIII COVID-19 Brazil Investigators. Rivaroxaban to prevent major clinical outcomes in non-hospitalised patients with COVID-19: the CARE - COALITION VIII randomised clinical trial. EClinicalMedicine 2023;60:102004
8 Ananworanich J, Mogg R, Dunne MW, et al. Randomized study of rivaroxaban vs placebo on disease progression and symptoms resolution in high-risk adults with mild coronavirus disease 2019. Clin Infect Dis 2022;75(01):e473–e481
9 Piazza G, Spyropoulos AC, Hsia J, et al; PREVENT-HD Investigators. Rivaroxaban for prevention of thrombotic events, hospitalization, and death in outpatients with COVID-19: a randomized clinical trial. Circulation 2023;147(25):1891–1901
10 Gonzalez-Ochoa A, Hernandez A, Raffetto J. Suldexide in the treatment of early stages of COVID-19. J Vasc Surg Venous Lymphat Disord 2021;9:539
11 Capell W, Barnatham E, Piazza G, et al. Rationale and design for the study of rivaroxaban to reduce the risk of major venous and arterial thrombotic events, hospitalization and death in medically ill outpatients with symptomatic COVID-19: the PREVENT-HD study. Am Heart J 2021;235:12–23
12 Spyropoulos AC, Ageno W, Albers GW, et al; MARINER Investigators. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. N Engl J Med 2018;379(12):1118–1127
13 Schulman S, Kearon C; the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(04):692–694
14 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(03):177–188
15 McFadyen JD, Stevens H, Peter K. The emerging threat of (micro) thrombosis in COVID-10 and its therapeutic implications. Circ Res 2020;127(04):571–587
16 Spyropoulos AC, Bonaca MP. Studying the coagulopathy of COVID-19. Lancet 2022;399(10320):118–119
17 Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med 2020;382(21):1994–2004
18 Piazza G, Campia U, Hurwitz S, et al. Registry of arterial and venous thromboembolic complications in patients with COVID-19. J Am Coll Cardiol 2020;76(18):2060–2072
19 COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) treatment guidelines. National Institutes of Health Accessed October 24, 2023 at: https://www.covid19treatmentguidelines.nih.gov/
20 Marani M, Katul GG, Pan WK, Parolari AJ. Intensity and frequency of extreme novel epidemics. Proc Natl Acad Sci U S A 2021;118(35):e2105482118