Therapeutic versus Prophylactic Bemiparin in Hospitalized Patients with Nonsevere COVID-19 Pneumonia (BEMICOP Study): An Open-Label, Multicenter, Randomized, Controlled Trial

María Marcos-Jubilar[1] Francisco Carmona-Torre[2] Rosa Vidal[3] Pedro Ruiz-Artacho[4,5] David Filella[6] Cristina Carbonell[7] Víctor Jiménez-Yuste[8] Juana Schwartz[9] Pilar Llamas[3] Félix Alegre[10] Belén Sádaba[9] Jorge Núñez-Córdoba[9] José R. Yuste[2] Javier Fernández-García[9] Ramón Lecumberri[1,11] and for the BEMICOP Investigators*

[1] Hematology Service, Clínica Universidad de Navarra, Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain
[2] Divison of Infectious Diseases, Clínica Universidad de Navarra, Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain
[3] Hematology Service, Hospital Universitario Fundación Jiménez-Díaz, Madrid, Spain
[4] Internal Medicine Department, Clínica Universidad de Navarra, Madrid, Spain
[5] CIBER Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain
[6] Internal Medicine Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[7] Internal Medicine Department, Hospital Universitario de Salamanca-IBSAL, Universidad de Salamanca, Salamanca, Spain
[8] Hematology Service, Hospital Universitario La Paz, Madrid, Spain
[9] Clinical Trials Unit, Clínica Universidad de Navarra, Pamplona, Spain
[10] Internal Medicine Department, Clínica Universidad de Navarra, Pamplona, Spain
[11] CIBER Cardiovascular (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain

Address for correspondence Ramón Lecumberri, MD, PhD, Servicio de Hematología, Clínica Universidad de Navarra, Avda. Pío XII, 36. CP: 31008, Pamplona, Spain (e-mail: rlecumber@unav.es).

Thromb Haemost 2022;122:295–299.

Abstract

Thromboprophylaxis with low molecular weight heparin in hospitalized patients with COVID-19 is mandatory, unless contraindicated. Given the links between inflammation and thrombosis, the use of higher doses of anticoagulants could improve outcomes. We conducted an open-label, multicenter, randomized, controlled trial in adult patients hospitalized with nonsevere COVID-19 pneumonia and elevated D-dimer. Patients were randomized to therapeutic-dose bemiparin (115 IU/kg daily) versus standard prophylaxis (bemiparin 3,500 IU daily), for 10 days. The primary efficacy outcome was a composite of death, intensive care unit admission, need of mechanical ventilation support, development of moderate/severe acute respiratory distress, and venous or

Keywords
- COVID-19
- low molecular weight heparin
- outcomes
- prophylactic therapeutic

* A full list of the BEMICOP investigators is included in the ►**Supplementary Appendix**.

received
August 21, 2021
accepted after revision
October 10, 2021
published online
October 12, 2021

DOI https://doi.org/10.1055/a-1667-7534.
ISSN 0340-6245.

arterial thrombosis within 10 days of enrollment. The primary safety outcome was major bleeding (International Society on Thrombosis and Haemostasis criteria). A prespecified interim analysis was performed when 40% of the planned study population was reached. From October 2020 to May 2021, 70 patients were randomized at 5 sites and 65 were included in the primary analysis; 32 patients allocated to therapeutic dose and 33 to standard prophylactic dose. The primary efficacy outcome occurred in 7 patients (22%) in the therapeutic-dose group and 6 patients (18%) in the prophylactic-dose (absolute risk difference 3.6% [95% confidence interval [CI], −16% −24%]; odds ratio 1.26 [95% CI, 0.37–4.26]; $p = 0.95$). Discharge in the first 10 days was possible in 66 and 79% of patients, respectively. No major bleeding event was registered. Therefore, in patients with COVID-19 hospitalized with nonsevere pneumonia but elevated D-dimer, the use of a short course of therapeutic-dose bemiparin does not appear to improve clinical outcomes compared with standard prophylactic doses. *Trial Registration:* ClinicalTrials.gov NCT04604327.

