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Prophylactic vs Therapeutic Anticoagulation in Hospitalized Patients With COVID-19

A Randomized Clinical Trial

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Abstract

IMPORTANCE Coagulopathy in the context of COVID-19 is a major threat due to deep vein thromboses and pulmonary embolisms.

OBJECTIVE To assess whether therapeutic anticoagulation on top of standard of care (SOC) compared with prophylactic anticoagulation as part of SOC can improve objective patient-relevant end points.

DESIGN, SETTING, AND PARTICIPANTS This prospective, assessor-blinded, multicenter, parallel-group (1:1), placebo-controlled, superiority randomized clinical trial (HERO-19) assessed patients with a confirmed diagnosis of COVID-19 who were hospitalized in an intensive care unit or non–intensive care ward at 1 of 10 university hospitals in Germany from November 12, 2020, to January 15, 2023. Data analysis was conducted after the final database lock in February 2024.

INTERVENTIONS Patients were treated for 42 days. Patients enrolled in the experimental group received therapeutic anticoagulation using low-molecular-weight heparin (LMWH) body weight adapted during the hospital stay and oral anticoagulation using edoxaban, 60 mg daily, after being discharged from the hospital. Patients enrolled in the control group received prophylactic anticoagulation using LMWH as part of SOC while in the hospital and placebo after discharge.

MAIN OUTCOMES AND MEASURES The primary end point was time to the first occurrence of all-cause mortality and/or venous thromboembolism and/or arterial thromboembolism within up to 42 days. Potential thromboembolic events were assessed by duplex ultrasonography of arms and legs at day 14 or discharge and day 42. The primary safety outcome was major and clinically relevant nonmajor bleeding according to International Society on Thrombosis and Haemostasis classification.

RESULTS A total of 139 patients (mean [SD] age, 58.4 [13.7] years; 93 [67%] male and 46 [33%] female) were included in the study. Of these, 71 patients (51%) were randomized to prophylactic anticoagulation group, whereas 68 (49%) were randomized to the therapeutic anticoagulation group. The primary outcome occurred in 14 of 67 patients (21%; 2.31 incidence per patient-year) assigned to therapeutic anticoagulation and 20 of 70 (29%; 3.37 incidence per patient-year) assigned to prophylactic anticoagulation (primary end point assessment not available for 2 patients) with primary end point assessment (hazard ratio, 0.74; 95% CI, 0.38-1.48; P = .40). In the per-protocol analysis, the hazard ratio was 0.66 (95% CI, 0.32-1.37; P = .26). A total of 7 bleeding events occurred in the intervention group, whereas 6 bleeding events occurred in the control group.

(continued)

Key Points

Question Can therapeutic anticoagulation plus standard of care improve clinically relevant outcomes in hospitalized patients with COVID-19?

Findings This randomized clinical trial of 139 patients found that in-hospital therapeutic anticoagulation with low-molecular weight heparin followed by edoxaban was well tolerated but did not statistically significantly reduce death and/or thromboembolic events compared with prophylactic anticoagulation followed by placebo.

Meaning These findings do not support routine therapeutic anticoagulation in hospitalized patients with COVID-19 to reduce death or thromboembolic events compared with prophylactic anticoagulation.

+ Visual Abstract

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Abstract (continued)

CONCLUSIONS AND RELEVANCE In patients hospitalized with COVID-19, in-hospital therapeutic anticoagulation with LMWH followed by edoxaban to day 42 did not statistically significantly reduce death and/or thromboembolic events compared with prophylactic anticoagulation followed by placebo.

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Introduction

Coagulopathy in the context of COVID-19 is a major threat to affected patients due to deep vein thromboses and pulmonary embolisms.[1] Previous data show a high incidence of complications associated with increased morbidity and mortality, sometimes occurring without prior clinical evidence.[2-4] It is hypothesized that COVID-19 induces a proinflammatory state, which is associated with endothelial dysfunction and hypercoagulability, and thereby increases the risk of microvascular and macrovascular thrombosis.[5] In turn, the hypercoagulatory state and resulting microvascular thrombotic complications contribute to and aggravate the pulmonary injury itself.[5]

Previous studies[6] have reported mixed results regarding anticoagulation strategies in patients hospitalized with COVID-19, with therapeutic dose anticoagulation associated with reduced mortality compared with prophylactic dosing in some analyses, whereas comparisons with intermediate dose regimens remain inconclusive. Prophylactic dose anticoagulation, also referred to as thromboprophylaxis, uses lower doses intended to prevent venous thromboembolism, whereas therapeutic dose anticoagulation uses full treatment doses, generally adjusted for body weight and kidney function. Intermediate dose regimens fall between these 2 dose levels; no intermediate dose regimen was used in HERO-19. In addition, previous studies[7,8] comparing anticoagulation strategies often focused on clinically apparent thrombotic events only, which may lead to an underestimation of the true thromboembolic burden and introduce detection bias if asymptomatic events are not systematically assessed.