Pharmacological thromboprophylaxis is mandatory in hospitalized patients with COVID-19, unless contraindicated.[1,2] However, different series reported a high incidence of thrombotic events among patients with COVID-19 despite its use, particularly if intensive care unit (ICU) admission was required.[3,4] Consequently, the use of higher doses of anticoagulants for venous thromboembolism prevention among COVID-19 patients with additional risk factors was encouraged by several scientific societies guidances.[5–7] Subsequent retrospective studies showed conflicting results regarding the efficacy and safety of "supraprophylactic" doses.[8] Interestingly, heparins interfere with cellular invasiveness of severe acute respiratory syndrome coronavirus 2[9] and, together with other anti-inflammatory properties, could favorably impact the outcome of COVID-19 patients beyond the prevention of thrombotic events, particularly if administered early in the course of the disease. This hypothesis was the rationale for the design of numerous randomized clinical trials (RCTs) (**Supplementary Material**, available in the online version).

The BEMICOP study (NCT04604327) was an investigator-initiated, open-label, multicenter, randomized, controlled trial in patients with COVID-19 hospitalized in a conventional ward, conducted at five Spanish hospitals. The Clínica Universidad de Navarra served as sponsor and coordinating center. The study protocol was approved by the Agencia Española de Medicamentos y Productos Sanitarios and the Drug Research Ethics Committee of the Hospital Universitario Puerta de Hierro. All patients provided a written informed consent prior to participation.

We included adult patients who required admission due to nonsevere (CURB65 $\leq$ 2 points and baseline oxygen saturation $\geq$ 90%) COVID-19 pneumonia, with baseline D-dimer $>$ 500 ng/mL. The study design and the full list of eligibility criteria are provided in ►**Supplementary Appendix** (available in the online version).

Randomization was performed in a 1:1 ratio using a central, electronic, automated system with permuted blocks of 4. There was no blinding of patients or investigators to group allocation. Patients allocated to the control arm received standard prophylaxis with subcutaneous bemiparin 3,500 IU once daily. Patients in the experimental arm received bemiparin 115 IU/kg once daily, adjusted to body weight (7,500 IU for patients between 50 and 70 kg; 10,000 IU for patients weighing $>$ 70–100 kg; 12,500 IU for patients who weighed $>$ 100 kg). The assigned treatments were planned for a 10-day period, independently of early hospital discharge. After that period, thromboprophylaxis use was left at investigators' choice. In case of ICU requirement during the study treatment period, it was at the discretion of the treating physician to continue the study drug or not, according to local practices. Except for the assigned anticoagulant therapy, all other clinical care was provided according to local protocols.

The primary efficacy outcome was a composite of death, ICU admission, need of mechanical ventilation support, development of moderate/severe acute respiratory distress syndrome, and venous or arterial thrombosis within 10 days of enrollment. Secondary efficacy outcomes included those same endpoints separately at 10 and 30 days, as well as hospital discharge and negativization of the polymerase chain reaction test at 10 days. Safety outcomes were major bleeding and nonmajor clinically relevant bleeding (NMCRB), as defined by the International Society on Thrombosis and Haemostasis[10,11] and any adverse event not related with COVID-19 itself. The full list of study outcomes and definitions is provided in ►**Supplementary Appendix** (available in the online version). In this study, there was not an independent Endpoint Adjudication Committee.

Assuming an incidence of the main efficacy outcome of 40% in the control group and 20% in the experimental arm, with a two-sided *p*-value of 0.05 and 80% statistical power, a total of 164 patients, 82 in each arm, were needed. The study protocol included an interim analysis when 40% of the target population was reached. After the results of this interim analysis, presented herein, the Steering Committee decided

to prematurely stop the clinical trial, based on both, slow recruitment rate (in part related with the vaccination campaign) and futility. Details of the statistical analysis applied are shown in ►**Supplementary Appendix** (available in the online version).

Between October 2020 and May 2021, 72 patients were enrolled. Six patients were excluded due to consent withdrawal or not meeting eligibility criteria (►**Supplementary Fig. S1**, available in the online version). Of the remaining patients, 33 were allocated to standard thromboprophylaxis and 33 to therapeutic-dose bemiparin. A patient in the therapeutic-dose arm did not start the assigned treatment due to ICU transfer before its first administration, and was excluded from primary analysis. Baseline characteristics are shown in ►**Table 1**. Overall, there was a good balance between both study arms. All patients received the study drug in accordance to the study protocol. After completion of the study treatment period, two-thirds of patients continued extended prophylaxis for a median of 10 additional days. No patient was lost during follow-up.

Study outcomes are shown in ►**Table 2**. The primary efficacy outcome was observed in 6/33 (18%) of patients receiving prophylactic-dose bemiparin and in 7/32 (22%) of patients treated with therapeutic dose. No major or NMCRB events during the study treatment period were registered. No serious adverse event, unrelated with evolution of COVID-19, was recorded either.

In an exploratory analysis, a significantly larger decrease in ferritin levels was found in patients receiving prophylactic-dose bemiparin, compared with those treated with therapeutic dose. In contrast, similar reductions of D-dimer and interleukin-6 levels were observed (►**Supplementary Tables S1** and **S2**, available in the online version).

Several RCTs addressing the optimal intensity of anticoagulants in hospitalized patients with COVID-19 have been initiated.[12,13] In severe COVID-19 increasing the dose of heparin appears insufficient to cool down the intense underlying inflammatory and thrombotic stimuli, as recently suggested by the INSPIRATION and the multiplatform REMAP-CAP, ACTIV-4a, and ATTAC studies.[14,15]

Focusing on nonsevere COVID-19 hospitalized patients, in the ACTION trial the use of therapeutic rivaroxaban did not improve survival or duration of hospitalization compared with standard thromboprophylaxis.[16] Similarly, in the RAPID

Table 1 Characteristics of patients

	Bemiparin 3,500 IU	Bemiparin 115 IU/kg
N	33	32
Age (y); mean ± SD	62.3 ± 12.2	63.0 ± 13.7
Sex (male/female); *n* (%)/*n* (%)	24 (72.7)/9 (27.3)	17 (53.1)/15 (46.9)
BMI (kg/m^2); median (IQR) BMI > 30; *n* (%)	26.1 (24.1–28.8) 4 (12.1)	25.8 (24.0–29.4) 5 (15.6)
Comorbidities Hypertension; *n* (%) Diabetes mellitus; *n* (%) Chronic pulmonary disease; *n* (%) Cardiopathy; *n* (%) Previous arterial or venous thrombosis; *n* (%) Current or former smoking habit; *n* (%) Cancer; *n* (%)	 12 (36.3) 3 (9.1) 6 (18.2) 1 (3.0) 0 10 (30.3) 1 (3.0)	 10 (31.2) 2 (6.3) 5 (15.6) 3 (9.3) 0 16 (50.0) 1 (3.1)
Days since COVID-19 diagnosis; median (IQR)	6 (3–8)	5 (2–8)
Days since symptoms onset; median (IQR)	8 (6–10)	8 (7–10)
Status at inclusion Oxygen requirement; *n* (%) D-dimer; median (IQR) Ferritin; median (IQR) IL-6; median (IQR) Brescia COVID-19 score ≥2; *n* (%) SIC score ≥ 4; *n* (%)	 18 (54.5) 770 (590–1,030) 1,093 (514–1,751) 24.8 (5.1–57.9) 3 (9.1) 1 (3.0)	 20 (62.5) 780 (600–1,125) 518 (287–1,248) 34.1 (15.7–77.7) 1 (3.1) 0
COVID-19 therapy Steroids; *n* (%) Statins; *n* (%) Remdesivir; *n* (%) Tocilizumab; *n* (%)	 30 (90.9) 20 (60.6) 5 (15.2) 8 (24.2)	 32 (100) 23 (71.9) 4 (12.5) 7 (21.9)
Extended prophylaxis After end of study treatment; *n* (%) Duration (d); median (IQR)	 21 (63.6) 10 (7–14)	 23 (71.9) 10 (8–14)

Abbreviations: BMI, body mass index; IL-6, interleukin-6; IQR, interquartile range; SD, standard deviation; SIC, sepsis-induced coagulopathy.
Note: Absence of statistically significant differences between groups for all variables.