Edoxaban is a widely used direct oral inhibitor of factor Xa that is recommended for thromboprophylaxis in a variety of clinical indications, including deep vein thrombosis, pulmonary embolism, and stroke prevention.[9] HERO-19 compared a 2-stage therapeutic anticoagulation strategy—full therapeutic dose low-molecular-weight heparin (LMWH) or fondaparinux during hospitalization followed by edoxaban after discharge until day 42—with standard thromboprophylaxis using prophylactic dose LMWH or fondaparinux during hospitalization followed by placebo after discharge. The trial assessed whether the therapeutic anticoagulation strategy improved clinically relevant outcomes based on thorough clinical follow-up and systematic evaluation of thromboembolic events, including serial duplex ultrasonography of the arms and legs.

Methods

Study Design

The HERO-19 study was an assessor-blinded, multicenter, parallel-group (1:1), placebo-controlled, superiority randomized clinical trial that recruited patients at 10 university hospitals in Germany. The study protocol was approved by the federal authorities and the local ethics committees at each participating institution. The first and last versions of the protocol and a summary of changes, with their respective dates, are included in the trial protocol in Supplement 1. No changes to the trial design or analysis were made after unblinding. An independent data and safety monitoring board reviewed unmasked patient-level data for safety on an ongoing basis during the trial. In accordance

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with national regulations and requirements as well as the Declaration of Helsinki,[10] written informed consent was obtained from all patients or from the patients' legal representatives. The protocol was designed by the study group. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[11]

Sample Size

Sample size was calculated based on data from previous COVID-19 trials, data from our intensive care unit (ICU) database, and the Hamburg COVID-19 postmortem database. The assumed event rate refers to the composite primary end point, defined as the first occurrence of all-cause mortality, venous thromboembolism, or arterial thromboembolism within 42 days. The event rate was estimated to be 45% after 42 days within the control group. An absolute decrease of 20 percentage points (45% vs 25%) in the primary outcome measure was assumed. The 2-sided α level was set to .05. With a fixed follow-up of 42 days and no assumed dropouts or treatment switches, 86 patients per group (172 overall) were needed to achieve a statistical power of 80%. Power calculations were performed using PASS software, version 16.0.3 (NCSS LLC) with a 2-sided log-rank test.

As these assumptions may comprise a certain imprecision, 2 blinded sample size reestimations based on the overall event rate were planned to be performed after 50% and 75% of patients had been recruited. As within the first blinded analysis, the total event rate was lower than expected (26%); sample size recalculation resulted in a sample size of 266 patients in total. Due to recruitment problems, we decided not to increase the sample size, to skip the second blinded interim analysis, and to finish recruitment of the originally intended 172 patients. Nevertheless, the recruitment problems remained and enrollment was finished on January 15, 2023, after randomization of 140 patients.

Patients and Study Intervention

Full eligibility criteria are provided in Supplement 1. Of 140 patients randomized, 1 patient was classified as being a postrandomization screening failure due to preexisting atrial fibrillation, leaving 139 patients for analysis. Overall, 21 patients discontinued the trial (10 withdrew, 4 were unavailable for follow-up, 2 discontinued due to adverse events, and 5 discontinued for other reasons). Primary end-point data were missing for 2 patients. We included patients hospitalized in an ICU or non-ICU ward with a confirmed diagnosis of COVID-19. Although ambulatory patients with a diagnosis of COVID-19 within the last 10 days were formally allowed in this trial, in case they had a D-dimer and/or high-sensitivity troponin concentration above the upper limit of normal reference range per local laboratory, no individual from this patient group could be randomized. Study entry required confirmation of COVID-19 based on specific tests used in clinical practice (eg, reverse transcriptase–polymerase chain reaction, antigen test, or IgM test). Exclusion criteria included a formal indication of therapeutic anticoagulation, contraindications to edoxaban or heparin, and conditions placing patients at high risk for bleeding. **Figure 1** shows the CONSORT flow diagram. Full eligibility criteria are provided in the trial protocol in Supplement 1.

Randomization and Masking

A block randomization procedure was applied with stratification by ICU status (ICU vs non-ICU) and sex (male vs female). The script for the randomization list was written by the responsible statistician (A.Z.), and the list was created using a new seed by a member of the statistics team not otherwise involved in the trial. This list was implemented in SecuTrial and administered centrally via the internet-based system, ensuring allocation concealment until assignment. There was no blinding of patients or treating physicians to group allocation. Outcome assessors were blinded to treatment allocation, and the statistical analysis team remained blinded until database lock in February 2024. Other study personnel were not involved in outcome assessment or data analysis. Additional therapy was provided in accordance with national and international guidelines.[12]

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Procedures

In the experimental arm, during hospitalization the study treatment administered was LMWH and fondaparinux at a therapeutic dose according to the respective summary of product characteristics (SmPC) (therapeutic dosing) on top of standard of care (SOC). After discharge and for ambulatory patients, oral administration of edoxaban (off-label) on top of SOC was performed according to SmPC (standard: 60 mg, 30 mg if glomerular filtration rate is 15-50 mL/min/1.73 m^2 or body weight is ≤60 kg, once daily) until day 42. In the control arm, in-hospital (ICU and non-ICU ward) patients received LMWH and fondaparinux in a prophylactic dose according to SmPC as part of SOC. After discharge and for ambulatory patients, oral placebo (open-label) was administered according to the dosing rules for edoxaban until day 42.

This treatment strategy reflects a pragmatic approach combining established in-hospital anticoagulation with LMWH and continuation of anticoagulation after discharge using an oral factor Xa inhibitor. At the time of study design, LMWH represented SOC for hospitalized patients, whereas extended thromboprophylaxis after discharge was an emerging concept in high-risk populations.

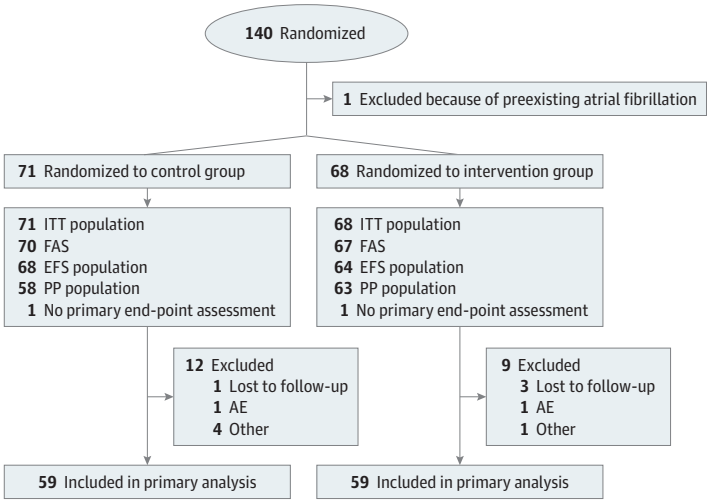
Edoxaban was selected as a well-established oral anticoagulant with a favorable efficacy and safety profile, enabling continuation of anticoagulation in the outpatient setting. The 42-day treatment period was chosen to cover both the short-term phase of hospitalization and the early postdischarge period, during which thromboembolic risk was considered to remain elevated.

Outcomes and Procedures

The primary outcome was time from randomization to the first occurrence of all-cause mortality, venous thromboembolism, or arterial thromboembolism within 42 days. Secondary outcomes included all-cause mortality, mortality related to thromboembolic events, rates of venous and arterial thromboembolism, need for and duration of mechanical ventilatory support, length of ICU stay, rehospitalization, kidney replacement therapy, and cardiac arrest or cardiopulmonary resuscitation. Safety outcomes included major and clinically relevant nonmajor bleeding according to International Society on Thrombosis and Haemostasis criteria.

Thromboembolic events were assessed by trained investigators using serial duplex ultrasonography of the upper and lower extremities at predefined time points (day 14 or at hospital discharge, whichever occurred first, and at day 42). Ultrasonography followed a standardized protocol and was applied uniformly across treatment groups to minimize detection bias. Assessments were performed by outcome assessors who were blinded to treatment allocation.