Table 2 Primary and secondary outcomes

Outcome	Control (3,500 IU) *N* (%)	Experimental (115 IU/kg) *N* (%)	Absolute difference (95% CI)	Odds ratio (95% CI)	*p*-Value
Primary efficacy outcome (day 10)[a]	6 (18.2)	7 (21.9)	0.04 (−0.16 to 0.24)	1.26 (0.37 to 4.26)	0.95
Secondary outcomes					
Death (day 10)	0	0	–	–	–
Death (day 30)	1 (3.0)	2 (6.3)	0.03 (−0.07 to 0.13)	2.13 (0.18 to 24.76)	0.61
Need of ICU (day 10)	4 (12.1)	4 (12.5)	0.004 (−0.16 to 0.16)	1.03 (0.24 to 4.55)	1.0
Need of ICU (day 30)	4 (12.1)	5 (15.6)	0.04 (−0.13 to 0.20)	1.34 (0.33 to 5.53)	0.73
ATE/VTE (day 10)	1 (3.0)	0	–	–	–
ATE/VTE (day 30)	2 (6.1)	0	–	–	–
Discharge in first 10 days	26 (78.8)	21 (65.6)	−0.13 (−0.35 to 0.08)	0.51 (0.17 to 1.56)	0.36
Negative PCR[b] at day 10	15/25 (60.0)	18/27 (66.7)	0.07 (−0.20 to 0.33)	1.33 (0.43 to 4.13)	0.83
Major or clinically relevant bleeding (day 10)	0	0	–	–	–

Abbreviations: ATE, arterial thromboembolism; CI, confidence interval; ICU, intensive care unit; PCR, polymerase chain reaction; VTE, venous thromboembolism.

[a]The primary efficacy outcome was a composite of death, admission at ICU, need of mechanical ventilation support, development of moderate/severe acute respiratory distress syndrome, and venous or arterial thrombosis within 10 days of enrollment.

[b]Negative or cycle threshold (Ct) value > 30.

trial no significant differences between therapeutic or prophylactic heparin for the composite outcome of death, need of mechanical ventilation, or ICU admission were found.[17] On the contrary, in 2,219 noncritically ill patients included in the aforementioned multiplatform RCT the use of therapeutic anticoagulation was associated with a 4.0% increased probability of survival to hospital discharge without need of organ support, although in-hospital mortality was similar (7.3% vs. 8.2%).[18] The multiplatform design favors evaluation of larger number of patients but the nonconcurrent nature of experimental and control groups is a potential source of bias.[19]

Some factors such as the time gap between admission and treatment onset, heterogeneity of study drugs, or other concomitant therapies could influence the results. Of note, the use of steroids was higher in our study. We selected a relatively lower-risk population; all patients received the same anticoagulant molecule, changing only the dose, and the maximum time gap between admission and randomization was 2 days, shorter than other RCTs. A short duration of the study treatment period was chosen since a high rate of early discharge was anticipated.

Safety data seem much more uniform, instead. The risk of bleeding increases with the use of higher-intensity anticoagulation in most studies, either RCT or large cohorts.[8,14–18,20] However, in the BEMICOP study no major bleeding event was recorded, in part due to the short duration of the study treatment period.

We acknowledge some limitations. First, the open-label design and the lack of an independent adjudication committee, although the primary outcome included a combination of objective variables. Second, some differences between participating sites in the management of COVID-19 patients could exist, although the distribution of concomitant therapies was similar in both study groups. Third, the relatively short duration of study treatment limits the evaluation of long-term impact. Finally, the limited number of patients implies a reduction of the statistical power. However, given the low absolute number of events in both arms, it seems unlikely that significant differences could be reached after completion of the initially planned recruitment.

In conclusion, in COVID-19 patients hospitalized with nonsevere pneumonia but elevated D-dimer, the use of a 10-day course of therapeutic-dose bemiparin does not seem to improve clinical outcomes compared with prophylactic doses. Further research is needed to evaluate other therapeutic strategies and identify subgroups of COVID-19 patients who benefit most of them.

Author Contributions

R.L., J.S., M.B.S., and J.J.F.G. designed and drafted the study protocol, which was reviewed by all other authors. M.M.J., F. C., R.V., P.R.A., D.F., C.C., V.J.Y., P.L., F.A., J.R.Y., and R.L. enrolled and/or followed-up patients. R.L. and J.J.F.G. analyzed the data. R.L. drafted the manuscript, which was critically reviewed by all the authors, who approved the final version.

Data Sharing

Anonymized participant data can be made available upon request directed to the corresponding author. Proposals will be reviewed by the sponsor. Once approved, a signed data access agreement will be required.