Figure 1. CONSORT Flow Diagram of the HERO-19 Study[a]



The investigators did not document the number of patients assessed for eligibility. AE indicates adverse event; EFS, event-free survival; FAS, full analysis sample; ITT, intention to treat; PP, per protocol.

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Venous thromboembolism was defined as the presence of deep vein thrombosis or pulmonary embolism, as detected by imaging according to standard clinical criteria. Arterial thromboembolism was defined as the occurrence of ischemic stroke, myocardial infarction, or peripheral arterial thrombosis based on clinical diagnosis supported by appropriate imaging or laboratory findings.

Statistical Analysis

The statistical analysis plan was completed before the end of the study and unblinding of the study results and is available in Supplement 1. The analyses followed the intention-to-treat principle, including all randomly allocated participants. The statistical analysis of the primary end point was based on a mixed Cox proportional hazards regression analysis with treatment group and stratification factors of the randomization (ICU status and sex) as fixed effects and a shared frailty term for center to account for potential heterogeneity among the study centers. A 2-sided $P < .05$ was considered statistically significant. Subgroup analyses were prespecified and performed by the appropriate interaction tests. The primary analysis was repeated within the per-protocol population (consisting of all randomized patients as belonging to their randomized arm, without a major protocol deviation; patients were censored at the time of a major protocol deviation) as a sensitivity analysis. Secondary end points were analyzed in an analogous way according to their underlying scale level. Safety end points were analyzed descriptively (ie, event numbers on patient and event levels). All analyses besides the primary analysis model are considered exploratory and should not be interpreted as confirmatory. The reported *P* values are provided for descriptive purposes only; therefore, no adjustment for multiple testing was applied. In the primary analysis and other time-to-event analyses, dropout was handled as independent right censoring. No imputation of missing data was performed. No further additional or sensitivity analyses were conducted. Data are presented as number (percentage) for categorical variables and as mean (SD) or median (IQR) for continuous variables. All analyses were performed with R software, version 4.2.3 (R Foundation for Statistical Computing). Data analysis was conducted after the final database lock in February 2024.

Results

A total of 139 patients (mean [SD] age, 58.4 [13.7] years; 93 [67%] male and 46 [33%] female) were included in the study, with 68 (49%) assigned to therapeutic anticoagulation and 71 (51%) to prophylactic anticoagulation. **Table 1** gives the baseline characteristics of the study population, which were well balanced between the 2 groups. At baseline, 55 of the 139 patients (40%) were in the ICU, whereas 84 (60%) were in a non-ICU ward.

Figure 2 displays the cumulative incidence for the primary end point until day 42. **Table 2** gives the results for the primary and secondary end points. In patients hospitalized with COVID-19, in-hospital therapeutic anticoagulation with LMWH followed by edoxaban through day 42 was well

Table 1. Characteristics of the Study Patients at Baseline

Characteristic	Therapeutic anticoagulation (n = 68)	Prophylactic anticoagulation (n = 71)
Age, mean (SD), y	58.5 (14.1)	58.3 (13.4)
Sex, No. (%)		
Male	46 (68)	47 (66)
Female	22 (32)	24 (34)
Ward at randomization, No. (%)		
Non-ICU	41 (60)	43 (61)
ICU	27 (40)	28 (39)
Body weight, mean (SD), kg	90.4 (21.4)	91.5 (20.7)
Systolic blood pressure, mean (SD), mm Hg	127.2 (18.7)	127.4 (18.8)
Diastolic blood pressure, mean (SD), mm Hg	70.7 (11.9)	72.3 (12.2)

Abbreviation: ICU, intensive care unit.

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tolerated, with no treatment interruptions due to LMWH or edoxaban intolerance and no new treatment-emergent adverse events, or increases in their severity or frequency, considered related to LMWH or edoxaban. Therapeutic intervention did not statistically significantly reduce time to a composite of death and/or arterial and/or venous thromboembolic events compared with prophylactic anticoagulation followed by placebo (hazard ratio [HR], 0.74; 95% CI, 0.38-1.48; *P* = .40). Mortality in hospitalized patients with COVID-19 reached 11% during the 42-day follow-up, with a 10% arterial event rate and a 6% venous thromboembolic event rate.

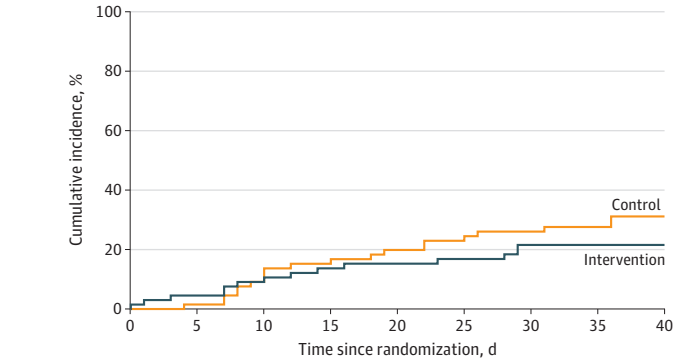
For 2 patients, a primary end-point assessment was not available. The primary outcome occurred in 14 of 67 patients (21%; 2.21 incidence per patient-years) assigned to therapeutic anticoagulation and 20 of 70 patients (29%; 3.37 incidence per patient-years) assigned to prophylactic anticoagulation (HR, 0.74; 95% CI, 0.38-1.48; *P* = .40). In the per-protocol analysis, the HR was even lower (HR, 0.66; 95% CI, 0.32-1.37; *P* = .26). Fewer rehospitalizations within 42 days were observed in the therapeutic anticoagulation group (1 vs 6 events; odds ratio, 0.16; 95% CI, 0.02-1.37; *P* = .09). Whereas 25 patients in each group were receiving mechanical ventilatory support, mean (SD) length of this support was shorter in the therapeutic dose group (249.7 [251.6] vs 281.1 [215.8] hours). In line with this finding, mean (SD) length of kidney replacement therapy was also shorter in the therapeutic dosing group (14.0 [14.1] vs 20.8 [14.9] days). Prespecified subgroup analyses revealed consistent results across all subgroups (**Figure 3**).

Serious adverse events were less frequent in patients receiving intensive anticoagulation, with 21 events (39.6%) in the experimental group and 32 (60.4%) in the conventional group. During the study, no suspected unexpected serious adverse reactions occurred, and investigators did not report any study drug–related deaths or new treatment emergent adverse events. A total of 7 bleeding events occurred in the intervention group, whereas 6 bleeding events occurred in the control group. Seven major and clinically relevant nonmajor bleeding events occurred in the therapeutic anticoagulation group vs 4 in the prophylactic anticoagulation group.

Discussion

Anticoagulation in COVID-19 essentially pursues 2 goals: (1) prevention of thromboembolic complications by inhibiting intravascular thrombin generation, fibrin formation, and platelet activation to prevent thrombotic events in the venous or arterial circulation and (2) prevention of disease progression with end-organ damage by inhibiting SARS-CoV-2–induced thromboinflammation to reduce clinically relevant end points, such as hospitalization, the need for organ support measures, and mortality.[12] This study evaluated the effect of a therapeutic

Figure 2. Kaplan-Meier Curve of the Cumulative Incidence of Time to First Occurrence of All-Cause Mortality and/or Venous Thromboembolism and/or Arterial Thromboembolism Within Up to 42 Days



No. at risk									
Control	70	65	60	55	52	50	48	44	35
Intervention	67	63	60	55	54	53	50	44	36

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anticoagulation on top of SOC compared with prophylactic anticoagulation as part of SOC in hospitalized patients with COVID-19. We report 4 major findings. First, in patients hospitalized with COVID-19, in-hospital therapeutic anticoagulation with LMWH followed by edoxaban to day 42 was well tolerated. Second, in patients hospitalized with COVID-19, in-hospital therapeutic anticoagulation with LMWH followed by edoxaban to day 42 did not statistically significantly reduce time to a composite of death and/or arterial and/or venous thromboembolic events compared with prophylactic anticoagulation followed by placebo. Third, despite improved treatment options during the COVID-19 pandemic, mortality in hospitalized patients with COVID-19 remains high and reached 11% during a 42-day follow-up in this study. Fourth, with an event rate of 10% for arterial and 6% for venous thromboembolic events in this study, arterial events seem an overlooked hazard in COVID-19.