Conflict of Interest

R.L. reports investigation grants from Rovi, consultant fees from Aspen and Leo-Pharma, and lecture fees from BMS, Boehringer Ingelheim, Daiichi-Sankyo, Leo Pharma, Rovi, and Sanofi, outside of the submitted work. P.R.A. reports investigation grants from Rovi, consultant fees from Viatris, BMS, Pfizer, and Leo Pharma, and lecture fees from BMS, Daiichi-Sankyo, Leo Pharma, Viatris, and Rovi, outside of the submitted work. All other authors declare no competing interests.

Acknowledgments

This trial was an investigator-initiated study. Laboratorios Farmacéuticos ROVI kindly provided the study drugs, but did not participate in any other step of the clinical trial process. We are grateful to all site staff who contributed to the development of the study and all health care professionals that enrolled participants or cared of them during the study.

References

1 Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report. Chest 2020;158(03): 1143–1163

2 Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv 2021; 5(03):872–888

3 Jiménez D, García-Sanchez A, Rali P, et al. Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. Chest 2021;159 (03):1182–1196

4 Mackman N, Antoniak S, Wolberg AS, Kasthuri R, Key NS. Coagulation abnormalities and thrombosis in patients infected with SARS-CoV-2 and other pandemic viruses. Arterioscler Thromb Vasc Biol 2020;40(09):2033–2044

5 Recomendaciones de tromboprofilaxis y tratamiento antitrombótico en pacientes con COVID-19. Available at: https://www.covid-19.seth.es/recomendaciones-de-tromboprofilaxis-y-tratamiento-antitrombotico-en-pacientes-con-covid-19/

6 Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfus 2020;18(03):167–169

7 Spyropoulos AC, Levy JH, Ageno W, et al; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020;18 (08):1859–1865

8 Patell R, Chiasakul T, Bauer E, Zwicker JI. Pharmacologic thromboprophylaxis and thrombosis in hospitalized patients with COVID-19: a pooled analysis. Thromb Haemost 2021;121(01):76–85

9 Mycroft-West CJ, Su D, Pagani I, et al. Heparin inhibits cellular invasion by SARS-CoV-2: structural dependence of the interaction of the spike S1 receptor-binding domain with heparin. Thromb Haemost 2020;120(12):1700–1715

10 Schulman S, Kearon CSubcommittee 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

11 Kaatz S, Ahmad D, Spyropoulos AC, Schulman SSubcommittee on Control of Anticoagulation. Definition of clinically relevant nonmajor bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13(11):2119–2126

12 Talasaz AH, Sadeghipour P, Kakavand H, et al. Recent randomized trials of antithrombotic therapy for patients with COVID-19: JACC state-of-the-art review. J Am Coll Cardiol 2021;77(15): 1903–1921

13 Tritschler T, Mathieu ME, Skeith L, et al; International Network of VENous Thromboembolism Clinical Research Networks INVENT-VTE. Anticoagulant interventions in hospitalized patients with COVID-19: a scoping review of randomized controlled trials and call for international collaboration. J Thromb Haemost 2020;18 (11):2958–2967

14 Sadeghipour P, Talasaz AH, Rashidi F, et al; INSPIRATION Investigators. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA 2021;325(16): 1620–1630

15 Goligher EC, Bradbury CA, McVerry BJ, et al; REMAP-CAP Investigators ACTIV-4a Investigators ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. N Engl J Med 2021;385(09):777–789

16 Lopes RD, de Barros E Silva PGM, Furtado RHM, et al; ACTION Coalition COVID-19 Brazil IV Investigators. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. Lancet 2021;397(10291):2253–2263

17 Sholzberg M, Tang GH, Rahhal H, et al. Heparin for moderately ill patients with Covid-19. MedRxiv 2021. Doi: 2021.07.08.21259351

18 Lawler PR, Goligher EC, Berger JS, et al; ATTACC Investigators ACTIV-4a Investigators REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. N Engl J Med 2021;385(09):790–802

19 Dodd LE, Freidlin B, Korn EL. Platform trials - beware the noncomparable control group. N Engl J Med 2021;384(16): 1572–1573

20 Demelo-Rodriguez P, Farfán-Sedano AI, Pedrajas JM, et al; RIETE-BLEEDING Investigators. Bleeding risk in hospitalized patients with COVID-19 receiving intermediate- or therapeutic doses of thromboprophylaxis. J Thromb Haemost 2021;19(08): 1981–1989