In light of the waning COVID-19 pandemic and the threat of new pandemics, identifying therapies that improve outcomes in severe pneumonic disease seems crucial. The HERO-19 trial used a pragmatic approach, including serial arterial and venous duplex ultrasonography of the arms and legs. Edoxaban, the anticoagulant used in the therapeutic group after discharge, was selected because it has been studied in a comprehensive cardiovascular program and found to reduce the risk of venous and arterial thrombotic events in a variety of clinical settings.[9]

Randomized clinical trials of the use of therapeutic anticoagulation in patients hospitalized with COVID-19 have produced divergent results, whereas the recent systematic review and meta-analysis[6] by the World Health Organization REACT Working Group indicated lower 28-day

Table 2. Primary, Secondary, and Safety End-Point Results

End point[a]	Therapeutic anticoagulation	Prophylactic anticoagulation	HR or OR (95% CI)[b]	*P* value
Primary end point, Events, No. (incidence per patient-years)				
Intention-to-treat analysis (n = 137)	14 (2.31)	20 (3.37)	0.74 (0.38-1.48)	.40
Per-protocol analysis (n = 121)	13 (2.42)	17 (3.24)	0.66 (0.32-1.37)	.26
Components				
All-cause death (n = 139)	7 (1.10)	8 (1.30)	0.89 (0.32-2.45)	.82
Arterial thromboembolism (n = 137)	7 (1.16)	7 (1.18)	1.05 (0.37-3.00)	.93
Venous thromboembolism (n = 137)	3 (0.49)	5 (0.84)	0.60 (0.14-2.53)	.49
Dichotomous secondary end points, No. (%) (n = 139)				
Rehospitalization during follow-up	1 (1)	6 (8)	0.16 (0.02-1.37)	.09
Kidney replacement therapy	4 (6)	4 (6)	1.07 (0.25-4.53)	.93
Cardiac arrest or CPR	2 (3)	0	NA	NA
Mechanical ventilatory support	25 (37)	25 (35)	1.13 (0.42-3.03)	.81
Continuous secondary end points, mean (SD)				
Length of mechanical ventilation, h	249.7 (251.6)	281.1 (215.8)	NA	NA
Length of kidney replacement therapy, d	14.0 (14.1)	20.8 (14.9)	NA	NA
Length of initial stay at ICU, d	10.7 (11.9)	10.1 (10.9)	NA	NA
Length of total initial stay in hospital, d	12.5 (11.8)	11.9 (10.5)	NA	NA
Safety end points, No./total No. (%)				
Adverse events	32/90 (35.6)	42/101 (41.6)	NA	NA
Severe adverse events	15/21 (71.4)	25/32 (78.1)	NA	NA
SUSARs	0	0	NA	NA
Death	7/7	8/8	NA	NA
Major and clinically relevant nonmajor bleeding	7/7	4/4	NA	NA
Bleeding event	7/7	6/6	NA	NA
Rate of rehospitalization	1/1	6/6	NA	NA
Myocardial infarction	0	1/1	NA	NA
Ischemic stroke	0	1/1	NA	NA
Acute kidney injury	3/4	2/2	NA	NA
Gastrointestinal disorder	4/4	3/3	NA	NA

Abbreviations: CPR, cardiopulmonary resuscitation; HR, hazard ratio; ICU, intensive care unit; NA, not applicable; OR, odds ratio; SUSARs, suspected unexpected serious adverse reactions.

[a] The primary end point was time to first occurrence of all-cause mortality and/or venous thromboembolism and/or arterial thromboembolism within up to 42 days.

[b] HRs for primary end points and ORs for secondary end points.

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mortality and thromboembolic event rates for therapeutic dose compared with prophylactic dose anticoagulation. With regard to their primary end points, the largest randomized clinical trials, the FREEDOM COVID trial and the multiplatform ATTAC study, ACTIV-4A, and REMAP-CAP randomized clinical trial,[7,8,13] which together accounted for two-thirds of the patients in the World Health Organization REACT meta-analysis,[6] were unable to demonstrate a clear superiority for therapeutic anticoagulation in hospitalized patients.

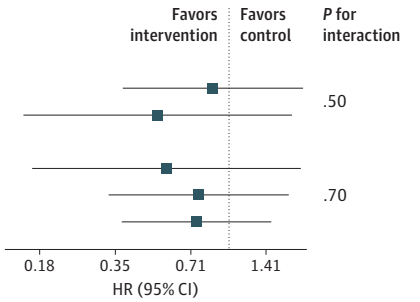
The FREEDOM COVID trial[7] compared the outcomes of therapeutic anticoagulation with enoxaparin or apixaban with prophylactic anticoagulation with enoxaparin in 3398 hospitalized patients with COVID-19 who did not require ICU-level care at admission.[7] Therapeutic dose anticoagulation failed to significantly reduce the 30-day composite primary end point of all-cause mortality, requirement for ICU-level care, systemic thromboembolism, or ischemic stroke.[7] In the open-label, multiplatform ATTAC study, ACTIV-4A, and REMAP-CAP randomized clinical trial, involving more than 1000 critically ill patients with confirmed COVID-19, therapeutic anticoagulation did not increase the probability of the primary end point of survival to hospital discharge or number of days free of cardiovascular or respiratory organ support and had a 95% probability of being inferior to usual care pharmacologic thromboprophylaxis.[8] There was even an 89% probability that therapeutic dose anticoagulation led to a lower probability of survival to hospital discharge than usual care thromboprophylaxis.[8] In contrast, the multiplatform trial[13] reported differential effects of therapeutic anticoagulation in patients with noncritical conditions: the trial arm that was conducted in more than 2200 noncritically ill patients with COVID-19 documented an increased probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support using therapeutic dose anticoagulation with heparin compared with usual care thromboprophylaxis.

HERO-19 represents the first anticoagulation study, to our knowledge, to apply thorough clinical follow-up with serial duplex ultrasonography of the arms and legs. Consequently, an important and new finding of our study is that most contemporary anticoagulation trials seem to have underestimated the rates of thromboembolic events because they only assessed clinically apparent events. We documented a very high incidence of 10% for arterial and 6% for venous thromboembolic events in HERO-19, which is clearly higher than in other current anticoagulation trials. In contrast, the so far largest COVID-19 anticoagulation study, the FREEDOM COVID trial,[7] (under)reported a 30-day incidence of venous or arterial thrombosis (including ischemic stroke and pulmonary embolism) of clearly less than 1% in its 3398 hospitalized patients.

In terms of choice of anticoagulatory substance, the formally neutral FREEDOM COVID study[7] yielded similar efficacy across the subgroups in the heparin and the factor Xa inhibitor groups, whereas other smaller trials[14,15] indicated potentially better outcomes using an initial strategy of therapeutic dose anticoagulation with heparin. It was hypothesized that the potential therapeutic superiority of heparins over factor Xa inhibitors might be explained by previously reported antithrombotic, anti-inflammatory, and possibly antiviral properties of heparins, some of which might be specific to COVID-19.[16-18] However, in our study, data do not indicate any superiority of

Figure 3. Dot Plot of Time to First Occurrence of All-Cause Mortality and/or Venous Thromboembolism and/or Arterial Thromboembolism Within Up to 42 Days for Prespecified Subgroups

Subgroup	No. of patients, %	Adjusted HR (95% CI)	*P* for interaction
Status			
ICU	54 (39)	0.87 (0.38-1.98)	.50
Non-ICU ward	83 (61)	0.52 (0.15-1.79)	
Sex			
Female	44 (32)	0.56 (0.17-1.93)	.70
Male	93 (68)	0.76 (0.33-1.73)	
All patients intervention vs control	137	0.74 (0.37-1.47)	



HR indicates hazard ratio.

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heparins against edoxaban. In contrast, the Kaplan-Meier analysis indicates a better efficacy of edoxaban: given that the initial hospital stay was 12 days, significantly more primary events occurred in the therapeutic dose arm than in the prophylactic dose arm up to day 10 after randomization (where heparins at therapeutic doses were predominantly used). In contrast, between days 10 and 30, the ratio reversed, and significantly fewer primary end points occurred in the therapeutic dose arm (where edoxaban was now predominantly used) than in the prophylactic dose arm. This observation raises the hypothesis that prolonged, low-intensity anticoagulation after discharge may be more effective and safer than intensive full-dose regimens during the short-term phase, in line with recent data supporting extended thromboprophylaxis in high-risk medical patients. Additional studies specifically addressing the optimal dose and duration of postdischarge anticoagulation in COVID-19 are warranted. Lastly, the study recruited patients between November 2020 and January 2023, encompassing several phases of the COVID-19 pandemic in Germany, including periods dominated by the ancestral strain, Alpha (B.1.1.7), Delta (B.1.617.2), and later Omicron (B.1.1.529) variants. These phases are associated with differences in disease severity, pathogenicity, and thrombotic risk, which may have influenced the study population and outcomes; therefore, again, additional analyses, including meta-analyses, across different trials are warranted.

Strengths and Limitations

This study has several strengths. First, because this trial was conducted in the mid and late phase of the COVID-19 pandemic and even after the World Health Organization declared the pandemic to be over, its results are much more generalizable to current COVID-19 disease than the results of earlier trials that were conducted before evolution of variants, population factors, and specific therapeutic measures. Second, the obligatory serial assessment of potential arterial and/or venous thromboembolic events via duplex ultrasonography allowed for thorough end-point assessment, thereby making the study more efficient in terms of statistical power than comparable studies assessing only clinical apparent events. Third, despite well-known challenges of COVID-19 studies, this adaptive sample–sized study, which aimed to randomize 86 to 258 patients (primary target, 172), was able to complete recruitment with 140 randomized patients. After the planned sample size reestimation, a larger total sample size was indicated; however, recruitment was discontinued prematurely due to operational challenges and limited patient enrollment. Recruitment was affected by several operational challenges during the COVID-19 pandemic, including high clinical workload, competing clinical priorities, and logistical constraints across participating centers. In addition, evolving treatment standards and changing patient populations during the pandemic contributed to slower enrollment than initially anticipated. Lastly, 33% of the patients in our study were female. Although our subgroup analyses did not indicate any interaction with sex, our study represents one of the few interventional studies of intensive care with women making up one-third or more of the study patients.

Several limitations also need to be mentioned. The sample size calculations were based on limited evidence available during the early phase of the COVID-19 pandemic, including data from local cohorts and early reports suggesting a high thromboembolic event rate. As a result, the assumed control event rate of 45% and the anticipated absolute risk reduction of 20 percentage points may have been overestimated in retrospect, given the subsequently lower observed event rates and evolving clinical management. Consequently, the study may have been underpowered to detect treatment effects smaller than those assumed in the original sample size calculation. Taking into account that the event rate in the experimental arm was numerically clearly lower, especially in the per-protocol analysis, a larger study might have led to a statistically significant benefit of the intervention. Moreover, the open-label design has a potential risk of bias, which was minimized by serial duplex ultrasonography and by blinding the assessors. An additional limitation is a potential bias in the assessment of secondary end points. After occurrence of a first primary event, a study end date was documented for the corresponding patient, so no further possible events or other secondary outcomes were documented. This might have led to an underestimation of event rates

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and biased estimates of continuous outcomes. Moreover, the composite end point included components with differing clinical relevance, such as all-cause mortality and imaging-detected thromboembolic events. Although this approach allowed for a more comprehensive assessment of thromboembolic burden, it may limit clinical interpretability and should be considered when interpreting the results. Another limitation is the limited availability of detailed baseline characteristics. As this investigator-initiated trial was conducted under the exceptional constraints of the COVID-19 pandemic, including high clinical workload and restricted resources, data collection was intentionally focused on essential variables. In particular, documentation requirements were kept feasible to ensure study conduct in a highly strained clinical environment. Available resources were prioritized toward rigorous end-point assessment, including systematic serial duplex ultrasonography, and to ensure high overall data quality. Nevertheless, the absence of additional baseline variables may limit the assessment of generalizability of the study population. Moreover, for the secondary outcome of mechanical ventilatory support, baseline ventilatory support status was not explicitly accounted for, which may limit interpretability of the binary end point. In this context, the end point of duration of mechanical ventilatory support may represent a more informative measure because it better reflects the overall burden of respiratory support. Lastly, because edoxaban was administered only after hospital discharge, patients with prolonged hospitalization had limited or no exposure to the postdischarge component before day 42. This may have attenuated any treatment effect attributable specifically to edoxaban, although the mean duration of the initial hospital stay was similar between treatment groups and these patients continued to receive their assigned in-hospital anticoagulation strategy.

Conclusions

In patients hospitalized with COVID-19, in-hospital therapeutic anticoagulation with LMWH followed by edoxaban to day 42 was well tolerated but did not statistically significantly reduce death and/or thromboembolic events, compared with prophylactic anticoagulation followed by placebo. These findings do not provide evidence to support routine escalation from prophylactic to therapeutic anticoagulation. However, systematic vascular surveillance revealed a substantial thromboembolic burden and underscores the need to identify patients who may benefit from intensified or extended anticoagulation.

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
Data Sharing Statement

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